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Salvage chemotherapy with 5-fluorouracil and actinomycin D for advanced testicular germ cell tumor: A case with elevated human chorionic gonadotropin

Tatsuro Sanami, Akiyoshi Katagiri, Kentaro Arinami, Kazuhiro Watanabe, Kohei Inui, Shunsuke Yamaguchi

ABSTRACT

Introduction: Platinum-based chemotherapy is the standard treatment for advanced testicular germ cell tumors. However, selecting third-line and further regimens is difficult in refractory cases. We report a case of testicular mixed germ cell tumor treated with a salvage regimen for high-risk gestational trophoblastic tumor.

Case Report: A 48-year-old male was diagnosed with an advanced mixed germ cell tumor of the right testis with markedly elevated human chorionic gonadotropin levels. Induction and second-line chemotherapy with platinum-based regimens did not achieve normalization of the tumor marker. As salvage chemotherapy, a regimen of 5-fluorouracil and actinomycin D was applied, which led to remission of the tumor marker. However, additional consolidation courses were discontinued due to cumulative adverse events and the patient's wishes. Ultimately the patient died of tumor recurrence.

Conclusion: We report the first case of testicular germ cell tumor in which a regimen of 5-fluorouracil and actinomycin D showed effectiveness. This regimen for high-risk gestational trophoblastic tumor is also considered a promising treatment option for testicular germ cell tumors with a choriocarcinoma element.

Keywords: Choriocarcinoma, FA, Human chorionic gonadotropin, Testicular tumor

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INTRODUCTION

Until the 1960s, antimetabolites and antitumor antibiotics have been commonly used in chemotherapy for testicular tumors, although with low response rates [1]. Treatment outcomes improved dramatically after the introduction of cisplatin, and various platinum-based regimens were established [2]. However, even in current guidelines, it is difficult to determine appropriate regimens for refractory cases [3]. We report an advanced case of mixed germ cell tumor (GCT) of the testis with markedly elevated human chorionic gonadotropin (HCG), in which a salvage regimen of 5-fluorouracil and actinomycin D (FA) achieved serological remission.

CASE REPORT

A 48-year-old male presented to our hospital with cough, gynecomastia, lumbar pain, and right testicular swelling. Computed tomography revealed retroperitoneal multiple lymph node metastases with right hydronephrosis and bilateral multiple lung metastases; each metastatic tumor showed hemorrhagic

necrosis (Figure 1). Laboratory tests revealed elevation of lactate dehydrogenase levels (524 IU/L), α-fetoprotein (AFP; 196 ng/mL), and HCG (365,122 mIU/mL). He underwent right radical orchiectomy and right ureteral stenting. The pathological diagnosis was mixed GCT consisting of embryonal carcinoma, teratoma, and yolk sac tumor. Although syncytiotrophoblasts were scattered, the pathological diagnosis of choriocarcinoma was not definite (Figure 2). Treatment commenced with induction chemotherapy, which included bleomycin, etoposide, and cisplatin (BEP). Although tumor marker levels gradually decreased, AFP rose again after three cycles of BEP. Therefore, treatment was changed to a second-line chemotherapy regimen: TIP (paclitaxel, ifosfamide, and cisplatin). After four TIP cycles, AFP normalized, and there was a slight reduction in tumor size. However, abnormal HCG levels persisted, and he developed a severe peripheral neuropathy. As a third-line chemotherapy, MEA (methotrexate, etoposide, and actinomycin D), a regimen for high-risk gestational trophoblastic tumor (HRGTT), was applied. Twelve days after MEA initiation, he suffered from breathlessness and was diagnosed with drug-induced pneumonitis. After steroid pulse therapy, chemotherapy was resumed with FA, another regimen for HRGTT with shortening of the regimen to three days because of exhausted bone marrow function. Although HCG normalized after five FA cycles (Figure 3), treatment was discontinued after one more cycle due to recurrence of drug-induced pneumonitis. At this point, significant multiple residual tumors remained (Figure 1), and its complete extirpation was considered to be difficult. Considering the patient's financial burden and comorbidities including peripheral neuropathy, pneumonitis, and poor bone marrow function, we followed him without further treatments. Four months after the last chemotherapy, the left pleural effusion with elevated HCG appeared (Figure 3). Ultimately, the patient died 22 months after the initial diagnosis.

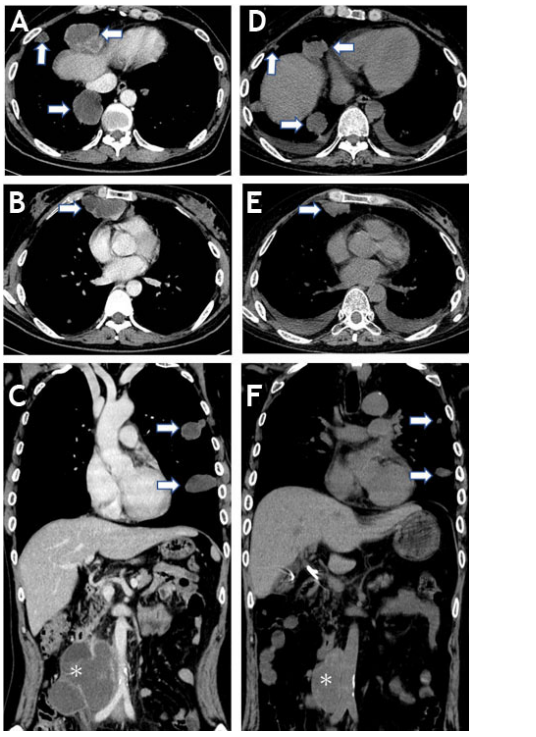

Figure 1: Computed tomography findings before (A–C) and after whole chemotherapy (D–F). (A, B, D, E) Lung metastases (arrows), (C, F) retroperitoneal lymphadenopathies (asterisks). Each metastatic tumor showed severe necrosis with heterogenous opacity suggesting hemorrhagic necrosis (A–C). Despite the partial response to chemotherapy, significant multiple tumors remained.

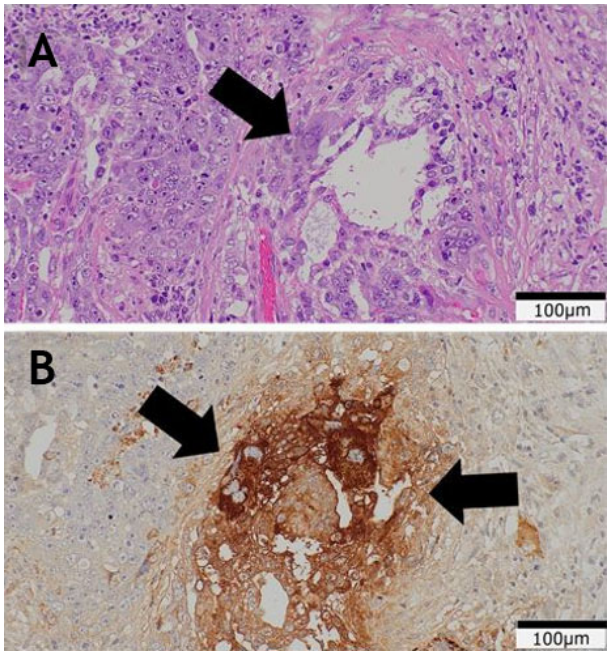

Figure 2: Pathological findings of the testicular tumor. (A) Hematoxylin-eosin staining, (B) immunohistochemistry for human chorionic gonadotropin. Arrows show syncytiotrophoblasts demonstrating positive staining for human chorionic gonadotropin.

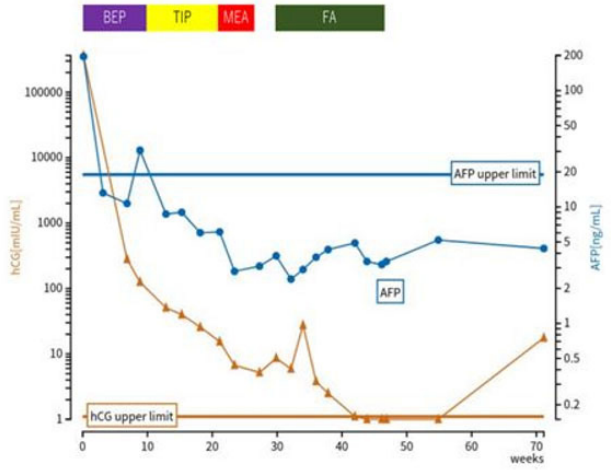

Figure 3: Tumor markers and treatment course. AFP, α-fetoprotein; HCG, human chorionic gonadotropin; BEP, bleomycin, etoposide, and cisplatin; TIP, paclitaxel, ifosfamide, and cisplatin; MEA, methotrexate, etoposide, and actinomycin D; FA, 5-fluorouracil and actinomycin D.

DISCUSSION

Approximately 95% of testicular tumors are GCTs, which comprise five main subtypes: seminoma, teratoma, embryonal carcinoma, yolk sac tumor, and choriocarcinoma [3]. Choriocarcinoma is characterized by elevated HCG levels, and it often presents with hemorrhagic and necrotic features on imaging [4]. Pathologically, choriocarcinoma is diagnosed by the presence of syncytiotrophoblasts and cytotrophoblasts [4, 5]. Testicular tumors containing a choriocarcinoma element have lower overall and cancer-specific survival rates [6]. Prognosis is notably poorer when HCG levels exceed 50,000 mIU/mL, with a reported median overall survival of 13 months [5]. Although this case was not diagnosed with definite choriocarcinoma pathologically, markedly elevated HCG levels and hemorrhagic necrosis in metastatic lesions strongly suggested the existence of a choriocarcinoma element. In the treatment of advanced testicular GCT, platinum-based regimens are generally used as induction and second-line chemotherapies. From third-line chemotherapy onward, regimens with various combinations of gemcitabine, oxaliplatin, and paclitaxel, high-dose chemotherapy, pembrolizumab, and others are selected, while there is no definite consensus [3]. In this case, HCG levels remained abnormal even after treatment with BEP and TIP. As this case was clinically considered to have a choriocarcinoma element as described above, we introduced a regimen for HRGTT as a third-line chemotherapy.

In chemotherapy for HRGTT including choriocarcinoma, combination regimens containing actinomycin D and methotrexate are popular. First-line regimens include EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine), EP/EMA (etoposide and cisplatin alternating with etoposide, methotrexate, and actinomycin D), FA, and MEA [7]. Generally, EMA/CO is the treatment of choice, as it has a high initial complete response rate of 62–78% [7]. In the treatment of testicular tumor including choriocarcinoma, actinomycin D and its related regimens have historically been used and have demonstrated some efficacy [1, 8, 9]. In a study of EMA/CO for male GCT with HCG expression, Raggi et al. reported four complete and five partial responses with HCG normalization in 41 patients [10]. Terakawa et al. reported salvage chemotherapy with MEA for male non-seminomatous GCT with a choriocarcinoma component, which achieved HCG normalization in five of nine cases [11]. Regarding FA, Matsui et al. reported a remission rate of 80% with a mean follow-up of 10 years in 10 refractory HRGTT cases [12]. As far as we know, this is the first case of testicular GCT with a choriocarcinoma element treated with FA. In this case, refractory HCG normalized with salvage FA, which may have contributed to the patient's survival over 20 months despite a poor prognostic factor, markedly elevated HCG levels at presentation.

In this case, multiple tumors that were difficult to extirpate surgically remained after HCG normalization. Nonetheless, additional chemotherapy was abandoned, considering cumulative adverse events and the patient's wishes. In chemotherapy for HRGTT, several additional courses are recommended even after the normalization of HCG levels [13]. In a report of MEA therapy for male GCT with a choriocarcinoma component, three of four patients with prolonged survival received surgical resection of the residual tumor after HCG normalization [11]. Resection of residual tumors in testicular non-seminomatous GCT after the normalization of tumor markers reveals fibrosis or necrosis in 45–50% of cases [14]. Higher viable cancer rates have also been reported after salvage chemotherapy compared with first-line chemotherapy [15]. Although normalization of tumor markers leaves the possibility of pathological remission, this case practically resulted in recurrence with elevated HCG levels. In regard to consolidation chemotherapy in testicular tumor, there have been no definite evidences and adjuvant chemotherapy after consolidation surgery is also controversial. However, a similar efficacy of consolidation chemotherapy after serological remission as in HRGTT is presumed in testicular choriocarcinoma, almost the same pathological entity as HRGTT. Taken together, consolidation treatment with chemotherapy and/or surgery is considered to be essential even after HCG normalization in refractory testicular GCT with a choriocarcinoma element.

In view of global effect of standard regimens on histological subtypes other than choriocarcinoma in mixed GCT, this regimen could be applied in the salvage setting for selected cases with residual HCG. As testicular choriocarcinoma is rare, we consider that this regimen should be validated by cautious application and could be integrated as a salvage option in testicular GCT with a choriocarcinoma element.

CONCLUSION

We reported a case of advanced testicular GCT with elevated HCG levels, in which the effectiveness of FA therapy was demonstrated. This regimen could be an option as salvage chemotherapy in cases of testicular GCT with residual HCG.

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Author Contributions

Tatsuro Sanami – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Akiyoshi Katagiri – Acquisition of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Kentaro Arinami – Acquisition of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.