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CASE SERIES OPEN ACCESS

Management of osseous defects in aggressive periodontitis: A report of four cases using different techniques

Sangeeta Singh, Parul Sharma

ABSTRACT

Introduction: Successful treatment of aggressive periodontitis is considered to be dependent on early diagnosis, targeted antimicrobial therapy and modifying the tissue architecture that is conducive to long-term maintenance. Osseous defects present a challenge in periodontal practice and successful treatment depends primarily on selection of the correct technique and materials. Case Series: This case series presents four cases and a total of eight defects treated with different techniques and materials. One defect was treated using a combination of platelet-rich plasma (PRP) with bone graft substitute, three defects were treated using bone graft substitute with resorbable membrane, one using autogenous bone graft combined with bone graft substitute, one using bone graft substitute alone, one using resection technique and the last one was managed as an endo-perio lesion. The results in all four cases discussed here are satisfactory and have shown long-term stability emphasizing the importance of selection of technique and material. Conclusion: There are different techniques and a variety of newer materials available for elimination of osseous defects. The key to successful management of such defects is correct diagnosis, early intervention and proper selection of technique and materials.

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INTRODUCTION

Aggressive periodontitis by definition comprises a group of rare, often severe, rapidly progressing forms of periodontitis often characterized by an early age of clinical manifestation and a distinctive tendency to aggregate in families. The 1999 international classification workshop identified clinical and laboratory features and further sub-classified as aggressive periodontitis into localized and generalized forms [1]. Localized aggressive periodontitis cases generally present isolated osseous defects, which need early intervention to improve prognosis.

The regeneration of periodontal tissues lost due to destructive inflammatory process has been the ultimate goal of any periodontal therapy. However, despite the development of a wide range of regenerative surgical techniques, this goal remains difficult if not impossible to achieve. Two techniques with the most successful documentation of periodontal regeneration are osseous grafting and guided tissue regeneration [2].

CASE SERIES

Case 1: A 36-year-old male reported with the chief complaint of pain and bleeding from gums since three months. He also complained of pus discharge from maxillary left last molar since one month. On clinical

examination, there were deep pockets > 5 mm in 46, 36 and 27. There was bleeding on probing in all the three teeth involved. The tooth #27 also had Grade II mobility with purulent discharge from the pocket on probing. An orthopantomogram (OPG) revealed infrabony defects on distal aspect of 46 and 36. The tooth #27 had a large periapical radiolucency surrounding the root (Figure 1A). Based on history, clinical findings and radiographic evaluation a diagnosis of Localised Aggressive Periodontitis with an endo-perio lesion in 27 was arrived at.

After phase I therapy and endodontic treatment 27, three different procedures were planned to correct the osseous defects. The first surgery was carried out in 36 region. After debridement, bone graft substitute mixed with platelet-rich plasma (PRP) was placed inside the defect (Figure 1B). In the second surgery involving 46, a bone graft substitute was placed which was covered with a resorbable membrane (Figure 1C). In 27, a complete debridement was carried out.

Case 2: A 29-year-old male reported with the chief complaint of pain and bleeding in relation to upper left tooth since one month. He also complained of dull pain in lower left tooth since three months. Clinically, there were deep periodontal pockets on both mesial and distal aspects of 25 and mesial aspect of 35. Radiographic picture showed osseous defects on mesial and distal aspects of 25 and on mesial aspect of 35 (Figure 2A). A diagnosis of localized aggressive periodontitis was made taking into consideration his positive family history, clinical evaluation and X-rays. After completing phase therapy, surgeries were planned for 25 and 35 using a bone graft substitute in combination with a resorbable membrane (Figure 2B–C).

Case 3: A 34-year-old male reported with the chief complaint of pain, bleeding and pus discharge in relation to upper left tooth since two months. He also complained of bleeding from gums in lower posteriors since one year. Clinically, there was bleeding and pus discharge on probing from 26 region. There was a deep periodontal pocket and Grade III furcation involvement. There were pockets > 6 mm on distal aspect of 46, 47 and 36 regions. An OPG revealed infrabony defects on distal aspect of 46, 47 and 36. There was a large radiolucency around the roots of 26 and severe bone loss especially around the distobuccal root of 26 (Figure 3A). After phase I therapy and endodontic treatment in 26, root resective surgery was planned. The distobuccal root was resected out since there was complete absence of bone around it. After thorough debridement, a bone graft substitute was placed and flap sutured (Figure 3B). Further surgeries were planned to eliminate the osseous defects in 46, 47 and 36 regions. In 36, 46 area, the plan was to use autogenous bone chips from maxillary tuberosity mixed with bone graft substitute making a composite graft. After debridement, the defects were filled with this composite graft (Figure 3C). In 36 region, a debridement followed by placement of bone graft substitute was carried out.

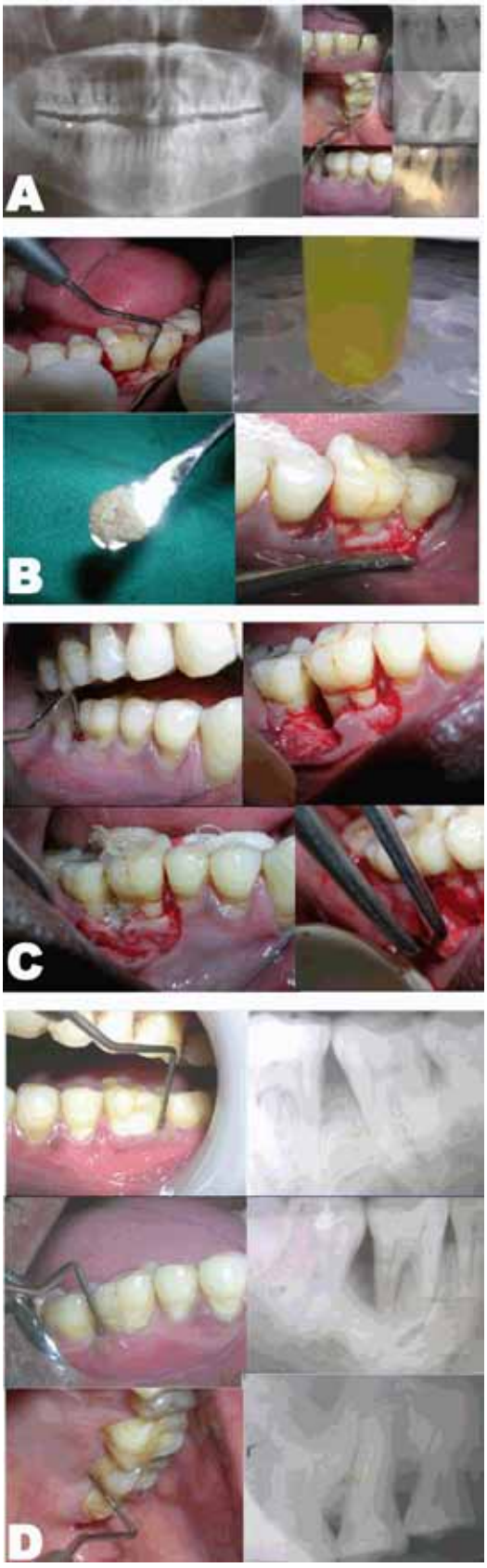

Figure 1: (A) Preoperative, orthopantomogram and clinical evaluation, (B) Tooth #36 treated with platelet-rich plasma bone graft substitute. (C) Tooth # 46 treated using resorbable membrane with bone graft substitute. (D) Postoperative clinical and radiographic evaluation (Case 1).

Case 4: A 17-year-old female reported with the chief complaint of pus discharge and mobility in relation to lower anterior tooth since two months. She had first noticed dull ache in the tooth six months back, which subsided after taking medication. Her main concern was loss of tooth. Clinically, there was a deep pocket on both mesial and distal aspects of the tooth # 31. There was bleeding on probing and advanced grade II mobility. Radiograph revealed a significant osseous destruction around 31, 32 and 41. After endodontice therapy I 31, splinting was done to stabilize the tooth and improve healing. After complete debridement a deep intraosseous defect was evident. A bone graft substitute was placed and flap sutured.

In the Case 1, clinical as well as radiographic picture at sixth month showed reduction in pocket depth and osseous lesions in 36, 46 and 27 (Figure 1). In Case 2, at the time of evaluation at ninth month postoperative, there was significant decrease in the radiolucency in 25, 35 as well as reduction in the pocket depth (Figure 2). In Case 3, following root resection, 26 was clinically healthy and a radiograph at sixth month revealed reduction in radiolucency around the roots (Figure 3D). In Case 4 involving tooth #31, the tooth appeared healthy with no pain or pus discharge. Radiograph showed some amount of bone fill.

DISCUSSION

Aggressive periodontitis results in a very rapid and severe attachment loss which needs immediate corrective measures to arrest progression and prevent further loss. An infrabony defect results when the junctional epithelium is apical to the alveolar crest. These kind of defects are frequently found in areas of the mouth where the cortical bone is thick and is separated by large volume of cancellous bone. The most common location of infrabony defects is the mesial interproximal location between maxillary and mandibular second molars. Since the mandible widens anteroposteriorly, the incidence of infrabony defects increases in the posterior region [3]. Most of the defects in the case series presented here were in mandibular molars. Literature supports the concept that periodontal pockets associated with intrabony lesions are at higher risk of disease progression in patients who do not receive timely and systematic periodontal therapy [4].

A periodontally compromised patient is considered to have poor prognosis when there is moderate to advanced bone loss around one or more teeth leading to tooth mobility of grade II or I. Furcation involvement in difficult to maintain areas, doubtful patient cooperation and presence of coexisting systemic or environmental factors also lead to poor prognosis. Poor prognosis depends on a large number of factors that can interact in an unpredictable number of ways. Prognosis of individual tooth is determined after the overall prognosis and is affected by it.

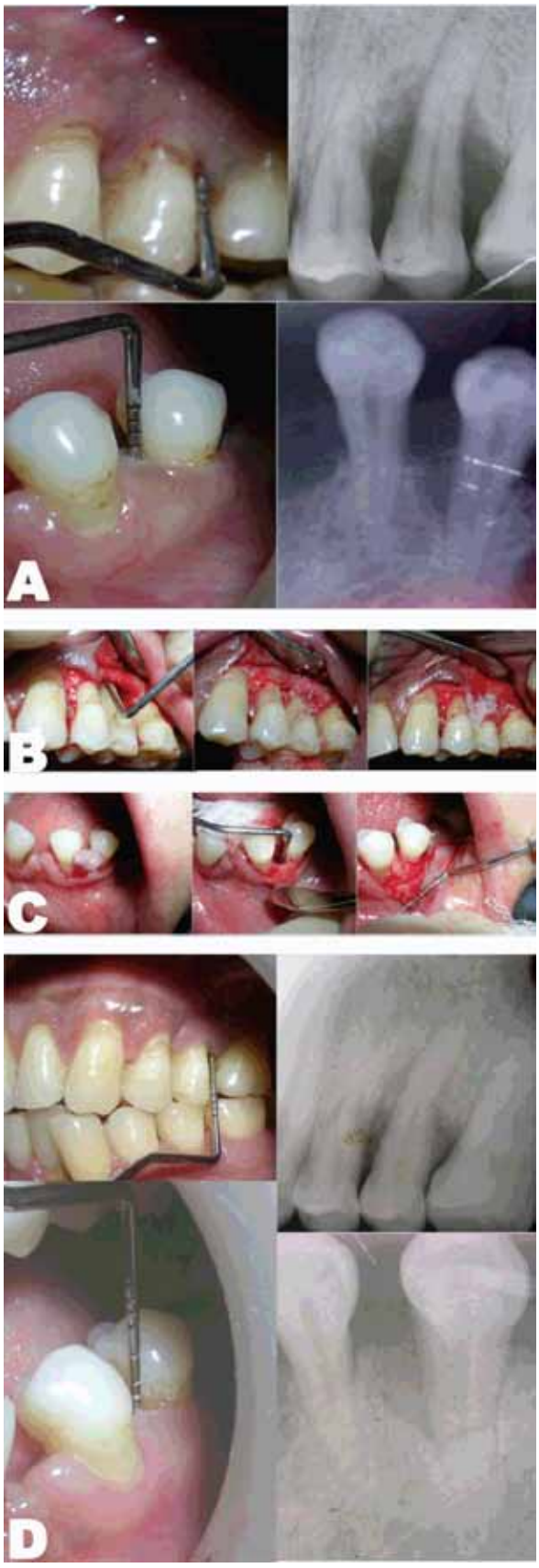

Figure 2: (A) Preoperative clinical evaluation and radiographs. (B) Tooth #25 treated using bone graft substitute with resorbable membrane. (C) Tooth #35 treated using bone graft substitute with resorbabale membrane. (D) Postoperative clincial and radiographic evaluation (Case 2).

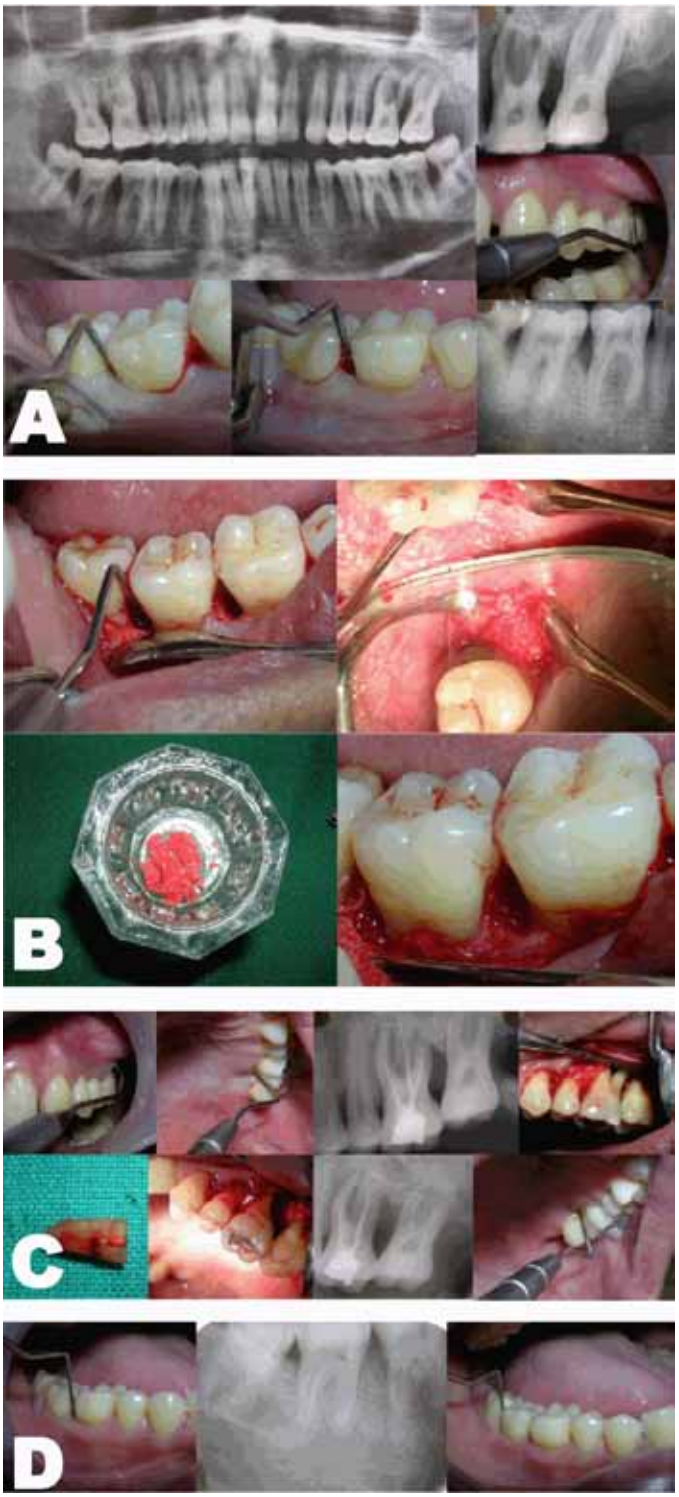

Figure 3: (A) Preoperative clinical evaluation and OPG. (B) Tooth #46, 47 treated using autogenous graft. (C) Tooth #26 treated using root resective surgery. (D) Tooth #46, 47 Postoperative radiographic evaluation (Case 3).

In patients with poor prognosis, the following points should be considered:

(i) Should surgical treatment be undertaken?
(ii) Is it likely to succeed?

Figure 4: Case 4 tooth #31.

(iii) When prosthetic replacements are needed are the remaining teeth capable of supporting the added burden of prosthesis?

In the following conditions decision to save the tooth may be taken:

(i) When endodontic treatment (if necessary) can be performed and the tooth can be sealed with well fitted single tooth restoration with adequate ferrule.
(ii) When vertical osseous defects can be grafted predictably.
(iii) When patient is psychologically motivated to keep his/her teeth and has been informed of various options.
(iv) When patient has very good compliance and maintains good oral hygiene.

Numerous factors must be considered in the treatment planning process when cases present with advanced periodontal disease. The procedure is selected based the clinical findings and in cases with poor prognosis the ultimate decision must be made considering all the presenting factors in that particular case.

With proper management and adequate maintenance even hopeless prognosis teeth can be maintained for a long time.

Despite advent of numeraous alloplastic materials, Autogenous grafts continue to be the gold standard among graft materials with documented excellent regenerative potential proven earlier with histologic evidence [5]. In Case 3, the defects in 46, 47 were treated using autogenous graft from maxillary tuberosity and the results achieved were excellent in terms of reduction in probing depth and radiographic evidence of bony fill.

Alloplastic bone graft substitutes are widely used treatment options for the correction of osseous defects [6, 7]. In this case series, these have been used in all the defects combining them with either resorbable membranes or platelet-rich plasma (PRP) or autogenous graft. The use of PRP combined with bone graft substitute has given excellent results in treatment of infrabony defects [8]. In Case 1, the tooth #36 was treated using PRP combined with a bone graft substitute. There was significant reduction in probing depth and evidence of bony fill on the radiograph.

Endoperio lesions are fairly common conditions that are often difficult to diagnose and if not treated completely can recur. However with proper diagnosis and treatment planning, these lesions can be completely eliminated to give predictable results. At times, a properly done endodontic treatment is sufficient to eliminate the infection. Whenever secondary periodontal involvement exists, it requires periodontal therapy to achieve success. These lesions generally have a vertical osseous defect and periodontal regenerative therapy gives excellent results [8].

In Case 1, tooth #27 had a large endo-perio lesion with Grade II mobility. This tooth could be successfully conserved by a proper endodontic therapy and subsequent complete debridement. Postoperative follow up showed a functional tooth with elimination of periodontal pocket and bony fill evident radiographically. In Case 3, the defect in 26 was very large. There was Grade III furcation involvement and the entire distobuccal root had lost significant bone around it. The tooth was first treated endodontically and then the distobuccal root was resected out. After thorough debridement, a bone graft substitute was placed to fill the defect. In Case #4, the bone loss was quite extensive. The tooth was mobile and required splinting to stabilize it to enhance healing. After debridement, a bone graft substitute was placed to fill the defect.

All four cases in this case series had isolated infrabony defects as a result of the extensive destruction associated with Aggressive periodontitis. The regenerative surgeries carried out to eliminate these defects resulted in successfully conserving the teeth with improved overall long term stability.

CONCLUSION

Aggressive periodontitis is associated with severe and rapid destruction of the attachment apparatus leading to infrabony osseous defects. The treatment plan for these patients must address these defects with the aim of providing a stable environment to prevent recurrence. Newer treatment modalities are being introduced and researched all over the world providing the clinicians with a wide range of options to achieve a more predictable regeneration of the periodontium.

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Author Contributions

Sangeeta Singh – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Parul Sharma – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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CASE SERIES OPEN ACCESS

Massive transfusion in multi-trauma patients

Karlijn JP Van Wessem, Bas A Twigt, Kaj ten Duis, Luke PH Leenen

ABSTRACT

Introduction: Trauma is not only the leading cause of death in patients under 45 years of age, but also the most common cause for massive transfusion. Adequate recognition of the need for massive transfusion is paramount to decrease early mortality. Massive transfusion protocols have been developed to simplify and standardize transfusion administration are based on prevention of coagulopathy, acidosis and hypothermia. Transfusion not only refers to administering packed red blood cells (PRBC), but also limiting coagulopathy by means of using essential hemostatic blood products, such as fresh frozen plasma (FFP) and platelets (PLT). Case Series: In this article, current opinions on massive transfusion will be discussed, based on three patients who received massive transfusion after major injury. All of the three described patients in this article developed coagulopathy, acidosis and hypothermia. Their physiology was corrected by a combination of damage control surgery and early hemostatic blood transfusion. The two surviving patients did not develop any septic complications caused by massive transfusion. At our institution, a 1:1:1 ratio of PRBC:FFP:PLT is advocated, in concordance with most current literature. Massive transfusion, however, can lead to complications such as transfusion induced lung injury, acute respiratory distress syndrome and multiple organ dysfunction syndrome. Conclusion: In this article, current literature is reviewed, and new insights regarding coagulation measurements and hemostatic products including the influence of transfusion on the immune system have been discussed.

Keywords: Multi-trauma, Coagulopathy, Acidosis, Hypothermia, Massive transfusion

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INTRODUCTION

Trauma is the worldwide leading cause of death in people under 45 years of age. Yearly, more than five million people die due to trauma related injuries [1, 2]. Trauma is also the most frequent cause of massive blood transfusion. After brain injury (60%), hemorrhagic shock (30–40%) is the most common cause of death in trauma patients [3–5]. Resuscitation strategies during damage control surgery may be as important as anatomical repair in order to improve long-term outcomes [6]. Early recognition of the need for massive transfusion, in combination with aggressive surgical and non-surgical hemorrhage control, results in significant decrease of early mortality. However, massive blood transfusion is associated with high morbidity and mortality rates.

Herein, we will discuss three patients who received massive blood transfusion after sustaining severe

traumatic injuries, and describe the effects of receiving massive transfusion. At our institution, we advocate a 1:1:1 ratio of PRBC:FFP:PLT transfusion. Our protocol will be discussed and compared to current literature. Furthermore, recent developments and opinions on blood product ratios, clotting assays and hemostatic products will be reviewed.

CASE SERIES

Case 1: Patient A , a 74-year-old male cyclist, was hit by a car. At the scene, he was intubated because of respiratory distress and two large bore cannulas were inserted. In the emergency department, soft but symmetric breathing sounds were heard and several rib fractures were palpable on the right side. Saturation was 90%, blood pressure 63/27 mmHg and pulse 133/min. The abdomen was not tender and the pelvis was stable. The right tibia had a Gustilo-Anderson grade IIIA open fracture and was actively bleeding; a pressure bandage was applied. The chest X-ray showed a right sided hemothorax and therefore a chest tube was inserted and three litres of bloody fluid was drained. Pelvic X-ray showed an acetabular and subtrochanteric fracture on the right, a bilateral pubic fracture, as well as a suspicion for widened sacroiliac joints. Focussed assessment with sonography for trauma (FAST) was negative. Blood pressure stayed low despite two litres of normal saline and five packed red blood cells (PRBC). The laboratory values at the time of presentation is: hemoglobin (Hb) 4.9 mmol/L, pH 7.00, base excess (BE) -17.2 mEq/L and temperature 35.5^{0}C. The patient was taken to the operating theatre for a right sided thoracotomy. No active bleeding was found from either the lung or the pulmonary vessels. However, a right diaphragmatic rupture was diagnosed. In a subsequent laparotomy, a ruptured bladder along with a retroperitoneal hematoma was found. During the procedure, blood pressure remained low (90/50 mmHg) despite massive transfusion of blood products. After placing a C-clamp to stabilize the pelvis, blood pressure rose to 110/50 mmHg and pulse decreased to 100/min. The chest was primarily closed and the abdomen was temporarily closed by a vacuum pack. Postoperative angiography showed contrast blushes from both internal iliac arteries. Therefore, both internal iliac arteries were coiled. After angiography a computed tomography (CT) scan showed a skull fracture with a subdural hematoma. The patient was then taken to the intensive care unit (ICU), having received 28 units of PRBCs, 21 fresh frozen plasma (FFP), and 30 units of platelets (PLT). After transfusion, Hb was 4.4 mmol/L, pH 7.19, BE -14.6 mEq/L, activated partial thromboplastin time (APTT) >120 sec, prothrombin time (PT) was 26.2 sec, International Normalized Ratio (INR) 1.80, platelets 94x10^{9}/L. His temperature was 33.7^{0}C. The patient's neurological condition deteriorated during the following hours in the ICU. A cranial CT scan was repeated and showed more diffuse cerebral swelling with herniation. Due to a futile prognosis, treatment was withdrawn and the patient died.

Case 2: Patient B, a 49-year-old male cyclist, was hit by a sports utility vehicle. On arrival in the emergency department, he was intubated because of respiratory distress and multiple facial fractures. He had symmetric bilateral breath sounds, but subcutaneous emphysema on the left side. A chest tube was inserted, which drained 300 mL of blood. His blood pressure was 60/40 mmHg and pulse 130/min. His abdomen was distended and the pelvis was stable as were both femurs. His Glasgow Coma Scale (GCS) was 15. Chest X-ray showed a chest tube on the left side in good position, lung contusion and several rib fractures. The FAST showed free fluid. The laboratory values at the time of presentation is: Hb 2.7 mmol/L, BE -11.5 mEq/L, APTT >120 sec, PT 34.6 s, and INR 2.33. Our massive transfusion protocol was initiated and the patient was immediately transported to the operating theatre. During laparotomy a splenic rupture and an avulsed left kidney were found, requiring splenectomy and nephrectomy. The abdomen was packed and a vacuum dressing was applied. After being transported to the ICU, he had received 5.5 liters of Ringer's lactate, 11 units of PRBCs, 6 FFPs and 10 PLT units. Despite massive transfusion, the patient was transported to the theatre twice again during the next few hours due to hemodynamic instability. The second operation showed diffuse oozing from the kidney bed. A few hours later, an ischemic transverse colon was found and resected based on a ruptured middle colic artery. At that time, he had received 51 PRBC units, 50 FFPs, 45 PLTs. The hemogblobin then was 6.0 mmol/L, pH 7.37, BE -2.8 mEq/L, platelets 58x10^{9}/L, APTT 38 s, PT 10 s, and his temperature was 35.9^{0}C. After stabilization, a CT scan was performed a few hours later which showed a subdural hematoma on the right frontotemporal side, a Le Fort I facial fracture, C6 facet joint fracture, transverse process fractures of L2-L4, and several rib fractures on the left side. On the third day his colon was anastomosed, on eight day the abdomen was closed, and on day ten and fifteen his facial fractures were repaired. Apart from a bleeding peptic ulcer postoperatively, no further complications occurred, and six weeks after arrival, he was discharged to a rehabilitation center.

Case 3: Patient C, a 48-year-old male driver hit a tree. Upon arrival in the emergency department his airway was threatened because of blood in his mouth. There were bilateral soft but symmetric breathing sounds and the left side of his chest was painful on palpation. Saturation was 75%, blood pressure 125/75 mmHg, pulse 125/min, and GCS 11 (E3M6V2). A chest X-ray showed multiple fractured ribs on the left side, but no pneumothorax. A pelvic X-ray showed no abnormalities. His abdomen was not tender, but a FAST of the abdomen showed free fluid. The patient was intubated and a left chest tube was inserted. Additional X-rays revealed a comminuted femur and patella fracture on the left side.

The first measured Hb was 8.4 mmol/L, pH 7.40, BE -7.0 mEq/L, platelets 154x10^9/L, PT 15 s and APTT 32 s, and INR 1.10. The patient was prepared for CT scan, but because of hemodynamic instability despite resuscitation he was transported to theatre for a laparotomy. A caval vein injury was diagnosed with a partially avulsed left kidney, a contused transverse colon with several serosal tears and a vascular pancreatic injury. The caval vein injury was sutured, a left nephrectomy was performed, the transverse colon resected and the abdomen was packed and a vacuum pack was applied. The femur was stabilized with an external fixator. By then the patient received 18 PRBC units, 18 FFPs and 20 PLTs. The hemoglobin was 4.5 mmol/L, pH 7.10, BE -9.7 mEq/L, platelets 116x10^9/L, PT 16.6 s, APTT 42 s, and INR 1.20. After 24 hours, a second look laparotomy was performed whereby the colon was anastomosed and the abdomen closed. On third day, the patient developed respiratory distress despite being on a ventilator with high pressures and high FiO2 values. Therefore, the femur was left with the external fixator and no intramedullary nailing was performed. The CT angiography of the chest revealed no abnormalities [no signs of pulmonary emboli, Adult Respiratory Distress Syndrome (ARDS) or pneumonia]. A few days later, he developed fever and a relaparotomy was done and large amounts of pancreatic necrosis were found and resected. The colon anastomosis was intact. On day 21, he developed chylous leakage and was put on total parenteral feeds. Chylous leakage ceased and oral feeding could be resumed after a few weeks. Four weeks after the accident the patellar fracture was fixed, and three weeks later, the patient was discharged to a rehabilitation center.

DISCUSSION

Lethal triad of hypothermia, acidosis and coagulopathy

The three described cases show severely injured patients with persisting hemodynamic instability based on hypovolemic shock. Shock causes a shift from aeroob to anaeroob metabolism resulting in acidosis. Furthermore, patients in shock develop hypothermia; they do not only lose warmth during the trauma itself, initial assessment and operations, but also because of massive transfusion of blood products. Hypothermia causes arrhythmias, decreased heart minute volume, increased vascular resistance and a shift to the left in the oxygen-hemoglobin saturation curve. Thirdly, these severely injured patients develop coagulopathy. Previously, it was assumed that dilution by resuscitation was the most important factor causing coagulopathy. Current insights, however, show that coagulation cascade and platelets are not only influenced by hemodilution but also by acidosis and hypothermia. A temperature of 32°C equates to clotting factor activity of 2.5% of normal. It is postulated that the major effect on clotting factors during hypothermia is on the kinetic activity of clotting enzymes. Therefore, the appropriate treatment for hypothermia induced coagulopathy is rewarming rather than administration of clotting factors [6]. Coagulopathy develops in the early phase after injury and is not related to fluid resuscitation. Coagulopathy is a marker for injury severity and is related to mortality [7]. Moreover, hypovolemic shock and transfusion itself induce fibrinolytic system consumption by activating the coagulation cascade [7]. In international literature the combination of hypovolemia, hypothermia and acidosis is called the 'lethal triad'. The treatment of patients is focussed on preventing this dangerous vicious cycle.

Massive transfusion of blood products

The presented patients all received massive transfusion of blood products after sustaining severe injuries [8]. The definition of massive transfusion is administration of more than ten PRBCs in 24 hours, more than one entire blood volume in 24 hours, more than four PRBCs in one hour, or more than 50% of total blood volume within the first three hours [9, 10]. Massive transfusion is associated with increased mortality: more than six PRBCs within 24 hours have a mortality of 20–30%, more than 10 PRBCs within 24 hours are associated with mortality as high as 50% [11]. Length of stay in ICU is longer if patients receive more than six PRBCs (more than ten days versus four days if the patient received less than four PRBCs). If transfusion exceeds six PRBCs the total hospital stay is also longer. Blood product transfusion can cause adverse effects such as transfusion reactions, infection transmission and has an immune modulatory response. After blood product transfusions, an increase is seen in wound infections, pneumonias, sepsis, systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), transfusion related acute lung injury (TRALI) and multiple organ dysfunction syndrome (MODS) [12, 13].

For a long time, it has been unclear what transfusion protocol was associated with lower morbidity and mortality. In the military, it has already been long advocated to use massive transfusion protocols in which the administration of blood product combinations resembled whole blood [14, 15]. It is clear now that in the civilian population the administration of a higher FFP:PLT:PRBC ratio is also associated with lower mortality [5]. It became also clear that a good-working massive transfusion protocol is paramount for optimal results. Cotton et al. demonstrated that administration of blood products according to a predefined protocol in the early phase of resuscitation leads to less MODS, less infectious complications, decrease in ventilation days and reduction of abdominal compartment syndrome and incidence of open abdomens [16].

Several studies have shown that early correction of coagulopathy is associated with increased survival [5,

8, 9, 14–19]. In other words, massive transfusion based on a more physiologic regime resembling whole blood will improve survival. With reference to good results in several studies a new international consensus has been developed: A ratio of 1:1:1 in PRBC:FFP:PLT is advocated [9, 20–22]. This ratio results in decreased mortality, less blood products needed and decreased costs per patient. In our hospital, we also strive towards a 1:1:1 ratio. The pillars of our protocol are: stop the bleeding, be flexible regarding hypotension, perform damage control surgery when needed, minimizing the use of crystalloid fluids, start early with blood products (aiming at a ratio of 1:1:1), administer tranexamic acid and use thromboelastography in multiple transfusion patients (>5 PRBC).

In literature, it is mentioned that it might be difficult to reach a 1:1:1 ratio in practice because O negative PRBCs are readily available in the emergency department, while FFPs and PLTs usually need to be prepared. The transfusion ratios, obtained in patients A, B, and C were 1.3:1:1.4, 1.1:1.1:1, and 1:1:1.1, respectively. To reach these ratios it is paramount to optimize the cooperation between the blood bank and the anesthesiologist who coordinates blood product administration.

It is important to note that the transfusion consensus is mostly based on retrospective studies since it is very difficult to randomize severely injured patients for a specific transfusion ratio. Furthermore, there is evidence that this management may cause more complications such as SIRS, TRALI and MODS [12]. Possibly, this is caused by increased FFP and PLT administration. Due to this, some authors are warning against the development of protocols for empirical FFP transfusion [23]. Other authors stress the importance to administer FFP when it is physiologically necessary and not simply when there is laboratory evidence of coagulopathy [24]. This pleads for a more individual approach, adjusting the transfusion ratio on the basis of post-injury changes in the clotting and fibrinolysis cascade. In a recent review Sorensen et al. speculate that timely and rational use of systemic antifibrinolytics, local hemostatics and coagulation factor concentrates (fibrinogen, prothrombin complex concentrate, recombinant factor VIIa and factor XIII) will be more efficacious and safer than ratio-driven transfusions [25]. Innerhofer et al. have recently shown in a prospective cohort study that prothrombin complex concentrates (PCC) are effective in correcting coagulopathy and reducing the need for transfusion in patients with severe blunt trauma [26]. However, larger randomized trials need to be conducted to evaluate this effect since an increased risk of thromboembolic events has been reported in the past as well [27]. We believe until that time has come, it is safer and more useful to have an uniform protocol.

In the cases described above, none of the two surviving patients developed TRALI, ARDS or MODS despite massive transfusion administration. It could be noted that massive transfusion may have attributed to brain swelling causing patient A to develop cerebral herniation. However, it will remain unclear whether cerebral herniation would have been prevented if he had not received massive transfusion.

Thromboelastography

In massive transfusion patients APTT and PT have shown to be bad predictors for coagulopathy and the need for transfusion [28]. New insights regarding clotting measurements have led to the introduction of the thrombelastograph hemostasis analyzer (TEG). Thrombelastography has proven, in contrast to APTT and PT, to be a simple viscoelastic test of overall coagulation by measuring clot strength, which reflects the quantity and quality of both clotting factors and platelet function. Furthermore, it is a rapid (several minutes versus 45 minutes for APTT and PT) and inexpensive test. Treatment of coagulopathy can be focussed on the consumed clotting factors because TEG determines coagulation directly [4, 29]. The TEG has recently been implemented in our hospital and some studies indicate that transfusion ratios might be further adjusted even more, based on TEG measurements. Eventually, it might lead to transfusion ratios personalized to the specific patient's needs [24].

Blood product replacing therapies

In recent years, blood product replacing therapies have gained more and more interest. Several products are described below.

Recombinant activated factor VII (rFVIIa) has been used for some time for spontaneous bleeding in hemophilic patients. It enhances clot formation in combination with tissue factors expressed on damaged or ischemic vascular subendothelium. It binds directly to activated platelets, thereby stimulating a stable hemostatic plug formation. rFVIIa, however, is very expensive. Recently, a large multicentre trial studying rFVIIa in multi trauma patients has been terminated because no increased survival could be demonstrated, even though the number of blood products in rFVIIa-treated patients decreased [2].

Part of the response to trauma and surgery is fibrinolysis. This response can be so large that is becomes pathological due to hyperfibrinolysis. Antifibrinolytics decrease blood loss in patients with both normal and pathological responses without apparent increases in postoperative complications [30]. Tranexamic acid is a synthetic derivative of amino acid lysine that inhibits fibrinolysis by blocking lysine binding sites on plasminogen and in contrast to rFVIIa, the treatment is inexpensive. Several clinical studies have researched tranexamic acid in trauma patients. The Lancet has published a randomized clinical trial including more than 20,000 patients showing a significant decrease in mortality in multi trauma patients treated with tranexamic acid. Furthermore, mortality caused by bleeding was significantly lower when treated with tranexamic acid [31].

Fibrinogen plays an important part in hemostasis through its role in platelet aggregation formation and construction of a stable fibrin network. Current transfusion strategies are based on reaching adequate coagulation by administration of FFPs and PLTs. Cryoprecipitate (a combination of Factor VIII, fibrinogen, fibronectin, von Willebrand factor and Factor XIII) is mainly used when fibrinogen blood levels are too low. Fibrinogen concentrations in cryoprecipitate are much higher than in FFP. When cryoprecipitate is administered to correct fibrinogen levels, the volume added is much lower than when FFP is used. This is favorable in reducing complications related to massive fluid resuscitation. At this moment, it remains unclear whether normal fibrinogen levels in trauma patients are recommendable [32].

Hemoglobin based oxygen carriers (HBOC, hemtetrameres) are human blood derivates and developed in the United States for military purposes. Studies have demonstrated that HBOCs have a number of advantages, namely being always compatible, they do not transmit diseases, have no immunological side effects, and can be stored long-term [33]. In 2008, Moore et al. published a multicenter randomized double blind trial comparing HBOC administration in a pre-hospital setting with customary administration of crystalloids and PRBCs. No statistical significant difference could be demonstrated in a 30-day mortality between both groups. However, there were more complications reported in the HBOC treated group. Consequently, it was advised to consider HBOC treatment only if blood products are not available, such as in war or disaster situations [33].

Inflammatory response induced by massive resuscitation

Although blood transfusions are lifesaving, some studies suggest that patients receiving blood transfusions with older PRBCs have worse clinical outcomes including sepsis and MODS than patients who receive fresh blood [34, 35]. With increased storage time, PRBCs change in biochemical composition and morphology resulting in erythrocyte lysis. Neal et al. have shown that transfusion of intra-erythrocytic compounds may have adverse reactions, especially with long stored PRBC units or in massive transfusion. Free heme released from hemolysis exerts an impact on multiple components of the innate immune response, both through effects on NO depletion as well as cellular specific mechanisms [36].

Microparticles (MP) are vesicles that are thought to bud from apoptotic or activated cells and retain the surface markers of their parent cell [37]. It is likely that erythrocytes undergo MP formation as they age. These MPs appear to contribute to neutrophil priming and activation. The presence of MPs in stored units can be associated with adverse effects after transfusion, including lung injury [38].

During the last years the efficacy of various blood products used as resuscitation fluid on the acute inflammatory response after hemorrhagic shock has been investigated. Makely et al. have shown that resuscitation with fresh whole blood ameliorated the inflammatory response after hemorrhagic shock and that crystalloids in mice induced a larger inflammatory response compared with fresh whole blood [39]. Subsequently, they investigated the use of different ratios of PRBCs and plasma and found that a 1:1 ratio of PRBC to plasma is nearly as efficacious as fresh whole blood [40]. Further, removing MPs from aged blood before use proved to be beneficial because of the reduction in inflammatory response [40].

Not much is known about the influence of fresh frozen plasma administration on the immune system. The FFP contains leukocyte-derived bioactive substances that can sometimes cause transfusion related lung injury (TRALI) and/or anaphylactic shock [41]. These adverse reactions are thought to be an expression of a pro-inflammatory response. This was confirmed by in vitro studies by Urner et al. [42]. They found that blood products are able to provoke a pro-inflammatory response in endothelial cells, especially when cells are already pre-activated. Nohe et al. have investigated the role of FFP on the endothelial cell adhesion molecules and subsequent neutrophil-endothelial interactions in vitro. They found that FFP reduced the adhesion molecule expression and subsequent adhesion of neutrophils on the endothelium. This suggested that FFP also have an anti-inflammatory effect [43]. This can possibly attributed to fibrinogen. Several studies have shown that fibrinogen induces a pro-inflammatory response by interaction with neutrophil MAC-1 (complement receptor consisting of CD11b/CD18) facilitating neutrophil adhesion to the endothelial wall [44, 45]. In vitro studies from our own research group however have shown that fibrinogen has an anti-adhesive role in regulating neutrophil-endothelial interactions [46]. Cryoprecipitate contains higher concentrations of fibrinogen than FFP. Interestingly, a retrospective study analyzing polytrauma patients showed less organ failure when cryoprecipitate was administered instead of FFP [47]. One could speculate that the anti-inflammatory effect of fibrinogen has attributed to these results.

To date, the exact role of blood products in the inflammatory response remains unclear.

CONCLUSION

This case report shows that multi trauma patients in hypovolemic shock do not only benefit from damage control surgery but also from adequate transfusion management. It is paramount to prevent the 'lethal triad'. Transfusion management is not only focussed on packed red blood cells administration, but also on supplying necessary clotting factors to limit coagulopathy. We not only advocate a 1:1:1 transfusion ratio from a hemostatic point of view, but it has also a less detrimental effect on the inflammatory response. In two out of our three

patients a 1:1:1 transfusion ratio was feasible. Patient A had a 1.3:1:1.4 ratio. This was mainly due to lack of initial available fresh frozen plasma (FFP) in the emergency department. To solve this problem, it could be advocated to have FFPs readily available in emergency department at all times. In the near future, coagulation will be measured more quickly and more accurately by thromboelastograph hemostasis analyser. It is expected that this technique will soon be available in emergency department, ICU and operating theatres. This development will increase adequate coagulopathy correction. At the moment, tranexamic acid is the most promising blood replacing product.

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Author Contributions

Karlijn JP Van Wessem – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Bas A Twigt – Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Kaj ten Duis – Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Luke PH Leenen – Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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CASE SERIES OPEN ACCESS

Sarcoma botryoides a management dilemma: A review of two cases

Aliyu Labaran Dayyabu, Adogu IO, Makama BS

ABSTRACT

Introduction: Sarcoma botryoides is a rare and rapidly growing tumor affecting primarily the female genital tract of children. It presents as bleeding per vaginum or as a polypoid fleshy mass protruding through the vagina. Treatment is surgery combined with multidrug chemotherapy. In developing environment, one has to contend with late presentation, availability and affordability of cytotoxics and the surgical options available at advanced stage, their acceptability, their management postoperative and their impact on quality of life. Case Series: The first case was a four-year-old child who presented with a rapidly growing mass protruding per vaginum, intermittent vaginal bleeding and difficulty in passing stool and urine. She had examination under anesthesia and biopsy. Histology confirmed sarcoma botryoides. Her parents opted for multidrug chemotherapy and was treated with a combination of cylophosphamide, vincritine and doxorubicin. She had six courses of the drugs with remarkable improvement in symptoms and the tumor regressed almost completely. Patient was subsequently lost to follow-up. The second case was a six-month-old child who presented with vaginal bleeding, vaginal growth and abdominal swelling. Histology confirmed sarcoma botryoides and the parents were counselled on management options which they declined and took the child home. The child was brought back with obstructive uropathy and septicemia. She had suprapubic cystostomy to relieve the obstruction. However, her condition deteriorated and she died a week after admission. Conclusion: Sarcoma botryoides is a rapidly growing malignancy, early presentation and prompt and aggressive surgery combine with multidrug chemotherapy may be the answer if outcome is to be improved. To ensure this in low resource countries free health care for children and all individuals with malignancies and chronic debilitating diseases should be provided. In addition education and poverty alleviation will further save the situation.

Keywords: Sarcoma botryoides, Rhabdomyosarcoma, Multidrug chemotherapy

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INTRODUCTION

Sarcoma botryoides is a malignancy that arises from embryonal rhabdomyoblasts. It is also called embryonal rhabdomyosarcoma. The word botryoid in Greek means a bunch of grapes which characteristically describes the clinical appearance of the tumor. It is the most common soft tissue sarcoma in childhood and young adulthood, and account for 4–6% of all malignancies in this age group [1]. Sarcoma botryoides is usually reported as a

vaginal tumor in female reproductive tract of infants [2]. However, it also occurs rarely in the cervix or uterine fundus [3]. Unlike its counterpart in the vagina, which has poor prognosis, sarcoma botryoides of the cervix in young women has a favorable outlook [4]. Two other studies also reported better prognosis when the lesion affect the cervix [5, 6]. The survival rate of vaginal and cervical lesions has been reported to be 60–96%, respectively [7]. Vaginal bleeding is the most common presenting feature even though non-specific [8]. It may also present as a polypoid or fleshy mass in the vagina, or more classically projecting from the introitus. Other forms of presentations include urinary symptoms especially when the tumor is anteriorly situated or tenesmus where there is posterior extension [9].

There are different approaches in the management of this tumor, from simple excision to extensive radical mutilating procedures. These procedures may be combined with radiotherapy. However radiotherapy has been abandoned as it is now generally agreed that these tumors are not radiosensitive [9]. New multidrug chemotherapy regimens with or without radiotherapy are also used in combination with less radical surgery with good results, although outcome data are not yet available [10]. Radical surgery takes the centre stage in treatment as the disease is uniformly fatal with a five-year survival rate of between 10–35% [11]. Sarcoma botryoides has marked tendency for recurrence locally after excision and to invade adjacent organs [9].

We present two cases of Sarcoma botryoides to illustrate the difficulties encountered by Gynecologists in the management of this malignant and aggressive tumor (Sarcoma botryoides) in children in low resource environment and the benefit of multidrug chemotherapy when the disease is advanced.

CASE SERIES

Case 1: A four-year-old child was presented with a four-month history of serous vaginal discharge, three-month history of intermittent slight vaginal bleeding and two-month history of a mass protruding per vagina. The mass started increasing in size rapidly and occasionally bleeds on contact. Later, the mother noticed that the abdomen was progressively becoming distended with associated difficulty in passing stool and urine. There was also progressive weight loss. The mother started applying some herbal preparations on the mass without improvement. The child had five other siblings none of them had similar problem. Her pregnancy was carried to term and was uncomplicated. Mother had no antenatal care while carrying the child's pregnancy.

On examination the patient (child) was found to be slightly emaciated, mildly pale, afebrile and anicteric. Her chest was clinically clear with 18 respiratory cycles per minute. Her pulse rate was 74 beats per minute and had no abnormal heart sounds. Her abdomen was distended firm and there was a suprapubic mass about 16 cm in size firm slightly mobile, one can get above but not below it. There was no demonstrable ascites and liver, kidney and spleen cannot be palpated. Pelvic examination revealed a polypoid mass, pink in colour, covering the whole of vaginal introitus (Figure 1). Further examination of the vagina was not possible because it was filled with the mass. The mass bleeds on touching. Rectal examination revealed a smooth anterior rectal wall with a mass pushing into the rectum.

An abdomino-pelvic ultrasound revealed a distended bladder and a mass measuring 6.1×5.2 cm lying posterior to the bladder. Both kidneys, liver, gallbladder and pancreas were grossly normal. There was no ascites. She had some investigations such as full blood count and differential, electrolytes, urea and creatinine, liver function tests and chest X-ray. All the test results were within normal ranges.

The parents were counselled on need for biopsy to confirm diagnosis before further management.

An examination under anesthesia and biopsy was done. Histology result revealed embryonal rhabdomyosarcoma (Figure 2).

The parents were informed of the result and options of management were discussed. The parents opted for cytotoxic chemotherapy.

The child was prepared for chemotherapy and the plan was to give a combination of cyclophosphamide (300 mg iv), vincristine (0.9 mg iv) and doxorubicin (22 mg iv) which will be given at two weekly interval. Before each course of treatment, the following investigations were done: full blood count and differentials, liver function test and electrolytes, urea and creatinine and any abnormality corrected before the next course is given. After four courses, the mass was noted to have regressed significantly in size (Figure 3), and the abdominal swelling disappeared. The difficulty of passing urine and stool also improved. Before the last course, the vaginal mass had disappeared completely and five days after the last course, the patient was discharged to come for follow-up in two weeks.

On follow-up the mother complained that the child's underwear were stained with clear malodorous discharge. The patient was examined and vulva was found to be stained with serous discharge and after a course of antibiotics the discharge stopped. She had two more uncomplicated follow-up visits and was subsequently lost to follow-up.

Case 2: A six-month-old child was brought to the hospital with a complaint of a vaginal growth that appeared a month prior to presentation and vaginal bleeding. The mass bled intermittently especially on contact. There was also abdominal swelling which appeared about two weeks following the appearance of the vaginal mass. The vulva appeared normal at birth and pregnancy was uncomplicated and was carried to term. No history of similar problem in her siblings.

On examination the infant appeared stable, not pale and not febrile, no jaundice. Respiratory rate was 20 cycles per minute and her chest was clinically clear. Her pulse rate was 80 beats per minute and had no added heart sounds. Abdomen was slightly distended with a suprapubic mass of about 14 weeks size, firm, mobile and non-tender. Other organs were not palpably enlarged. Pelvic examination revealed a mass protruding through the vaginal introitus completely covering the urethral opening (Figure 4).

The parents were counseled on the need for biopsy before further management. The patient was admitted and the plan was to do a full blood count, liver function test, electrolyte, urea and creatinine and abdomino-pelvic ultrasound. Biopsy was taken and the result confirmed embryonal rhabdomyosarcoma (Figures 5 and 6) and the parent were informed of the result and counselled on the line of management. They signed against medical advice and left. After four weeks, the patient was brought back with complaints of inability to pass urine and constipation for three days.

Figure 1: Polypoid tumor mass.

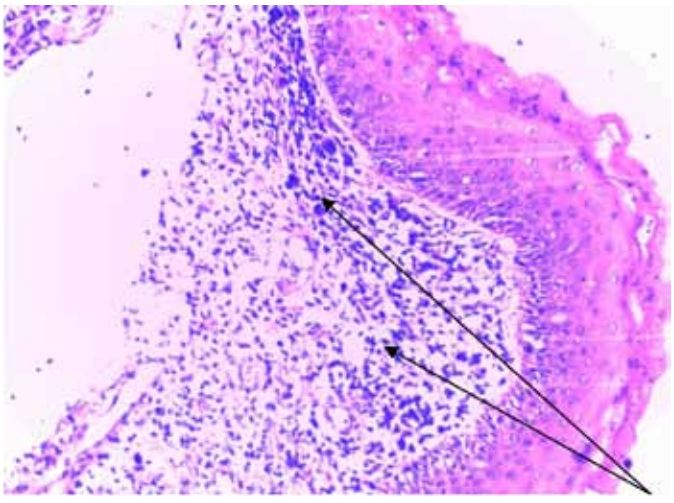

Figure 2: Cambium layer (H&E stain, ×100).

Figure 3: Residual tumor after four courses of cytotoxics.

Figure 4: Tumor mass filling the vaginal introitus.

On examination she was ill looking, dehydrated, febrile to touch (temp 38°C), pale but anicteric. Respiratory rate was 24 cycles per minute and there were fine basal crepitations in the lower lung fields. The pulse rate was 110 beats per minute and there were no added heart sounds. The abdomen was grossly distended and tender and organs could not be palpated. Pelvic examination revealed a large infected mass, with irregular

surface covering the whole of the vulva. Urethral opening could not be identified (Figure 7). Rectal examination revealed a mass bulging into the rectum with irregular surface and mobile anterior rectal wall mucosa.

An assessment of sarcoma botryoides, obstructive uropathy and septicemia was made.

Packed cell volume of the infant was 18%, urea level was elevated and electrolytes were derrange. Liver function was normal and urine microscopy and culture revealed a growth of *Escherichia coli*. She was rehydrated with intravenous fluid and was also transfused with packed cells and placed on parenteral antibiotics. She was also empirically treated for malaria parenterally. A Urologist was invited who suggested that suprapubic cystostomy was needed to relieve the urinary obstruction which was done. Patient's condition continued to deteriorate despite all the treatment and died after a week of admission.

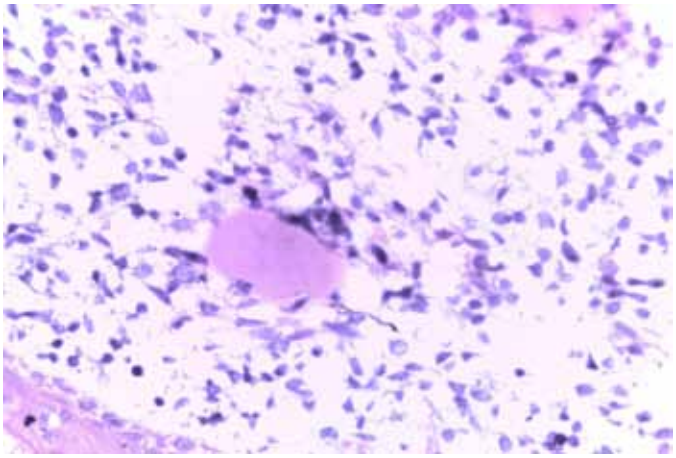

Figure 5: A slide showing multiple rhabdomyoblast in myxomatous stroma (H&E stain, ×200).

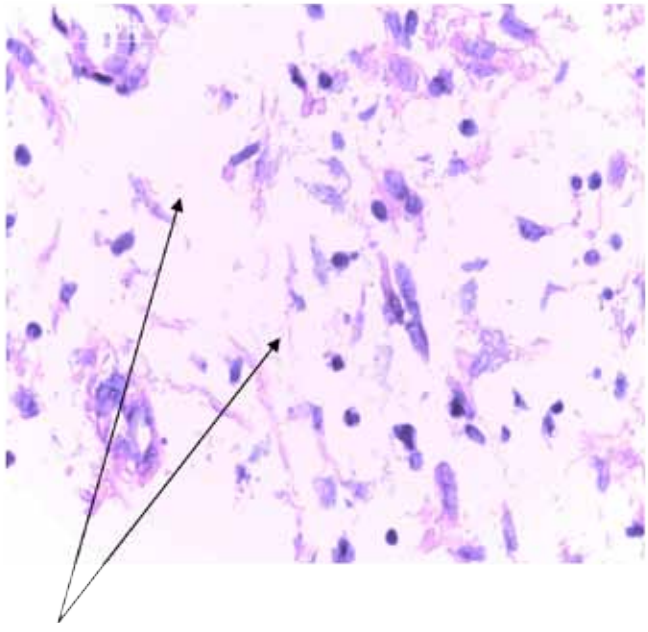

Figure 6: Strap cells (which are characteristic of Sarcoma botryoides) (H&E stain, ×400).

Figure 7: The same tumor mass at second presentation infected and degenerating.

DISCUSSION

Rhabdomyosarcoma is a malignant tumor which arises from embryonic muscle cells [12]. It present as a submucosal lesion giving the typical 'grape like' appearance and is usually seen in female infants and young children [13, 14]. Our two patients presented with grape-like, pinkish oedematous polyps filling the whole vagina. Other ways of presentation include recurrent vaginal bleeding, urinary symptoms and tenesmus [9]. The second patient presented with all these features while the first presented in a similar manner but with no tenesmus. A gynecologist managing such a case has to contend with a lot of issues which ultimately determines the outcome of treatment and the prognosis of the patient. One important issue is late presentation, this impact significantly on outcome. Some of the reasons for this is going to see traditional healers in the first instance and seeking modern medical care as the last resort. Both patients were initially treated by local traditional healers who gave them some herbal preparations to apply in the vagina. When the lesions continue to grow the parents brought the children to hospital. Financial constraints and lack of easily accessible health facilities also lead to late presentation. The parents of both children were peasant farmers living in remote villages very far from the nearest health facility. When eventually the patients presented the tumor had advanced to a stage where only palliative care is possible. The second problem encountered is refusal to accept the counselling given on the type of treatment which is likely to give a better result. In fact, after proper evaluation and counselling the mother of the second child signed against medical advice

and left only to come back when the child had developed obstructive uropathy, anemia and septicemia.

Our intention in the treatment of the first case was to do surgery and follow it up with multidrug chemotherapy, however, when the parents refused surgery we offered the patient multidrug chemotherapy. The child had remarkable improvement after six courses given at two weekly intervals and the tumor grossly disappeared. She had three symptoms free follow-up visits and was subsequently lost to further follow-up.

All these problems arise because of illiteracy and poverty which create a vicious circle which compound the management of patients not only for a malignant and aggressive disease like sarcoma botryoides but also in the treatment of simple diseases. The solution lies in elimination of poverty and illiteracy.

CONCLUSION

Sarcoma botryoides is a rapidly growing malignancy, early presentation and prompt and aggressive surgery combine with multidrug chemotherapy may be the answer if outcome is to be improved. To ensure this in low resource countries free health care for children and all individuals with malignancies and chronic debilitating diseases should be provided. In addition, education and poverty alleviation will further save the situation.

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Author Contributions
Aliyu Labaran Dayyabu – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Adogu IO – Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published
Makama BS – Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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CASE REPORT OPEN ACCESS

Triple simultaneous primary tumors of the head and neck: A rare case report

Hemavathi Umeshappa, Chandrashekhar M, Ashok M Shenoy, Dinesh Kumar GR

ABSTRACT

Introduction: Synchronous multiple tumors in the head and neck, has been reported to be around 0.5%. The development of simultaneous triple primary malignant neoplasms of different histology, confined to the head and neck region reported till now is very rare. Case Report: Herein, we report such a unique case where in three simultaneous neoplasms were diagnosed in single patient, with histology of different tissue origin and managed successfully by surgery. Conclusion: The risk of occurrence of new tumors in patients with multiple primary tumors should always be considered. Triple simultaneous primary tumors diagnosis reduces the incidence of secondary metastasis. It is essential to have regular checkups for better outcome of these patients.

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INTRODUCTION

Multiple malignant neoplasms are described based on their chronology of presentation as simultaneous, synchronous or metachronous. Tumors presenting at the same time in the initial examination are classified as simultaneous tumors, a terminology which has recently been introduced [1]. Tumors presenting within six months of diagnosis of index tumor is termed synchronous tumors. Metachronous tumors are those presenting after six months of diagnosis of index tumor. It is rare for a patient to suffer from three primary simultaneous malignancies of different histology. It is even rarer for these tumors to present at the same time in a confined anatomical region such as head and neck area. The prognosis of patients suffering from multiple primary cancer in head and neck is poor and early detection is essential. The development of second primary tumor was of equivalent prognosis to recurrence of primary tumor. The diagnosis of three simultaneous tumors during single visit, reduces the morbidity associated with the management of loco regionally advanced stage of the disease, and prolongs the survival thereby providing favorable outcome.

CASE REPORT

A 63-year-old female visited us with a chief complaint of swelling over the left side of neck since 16 years. Patient noticed mass in neck which was initially small and gradually increased to present size. She did not have difficulty in breathing or hoarseness of voice. Patient developed symptoms of dysarthria and difficulty in swallowing since six months. Patient does not have the history of exposure to ionizing radiation or tobacco habits or familial predisposition.

Clinical examination revealed an extra oral mass of size 5x6 cm involving the parapharyngeal space. There was no rise in ear lobule. No signs of facial nerve involvement was present. On palpation of neck lymph nodes were not enlarged. A second lesion of size 1x1 cm involving on the right side of the upper lip. A solitary lobulated, midline swelling of size 3.5x4.0 cm involving left lobe of the thyroid gland. Swelling moves with deglutition, non tender on palpation but the inferior border of thyroid gland was indistinct suggesting substernal extension. Mouth opening was adequate, intraorally there was bulging of pharyngeal mucosa of oropharynx with shift of uvula to right side (Figure 1).

Computed tomography (CT) scan showed 9.1x7.8 cm well circumscribed heterogeneously enhancing lobulated mass in the left upper neck predominantly involving the left parapharyngeal space probably arising from ectopic salivary tissue. No extension to involve the vagus nerve, IJV or carotid vessels. Another lesion of size 6.5x4.3 cm nodule in left lobe of thyroid with retrosternal extension into superior mediastinum and tracheal compression (Figure 2). Fine-needle aspiration cytology of left parapharyngeal mass proved to be Adenoid cystic carcinoma, and left thyroid nodule suspicious of follicular neoplasm.

After preoperative workup, the patient underwent three operative procedures (Figure 3).

Left Parapharyngeal Mass: Excision of tumor through transparotid-transcervical approach of left parapharyngeal space with supra omohyoid neck dissection on left side. Intraoperatively, tumor was well encapsulated, measuring 9x8 cm involving left parapharyngeal space. The main trunk of facial nerve identified and its branches preserved. Deep lobe of parotid gland was separated and the tumor excised.

Left Thyroid Nodule: Left thyroid lobectomy was done. Frozen section reported as follicular carcinoma. Completion thyroidectomy with central compartment neck dissection done. Intraoperatively, tumor was encapsulated measuring 5.5x5 cm involving left thyroid gland, without extrathyroidal extension, Recurrent laryngeal nerve was free of tumor and preserved. Parathyroid glands identified and preserved.

Upper lip lesion: Wide local excision of lesion involving the right side of the upper lip, followed by reconstruction with local advancement flap was done.

Postoperatively, patient was on endotracheal airway for two days and recovery was uneventful. Facial nerve function was intact. There was no change in voice.

Histopathology of specimens proved to be

(i) Adenoid cystic carcinoma of left parapharyngeal mass. Tumor size of 8x5 cm, no involvement of regional lymph nodes. Staging AJCC – pT3 pN0.

(ii) Follicular carcinoma of thyroid gland. Tumor size of 6.0x5.5 cm, presence of capsular invasion, with no lymphatic invasion. Staging AJCC – pT3 pN0.

(iii) Basal cell carcinoma of right upper lip. Tumor size of 1.5x1 cm.

Staging AJCC – pT1 pNx.

Based on HPR findings patient underwent radioactive iodine (I-131) therapy for thyroid and adjuvant radiotherapy for left parapharyngeal mass. Patient visited us after eight months for first follow-up after adjuvant therapy. Patient is free of disease and advised to come for regular follow-up biannually.

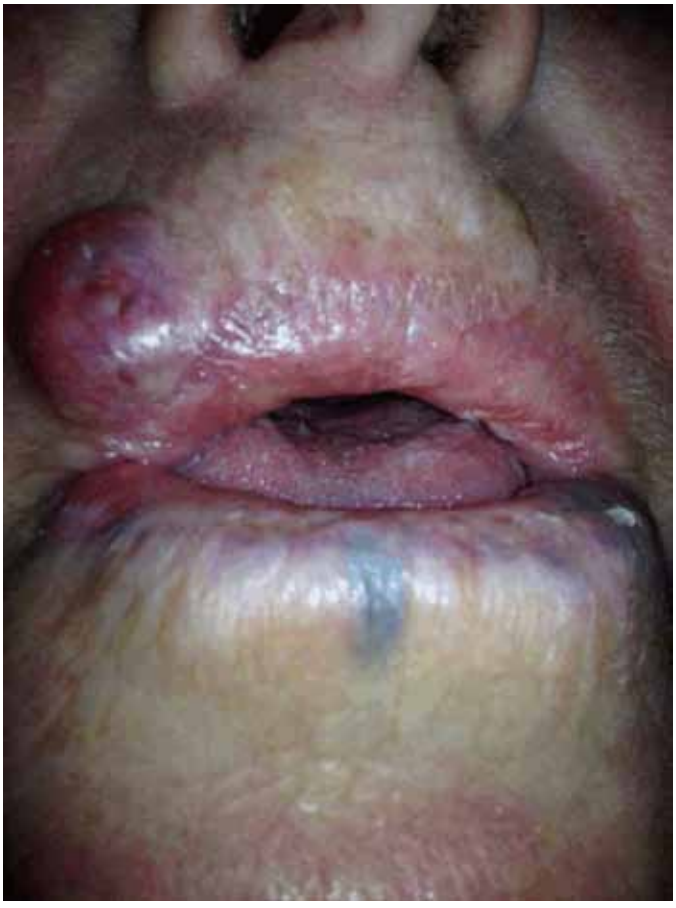

Figure 1: Preoperative image with lip lesion.

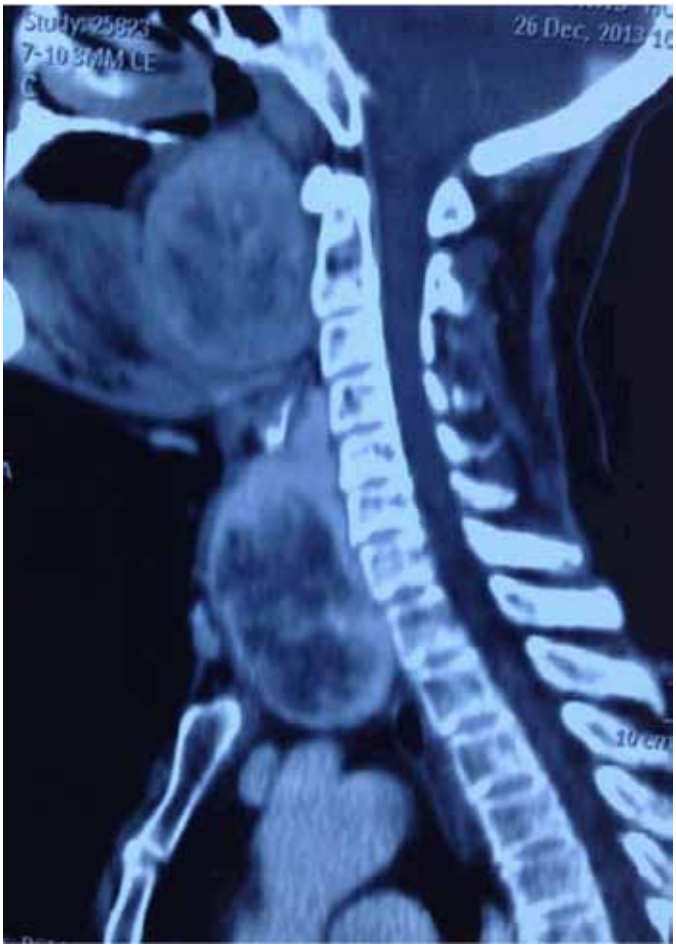

Figure 2: Computed tomography scan showing left parapharyngeal mass and retrosternal thyroid nodule.

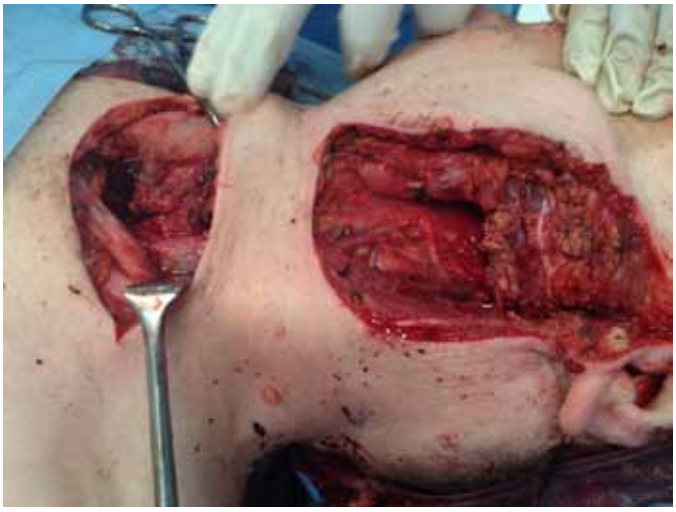

Figure 3: Intraoperative image after excision of parapharyngeal mass and total thyroidectomy.

DISCUSSION

Multiple synchronous primary neoplasms are increasing in literature and reported as high as 10% [2]. Patients of head and neck malignancies have increased risk of developing synchronous primary tumors. Tumors presenting within six months of diagnosis of index tumor is termed synchronous tumors. Synchronous primary tumors are commonly seen in upper aerodigestive tract such as oesophagus, with oropharynx in head and neck as index tumor. Initial workup with imaging and endoscopy is useful to diagnose the incidental finding of synchronous tumors. Survival of synchronous tumors is lower than the metachronous tumors. Synchronous/simultaneous neoplasms arising in the upper aero digestive tract are very common based on the concept of field cancerization [3]. The dysplastic changes of the mucosa produces tumors of monoclonal origin which shows the obvious relationship with the etiological factors such as smoking or tobacco chewing habits or previous ionizing radiation [4].

Cases of metachronous multiple neoplasms are very commonly reported in literature. Forrest et al. described a metachronous nine primary neoplasms over a 16-year period which were all treated by surgery. Taylor and Torrence reported a woman who suffered from metachronous six malignancies, accompanied by failure due to metastatic disease [3]. Multiple primary simultaneous neoplasms occurring in single patient are unusual. Cases of simultaneous triple primary neoplasms diagnosed and successful surgical management is very rare.

In this case, we have diagnosed all three neoplasms clinically and histologically proved to be of different tissue origin located in three different sites of the head and neck during first visit of the patient. The patient does not have the history of exposure to ionizing radiation or tobacco habits. All three neoplasms were managed surgically in her first visit successfully. Simultaneous multiple primary tumors in head and neck region, surgery seems to be superior to radiotherapy or chemotherapy in that surgery offers an effective simple, quick, low morbidity approach, especially in early stage disease. Radiotherapy and chemotherapy are the alternative modalities available and can be reserved for the management of secondary tumors. Radiotherapy and chemotherapy impairs the immunity resulting in increased incidence of new tumor developing. The diagnosis of the multiple tumors of head and neck during single visit at early stage, the morbidity associated with the management of loco-regionally advanced malignancies with multi-modality approach and also reduced the number of surgeries under anesthesia if tumors were diagnosed in a subsequent follow-up. The prognosis of the patient suffering from multiple primary tumors in head and neck is poor and early detection of these cases is mandatory to extend the survival of patients with a good prognosis by providing effective therapy at the initial stage of the cancer [5]. As per the prognosis considered Adenoid cystic carcinoma has increased incidence of local recurrence 42% and distant metastasis if managed with radiotherapy. Surgical management has reduced incidence of local recurrence of

these tumors thereby improving the survival rate of these patients. Basal cell carcinoma has excellent prognosis as it rarely metastasize. Follicular thyroid carcinoma also shows favorable outcome with radioactive iodine therapy.

CONCLUSION

The presentation of triple primary simultaneous tumors in head and neck of different histology is very rare. It is even more unusual for these tumors to present at the same time in a confined anatomical region such as head and neck area. The occurrence of multiple primary tumors have high risk of developing new tumors, should always be considered in any patient with malignant disease, if treatment is to be effective as possible. Triple simultaneous primary neoplasms diagnosis is essential to reduce the incidence of secondary metastasis and improve the survival rates. Besides interventions, it is ultimately important to have regular checkups in each visit for better outcome of the these patients.

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Author Contributions

Hemavathi Umeshappa – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Chandrashekhar M – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Ashok M Shenoy – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Dinesh Kumar GR – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT OPEN ACCESS

Vertical gaze palsy in Parkinsonism: An alternative diagnosis to progressive supranuclear palsy

Jonathan Hyer, Haziq Raees Chowdhury, Richard Men Ho Lee, Syed Taseer Hasan

ABSTRACT

Introduction: Vertical gaze palsy is a highly relevant clinical sign in Parkinsonian syndromes. As the eponymous sign of progressive supranuclear palsy (PSP), it is a core feature of this disease. However, the differential diagnosis of vertical gaze palsy in patients with Parkinsonism is rarely considered. Case Report: We present a case of a 65-year-old male with Parkinsonism who presented with diplopia secondary to oculomotor dysfunction and vertical gaze palsy. Computed tomography (CT) sacn demonstrated a thalamic hemorrhage with intraventricular extension. Neurosurgical intervention was not required. The patient's spectacles were fitted with a temporary Fresnel prism over the left lens to relieve diplopia. This progressively improved without the need for strabismus surgery. Conclusion: Vertical gaze dysfunction occurs in patients with thalamic hemorrhage and is an important differential diagnosis of vertical gaze palsy in Parkinsonism.

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INTRODUCTION

The differential diagnosis of Parkinsonism can be challenging. Despite consensus on diagnostic criteria for Parkinson's disease and the various atypical Parkinsonian disorders including progressive supranuclear palsy (PSP), there is a high rate of mis-diagnosis particularly in the early stages [1]. Furthermore, there is no diagnostic laboratory or imaging test for these atypical disorders. Conventional magnetic resonance imaging (MRI) is insufficiently sensitive or specific for routine workup of PSP or other neurodegenerative Parkinsonian disorders and is compounded by high variability based on the experience of the neuroradiologist [2].

Considerable overlap may exist in the clinical presentation of atypical Parkinsonian disorders and other diseases and as such, presence of vertical gaze palsy is open to error as a predictor of pathology. The presence of vertical gaze palsy may lead to significant false positive diagnosis of PSP. Furthermore, a weakness in the vertical gaze is often observed in elderly patients. Vertical gaze palsy on a background of Parkinsonism strongly suggests PSP but also rarely occurs in other atypical Parkinsonian disorders such as diffuse Lewy body disease [3]. Clinically, vertical gaze palsy appears relatively selective and typically affects primary vertical saccades as well as vertical smooth eye movements to varying degrees [4].

Vertical ocular palsies are most commonly in up-gaze, less frequently are combined up- and down-gaze and rarely pure down-gaze. The nature of the palsy helps define both clinical and anatomical diagnosis [5]. It is important to consider and exclude vascular lesions, neoplasia, demyelination and infection for which brain imaging can be particularly useful. Accurate and timely diagnosis of these differentials is imperative both therapeutically and prognostically.

CASE REPORT

A 65-year-old male with Parkinsonism presented to ophthalmology casualty with a two-day history of binocular diplopia and unsteadiness following an episode of dizziness three days previously. He was otherwise well in himself with no other neurological symptoms and in particular, no headache. There was no history of trauma. There was no significant past medical history and his only medication was levodopa. There was no past notable ocular history. On examination, uncorrected visual acuity was 6/12 in both eyes. Bilateral ptosis was noted. Examination of eye movements identified a vertical gaze palsy affecting up-gaze saccades and pursuit. There was a slight left sided exo-tropia and hypotropia in the primary position with mild weakness of medial rectus. There was no nystagmus. Pupil responses were equal and reactive to light and there was no relative afferent pupillary defect. Color vision was full on Ishihara plate testing and exophthalmometry revealed no proptosis. Dilated fundal examination was normal with a healthy optic disc appearance. Intraocular pressures were also normal. Blood pressure was 123/84 mmHg and random blood glucose was 5.3 mmol/L. Cardiovascular examination was normal with no heart murmurs or carotid bruits on auscultation.

Differential diagnosis prior to neuroimaging was that of an atypical Parkinsonian disorder such as PSP, multisystem atrophy, corticobasal degeneration and diffuse Lewy body disease. Other common causes of vertical gaze palsies were considered such as thalamic or brainstem stroke, neoplasm or hydrocephalus. Lack of pupil involvement and convergence nystagmus was against a diagnosis of Parinaud syndrome. Medical causes of third nerve palsy were also considered.

Computed tomography (CT) scan identified a thalamic bleed with intraventricular extension (Figure 1). MRI scan confirmed a focal bleed in the thalamus posteriorly in close proximity to the pulvinar nucleus projecting into the retrothalamic cistern (Figure 2). The radiographic findings suggested a hypertensive or other vasculopathic focus rather than an aneurysm.

The patient was admitted and kept under neurological observation. No neurosurgical intervention was required. His spectacles were fitted with a temporary Fresnel prism over the left lens to relieve diplopia which gradually resolved over the following two weeks with improvement in vertical gaze palsy (Figure 3). No strabismus surgery was required.

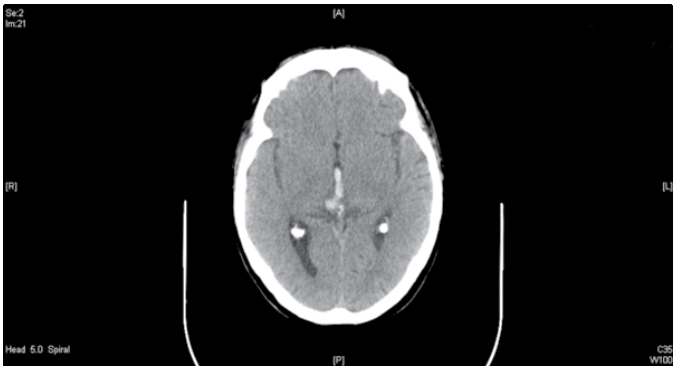

Figure 1: Non-contrast CT scan of head showing intraventricular extension of haemorrhage from right medial thalamic haemorrhage.

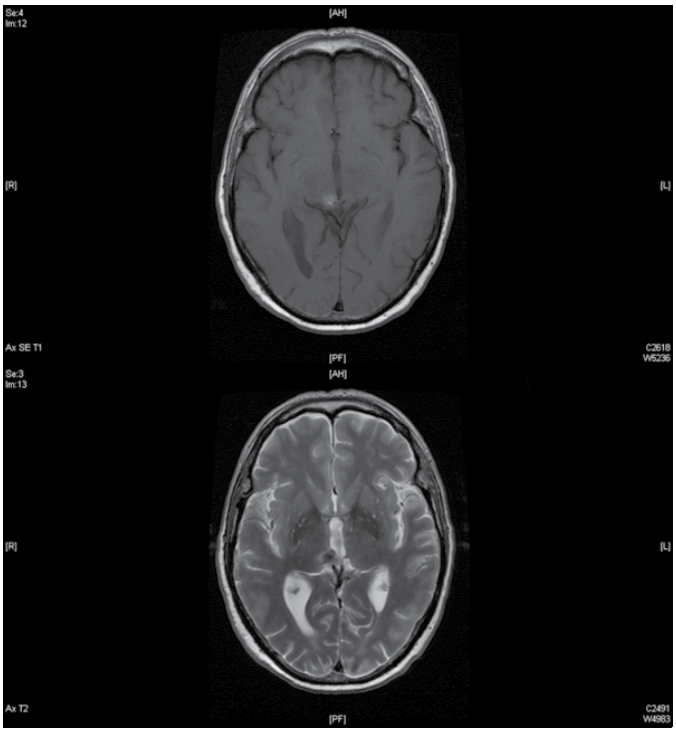

Figure 2: T1 and T2 weighted magnetic resonance imaging scan showing focus of right paramedian thalamic hemorrhage.

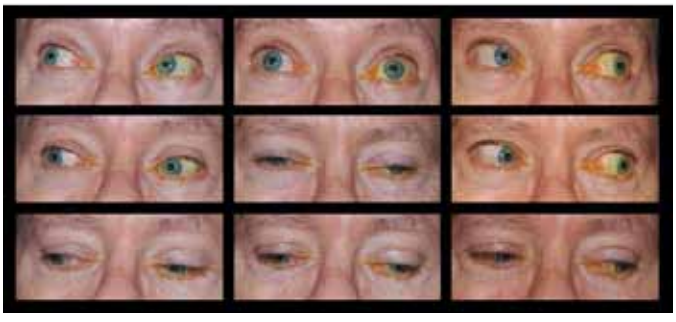

Figure 3: Eye Movements two weeks post presentation showing residual up-gaze palsy and bilateral ptosis in the primary position.

DISCUSSION

Acute thalamic stroke is an important cause of vertical gaze palsy and is common after thalamic hemorrhage, especially associated with intraventricular extension [6]. While acute thalamic infarction appears to carry an overall good prognosis, thalamic hemorrhage is frequently associated with early neurological deterioration, severe deficits and high mortality and requires urgent neurosurgical referral [6, 7]. Computed tomography (CT) scan of head is the imaging procedure of choice and once the diagnosis is confirmed blood pressure should be maintained below a mean arterial pressure of 130 mmHg in a person with no history of hypertension [8]. Standard craniotomy for surgical removal of thalamic hemorrhages has been all but abandoned because of extremely poor outcomes in most patients. Angiography is not required for older hypertensive patients with a thalamic haemorrhage and in whom CT scan findings do not suggest a structural lesion.

There are no reports of vertical gaze palsy having occurred co-incidentally in a patient with Parkinsonism. Kumral et al. [6] evaluated a cohort of patients with pure thalamic ischaemic stroke and identified up-gaze palsy in 50% patients with bilateral paramedian infarction and 25% with unilateral paramedian infarction [6]. A case of unilateral thalamic infarction presenting with vertical gaze palsy and skew deviation was reported [9]. Reversibility of ocular manifestations of thalamic hemorrhage following ventricular drainage has also been described [10, 11].

The excellent outcome in our case is unusual. It has been suggested that the up-gaze palsy in a case of Parinaud Syndrome associated with thalamic hemorrhage may be attributed to increased intracranial pressure resulting from a mass effect on the pre-tectal region and tectum, or to tightness in the incisura causing hydrocephalus secondary to aqueduct compression [11]. This may be relevant to our patient and help explain the improvement in eye movements as the hemorrhage was reabsorbed. Our patient benefited from the use of a prismatic spectacle lens. A study investigating prismatic spectacle lenses on symptoms of dizziness, headache and anxiety caused by vertical heterophoria is currently ongoing [12].

CONCLUSION

Alternative diagnoses other than progressive supranuclear palsy in patients with Parkinsonism and vertical gaze palsy should be considered as it is also featured in patients with thalamic hemorrhages, which can be easily identified on brain imaging. All patients presenting with an intraventricular hemorrhage need careful blood pressure monitoring and urgent neurosurgical review.

****

Author Contributions

Jonathan Hyer – Conception and design, Drafting the article, Final approval of the version to be published
Haziq Raees Chowdhury – Acquisition of data, Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published
Richard Men Ho Lee – Acquisition of data, Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published
Syed Taseer Hasan – Acquisition of data, Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT OPEN ACCESS

Primary duodenal adenocarcinoma of the fourth portion diagnosed using double-balloon enteroscopy and surgically resected: A case report

Shingo Kawano, Koichi Sato, Hiroshi Maekawa, Mutsumi Sakurada, Hajime Orita, Ryo Wada

ABSTRACT

Introduction: Primary duodenal adenocarcinoma is extremely rare. If this carcinoma occurs in fourth portion, it can now be diagnosed by recent developments in enteroscopy. Case Report: We report a rare case of primary duodenal adenocarcinoma of the fourth portion diagnosed by double-balloon enteroscopy and resected surgically. A 57-year-old male was anemic. Positron emission tomography – computed tomography revealed accumulation in the fourth portion of the duodenum. Double-balloon enteroscope showed circular tumor of the fourth portion of the duodenum, and biopsy disclosed poorly differentiated adenocarcinoma. Partial duodenectomy and partial colonectomy were performed. The marginal artery of the transverse colon was invaded. Histological examination disclosed that the tumor was poorly differentiated adenocarcinoma and two lymph node metastases were seen. Conclusion: Primary duodenal adenocarcinoma of fourth portion can be diagnosed by double-ballon enteroscopy and treated by surgical resection.

Keywords: Double-balloon entroscopy, Primary duodenal adenocarcinoma, The fourth portion

How to cite this article

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INTRODUCTION

Primary duodenal adenocarcinoma is extremely rare, accounting for 0.3~0.4% of all gastrointestinal cancers [1]. It is too difficult to anatomically diagnose primary duodenal adenocarcinoma of the fourth portion. However, primary duodenal adenocarcinoma of the fourth portion can be diagnosed by recent developments in enteroscopy. Herein, we report a case of duodenal adenocarcinoma of the fourth portion diagnosed by double-balloon enteroscopy and resected surgically, and discuss it based on a review of literature.

CASE REPORT

A 57-year-old Japanese male was admitted to our hospital in December 2009 for evaluation of severe anemia. Past medical history included a gastric ulcer when he was 50-years-old. His family history was non-contributory. Physical examination on admission revealed

a body height 175 cm, weight 63 kg, blood pressure 112/61 mmHg, a regular pulse of 85/min, and body temperature 36.8°C. There was no sign of lymphadenopathy. His abdomen was soft and flat, and no abdominal, liver, or spleen masses were palpable.

There were no abnormal laboratory findings, except evidence of anemia (hemoglobin 6.6 g/dL) and an inflammatory reaction (white blood cell count was 8900/μg, and C-reactive protein was 3.7 mg/dL). Tumor markers, carcinoembryonic antigen (CEA) and carbohydrate antigen (CA19-9), were within normal ranges.

Abdominal computed tomography (CT) scan indicated a circumferential, thick, and unequally enhanced wall in the fourth portion of the duodenum, and showed no lymph node swelling or ascites. Upper gastrointestinal series demonstrated a 7-cm 'apple core' sign in the fourth portion of the duodenum (Figure 1). Double-balloon enteroscopy showed a circumferential tumor with ulceration in the fourth portion of the duodenum (Figure 2). The enteroscope could not pass the lesion. Biopsy specimen from the lesion disclosed poorly differentiated adenocarcinoma. Positron emission tomography (PET) scan revealed accumulation in the fourth portion of the duodenum (Figure 3). Based on these findings, the patient was diagnosed with primary duodenal adenocarcinoma of the fourth portion and underwent partial duodenectomy and partial colectomy because the marginal artery of the transverse colon was invaded by the tumor on January 22nd, 2010.

The resected tumor had deep ulceration with a round wall and measured 100×80 mm in size (Figure 4).

Histological examination disclosed that the tumor was poorly differentiated adenocarcinoma which invaded into the subserosal layer and two lymph node metastases were seen (Figure 5).

The patient had an uneventful postoperative course, and was discharged from hospital 40 days postoperatively. Combined chemotherapy of TS-1 and cisplatin was prescribed as neoadjuvant chemotherapy. TS-1 (80 mg/

Figure 1: Upper gastrointestinal series: A 7-cm 'apple core' sign was found in the fourth portion of the duodenum.

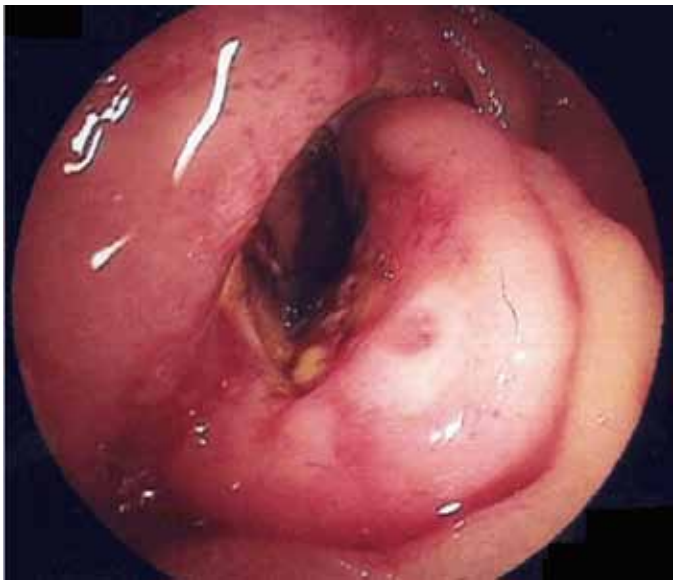

Figure 2: Double-balloon enteroscopy: A circumferential tumor with ulceration in the fourth portion of the duodenum.

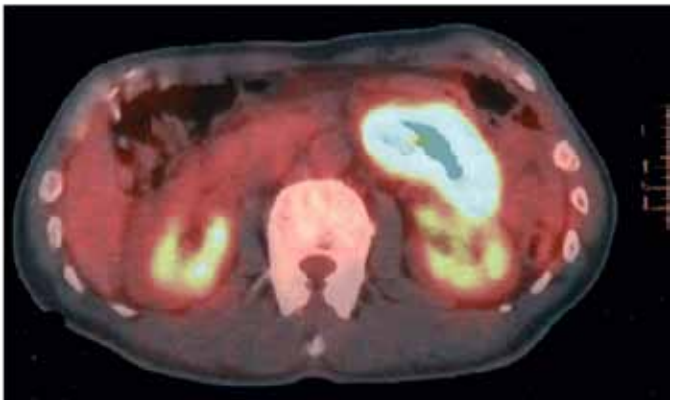

Figure 3: Positron Emission Tomography (PET): There was accumulation in the fourth portion of the duodenum.

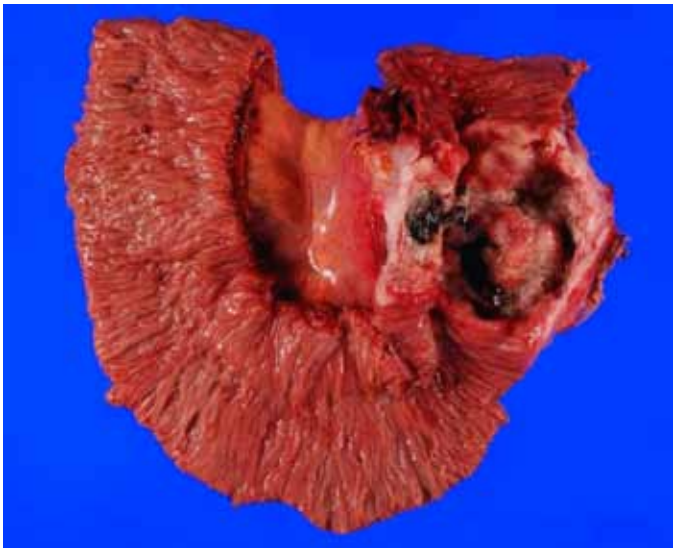

Figure 4: Surgical specimen: The resected tumor displayed deep ulceration with a round wall and measured 100×80 mm in size.

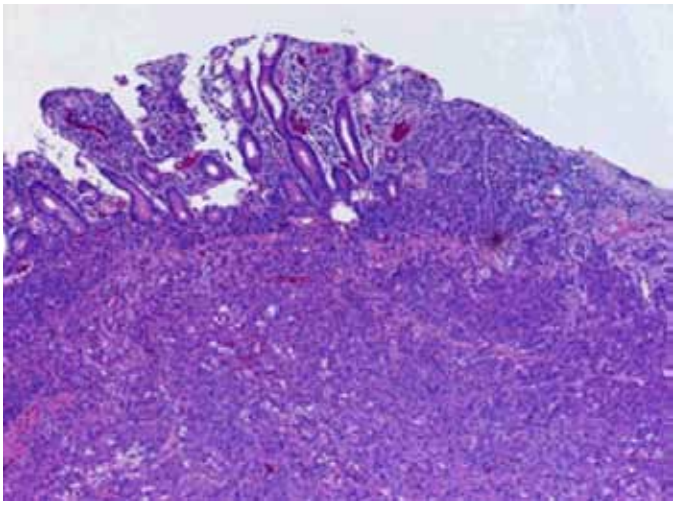

Figure 5: Histological findings: Poorly differentiated adenocarcinoma had invaded the subserosal layer. Two lymph node metastases were also detected.

m²) was administered 21 days, followed by 14 days rest as one course. Cisplatin (60 mg/m²) was administered on the eight day. Six courses of this adjuvant chemotherapy were administered. The patient is alive with no recurrence for one year.

DISCUSSION

Primary duodenal adenocarcinoma is extremely rare. Most primary duodenal adenocarcinomas are in the first and second portions, with 20% in the third portion, and 10% in the fourth portion [2]. Recently, reports of primary duodenal adenocarcinoma have been increasing because of progresses in gastric enteroscopy [3, 4]. However, it is impossible to diagnose primary duodenal adenocarcinoma of the third and fourth portions by gastric enteroscopy. There are still many cases to be diagnosed by the upper gastrointestinal series. In this case, primary duodenal adenocarcinoma of the fourth portion was diagnosed by double-balloon enteroscopy. In Japan, there are no case reports of primary duodenal adenocarcinoma of the fourth portion diagnosed by double-balloon enteroscopy. In Brazil, there is only one case report [5].

In Japan, there are eleven case reports of primary duodenal adenocarcinoma of the fourth portion resected surgically, including our case [5–16] (Table 1). The median age was 60.5 years (range 42–74 years). Six cases were men. Two cases invaded into the mucosal layer, three cases into the subserosal layer, and six cases went beyond the serosal layer. Seven cases had metastasis of the lymph nodes. According to these reports, there are two kinds of surgery, three cases of pylorus preserving pancreatoduodenectomy and partial

Table 1: Cases of the primary adenocarcinoma of the fourth portion of the duodenum reported in Japan

Author	Year	Age/Sex	Operation	Depth*	N	Prognosis
Adachi	1991	55/F	SD	SE	+	Unknown
Umehara	1996	42/F	PPPD	SE	+	24 mth. dead
Oshiro	2000	51/F	SD	SE	-	24 mth. alive
Saito	2001	54/M	SD	SE	+	Unknown
Hosokaewa	2003	74/F	SD	M	-	24 mth. alive
Maeda	2004	58/F	PPPD	SS	+	16 mth. alive
Suzuki	2005	66/M	PPPD	SE	+	24 mth. alive
Kinoshita	2006	65/M	SD	SS	-	11 mth. alive
Miyawaki	2006	72/M	SD	SE	+	30 mth. alive
Ishizaki	2008	72/M	SD	M	-	30 mth. alive
Our case	2010	57/M	SD	SS	+	12 mth. alive

PPPD - pylorus-preserving pancreatoduodectomy, DS - segmental duodectomy,
* Depth was expressed according to Japanese Classification of Gastric Carcinoma (The 14th edition), mth.: Month

duodenectomy and eight cases of partial duodenectomy with lymphadenectomy. In Kaklamanos's report, there was no significant difference in prognosis between pancreatoduodenectomy and partial duodenectomy in 63 cases of primary duodenal adenocarcinoma [16]. In Lowell's report, the seven cases of primary duodenal adenocarcinoma of the third or fourth portions are all alive after five years, except for those who died of another disease [17]. Five of seven cases underwent partial duodenectomy. There are many reports that partial duodenectomy is better in the case of primary duodenal adenocarcinoma in the third or fourth portions. Consequently, partial duodenectomy was thought to be a better surgery for primary distal duodenal adenocarcinoma. However, in Suzuki's report, a case of primary duodenal adenocarcinoma of the fourth portion underwent pancreatoduodenectomy [12]. There were metastases of the lymph nodes in No. 13 and No. 14 according to the Japanese classification of gastric carcinoma (The 14th Edition). That report insisted on the necessity of pancreatoduodenectomy with lymphadenectomy. Our case underwent partial duodenectomy with lymphadenectomy. There was no recurrence for one year in spite of advanced carcinoma and metastasis of the lymph nodes.

CONCLUSION

We reported an extremely rare case of primary duodenal adenocarcinoma of the fourth portion diagnosed by double-balloon enteroscopy and resected surgically.

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Author Contributions

Shingo Kawano – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Koichi Sato – Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published
Hiroshi Maekawa – Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published
Mutsumi Sakurada – Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published
Hajime Orita – Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published
Ryo Wada – Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT OPEN ACCESS

Palytoxin poisoning via inhalation in pediatric siblings

Martha M Rumore, Blaine M Houst

ABSTRACT

Introduction: Several cases of palytoxin poisoning have occurred during cleaning of aquariums. Case Report: We report a case of palytoxin inhalational toxicity in pediatric siblings following secondary exposure to vapors from cleaning of an aquarium containing Zoanthids. Symptoms included fever, tachycardia, leukocytosis and elevated lactic dehydrogenase. Both patients received supportive treatment in the pediatric intensive care unit and were discharged after 48 hours. Symptoms also occurred in children's parents including cleaning attendant. Conclusion: Herein, we present a rare case of inhalational toxicity from palytoxin.

Keywords: Palytoxin, Pediatric, Inhalation, Aquarium, Zoanthids

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INTRODUCTION

Zoanthid corals are often found in sea water aquaria. Touching the zoanthid corals results in palytoxin poisoning in patients with skin injuries and also through intact skin [1, 2]. Several cases of palytoxin poisoning have occurred during cleaning of aquarium by inhaling a water aerosol where toxin is dissolved [3, 4]. Herein, we report a case of inhalational toxicity affecting pediatric patients, as well as involving multiple individuals following cleaning of an aquarium. To our knowledge, this represents the first case of elevated lactic dehydrogenase (LDH) following inhalational exposure and the third case of leukocytosis.

CASE REPORT

A three-year-old boy and his two-month-old sister presented to the emergency department, both febrile after vomiting at home. The three-year-old also presented with tachycardia (heart rate 120 beats per minutes), cough and sleepiness whereas the two-month-old did not have cough, the cough reflex is unreliable at this age. Both patients had no known allergies. Since the children's parents were also ill with vomiting and a feeling of being hungover, an initial diagnosis of unspecified food poisoning was made.

The symptoms occurred after their aquarium attendant washed the coral in the tank with hot water. A short while after, the parents were both vomiting

and felt hungover while the children both vomited and spiked temperatures. The family received a call by the tank company three hours after the attendant left, were informed that the attendant was in emergency department with similar symptoms, and advised to seek medical treatment. At that point, palytoxin poisoning was suspected; both children were ultimately admitted to the pediatric intensive care unit (PICU).

On admission, chest X-rays and electrocardiograms of both the children were normal and oxygen saturation was 97% for both. Upon examination, both children showed leukocytosis and elevated LDH on blood analysis including elevated white blood cells. White blood cells of three-year-old was 34,000/μL and LDH levels was 331 U/L whereas white blood cells of two-month-old was 34,400/μL and LDH levels was 507 U/L (normal range 135–225 U/L). Laboratory examination of the three-year-old boy also revealed the following: elevated serum phosphorus 4.9 mg/dL, creatine kinase 78 U/L (normal 30–200 U/L), proteinuria 10 mg/dL. Alkaline phosphatase and all other laboratory values were normal.

The two-month-old female developed symptoms earlier than her brother and was considered more sick. Her laboratory values were more elevated than her brother. Her laboratory examination revealed the following: serum phosphorus 5.8 mg/dL, potassium 5.5 mmol/L, creatine kinase 169 U/L, aspartate aminotransferase/alanine aminotransferase (AST/ALT) (57/50 U/L) (normal 0–31 U/L), proteinuria 20 mg/dL. Mild metabolic acidosis was present— urine pH 6.5, blood pH 7.36, bicarbonate 17 mmol/L. The urine was hazy with trace blood. The patient was tachycardic (heart rate 156 beats per minutes) and hypotensive (blood pressure 102/65 mmHg). An echocardiogram on the two-month-old girl showed no findings. For both patients, serial extended monitoring of electrolyte levels was conducted.

Supportive therapy was given during the hospital stay, and the complete blood count and metabolic panels began to normalize. Both children received hydration (D5 ½ NS at 50 mL/hr); a one-time dose of acetaminophen suspension was administered to the three-year-old boy for a fever (100.4°F). The boy also received calamine lotion every 8 hours and diphenhydramine cream 1% for mosquito bites.

Within the next 24–48 hours, some of the laboratory values normalized while others remained elevated. The three-year-old was discharged 48 hours after admission with white blood cell 24,800/μL, creatine kinase 39 U/L, and LDH 253 U/L whereas the two-month-old was discharged at the same time with white blood cell 8,700/μL, creatine kinase 115 U/L and mildly elevated LDH 285 U/L.

Both children were discharged from the hospital within 48 hours.

DISCUSSION

Currently, there are no restrictions on the importation of toxic marine organisms into the United States if they are not ingested. Records regarding Zoanthidea are also not required. In some cases, Zoanthidea are not purchased at all, but are merely contaminants growing on rock or coral (e.g. frags). Recently, specimens of Zoanthids collected from home aquarium stores were analyzed and found to be highly toxic with palytoxin [5]. Palytoxin ($C_{129}H_{223}N_3O_{54}$), first isolated in 1971, is one of the largest and most complex natural products and is the second deadliest toxin known to man with an LD_{50} of 300 ng/kg in mice, 2 mg of toxin could kill 300,000 mice [5–7]. A toxic dose in humans may be about 4 μg. However, there are no reliable quantitative data on acute toxicity in humans. In our case, both identification of the toxin and quantification of levels were not performed, and palytoxin was implicated based on the exposure to Zoanthids and clinical symptomology. Palytoxin is one of the only marine toxins that are toxic to humans via ingestion, inhalation or dermal exposure. The toxin is heat stable and boiling or hot water used in cleaning aquaria does not inactivate the toxin.

Palytoxin binds to Na, K-ATPase, resulting in transformation of the sodium pump into a non-specific ion channel for monovalent cations causing a wide spectrum of secondary pharmacological actions [8]. More specifically, an increase in sodium may stimulate calcium-independent superoxide anions and oxidative stress, leading to cellular death [9]. The toxicity can be severe affecting multiple organ systems and takes place after a short-time of exposure at very low concentration. Clinically, patients can develop paresthesia, hypertension, dysgeusia, nausea, vomiting, diarrhea, rhabdomyolysis, cardiac dysrhythmias, respiratory depression, coma and death [10, 11].

Most cases involving aquarium Zoanthids have involved dermal exposure [1, 2, 12, 13]. While inhalational toxicity from marine aerosols is well known, the first case of inhalational toxicity from aquaria was reported in 2008, a second case was reported in 2010, and a third case in 2012 [3, 4, 14, 15]. This case report represents the fourth case of inhalational toxicity incidental to aquarium Zoanthids.

Very few data is available regarding inhalational toxicity. In 2003, 2006 and 2008 outbreaks of inhalational toxicity from blooms of algae occurred in Europe and the Mediterranean sea. All those affected needed medical attention for high fever, coughs and wheezing [16, 17]. Therefore, exposure to aerosolization results mostly in respiratory illness, fever, mild dyspnea, bronchoconstriction, cough, sore throat, headache, rhinorrhea, lacrimation, expectoration, myalgia, arthralgia, dermatitis, odynophagia, fatigue, dry throat and, occasionally, conjunctivitis. There are anecdotal reports in online marine aquarium forums of individuals poisoned via inhalation from cleaning organisms or

aquaria under steaming water. However, there are only a few published case reports of inhalational palytoxin toxicity from exposure to aquarium Zoanthids. The cases are summarized in Table 1.

In our case, the cleaning attendant became sick first, followed by the parents, and then the two children. The parent's complaint of feeling hungover is consistent with previous reports of poisoning from contact with aquarium Zoanthids. In one case, the patient exhibited dizziness, slurred speech, and glassy eyes [1]. Clearly, the symptoms in the adults in this case were of lesser severity than that in the children. Additionally, the two-month-old female developed symptoms earlier than her brother and was considered more sick. This would indicate greater susceptibility. However, the paucity of reported cases in children does not permit a comparison of inhalational toxicity from palytoxin in adults and children.

Creatine kinase levels of approximately 1000 U/L are suggestive of rhabdomyolysis. Creatine kinase levels were normal in the three-year-old, but mildly elevated in the two-month-old. However, elevated LDH in our patients may be indicative of mild rhabdomyolysis which was asymptomatic. Rhabdomyolysis is one of the most dangerous complications of palytoxin poisoning because it can lead to acute renal failure. Both patients also had hyperkalemia which is an early and fast-rising manifestation of rhabdomyolosis and mild hyperphosphatemia.

While all the cases were presumptive, the appearance of symptoms in five individuals simultaneously after cleaning an aquarium is highly suggestive of palytoxin toxicity.

Although animal studies have shown that vasodilators, such as papaverine and isosorbide dinitrate, can be used as antidotes if injected directly into the heart immediately following exposure [18], there is no specific antidote for palytoxin poisoning. Treatment is supportive. Both patients received hydration and were closely monitored in the PICU.

Table 1: Summary of Published Case Reports of Inhalational Palytoxin Toxicity.

Snoeks and Veenstra, 2012	4 individuals- husband, wife, twins Aquarium- attempted Zoanthid removal with boiling water Symptoms- fever, hypotension , metallic taste, nausea, headache, shivering, muscle cramps, leukocytosis, elevated CRP
Deeds and Schwartz, 2010 (occurred 2007)	1 case- Aquarium- attempted Zoanthid removal with boiling water Symptoms-within 20 minutes- rhinorrhea, coughing; within 4 hours- difficulty breathing, lightheadedness, chest pain, bronchial inflammation and bronchoconstriction, temperature not reported. Lab- No *creatine phosphokinase* levels reported Treatment- antihistamine, inhaled corticosteroid, analgesic, cough suppressant Two weeks post-exposure- bronchial inflammation; bronchoconstriction
Majilesi, 2008	1 case- Aquarium-attempted Zoanthid removal boiling water Symptoms- shortness of breath, chest pain, tachycardia, BP 140/80 mmHg, afebrile, respiratory rate 24, 100% oxygen saturation, wheezing, EKG-sinus tachycardia Chest X-ray- no infiltrates or pneumothorax Lab- Metabolic panel and cardiac enzymes were normal; leukocytosis (WBC 21,000/μL) Treatment- nebulized albuterol Recovery after 48 hours

CONCLUSION

Zoanthids are commonly sold by pet stores and found in home aquariums. Precautions should be taken as palytoxin can travel in water vapor and cause poisoning by inhalation. Cases of palytoxin toxicity via inhalational route, while rare, do occur. Exposure is characterized by vomiting, leukocytosis, elevations in lactic dehydrogenase, sometimes creatine kinase, and a febrile syndrome.

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Author Contributions

Martha M Rumore – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Blaine M Houst – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT OPEN ACCESS

Isolated plexiform neurofibroma presenting as white lesion of vulva: A case report

Sunita Arora, Rupneet Kaur, Poonam Goel, RPS Punia

ABSTRACT

Introduction: Neurofibromas commonly involve peripheral nervous system but rarely may involve genital organs such as labia, clitoris, vulva, vagina and cervix. Case Report: We present a case of isolated plexiform neurofibroma of vulva which presented as white lesion of vulva. A tissue biopsy was done and the histopathological analysis-demonstrated plexiform neurofibroma with spindle shaped cells with wavy nuclei and bland nuclear chromatin. The immunohistochemical staining showed strong positivity for S-100 protein which has a strong correlation with neurofibromatosis-1. No systemic sign of neurofibromatosis was found. Conclusion: Plexiform neurofibroma may present as isolated white lesion of the vulva without any systemic involvement in the form of neurofibromatosis. So a tissue biopsy is mandatory for definitive diagnosis of any white lesion of vulva.

Keywords: Vulva, White lesion, Plexiform neurofibroma

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INTRODUCTION

Neurofibroma is one of the uncommonly occurring mesenchymal lesions in vulvo-vaginal region. Neurofibroma as such is a disease of the peripheral nervous system and occurs most commonly in the extremities. Neurofibromas have been categorized as cutaneous neurofibromas (both localized and diffuse types), intraneural neurofibromas (localized and plexiform), massive soft tissue neurofibromas (solitary or multiple) and sporadic neurofibromas or those associated with neurofibromatosis-1 (NF-1) [1, 2]. Plexiform neurofibroma is usually recognized as a pathognomonic criterion of NF-1 (or von Recklinghausen's disease). It may also occur as a solitary lesion arising in a nerve root [3]. These lesions commonly involve labia and clitoris among the female genital tract. Lesions may also affect the vagina, cervix, endometrium myometrium, and ovary and may be associated with urinary tract neruofibromatosis [4]. We present a case of asymptomatic isolated vulvar neurofibroma with unusual presentation as white lesion of vulva without systemic involvement. Already known major differential diagnosis of hypopigmented lesion of vulva are lichen sclerosis, squamous cell hyperplasia, squamous cell carcinoma in situ and Paget's disease of vulva.

CASE REPORT

A 57-year-old female presented in the gynecology outpatient department with complains of postmenopausal

discharge per vaginam, irregular bleeding per vaginam and post coital bleeding since last 36 months. She was a multiparous female, a mother of five children and was menopausal for 15 years. She had past history of pulmonary Koch for which she took antitubercular treatment for two years. There was no family history of neurofibromatosis. On genital examination, she was found to have flat hypopigmented vulvar lesions involving labia minora and labia majora (Figure 1). Clitoris was healthy. Rest of the external genitalia looked healthy. The patient was aware of the lesion for past one year but did not seek any medical treatment. On speculum examination cervix was suspicious in appearance, flushed up with vaginal vault. Rest of the vaginal mucosa was healthy. On systemic examination, there were no swelling or café-au-lait spots over the body. No nerve involvement was observed. On ultrasonography uterus measured 7.53x3.99x2.95 cm with normal myometrium and endometrium. Thickness of endometrial cavity containing fluid measured 11.7 mm. Bilateral ovaries were normal. Cervical cytology showed atrophic smear. After a course of antibiotics for cervicitis, colposcopy showed inflammatory changes only and a punch biopsy was taken. A vulvar biopsy from the white lesion of vulva and an endometrial sampling were also taken.

Histopathologically, microscopic examination of vulvar biopsy revealed focally atrophic epidermis. Dermis showed fascicles and bundles. The tissue comprised of spindle shaped cells with wavy nuclei and bland nuclear chromatin. No atypia or necrosis was seen in the tissue. A diagnosis of plexiform neurofibroma was obvious on microscopic examination (Figure 2). Immunohistochemically, the tumor was strongly positive for S-100 protein (Figure 3) which is seen strongly in association with NF-1. Endometrial histopathology showed chronic endometritis and cervical biopsy showed

Figure 1: External genitalia on examination

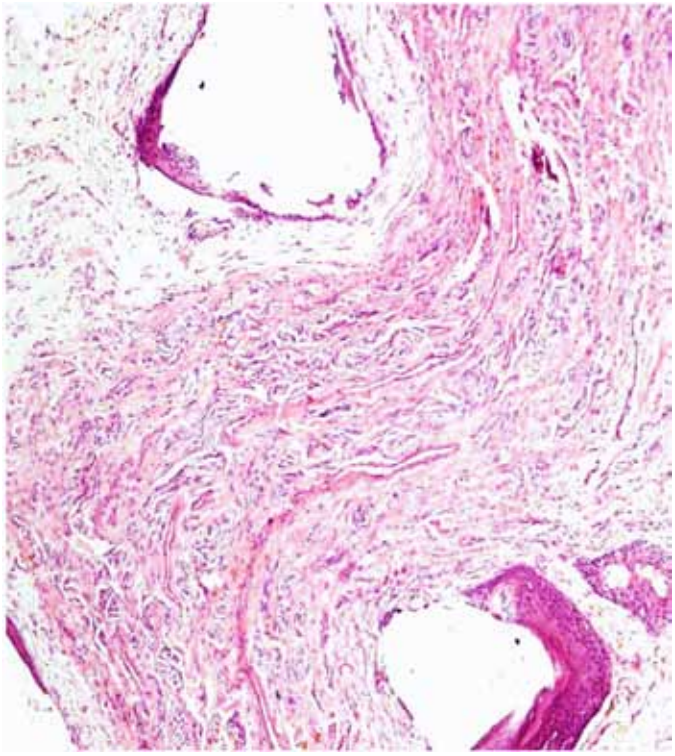

Figure 2: Microscopic examination of plexiform neurofibroma (H&E stain, x100).

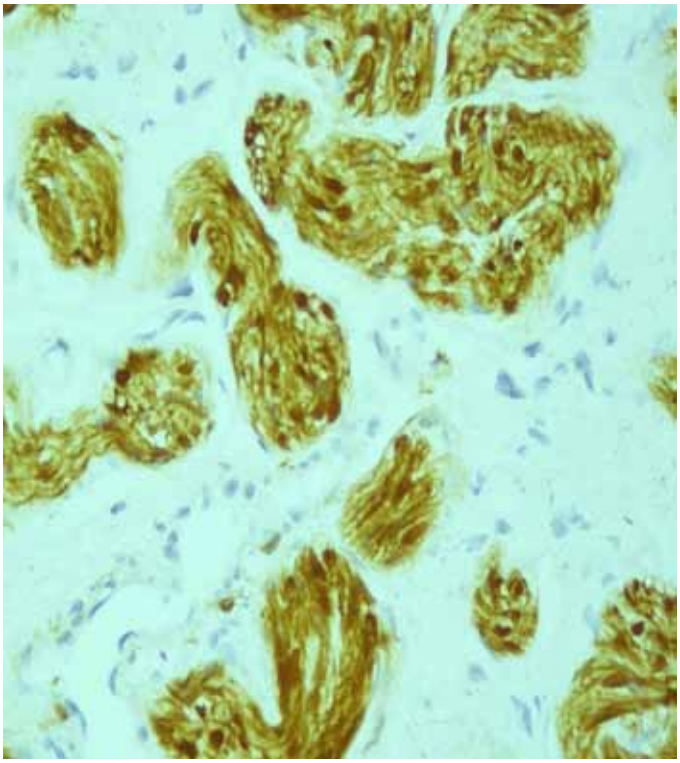

Figure 3: Immunohistochemical staining for S-100 protein was positive in plexiform neurofibroma (S-100, x200).

chronic cervicitis. At third, sixth and twelth month follow-up patient is healthy with no complains. There are no color changes, no mass lesion in (white lesion) involved area of vulva.

DISCUSSION

Neurofibroma of female genital system can be categorized according to organ involvement into three categories: 1. Vulvar 2. Clitoral 3. Pelvic (cervical, endometrial, myometrial and ovarian). Most of the cases reported to have vulvar, clitoral and pelvic neurofibromas presented as mass lesions. Till date, literature on isolated vulvar neurofibroma is scarce [5]. Among isolated vulvar neurofibromas, the association is found with trauma such as episiotomies or other vulvar injuries [6]. Approximately, half of all vulvar neurofibromas are found in women with neurofibromatosis. Our patient did not have any features of von Recklinghausen's disease.

There are two major concerns in such patients:

1) How these patients should be evaluated?

2) How these patients should be followed-up?

Our patient had hypopigmented lesion of vulva which was subsequently diagnosed to have plexiform neurofibroma. According to current nomenclature, such type of lesions is being categorized as non-neoplastic epithelial disorders of skin and mucosa (previously leukoplakia, etc). These lesions are associated with dysplasia and cancer. These lesions do not show significant colposcopic findings and hence the investigation of choice should be tissue diagnosis in such patients. The present case did not have any urinary symptoms so cystoscopy was not performed.

After 12 months of regular follow-up, our patient did not develop any new complains. She did not notice any change in color of the lesion, development of mass in external genital region, inguinal lymphadenopathy. We have planned to keep patient on regular follow-up every 2-3 monthly for external genital and pelvic examination.

Till date no such guidelines have been developed for investigations and management of vulvar neurofibromas. As per available literature, data on malignant transformation is also scarce.

CONCLUSION

We can conclude from the available literature that for women having hypopigmented lesions of vulva differential diagnosis of neurofibroma should be kept in mind. Systemic examination for the presence of café-au-lait spots should be performed. Also detailed examination of the genitourinary tract including cystoscopy should also be undertaken in such cases. In cases with no mass lesions the rate of growth of the lesion or change in color should be kept in mind for the possible development of malignancy.

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Author Contributions

Sunita Arora – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Rupneet Kaur – Substantial contributions to conception and design, Drafting the article, Final approval of the version to be published

Poonam Goel – Substantial contributions to conception and design, Drafting the article, Final approval of the version to be published

RPS Punia – Substantial contributions to conception and design, Drafting the article, Final approval of the version to be published

Guarantor

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Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT OPEN ACCESS

Amlodipine induced gingival overgrowth: A case report

Aditya Sinha, Sheetal Oswal, Ravindra Shivamurthy

ABSTRACT

Introduction: Drug-induced gingival overgrowth (DIGO) remains a significant problem for the dental clinicians and the periodontologists. Patients medicated with certain drugs may be implicated in this unwanted side effect, which may interfere with esthetics, mastication or speech. Case Report: The case presented here is a 60-year-old female patient with drug induced gingival enlargement. Patient was a known hypertensive and was on medication from past two years. Planned surgical intervention along with full mouth rehabilitation was the chosen treatment strategy. Clinical follow-up period lasted for one and a half years. Conclusion: With the consent of physician for substitution of the drug along with stringent maintenance of oral hygiene, surgical correction is required, and positive pressure appliance helps in preventing the recurrence of the gingival enlargement.

Keywords: Amlodipine, Gingival enlargement, Positive pressure appliance

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INTRODUCTION

Defining all the various clinical entities that affect the gingiva as gingivitis is too restrictive and at times confusing. Unlike the restrictive nomenclature of gingivitis, the term "gingival diseases" is a more comprehensive and encompassing definition of the different entities that affect the Gingival. Gingival disease is a diverse family of complex and distinct pathological entities found within the gingiva that are the result of a variety of etiologies. Increase in size of the gingiva is a common feature of gingival disease. Accepted terminology for this condition is gingival enlargement or gingival overgrowth. These are strictly clinical descriptive terms and avoid the erroneous pathologic connotations of terms used in the past, such as hypertrophic gingivitis or gingival hyperplasia.

Various drugs have been associated with an increased prevalence of gingival hyperplasia. The oldest and the most common of these is phenytoin (Dilantin), an anticonvulsant drug commonly used in the treatment of epilepsy. Recently, the number of offending drugs is increasing, with numerous calcium channel blockers, antiepileptic agent, sodium valproate, and the immunosuppressant drug cyclosporine joining the list. Of all calcium channel blocker, nifedipine is correlated with increased gingival hyperplasia most frequently, but an association with diltiazem, amlodipine, nitrendipine, and verapamil also has been shown. Drug-induced gingival overgrowth (DIGO) remains a challenging condition for diagnosis and treatment, the severity of the hyperplasia is correlated directly to the patient's susceptibility and the level of oral hygiene. With excellent oral hygiene, gingival

hyperplasia is reduced dramatically or is not present. Despite this, occasional susceptible patients demonstrate gingival hyperplasia which may interfere with esthetics, mastication, speech and affect access for oral hygiene resulting in an increased vulnerability to bacterial infection, caries and periodontal diseases.

Amlodipine is a dihydropyridine calcium channel blocker that is used in the treatment of both hypertension and angina. Ellis et al., first reported gingival sequestration of amlodipine and amlodipine-induced gingival overgrowth (AIGO) [1], since then, very few cases of AIGO have been reported.

After one month to three months of drug use, the overgrowth originate in the interdental papillae and spread across the tooth surfaces. The anterior and facial segments are the most frequently involved areas. In extensive cases, the hyperplastic gingival can cover a portion (or all) of the crowns of many of the involved teeth. Extension lingually and occlusally can interfere with speech and mastication. Gingival tissue appears pink color or they may be slightly paler than normal. The tissues are firm, hard, and lobulations are formed that may appear inflamed or fibrotic in nature depending on the degree of local factor induced inflammation. Different treatment options that have been explored in the management of DIGO. Such management strategies can most simply be categorized as either non-surgical or surgical approaches. Although a variety of non-surgical measures have been shown to be of some value in the management of DIGO, surgical correction of gingival overgrowth is still the most frequent treatment. Such treatment is only advocated when overgrowth is severe [2]. From the patient's prospective, surgical correction of DIGO should result in little or no postoperative pain or sequelae, good aesthetics and a reduced risk of recurrence. Currently, the surgical management of DIGO includes the scalpel gingivectomy, overgrowth flap surgery, electrosurgery and laser excision.

Electrosurgery techniques have been used in dentistry for the last 70 years. Although such techniques produce adequate hemostasis, they have the disadvantage of causing a surrounding zone of thermal necrosis, which may impede wound healing. This is probably due to the production and accumulation of excessive latent heat, which can be significant if electrosurgery is performed inappropriately. The amount of latent heat produced is dependant upon instrumentation variables, such as type of waveform, size of cutting electrode, time required for incision and the energy produced at operating site. Nevertheless, surgical intervention using conventional means (scalpel) may sometimes be technically difficult and/or impractical for example in children or mentally handicapped, or in patients suffering from impaired hemostasis. In these situations, the use of electrosurgery may be advantageous [2].

CASE REPORT

A 60-year-old female patient was referred to the department of periodontics at Sri Hasanamba Dental College and Hospital, Hassan with the chief complaint of swollen gums in the upper and lower front tooth region from past two months. Patient had noticed a small bead-like nodular enlargement of the gums that gradually progressed to the present size covering almost the entire front teeth in the upper and lower arches (Figure 1). There was no bleeding associated with the overgrowth of the gums. Patient periodontal condition was poor with generalized bone loss and teeth had generalized mobility. Medical history revealed that the patient was hypertensive from last two years and her medication was started four months earlier with amlodipine 5 mg, once daily. Patient did not suffer from any other form of systemic disease. Intraoral examination revealed overgrowth originating from the marginal, interdental and attached gingival extensively covering almost all of the crown of many of the involved teeth. The anterior and facial segments were severely involved areas. Gingiva was pink in color with erythematous area and lobulated surface. Palpation revealed, gingival to be firm and resilient in consistency.

Hypertrophied areas were painless and did not bleed on probing. Inflammatory component of the gingival enlargement was contributed by local irritating factors. Complete blood investigations was done for the patient and all the parameters were found to be within normal range. Patient's physician was consulted regarding substitution of the drug. The physician substituted the with Tab. losartan-H (50 mg). The treatment of the patient was started with full mouth extraction as most of the teeth had poor periodontal prognosis. After full mouth extraction there was a relatively minimal decrease in gingival enlargement. Electrosurgical excision of gingival hyperplastic tissue was planned and performed employing the techniques of gingivectomy to restore the normal shape and contour of the alveolar ridges after a period of one month (Figure 2).

Postoperatively, there was successful elimination of enlarged gingival tissue and restoration of a physiological gingival contour giving the patient an esthetically pleasing appearance to the alveolar ridges. Finally, prosthetic rehabilitation was done for the same patient by constructing complete dentures (Figure 3). Patient was followed postoperatively for a period of one and a half years and no signs of enlargement were reported (Figure 4).

Histopathological report revealed stratified squamous parakeratinized epithelium covering a fibrocellular tissue. The underlying connective tissue shows abundant collagen fibers admixed with spindle shaped fibroblast. Dispersion of numerous inflammatory cells throughout the connective tissue was evident (Figure 5). On the basis of the patient's history and clinical features, a clinical diagnosis of amlodipine induced gingival overgrowth (AIGO) was made.

DISCUSSION

Drug induced gingival overgrowth refers to an abnormal growth of the gingival tissue secondary to use of a systemic medication. The term is a misnomer because neither the epithelium nor the cells within the connective tissue exhibit either hyperplasia or hypertrophy. The increased gingival size is due to an increased amount of extracellular matrix, predominantly collagen. Therefore, it is designated as DIGO. The dihydropyridones (e.g., nifedipine) tend to be more commonly associated with the gingival overgrowth than with other sub groups of calcium channel antagonists such as amlodipine. It has a mode of action pharmacodynamically similar to nifedipine. However, amlodipine has a distinctive physiochemical profile, which is characterized by near complete absorption, late peak plasma concentrations, high bioavailability and slow hepatic biodegradation. The associated slow elimination of amlodipine with resulting long duration of its action means that only a single daily dose is required. This results in better patient compliance and has until now been associated with similar or reduced severity of side effects compared with nifedipine [3, 4].

The prevalence rates of gingival overgrowth has been reported in 15–83% of patients taking nifedipine [5], whereas the occurrence rate for amlodipine enlargement is very rare. Patients taking nifedipine appear to be at increased risk for developing significant overgrowth than those on amlodipine. The difference between nifedipine and amlodipine is of interest, Amlodipine is more polar than the other dihydropyridones, with a pKa value of 8.7. In contrast, nifedipine is intensely lipophilic and will readily dissolve within the cell membrane and pass into the cytoplasm. While the mechanism of drug-induced gingival overgrowth is considered to be multifactorial, the drug-cellular interaction is crucial in the pathogenesis of this effect [6].

The treatment should be based on the medication being used and the clinical appearance of the individual case. Initial consideration should be given to the possibility of discontinuing or substituting the drug. Either of that decision should be taken after consulting with patient's physician. Discontinuation of the aberrant drug is usually not a practical solution. However, its replacement with another medication might be the practical solution. If any drug substitution is attempted, it is important to allow for 6–12 months to elapse between discontinuation of the offending drug and possible resolution of gingival enlargement before a decision to implement surgical treatment is made. As in this case, most of the overgrowth was fibrotic and did not reduce even after full mouth extraction, and the patient had to be rehabilitated with complete denture so as to restore her esthetic and masticatory function, surgical modality was chosen as the treatment option followed by prosthetic rehabilitation.

Emphasis should be made on adequate plaque control as the initial step in the treatment of drug induced gingival overgrowth. Although the exact role played by bacteria plaque in DIGO is doubtful, there is evidence that good oral hygiene and frequent professional removal of plaque decreases the degree of gingival overgrowth present and improves gingival health. Also, adequate plaque control may aid in preventing or retarding the recurrence of gingival overgrowth in surgically treated cases.

Figure 1: Preoperative frontal, maxillary and mandibular view.

Figure 2: Intraoperative excision of fibrous tissue using electrosurgery.

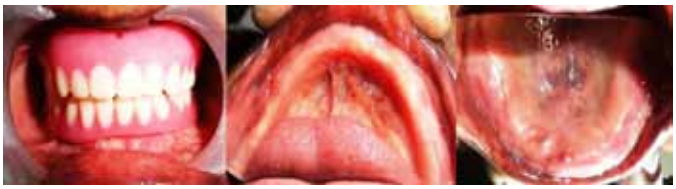

Figure 3: Postoperative healing after one month and complete full mouth rehabilitation.

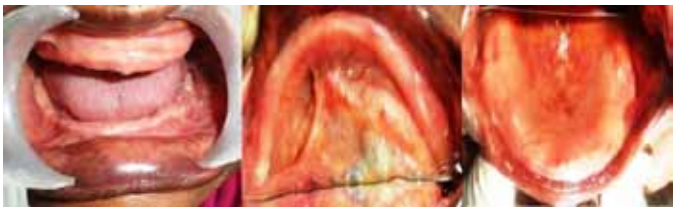

Figure 4: Postoperative view after one and half years.

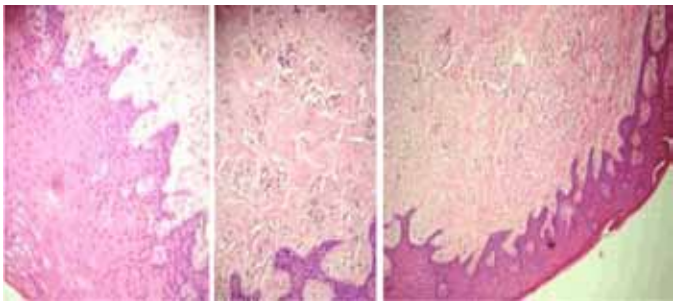

Figure 5: Histology showed parakeratinized epithelium which is hyperplastic in nature, underlying stroma comprising bundles of coarse fibers arranged in wavy fashion. (H&E stain, x40).

In this case, no recurrence of the enlargement after a period of one and, half years can be attributed to the substitution of the drug along with the complete denture acting as a positive pressure appliance (PPA). The effect of PPA in prevention of recurrence of enlargement has been reported in a previous study by Shreidan and Reeve [7]. The need for, and timing of, any surgical intervention needs to be carefully assessed. Surgery is normally performed for cosmetic/aesthetic needs before any functional consequences are present. In this report, as the gingival overgrowth was extensive and relatively minimal decrease in gingival enlargement was seen even after full mouth extraction, hence surgical intervention had been undertaken.

CONCLUSION

With the consent of physician for substitution of the drug along with stringent maintenance of oral hygiene, surgical correction is required, and positive pressure appliance helps in preventing the recurrence of the gingival overgrowth.

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Author Contributions
Aditya Sinha – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Sheetal Oswal – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Ravindra Shivamurthy – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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CASE REPORT OPEN ACCESS

A young female with catastrophic antiphospholipid syndrome

Vivekanandan Senthamil Pari, Lakshmi M, Sampath Kumar, Sathyamurthy P, Sudhakar MK, Sandhya Sundaram

ABSTRACT

Introduction: Antiphospholipid syndrome is characterized by recurrent thrombosis and/or pregnancy loss with the presence of circulating antiphospholipid antibodies. Its clinical manifestations range from asymptomatic to catastrophic antiphospholipid syndrome. This condition is a rare presentation of antiphospholipid syndrome and has a very high mortality rate. Case Report: Herein, we present a 20-year-old female patient are presented with peripheral cyanosis, computed tomography angiogram of abdomen and lower limb vessels showed arterial occlusion, and renal infarcts. She also developed seizures during hospital stay. With suspicion of vasculitis she was started on methyl prednisolone with other appropriate medications after sending blood for relevant investigations. She responded to medications, meanwhile her antiphospholipid antibody was positive with skin biopsy taken from affected limb showing microthrombi in dermal capillaries with inflammatory exudates. These features are in favor of a diagnosis of a catastrophic antiphospholipid syndrome, which will be discussed in this case report. Conclusion: Catastrophic antiphospholipid syndrome is a rare entity occurring in 0.8–1% of patients with antiphospholipid antibody syndrome and it has a very poor prognosis. But early, aggressive treatment improves the recovery rate and requires a high degree of suspicion.

Keywords: Recurrent thrombosis, Catastrophic antiphospholipid syndrome, Antiphospholipid antibodies

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INTRODUCTION

Antiphospholipid syndrome (APS) is characterized by recurrent thrombosis and/or pregnancy loss with the presence of circulating antiphospholipid antibodies. A severe, rapidly progressive form characterized by involvement of at least three different organ systems within one week duration with histopathological evidence of small and large vessel occlusion is termed catastrophic antiphospholipid syndrome. It occurs in 0.8–1% of cases

of APS as seen in various case series and has a mortality of about 50%. It presents with features suggestive of DIC (Disseminated intravascular coagulation) or TTP/HUS (thrombotic thrombocytopenic purpura/hemolytic uremic syndrome) and needs to be treated aggressively in view of the rapid progression and high mortality.

CASE REPORT

We present a case of a 20-year-old unmarried female presented to the emergency room with bluish discoloration of toes and fingers which started four days prior and was progressive, first involving the left and then the right leg toes and then fingers. It was associated with numbness and pricking type of pain. She also had breathlessness for three days which was insidious in onset, progressing from NYHA (New York Heart Association) class II to IV in three days. She also gave history of fever for four days which was low grade with no associated chills or rigors. She also had history of recurrent oral ulcers and rashes on the face on exposure to sunlight for the last six months. Her menstrual cycles were normal. She had no comorbid illnesses and no significant past medical history. On examination she was well oriented, febrile, pale, had peripheral cyanosis and bilateral pitting pedal edema. Her blood pressure was 200/110 mmHg, respiratory rate was 28 breaths/min. Chest examination revealed S3 gallop and there were crepitations heard in bilateral lung fields. Abdomen and nervous system were unremarkable. Arterial pulses distal to the femoral artery were absent in both lower limbs (Figure 1).

Baseline blood investigations revealed anemia, raised total counts, normal platelet counts, PTT (partial thromboplastin time) about twice the normal with normal prothrombin time and a serum creatinine of 1.3 mg/dL with urea of 41 mg/dL. Urinalysis revealed 2+ proteinuria and no sediments. Peripheral smear showed no evidence of hemolysis. Arterial blood gas analysis showed hypoxia and metabolic acidosis with partial respiratory compensation. Chest X-ray showed bilateral pulmonary congestion. Electrocardiography had T-wave inversion in leads V1-V4 and left ventricular hypertrophy. Echocardiography was essentially normal with an ejection fraction of 60%. However, the levels of cardiac enzymes CK-MB and troponin T were slightly elevated and BNP was high (5000 ng/L). Cultures which were sent came out to be negative later. Vasculitis with acute pulmonary edema was suspected and patient was started on nitroglycerine infusion, diuretics and antihypertensives and connective tissue work up sent. Meanwhile the computed tomography (CT) angiography of lower limbs and renal vessels showed complete occlusion of anterior tibial and peroneal artery a few centimeters above the ankle with complete occlusion of dorsalis pedis bilaterally; both kidneys showed multiple wedge shaped parenchymal defects and the mid, distal segments, branches of renal arteries were small in calibre.

By the second day of admission, the patient developed severe respiratory distress and had to be ventilated, started on imepenam, low molecular weight heparin and i.v. methyl prednisolone therapy (1g/day for 5 days followed by oral prednisolone) was initiated pending the connective tissue work up reports in view of the critical condition of the patient and strong suspicion of vasculitis. On the fourth day of hospital stay the patient had one episode of generalized tonic clonic seizures, the CT scan of brain done for the same which was unremarkable and patient was switched from imepenam to piperacillin-tazobactum along with levetriacetam for the seizures. Skin biopsy was taken at the line of demarcation on the gangrenous digits to look for evidence of vasculitis/microthrombi. The connective tissue work up revealed ANA (Antinuclear antibodies), ds-DNA (double stranded DNA) and APLA (antiphospholipid antibody) positivity and ANCAs (antinuclear cytoplasmic antibodies) were negative. Skin biopsy showed microthrombi in the dermal capillaries with surrounding inflammatory infiltrates (Figures 2–4).

Patient was gradually improving and was extubated, later switched to oral prednisolone and mycophenolate mofetil as per nephrologist's opinion. The patient's blood pressure was stable with oral antihypertensives and she was initiated on oral anticoagulant therapy. Amputation of the gangrenous digits/limbs was planned later. Her recovery was uneventful and was discharged on oral

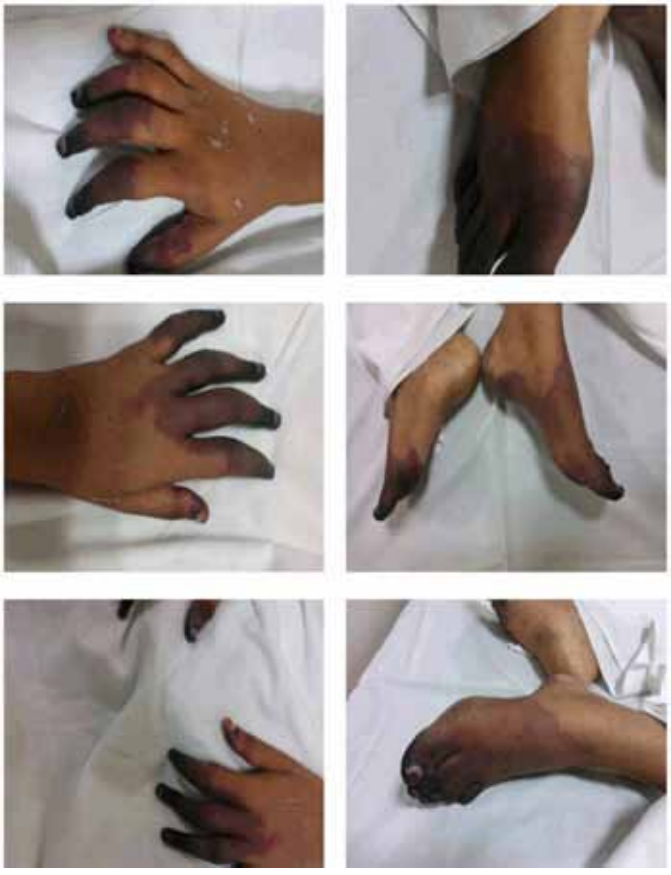

Figure 1: Photograph showing peripheral cyanosis.

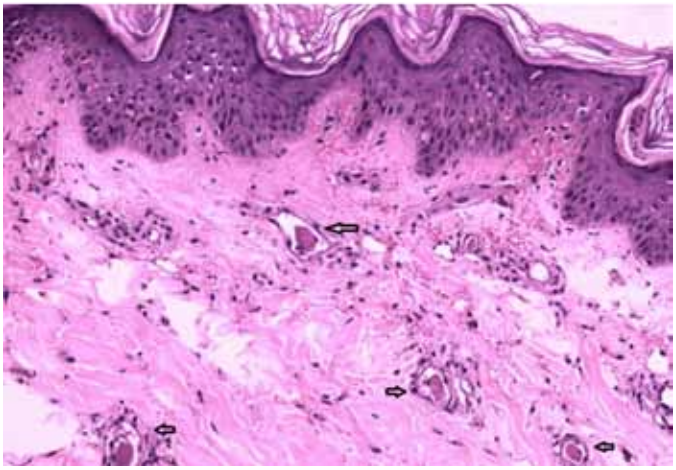

Figure 2: Micrograph of skin with dermal capillaries showing multiple microthrombi (H&E stain, x100).

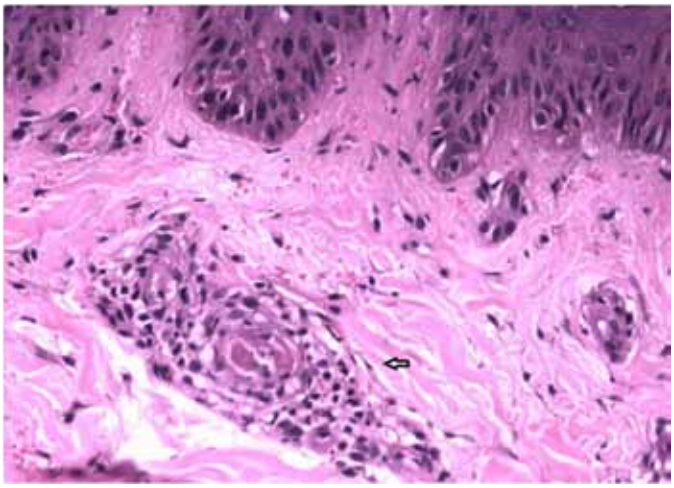

Figure 3: High power showing microthrombi within dermal vessels surrounded by inflammatory infiltrates (H&E stain, x200).

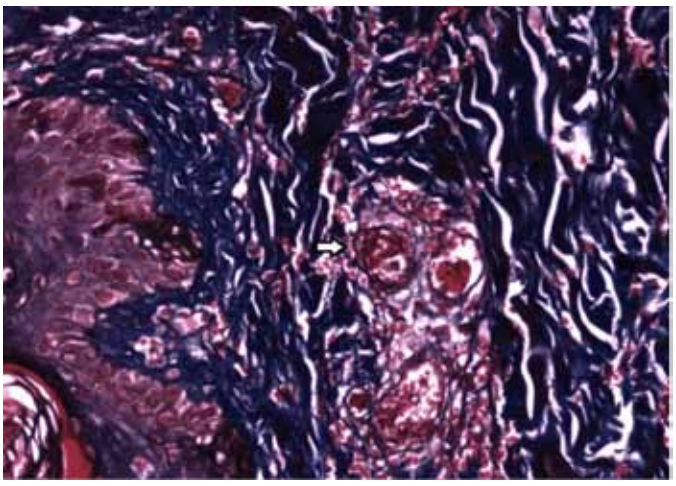

Figure 4: Special stain highlighting the microthrombi within the vessels (Masson trichrome stain, x200).

medications with advice to follow-up. On follow -up after 12 weeks repeat APLS was sent and it was positive. In this case, this is the first presentation of the patient and she came with features of limb ischemia secondary to microthrombosis, proteinuria with renal vascular changes and accelerated hypertension and she also had central nervous system involvement in the form of seizures. The above three features occurring within one week, with APLA positivity done twice more than six weeks apart, all point towards a diagnosis of catastrophic antiphospholipid syndrome (CAPS).

DISCUSSION

In this case, the initial differential diagnoses thought of were vasculitis, antiphospholipid syndrome with thromboses, sepsis with DIC, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome.

In view of probable clinical diagnosis of vasculitis and CT angiography was suggestive of arterial occlusion she was started on steroids but later c-ANCA and p-ANCA reports turned out to be negative and skin biopsy was not suggestive of any specific vasculitis.

Another differential diagnosis considered was sepsis with disseminated intravascular coagulation since patient had thrombocytopenia leukocytosis. Hence she was initiated on broad spectrum antibiotics, but there was no evidence of bleeding or consumptive coagulopathy and microbiological cultures were negative.

We had also thought of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome but there was no history of antecedent or current diarrhea, no evidence of hemolysis such as schistocytes on peripheral smear, hyperbilirubinemia or elevated LDH and no evidence of coagulopthy either.

So , putting all the positive findings together, we have acute ischemia of all four limbs, renal ischemia, acute pulmonary edema with normal left ventricular systolic function, central nervous system involvement in the form of seizures, deranged PTT and thrombocytopenia with normal PT and no evidence of bleeding or hemolysis with negative cultures and immunopathological evidence of systemic lupus erythematosis with antiphospholipid antibody positivitiy (ANA and ds-DNA, APLA positive and skin biopsy showing microthrombi with no evidence of vasculitis), all event occurring within a span of one week and thus fitting into the diagnosis of catastrophic antiphospholipid syndrome.

A small subset of patients with APS can go on to rapidly progressing widespread thrombotic disease with multiorgan failure, which is called “catastrophic APS” or Asherson syndrome and has a high mortality even with treatment. Hence the problem needs to be identified early and treated aggressively.

The current criteria for classification purposes and to facilitate early recognition of catastrophic APS as suggested by Asherson et al. are given in Table 1 [1].

Catastrophic APS occurs in 0.8–1% of the patients with APLA syndrome according to various studies [2, 3]. The basic pathology of the disease process remains the same as in antiphospholipid syndrome but at an accelerated

Table 1: Preliminary criteria for the classification of catastrophic antiphospholipid syndrome [4]

(1) Evidence of involvement of three or more organs, systems and/or tissues[a]
(2) Development of manifestations simultaneously or in less than a week
(3) Confirmation by histopathology of small vessel occlusion in at least one organ or tissue[b]
(4) Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)[c]
Definite catastrophic APS
• All four criteria
Probable catastrophic APS
• All four criteria, except for only two organs, systems and/or tissues involvement
• All four criteria, except for the absence of laboratory confirmation at least 6 weeks apart due to the early death of a patient never tested for aPL before the catastrophic APS
• 1, 2 and 4
• 1, 3 and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation

a. Usually, clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate. Renal involvement is defined by a 50% rise in serum creatinine, severe systemic hypertension (>180/100 mmHg) and/or proteinuria (> 500 mg/24 h).
b. For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally.
c. If the patient had not been previously diagnosed as having an APS, the laboratory confirmation requires that presence of antiphospholipid antibodies must be detected on two or more occasions at least six weeks apart (not necessarily at the time of the event) according to the proposed preliminary criteria for the classification of definits APS.

Abbreviations: APS – Anti-Phospholipid Syndrome

rate. The process of thrombosis and inflammation starts off with activation or apoptosis of platelets, endothelial cells, or trophoblasts. This causes negatively charged phosphatidylserine in the affected tissues to migrate from the inner to the outer cell membrane. Circulating β_2-glycoprotein I (β_2GPI) binds to phosphatidylserine on these cells, and then APL binds to a β_2GPI dimer. This leads to a series of events like activation of the complement cascade extracellularly, initiation of an intracellular signaling cascade, probably through the C5a and β_2GPI surface receptors and also recruits and activates inflammatory effector cells such as neutrophils, monocytes, and platelets, leading to the release of pro-inflammatory products (e.g., tumor necrosis factor [TNF]-α, oxidants, proteases) triggering off a prothrombotic state [4]. In a meta-analysis, it was found that in about one-fourth of the patients, precipitating factors contribute to the development of catastrophic APS (infections, drugs, minor surgical procedures, anticoagulation withdrawal, etc.) and none was found in the remaining 75–80% cases [3].

The prognosis for patients with CAPS is poor with 25–50% mortality unless treated aggressively. Various modalities of treatment have been tried (no randomized trials). The combination of anticoagulation, glucocorticoids, immunosuppressants and plasma exchange with or without intravenous immune globulin (IVIG) has been associated with recovery rates ranging from 50–8% [2, 3, 5]. As per the analysis of case reports of 250 patients included in the International CAPS Registry up to February 2005 by Bucciarelli et al., systemic lupus erythematosus was identified as prognostic of a higher mortality rate. A higher recovery rate was associated with combined treatment with anticoagulants plus corticosteroids plus plasma exchange (77.8%), whereas, concomitant treatment with cyclophosphamide did not demonstrate additional benefit [5]. In patients resistant to standard therapies, case reports indicate that use of monoclonal antibodies may be beneficial. In a case report by Shapira et al. of a patient with recurrent CAPS, despite maximal anticoagulation, immunosuppression, and plasma exchange, benefit was shown with eculizumab, a monoclonal antibody against the C5 component of complement [6]. In another case, rituximab, the B cell-depleting anti-CD20 monoclonal antibody, was successfully employed [7].

In another study, majority of patients with catastrophic APS who survived their initial illness remained free of further thromboembolic events when treated long-term with oral anticoagulants [8]. Approximately, 20-26% had recurrent APS-related events, but none had another episode of multiorgan failure. Among the recurrent thromboembolic events, 40% occurred in a perioperative period [8]. In another meta-analysis it was found that relapses occurred in about 3.2% of APLA positive patients and it was also suggested that there could be an association between MHA (microangiopathic hemolytic anemia) and relapse of catastrophic APS [9, 10].

CONCLUSION

Catastrophic antiphospholipid syndrome is a rare entity occurring in patients with antiphospholipid antibody syndrome and it has a very poor prognosis. But early, aggressive treatment which usually consists of a combination therapy of anticoagulation, corticosteroids, IVIG and plasma exchange, improves the recovery rate. Hence this diagnosis has to be kept in mind in a scenario of acute limb ischemia and patient started on treatment at the earliest.

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Author Contributions

Vivekanandan Senthamil Pari – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
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Conflict of Interest

Authors declare no conflict of interest.

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CASE REPORT OPEN ACCESS

Spontaneous spermatic vein thrombosis as a circumstance of discovery of the nutcracker syndrome: An exceptional entity

Faouzi Mallat, Wissem Hmida, Khaled Ben Ahmed, Sarra Mestiri, Faouzi Mosbah

ABSTRACT

Introduction: Spontaneous thrombosis of a varicocele is an extremely rare event. Preoperatively, it may be misdiagnosed due to non-specific presentation because of its clinically indistinguishable from many other inguinal conditions. Case Report: We report a case of left spermatic vein thrombosis extending to the nearby renal vein diagnosed by Doppler ultrasound, in a 28-year-old male. Blood congestion caused by the nutcracker syndrome, which was incidentally found by computed tomography angiography, may therefore have contributed to the pathogenesis of the thrombosis in our patient. After undergoing surgical treatment (complete resection of the spermatic vein thrombosis), our patient is asymptomatic, with complete resolution of his pathology. Watchful observation was our option for the nutcracker syndrome. Conclusion: The diagnosis of spontaneous thrombosis of varicocele is difficult and it may be misdiagnosed before ultrasound examination, and should be considered in patients without usual risk factors of thrombosis vein. Our purpose is to raise clinician's awareness for this condition so that they will be more likely to diagnose it. Our recommendation is: before classification of the left spermatic vein thrombosis as spontaneous in the absence of the usual risk factors for thrombosis, nutcracker syndrome should be sought especially among young males.

Keywords: Varicocele, Thrombosis, Nutcracker syndrome

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INTRODUCTION

Spontaneous thrombosis of a varicocele is a rare event; approximately less than 25 cases have been reported in literature.

Herein, we present a new case of spontaneous thrombosis of a varicocele in which pathogenesis is contributed to the blood congestion caused by the nutcracker syndrome. To the best of our knowledge, we present the first thromboembolic complication of this syndrome in literature, this report is the first to describe the spermatic vein thrombosis extending to the nearby renal vein as a circumstance of discovery of the nutcracker syndrome.

CASE REPORT

A 28-year-old male, with no previous major health problems, was presented to our department for an induration in the left inguinal region with tenderness associated with left abdominal and testicular pain. The condition had started 14 days before with moderate-in-severity dull, aching pain in the left groin and left testis.

Our patient denied any history of left inguinal swellings or hernia, and has no history of surgeries, chronic illness, allergy, or trauma. He did not present any thrombogenic factors.

Physical examination of the patient revealed a height of 182 cm and weight of 58 kg with a lower body mass index at 17.5, his blood pressure was 135/75 mmHg, and was significant only for tender, movable and firm to hard 7.0 cm mass extending from the left scrotum to the external inguinal region. The testes, prostate and contralateral scrotum were normal to palpation. Initial laboratory reports were within normal limits.

Doppler ultrasonography (Figure 1) confirmed the diagnosis of left thrombosed varicocele with complete cessation of blood flow in the left spermatic vein.

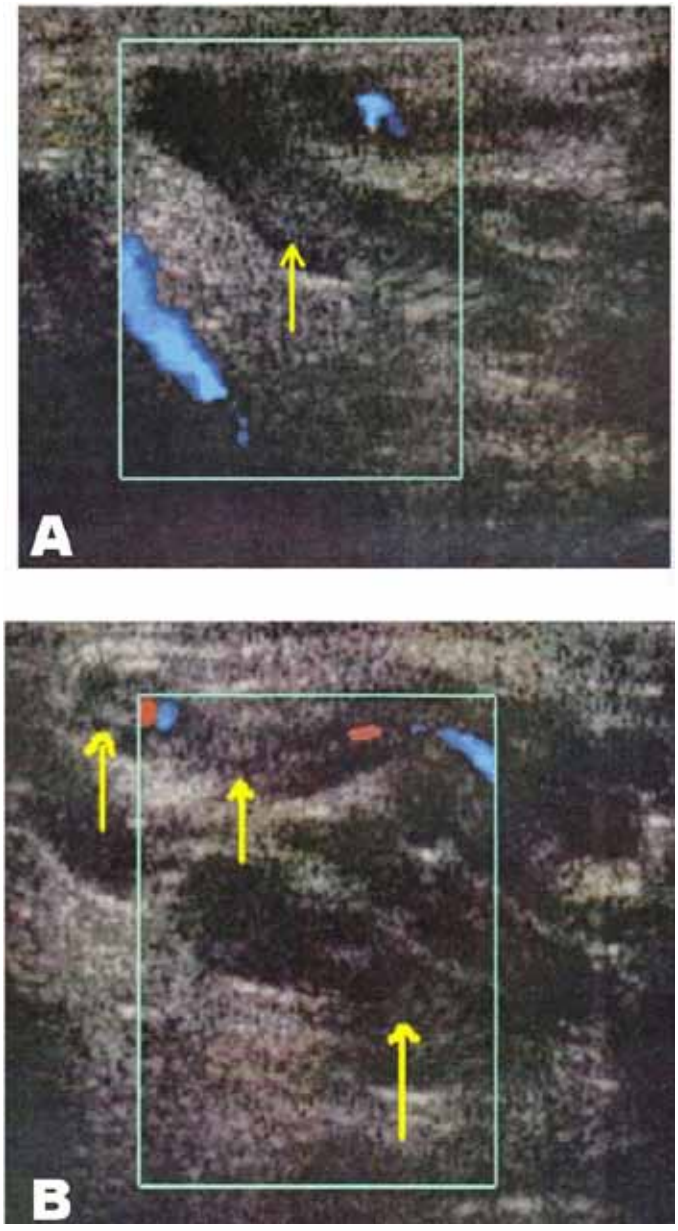

Figure 1: (A, B) Doppler ultrasound showing echogenic intraluminal thrombus in the dilated pampiniform plexus (yellow arrows).

Computed tomography angiography (CTA) revealed left spermatic vein thrombosis starting at the external inguinal ring and extending retroperitoneally to the nearby renal vein (Figure 2). The CTA also demonstrated a compression of the left renal vein between the aortic-mesenteric space, the angle between aorta and superior mesenteric artery was approximately 11°. The postero-anterior diameter of the hilar portion of the LRV was 9.8 mm and that of the aortico-mesenteric stenotic portion was 2.1 mm; suggesting anterior nutcracker syndrome (Figures 3 and 4). When we asked the patient again, he reported an intermittent macroscopic hematuria, and chronic left lumbar pain aggravated by physical activity; associated with systemic signs dominated by intermittent fatigue and headache; which lasted for his childhood.

Repeated laboratory tests revealed hemoglobin 12.0 mg/dL, microscopic hematuria, but 24-hour urine collection analysis did not show proteinuria.

Based on clinical presentation, urinary and systemic symptoms, laboratory reports, Doppler ultrasonography and computed tomography angiography finding, a diagnosis of anterior nutcracker syndrome leading to total left spermatic vein thrombosis was confirmed.

Surgical intervention was decided, and the patient consented to.

Left lumbar incision was done. There was a firm-to-hard swelling inside the dilated spermatic vein. Careful dissection and complete excision of the left spermatic vein was performed (Figure 5). All the veins draining into the left renal vein were ligated and bisected.

The patient had an uneventful postoperative hospital course and was discharged from the hospital four days later.

With eight months follow-up, the patient is doing well. The patient remained asymptomatic and had returned to his usual life. The varicocele improved significantly after operation.

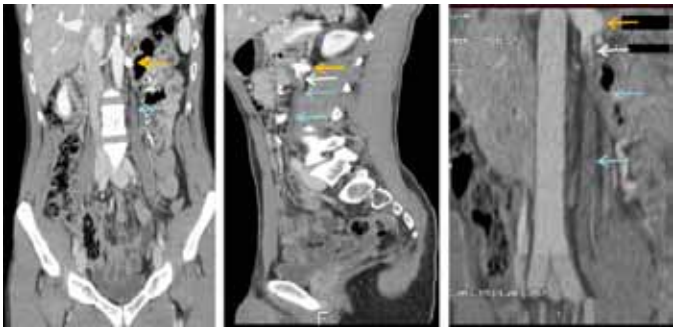

Figure 2: Computed tomography angiography (digital reconstruction) showing grossly distended and thrombosed gonadal vein: Yellow arrow: Left renal vein. White arrow: upper limit of the thrombosis of the spermatic vein to the nearby left renal vein. Blue arrow: extensive thrombosis of the spermatic vein.

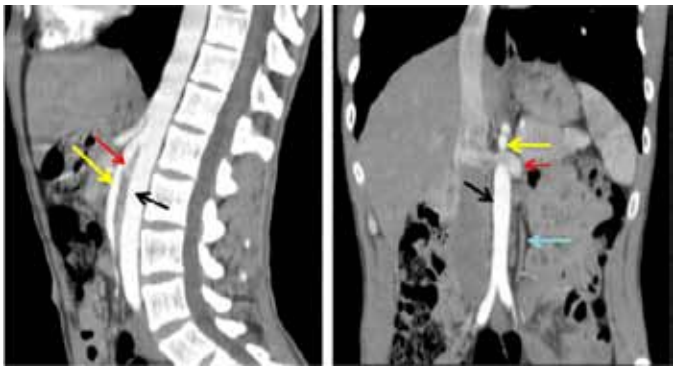

Figure 3: Computed tomography angiography showing nutcracker syndrome. Left renal vein (red arrow) is compressed between the aorta (black arrow) and the superior mesenteric artery (yellow arrow). Blue arrow showed the left spermatic vein thrombosis.

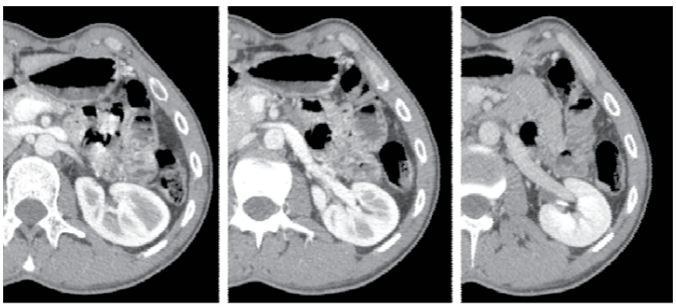

Figure 4: Computed tomography angiography showing Left renal vein compression between the aorta and the superior mesenteric artery with distended hilar portion of the left renal vein.

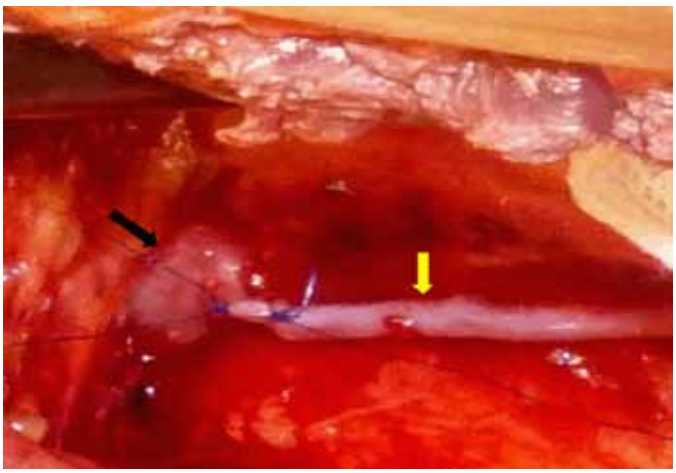

Figure 5: Intraoperative view showing ligation of the left spermatic vein (yellow arrow) to the nearby left renal vein (black arrow).

DISCUSSION

Spermatic vein thrombosis is a rare entity that is usually associated with a chromogenic background. In a review of literature, less than 25 cases of spontaneous thrombosis of the spermatic vein were found. The evolution of the spermatic vein thrombosis is unpredictable, it may disappear spontaneously [1], and in contrast it may be complicated by pulmonary embolism [2].

Three broad categories of factors, known as Virchow's triad, contribute to thrombosis: blood stasis, coagulation factors and mural factors.

Our case had no mural factors or prothrombotic coagulation factors. The nutcracker syndrome causing blood congestion may explain the pathogenesis in our present case.

The compression of the left renal vein in the aortico-mesenteric space is known as anterior nutcracker syndrome, and is responsible for the development of venous varicosities in the renal pelvis, ureter, and the gonadal vein [3]. Posterior nutcracker syndrome or entrapment of the left renal vein between the aorta and the vertebra is not rare [4, 5]. However, only a few cases showing clinical symptoms with this anomaly have been reported; and may lead to several urological problems such as varicocele, hematuria, and ureteropelvic junction obstruction [4, 5].

The extrinsic left renal vein (LRV) compression causes an impeded outflow from the LRV into the inferior vena cava, and is accompanied by LRV hypertension. Some authors contend that LRV hypertension is the usual cause of varicoceles; and it was admitted that the LRV was compressed in 50–100% of all patients with varicocele [3, 6, 7].

The pathogenesis of the varicocele thrombosis and its extension to the nearby renal vein, in our case, is explained by the chronic blood congestion in the left spermatic vein. Especially, when the diagnosis of NCS is commonly delayed.

In this case, we present the first thromboembolic complication of this syndrome in literature. To our knowledge, this report is the first to describe the spermatic vein thrombosis extending to the nearby renal vein as a circumstance of discovery of the nutcracker syndrome.

The higher sensitivity and specificity of Doppler examination, as well as its low cost and non-invasiveness, make this the procedure of choice in the diagnosis of the varicocele thrombosis and may have a role in differentiating this condition in men presenting with a history of acute idiopathic left inguinal pain; given that spermatic vein thrombosis is clinically indistinguishable from many other groin conditions. While CTA may help reveal whether the thrombus extends beyond the external inguinal ring, either externally or internally, and help to find aetiology such as the nutcracker syndrome especially in the young male.

The management of the spermatic vein thrombosis [8–16] is controversial. With regard to its management, Roach et al. recommended conservative management following their experience with a postoperative complication in a patient with bilateral thrombosis which resulted in left orchiectomy despite a satisfactory outcome on the right side with anticoagulation therapy alone [17]. In addition, no case of pulmonary embolism

from superficial spermatic vein thrombosis out of external inguinal ring has been reported.

In contrast, Castillo et al. reported a case of pulmonary thromboembolism associated with deep-seated spermatic vein thrombosis [2], and recommended spermatic vein ligation to prevent from pulmonary embolism.

From these findings, Yoko et al. [1] propose two strategies for the treatment of spontaneous thrombosis of the spermatic vein on the basis of anatomical location. Conservative management, including watchful observation, is acceptable for thrombosis of a peripheral vein localized out of external inguinal ring in the so-called pampiniform plexus. In contrast, surgical excision may prevent pulmonary embolism in deep-seated spermatic vein thrombus inside the external inguinal ring and extending to the nearby renal vein as in the present case.

Treatment options of nutcracker syndrome include follow-up, conservative treatment and surgical therapy and is still controversial.

The aim of treatment is to decrease LRV hypertension.

The procedures include intravascular or extravascular stents and open surgical options include the transposition of left renal vein, transposition of the superior mesenteric artery and renal autotransplantation.

These options should be considered only when the nutcracker syndrome was complicated by severe or persistent symptoms, such as severe pain, severe acute or chronic hematuria, not respond to conservative treatment or renal insufficiency [3].

In our case, the surgery was to prevent embolic phenomenon. Watchful waiting/observation was our strategy for the nutcracker syndrome, first because of the possible spontaneous improvement of the syndrome, and secondarily the operation is not denied of severe complications in our young and active patient with intermittent and not severe symptoms, which does not consent to. Possible intervention is considered to relieve the angulation between the aorta and superior mesenteric artery to correct LRV hypertension in case of no improvement or worsening of the symptoms or complications and when the consent of patient will be done.

CONCLUSION

Thrombosis of varicocele is a difficult clinical diagnosis and requires a high index of suspicion. Doppler ultrasonographic examination is the procedure of choice in the diagnosis of the varicocele thrombosis with higher sensitivity and specificity and may have a role in differentiating this condition in men presenting with a history of acute idiopathic left inguinal pain; given that spermatic vein thrombosis is clinically indistinguishable from many other groin conditions. Computed tomography angiography may help reveal whether the thrombus extends beyond the external inguinal ring, either externally or internally, and help to find aetiology for the spermatic vein thrombosis classified as spontaneous or idiopathic, such as nutcracker syndrome especially in the young male. If properly diagnosed, the extensive spermatic vein thrombosis must be treated surgically.

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Conflict of Interest
Authors declare no conflict of interest.

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CASE REPORT OPEN ACCESS

The effect of platelet-rich plasma injections in the non-surgical treatment of a partial rotator cuff tear

Julien Freitag, Ross Lenssen, Drew Slimmon, Simon Balster

ABSTRACT

Introduction: Rotator cuff tears are associated with significant morbidity and have a reported incidence of greater than 50% amongst the adult population. We present a case report of a partial rotator cuff tear treated with platelet-rich plasma injections. Case Report: A 60-year-old female was presented with a partial supraspinatus tear having failed to improve with physiotherapy. The patient underwent a course of three platelet-rich plasma injections to her tear. Patient outcome was measured using the numerical pain rating scale (NPRS), percentage perceived improvement (PPI) and also a handheld dynamometer assessment of rotator cuff strength. Repeat ultrasound examination was performed. The patient reported improvements in pain as measured by NPRS and PPI, though maximal improvement was not maintained through to final data collection at 52nd week. Dynamometer follow-up showed improvement in strength. Ultrasound at 52nd week showed evidence of ingrowth of tissue though this did not resemble normal tendon. The patient noted increased pain post her second platelet-rich plasma injection though this was self-limiting and managed with simple analgesia. Conclusion: In this case report, platelet-rich plasma injections for the treatment of a partial rotator cuff tear resulted in improvement in all recorded outcome measures. This highlights the need for more formal controlled trials to determine the use of platelet-rich plasma in the treatment of rotator cuff pathology.

Keywords: Rotator cuff tear, Shoulder, Platelet-rich plasma, Pain

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INTRODUCTION

Rotator cuff pathology is associated with significant morbidity and accounts for more than 4.5 million physician visits per year within the United States [1]. Incidence of rotator cuff tears has been reported as >50% amongst the adult population [2].

While surgical repair of full thickness tears show success rates of up to 85%, imaging post repair often reveals persistent cuff defects [3, 4]. This may explain recurrence of symptoms and re-tear rates reported to be as high as 57-90% [5, 6]. Furthermore, while primary surgical repair is an accepted treatment of full thickness tears there remains speculation about how best to treat symptomatic partial thickness tears.

Most classifications recognize bursal and joint surface partial rotator cuff tears. Intra-substance tears have more recently been formally described [7]. Studies have shown that bursal surface tears respond poorly to

conservative management and surgical interventions such as arthroscopic subacromial decompression, debridement and repair have all been suggested [8]. Similarly, arthroscopic follow-up of joint surface tears managed non-operatively has shown that 80% enlarge and/or progress to full thickness tears [9]. Laudicina et al. suggest that primary repair of partial tears >50% is an accepted practice, though there is no published data on its efficacy [10].

There has been growing interest in the area of biological therapies to assist musculoskeletal repair. Autologous platelet-rich plasma (PRP) is one such therapy that has gained much attention. Platelet-rich plasma is defined as a volume of the plasma fraction of whole blood having a platelet concentration above that of baseline. Several anabolic and trophic factors that participate in tissue repair processes have now been identified within PRP preparations [11]. These growth factors, including platelet derived growth factor (PDGF), transforming growth factor beta 1 (TGFβ1), insulin-like growth factor 1 (IGF1) and vascular endothelial growth factor (VEGF), have the ability to influence and direct tissue regeneration through angiogenesis, chemotaxis and cell proliferation and also effect the synthesis of extracellular matrix proteins. Platelets also release cell adhesion molecules such as fibronectin, fibrinogen and vitronectin which influence extracellular matrix synthesis and thus connective tissue development/ regeneration [12]. Recent review articles on PRP have suggested that it is being used increasingly in the clinical setting for the treatment of tendinopathy [13, 14].

Due to the significant incidence of post surgical tear recurrence, there has been considerable focus on improving long-term surgical outcome through the use of biological augmentation. The use of PRP matrices at time of surgical repair has been trialed with inconsistent results and is not widely practiced [15, 16]. Further, despite its growing use within clinical practice for the conservative management of tendinopathy there is a paucity of published data on its use in the non-surgical management of rotator cuff pathology.

Kesikburun et al. have published a randomized control trial on the use of PRP in the treatment of chronic rotator cuff tendinopathy showing no improvement beyond that achieved with a traditional conservative exercise program [17]. Interestingly, however, the PRP was injected into the subacromial space and not the tendon itself. O'Donnell et al. compared intra-tendinous injections of PRP to subacromial corticosteroids and showed both significant improvement in pain and function but also a significant reduction in the later requirement for surgical repair at 12th month follow-up [18]. This result, however, may be complicated by the growing awareness that long-term outcome in tendinopathy is worse in those treated with corticosteroid injections [19].

Despite its theoretical potential in therapeutic applications within musculoskeletal medicine, trials on the use of PRP in tendon pathology have been inconclusive [20, 21]. Both the lack of uniformity in treatment protocols and differing preparation techniques have meant vastly conflicting results between publications on PRP treatments, leading to disagreement on whether PRP is an effective therapeutic modality. It is yet to be determined whether good theory equates to a successful clinical outcome.

CASE REPORT

Case Presentation

A 60-year-old female presented with gradual onset of shoulder pain with lifting and overhead activities over the last six months. She worked as an aged care assistant and had failed to improve with a physiotherapy guided scapular control and rotator cuff strengthening program. The patient had received an ultrasound-guided subacromial cortisone injection with good but, unfortunately, only short-term relief. Formal ultrasound showed evidence of a partial insertional tear of the supraspinatus tendon (Figure 1A). The physician who treated her had discussed the possibility of surgical subacromial decompression and rotator cuff repair but she was hesitant to consider surgery. Her physician referred her for consideration of autologous platelet-rich plasma (PRP) therapy.

On initial examination, the patient had normal shoulder range of motion but exhibited a painful arc from 90–180 degrees of abduction. She had pain and weakness on rotator cuff testing. Radiological examination confirmed a type I acromion, no subacromial spur and no glenohumeral osteoarthritis.

Given that the patient had failed to improve with conservative management of her partial rotator cuff tear, the trial of PRP therapy in conjunction with a continued rehabilitation program was deemed appropriate. Written information and education was provided regarding PRP and its use within tendinopathy, including relevant alternatives (i.e. surgery) and possible risks involved.

The patient underwent a course of ultrasound guided PRP injections to her insertional tear. Patient outcome was measured using the numerical pain rating scale, percentage perceived improvement and also dynamometer assessment of rotator cuff strength.

Investigations

Ultrasound examination prior to treatment confirmed a partial insertional supraspinatus tear (Figure 1A). Repeat ultrasound was performed at 12th month post-PRP therapy (Figure 1B).

X-ray confirmed a type I acromion, no subacromial spur and no glenohumeral osteoarthritis.

Treatment

Analysis Method

Prospective analysis of patient outcome to intra-tendinous PRP injection included the numerical pain rating scale (NPRS) [22], patient percentage perceived improvement (PPI) and a handheld isometric dynamometer assessment of rotator cuff strength.

NPRS was recorded prior to each injection, with follow-up intervals occurring at 6th, 17th, 25th and 52nd weeks. Percentage perceived improvement was recorded at 17th and 52nd weeks. Dynamometer testing was recorded immediately prior to the initial injection and again at 6th and 18th weeks.

Isometric dynamometer testing has been validated as a reliable assessment of rotator cuff strength and function [23–25]. Eleven isometric resisted glenohumeral tests were performed using a handheld dynamometer (Figure 2), with supraspinatus being particularly active in the 'empty can' and external rotation positions [26]. Every position was loaded isometrically for five seconds at a maximum tolerated contraction. Each test was performed after a demonstration so to ensure that the participant and clinician used correct technique and avoided any unwanted movements or body swaying. If a test was performed incorrectly, it was repeated to ensure it was done properly. If performed correctly, no re-test was performed as Kolber et al. have shown excellent reliability with high intra-class correlation coefficients of 0.971–0.972 [23].

Platelet-Rich Plasma Preparation

The patient received three PRP injections (weeks 0, 1 and 2).

Autologous blood (24 mL) was withdrawn from the study participant and separated into 3x8.5 mL BD Vacutainers (BD, Franklin Lakes, NJ, USA) containing ACD (trisodium citrate 22.0 g/L, citric acid 8.0 g/L, and dextrose 24.5 g/L) to prevent clotting. BD vacutainers undergo gamma irradiation to ensure internal sterility. Gamma irradiation has also been shown to reduce endotoxin expression [27]. Using a bench-top XC 2000 centrifuge the tubes were centrifuged at 1000 rpm (110×G) for 10 minutes to create a platelet-poor plasma (PPP) level, a middle buffy coat level (high in platelets and leukocytes) and a lower red blood cell layer.

Platelet-poor plasma was withdrawn from each tube to the level of the red blood cell layer and placed in a single sterile vacutainer (BD, Franklin Lakes, NJ, USA) which was re-centrifuged at 3500 rpm (1370×G) for three minutes resulting in the formation of a platelet plug and PPP. Platelet-poor plasma was withdrawn to 30 mm and discarded. The remaining PPP and platelet plug were re-constituted using gentle manual agitation resulting in leukocytes rich platelet-rich plasma medium. The PRP underwent photo-modulation using the commercial Adi-Light 2 device (AdiStem Ltd, Hong Kong). Photo-modulation –polychromatic light– therapy has been

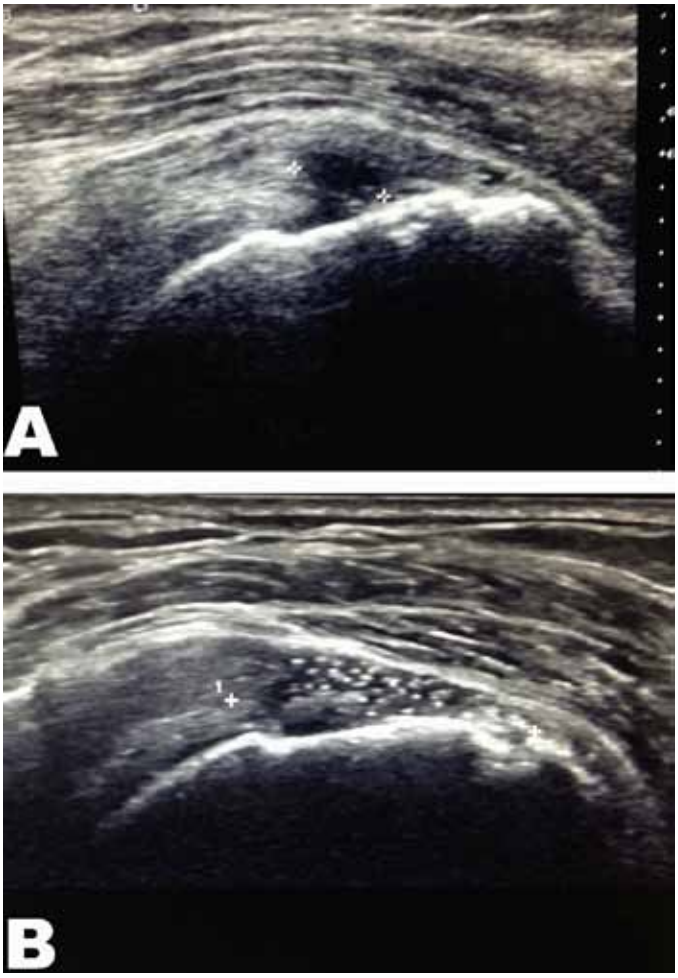

Figure 1: (A) Ultrasound examination prior to PRP therapy showing the insertional supraspinatus partial tear (B) Ultrasound examination at 52nd week post-commencement of PRP therapy showing ingrowth of hyper-echoic fibrous tissue which does not exhibit tendon 'like' structure.

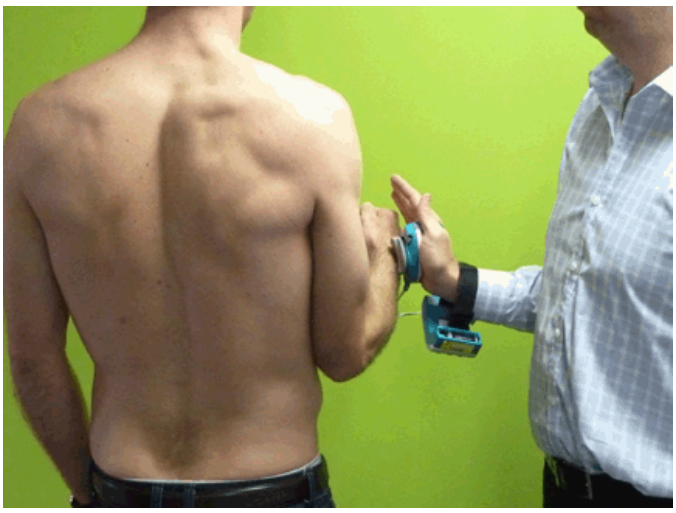

Figure 2: Dynamometer assessment.

shown to increase expression of leucocyte-derived anti-inflammatory cytokines (IL-1RA) and also to cause reduction in pro-inflammatory cytokines (IL-2 and 6) [28, 29].

Inflammatory cells such as neutrophils and macrophages play an important role in the initiation of tendon/soft tissue healing through phagocytosis of degenerative/necrotic tissue [30]. Unfortunately, the presence of leukocytes can also result in a pro-inflammatory environment leading to further damage [31]. Adapting these theories to clinical practice it was decided that the injection protocol would utilize a leukocyte rich PRP preparation for the initial injection but that a five-micron filter (GVS, Bologna, Italy) would be used in the subsequent injections resulting in a leukocyte poor PRP. This protocol has not previously been described.

Injection Method

Under sterile conditions and ultrasound guidance, a sterile 22-gauge needle was inserted into the partial supraspinatus tear using a lateral approach. On the initial injection two milliliters of leukocytes rich PRP was injected with no concurrent use of local anesthetic. For the following two injections a five-micron filter was placed between the needle and syringe resulting in a leukocyte poor PRP preparation upon injection.

Potential Adverse Effects

Previous studies using PRP therapy have indicated minimal adverse effects [20, 21]. Mishra et al. documented self-limiting discomfort post intra-tendinous injections [21].

Strengthening/Physiotherapy Program

The patient continued the physiotherapy guided progressive strengthening program which had commenced prior to receiving PRP therapy. This program initially consisted of two low graded exercises for three sessions per day. When the patient was able to demonstrate adequate progress, the program was gradually progressed to eight more difficult exercises 1–2 sessions per day. The intensity of the exercises gradually progressed as tolerated by increasing the weight/resistance used and by altering the type of exercise to increase the lever arm/torque and to work different muscle groups. Combinations of hand weight and theraband exercises were utilised.

RESULTS

The NPRS gradually improved after commencing PRP treatment and reached 0 at 17th week. NPRS remained improved though had increased to three by completion of data collection at 52nd week (Figure 3).

At 17th week following the initial PRP injection, a percentage perceived improvement of 90% was reported by the patient. At 52nd week, PPI remained improved though was now only 70% (Figure 4).

Dynamometer testing (performed by the same clinician to prevent inter-examiner variability) showed progressive improvement in strength across all movements (Figures 5 and 6). Isolated supraspinatus activation in the 'empty can' position showed improvement of 26.93% at 6th week and 32.15% by 18th week. Loaded external rotation with elbow by side (ER at 00) showed improvement of 32.15% by 6th week and 51.29% by 18th week. Unfortunately, dynamometer testing was not continued after 18th week due to the significant distance the patient had to travel to have this assessment.

Repeat ultrasound at 52nd week showed ingrowth of hyper-echoic tissue into the partial tear defect. This tissue did not, however, resemble tendon like structure (Figure 1B).

The patient noted a significant flare up of shoulder discomfort following the 2nd PRP injection. This was self limiting (lasting 3 days) and managed with simple analgesics (paracetamol). No other complications were noted.

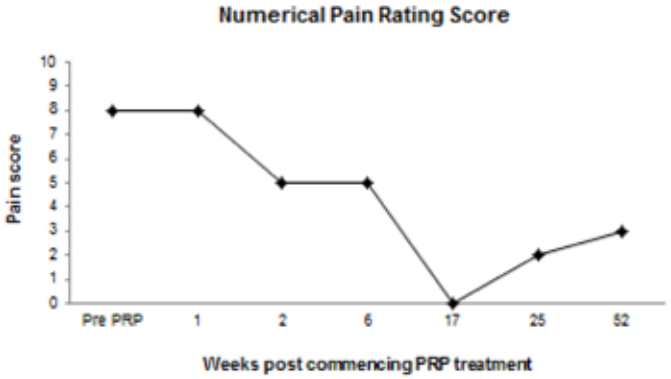

Figure 3: Numerical pain rating scale.

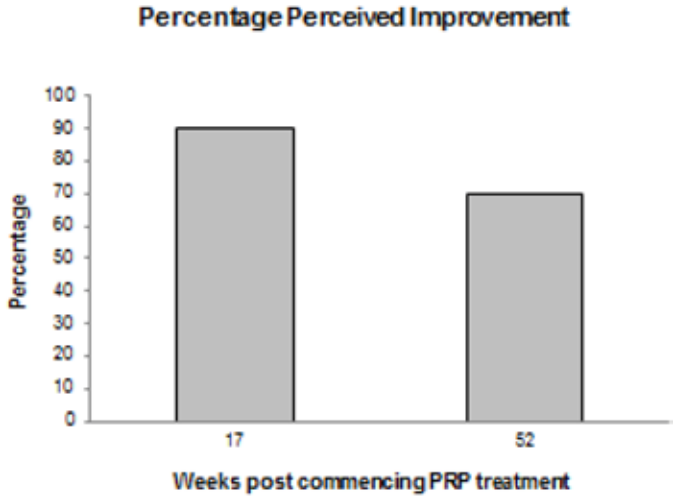

Figure 4: Patient perceived percentage improvement (PPI).

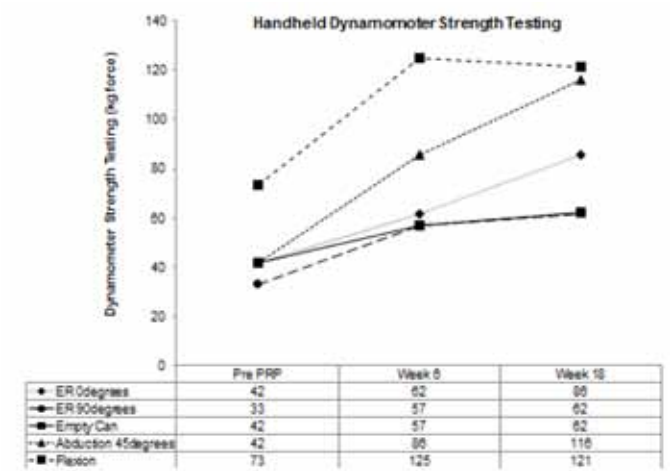

Figure 5: Digital handheld isometric dynamometer testing results (units = Kg).
ER 0° – External rotation with arm by side. ER 90° – External rotation with arm abducted to 90°. IR 0° – Internal rotation with arm by side. IR 90° – Internal rotation with arm abducted to 90°. Empty can – as described by Jobe et al. [26]. Lift Off and Press Belly – subscapularis specific test.

Table 1: Isometric rotator cuff dynamometer test results (units = Kg).

Test	Pre-PRP	Week 6	Week 18
ER 0°	41.8	61.6	85.8
ER 90°	33	57.2	61.6
Empty Can	41.8	52.8	61.6
Abduction 45°	41.8	85.8	116
Flexion	72.6	125	121
Extension	81.4	121	138
IR 0°	28.6	118	121
IR 90°	35.2	90.2	100
Lift Off	41.8	52.8	85.8
Press Belly	68.2	88	103

DISCUSSION

This case study describes the use of platelet-rich plasma in the treatment of a symptomatic partial rotator cuff tear. It also documents the use of dynamometer assessment of rotator cuff strength enabling further quantitative analysis of patient response beyond that achieved with questionnaires.

Post-PRP the patient demonstrated improvement in all recorded outcome measures. NPRS improved to 0 by 17th week and remained improved —though had increased to 3 — by completion of data collection at 52nd week. The PPI was recorded as 90% at 17th week and whilst remaining improved had reduced to 70% by week 52. Dynamometer testing recorded an improvement in supraspinatus activation over 18 weeks of follow-up.

Interestingly, all values of dynamometer testing – including those not assessing supraspinatus function– improved over the course of follow-up. This supports the concept that the individual muscles of the rotator cuff work in cohesion to assist with glenohumeral control during active movement of the shoulder [32]. Unfortunately, dynamometer testing was not continued after 18th week and we do not know whether increased values of NPRS and reduced PPI would have correlated with reduction in dynamometer values.

Repeat ultrasound at 52nd week showed development of tissue ingrowth into the tear though this did not resemble tendon tissue. This imperfect healing response perhaps explains why the patient, after an initial significant improvement in NPRS and PPI, showed some regression in these values by week 52. This highlights the difficulty in assessing PRP as an adjuvant biological therapy in tendon pathology. The protocol used in the case study involved three injections of PRP at weekly intervals. It is accepted that tendon healing occurs in 3 overlapping phases of inflammation, proliferation and remodeling [33]. As the remodeling phase may extend over 12 months it is conceivable that further injections of PRP are required to stimulate a more appropriate healing response.

Further, this case study uses a PRP preparation method that is not common to all published research and its use of a five-micron filter to create a leukocyte poor PRP has not to our knowledge been previously published in literature. The injection protocol and PRP preparation all add to a treatment `recipe' with significant possible variables that will influence the outcome. This lack of `recipe' uniformity makes it difficult to compare research papers on PRP. DeLong et al. have suggested the use of a PAW classification system (platelet count, activated versus inactivated, presence or absence of white blood cells) to enable formal comparison of PRP publications and this should be adopted if a more controlled trial/ study was performed [34].

The complex nature of rotator cuff pathology is another area that may influence the effectiveness of biological therapies such as PRP. Understandably, it is questionable whether the results of this study would have reliable external validity if used for other patients with similar but not exactly the same pathology. It is unlikely that PRP would be beneficial for under-surface/ joint or top-surface/bursal partial thickness rotator cuff tears where there is no contained defect in which to inject PRP.

Despite the aforementioned protocol and tendon pathology variables, and whilst recognizing the low level of evidence, the results of this case study indicate that in a well-selected patient population, PRP may assist in the non-surgical management of partial rotator cuff tears. Further investigation with an appropriately powered randomized control trial is needed to confirm the external validity of this treatment and use within clinical practice.

CONCLUSION

Partial rotator cuff tears are a cause of significant shoulder disability. Surgical repair of rotator cuff tears are complicated by significant re-tear rates and recurrence of symptoms. The use of platelet-rich plasma in partial rotator cuff tears may offer a non-surgical treatment for patients who do not respond to conservative rehabilitation methods. Platelet-rich plasma is an autologous medium that offers promise in the treatment of tendinopathies yet current evidence is inconclusive and further controlled research is needed.

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Author Contributions

Julien Freitag – Conception and design, acquisition of data, Analysis and interpretation of data, Drafting the article, Critical revision of the article, Final approval of the version to be published
Ross Lenssen – Acquisition of data, Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published
Drew Slimmon – Acquisition of data, Critical revision of the article, Final approval of the version to be published
Simon Balster – Acquisition of data, Critical revision of the article, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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CLINICAL IMAGE OPEN ACCESS

Deforming tophaceous gout

Lénea Porto, Eurico Oliveira, Jorge Correia, Fernando Girão

CASE REPORT

A 78-year-old male with a history of smoking, dietary excesses, hyperuricemia (serum uric acid level of 11 mg/dL) and renal chronic disease (creatinine clearance rate of 30 mL/min per 1.73 m^2 of the body-surface area) presented with multiple tophi on the hands, elbows, feet, knees, and auricular surfaces, with hand bone associated deformities (Figure 1).

He described a long past of multiple episodes of confirmed acute uric arthritis improperly treated. He had also been medicated with allopurinol but with a patient poor concordance and advised to take a dietary regimen, which he refused. After thirty years, daily activities such as holding a fork, etc. were severely impaired.

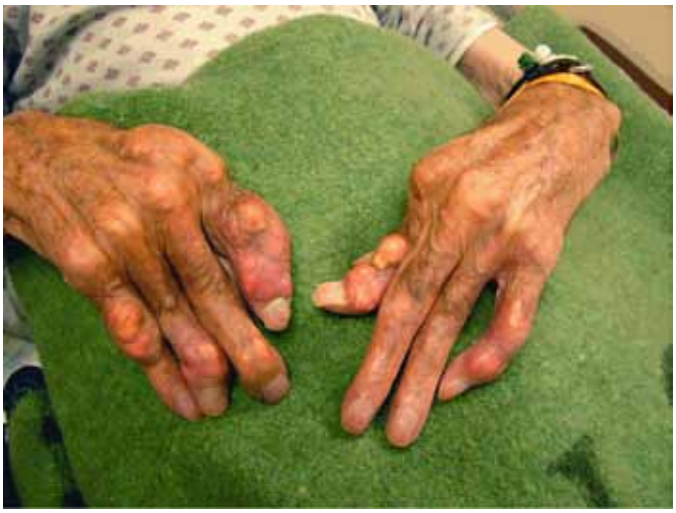

Figure 1: Multiple yellowish-white tophi on the hands deforming bone structure.

DISCUSSION

Gout is the most common form of inflammatory arthropathy and affects at least 1% of the population in the western countries [1, 2]. Several studies suggest that its prevalence and incidence, in recent decades, have risen [1, 3]. Men have a greater risk of developing gout. The overall men and women ratio ranges between 7:1 and 9:1, but more recent studies suggest, a smaller difference and point ratios of 4:1 [1]. Gout prevalence also presents a direct association with age, and the increased population longevity may be contributing to its present higher prevalence [3].

Numerous risk factors seem to associate to the development of gout, such as hyperuricemia, genetics, diet and alcohol consumption, hypertension, obesity, diuretic use and chronic renal disease. Of these, hyperuricemia is considered to be the most important [1, 3].

As serum uric acid levels rise and its physiological saturation threshold in body fluids is exceeded, the formation and deposition of monosodium urate crystals occurs, in and around joints.

A typical gout attack is characterized by the sudden onset of severe pain, swelling, warmth, and redness of a joint. The joint most commonly involved is the first metatarsophalangeal joint but any joint may be involved. Some patients have a chronic form of gout with relapsing acute episodes.

Gout is strongly suspected by a clinical course of acute episodes of joint pain with complete resolution of symptoms between attacks associated with high levels of urate in blood analysis. However, the best way to diagnose gout is to examine synovial fluid from an affected joint to look for urate crystals in the sample. Crystals of

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monosodium urate appear as needle-shaped negatively birefringent (polarize microscopy) crystals [4].

Anti-inflammatory medications are the best treatment for acute gout attacks. Prophylactic therapy includes dietary changes and urate-lowering medications. These are effective options. Repeated episodes of acute gout when sustained for several years without treatment may lead to the accumulation of a large number of urate crystals in masses called tophi (potentially treatable) and to joint deformity and destruction (irreversible) [5].

CONCLUSION

Gout, if untreated, can be deforming and severally disabling.

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Lénea Porto – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Final approval of the version published

Eurico Oliveira – Substantial contributions to conception and design, Analysis and interpretation of data, Drafting the article, Final approval of the version published

Jorge Correia – Substantial contributions to conception and design, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version published

Fernando Girão – Substantial contributions to conception and design, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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