

## CASE REPORT

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# High-grade undifferentiated pleomorphic sarcoma of the colon with node positivity and literature review of current therapeutic targets and future perspectives

Gogo-Ogute E Ibodeng, Jaime Said, Marcus Kwon, Jennifer Ra, Christopher D Johnson, John J Richards

## ABSTRACT

Undifferentiated pleomorphic sarcoma (UPS) arises from mesenchymal tissues and accounts for approximately 1% of adult malignancies. It is the most common type of malignant soft tissue sarcoma, primarily found in the extremities and retroperitoneum, but rarely presents in the gastrointestinal tract. Primary tumors of the mesentery are rare, though metastases to the mesentery from other anatomical sites are frequent. The standard of care of UPS involves surgical resection followed by adjuvant chemotherapy or radiation, though these treatments are often only partially effective.

We report a case of high-grade UPS of the sigmoid colon with node positivity and local extension to the small bowel. The patient underwent an open en bloc resection of the sigmoid colon and small bowel, followed by adjuvant chemotherapy and radiation therapy, resulting in transient clinical improvement. However, the patient returned to the ER 12.5 weeks post-initial surgical resection with complaints of abdominal pain, nausea, vomiting, and diarrhea. An exploratory laparotomy revealed a new intra-abdominal mass, leading to a palliative resection. This case highlights the aggressive

nature and poor prognosis of UPS, even with standard treatment. Ongoing clinical trials and emerging therapies are crucial for improving outcomes in UPS. Access to tumor profiling and precision therapies is essential for managing rare cancers like UPS. Further studies and clinical trials are imperative to develop more effective treatments and improve patient prognosis.

**Keywords:** Malignant fibrous histiocytoma, Metastasis, Sarcoma, Undifferentiated pleomorphic sarcoma

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Gogo-Ogute E Ibodeng<sup>1</sup>, MD, Jaime Said<sup>2</sup>, BS, DO, Marcus Kwon<sup>2</sup>, BS, DO, Jennifer Ra<sup>2</sup>, BS, DO, Christopher D Johnson<sup>3</sup>, MD, FACS, John J Richards<sup>3</sup>, MD, FACS

**Affiliations:** <sup>1</sup>Department of Internal Medicine, Thomas Hospital Internal Medicine Residency, 750 Morphy Avenue, Fairhope, Alabama 36532, USA; <sup>2</sup>Alabama College of Osteopathic Medicine, 445 Health Sciences Boulevard, Dothan, Alabama 36303, USA; <sup>3</sup>Department of Surgery, Ascension Sacred Heart Medical Group, 801 E 6th St #606, Panama City, Florida 32401, USA.

**Corresponding Author:** Gogo-Ogute E Ibodeng, Department of Internal Medicine, Thomas Hospital Internal Medicine Residency, 750 Morphy Avenue, Fairhope, Alabama 36532, USA; Email: gogo.ibodeng@gmail.com

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## INTRODUCTION

Undifferentiated pleomorphic sarcoma (UPS) is the most common type of malignant soft tissue sarcoma, making up about 28% of all soft tissue sarcomas [1]. It is primarily found in the extremities and retroperitoneum, and rarely presents in the gastrointestinal tract [2]. Current treatment involves surgical resection and adjuvant chemotherapy or radiation, which are partially effective. Prognosis for intra-abdominal UPS is considered particularly poor with high recurrence rates [3]. We report a case of undifferentiated high-grade pleomorphic sarcoma of the sigmoid colon with node positivity and recurrence in the retroperitoneum with a

review of the literature of current therapeutic targets and future perspectives.

## CASE REPORT

A 68-year-old Caucasian male with hypertension, hyperlipidemia, glaucoma, benign prostatic hyperplasia (BPH), gastroesophageal reflux disease (GERD), alcohol abuse, and chronic low back pain presented to the emergency room (ER) with constipation and worsening abdominal pain. He reported no bowel movement for four days and abdominal pain for 1.5 months. His abdominal pain was dull, constant, and localized to the lower quadrants. The patient admitted to nausea and weakness. He had no chest pain, dyspnea, fevers, chills, vomiting, hematemesis, hematochezia, or weight loss. On physical exam, the abdomen was soft and distended, with tenderness in the left upper quadrant and lower abdomen, but no rebound or guarding. Laboratory abnormalities showed leukocytosis (white blood cell count of  $18.2 \times 10^9/L$ ), hyponatremia (sodium of 127 mmol/L), and hyperbilirubinemia (total bilirubin of 1.8 mg/dL). Contrast computed tomography (CT) of the abdomen and pelvis showed a large sigmoid mass measuring approximately  $7.0 \times 5.2$  cm with surrounding edema and ill-defined hypodense lesions in the liver suggesting metastatic disease (Figure 1A and B). A liver core needle biopsy of a hypodense area previously seen on the initial CT showed marked acute and chronic inflammation fibrosis with reactive changes; however, malignancy was not identified. Flexible sigmoidoscopy revealed a friable 7 cm near-obstructing colon mass 40 cm proximal to the anal verge (Figure 2A–C). Because of the near-obstruction, the patient underwent surgical intervention. At the time of operation, he was found to have a large sigmoid mass with direct extension to the terminal ileum. He underwent an open sigmoid colectomy with en bloc ileocecectomy due to direct invasion. Intestinal continuity was restored with linear stapled ileocolic anastomosis and circular stapled colorectal anastomosis. Gross inspection of the abdominal cavity including the small bowel, colon, and rectum appeared normal.

Histopathological analysis revealed a high-grade pleomorphic sarcoma measuring  $8.5 \times 8.0 \times 6.0$  cm originating from the sigmoid colon with direct invasion into the ileum, and metastasis to 4–15 lymph nodes. Hematoxylin and Eosin (H&E) stain revealed pleomorphic spindle cells (Figure 3A). Immunohistochemistry (IHC) performed on the resected sigmoid colon mass returned positive for vimentin and smooth muscle actin (Figure 3B and C). The mass stained negative for desmin, myosin, calponin B, DOG-1, CD117, CD34, S100, CD31, pan-cytokeratin, and CAM 5.2. Ki-67 revealed a proliferation rate in areas of 60% and numerous mitoses were readily identified. After discharge, the patient began pelvic radiotherapy (RT) to the area of the positive lymph nodes that were removed at the time of operation. Radiation

therapy included 1980/4500 cGy over 25 elapsed days, 11/25 fractions of 180 cGy/fraction.

The patient returned to the ER 12.5 weeks post-initial surgical resection with complaints of abdominal pain, nausea, vomiting, and diarrhea. Non-contrast CT of the abdomen and pelvis showed a mid-abdominal and upper pelvic mesenteric mass measuring  $7.8 \times 5.1$  cm concerning for disease recurrence (Figure 4A and B). This area was superior to the radiation field used to treat the previously removed positive nodes. There was no evidence of inflammation or perforation around the abdominal mass. Exploratory laparotomy with palliative resection of the intra-abdominal mass and small bowel resection with primary anastomosis was subsequently performed. The mass was found to be fragile, multilobulated, and encased within a pseudo-capsule (Figure 4C). The tumor originated in the area of the aortic bifurcation and came out of the retroperitoneum into the mesentery of the small bowel, which was splayed over the main tumor, necessitating resection of the two sections of the small bowel. The entire tumor could not be removed. The surgical pathology report of this specimen revealed recurrent high-grade pleomorphic sarcoma involving two segments of the small bowel, measuring  $8.0 \times 5.0 \times 5.0$  cm, and separately received fragments measuring  $6.0 \times 4.0 \times 3.0$  cm. The proximal and distal enteric surgical resection margins were free by 3 cm. Lymph nodes were not identified. Immunohistochemistry and results were identical to the initial staining. Given the extent of the invasion of the tumor and node positivity, his prognosis is poor.

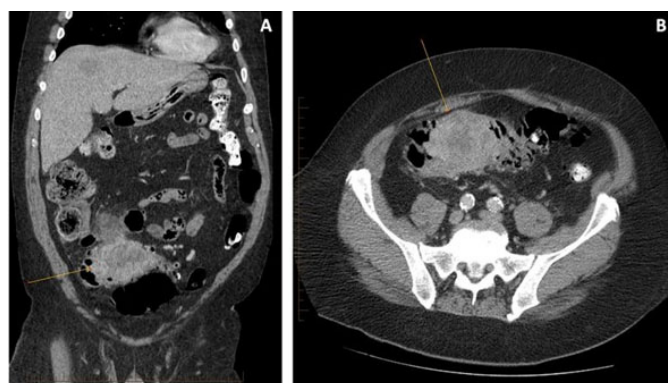


Figure 1: CT with contrast of the abdomen and pelvis showing large sigmoid mass. Coronal (A) and axial (B) images showing a large sigmoid mass approximately  $7 \times 5.2$  cm as well as a 4.8 cm lesion in the liver segment 7/8.

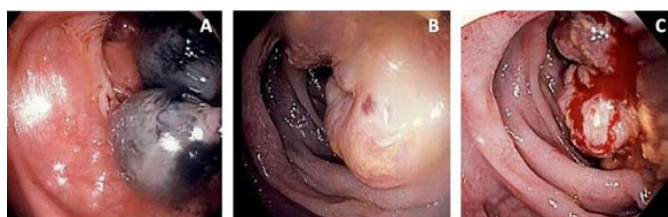


Figure 2: Presenting flexible sigmoidoscopy (A–C): 7 cm obstructing mass friable in nature at 40 cm in the sigmoid colon with some diverticulosis in the sigmoid colon.

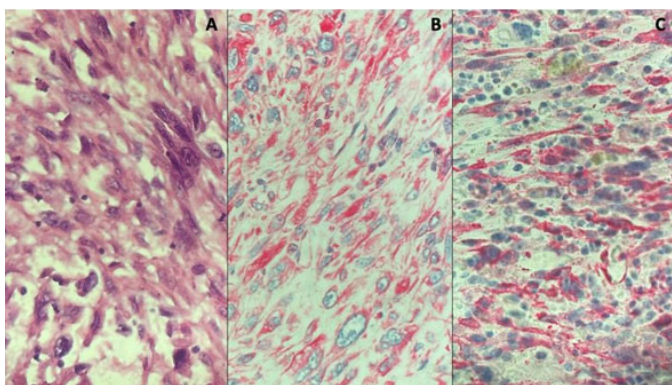


Figure 3: H&E and IHC stain performed on the sigmoid colon mass resection. (A) Histology demonstrating pleomorphic spindle cells on H&E stain (400× magnification). (B) The tumor cells are positive for SMA by immunohistochemistry (400× magnification). (C) The tumor cells are positive for vimentin by immunohistochemistry (400× magnification).

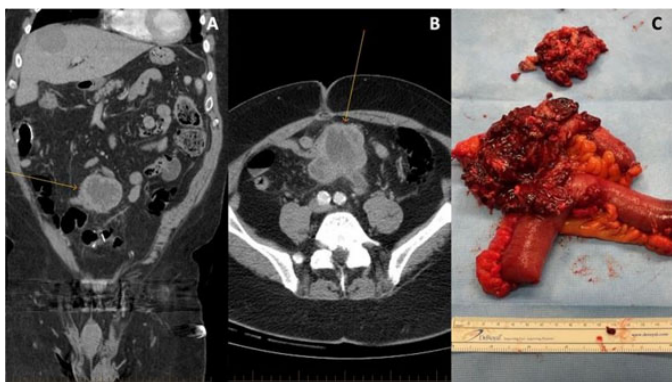


Figure 4: CT without contrast of the abdomen and pelvis showing new mass. Coronal (A) and axial (B) images showing a new mid-abdominal and upper pelvic mesenteric mass measuring 7.8 × 5.1 cm concerning for disease recurrence. (C) Gross specimen of a mass involving two segments of the small bowel, measuring 8.0 × 5.0 × 5.0 cm, and separated fragments measuring 6.0 × 4.0 × 3.0 cm. The mass was fragile, multilobulated, and encased within a pseudo capsule.

## DISCUSSION

Sarcomas are malignant tumors with heterogeneous features that arise from mesenchymal tissues and account for about 1% of adult malignancies [3]. Primary tumors of the mesentery are rare; however, metastasis to the mesentery from primary malignancies at other anatomical sites is frequent [2, 4]. Some common primary mesenteric tumors include desmoid tumors, lipomas, schwannomas, smooth muscle tumors, and sarcomas which may be low or high-grade [4].

Undifferentiated pleomorphic sarcoma, previously known as malignant fibrous histiocytoma (MFH), was first described by Ozzello and his colleagues in 1963 and was histologically subclassified into inflammatory, giant cell, storiform pleomorphic, and myxoid tumors. The World Health Organization (WHO) subsequently reclassified MFH in 2002 based on the line of differentiation rather

than histopathogenesis into UPS, UPS with giant cells, and UPS with prominent inflammation [2, 5]. Undifferentiated pleomorphic sarcoma is usually diagnosed in the sixth and seventh decade of life with a median age of 62 years; however, cases have been identified between ages 12 and 80 years [2, 5]. The incidence is predominantly more observed in males than females and UPS mostly involves the extremity (lower: 49% and upper: 19%), abdominal, and retroperitoneal cavity (16%) but rarely involves the gastrointestinal tract [2, 5]. Primary UPS of the large intestine is extremely rare and usually aggressive with poor prognosis as they tend to present late. In a few cases of large bowel UPS, synchronous metastasis to the lymph nodes has been reported, along with observed disease recurrence in affected patients [5]. Our patient presented with high-grade undifferentiated pleomorphic sarcoma of the sigmoid colon with node positivity and disease recurrence following surgical resection. This adds to the limited literature as only six cases of UPS of the sigmoid colon have been reported in the existing English literature (Table 1).

Undifferentiated pleomorphic sarcoma of the colon commonly presents with abdominal symptoms such as abdominal pain, abdominal distension, constipation/obstipation, nausea, vomiting, and sometimes could present with rectal bleeding which may overlap with clinical features of colorectal cancer. Thus, this creates a diagnostic challenge clinically as the presenting symptoms are non-specific and usually not identified endoscopically in the early stages. However, colonoscopy/sigmoidoscopy becomes a useful diagnostic tool as most cases present after disease progression, especially, if there is a large and obstructing tumor [2, 3].

Abdominal imaging with CT usually demonstrates a well-circumscribed and homogeneously enhanced mass or a mass with internal low density which occurs as a result of hemorrhage or necrosis [2] with similar findings on CT abdomen (Figure 4A) in the index case.

Undifferentiated pleomorphic sarcoma is characterized histopathologically by a disorganized and storiform arrangement of pleomorphic spindle-shaped cells with abnormal cytology and pleomorphic nuclear atypia.

Tissue biopsy with immunohistochemical assay remains the gold standard for the diagnosis of UPS. Common immunohistochemical stains that are frequently positive in UPS include vimentin, actin, CD68, Alpha 1-antitrypsin, and laminin mRNA. However, other immunohistochemical stains such as smooth muscle actin (SMA), S-100 protein, Keratins, and Desmin are frequently positive in pleomorphic sarcoma while S-100 protein and other melanocytic markers are positive in melanoma, which should always be considered as differential diagnoses for UPS. Other pathologies which should be excluded when making a diagnosis of UPS include leiomyosarcoma, rhabdomyosarcoma, and myxofibrosarcoma [2, 3]. In our case, the immunohistochemistry returned positive for vimentin and smooth muscle actin which

are frequently encountered in UPS; however, vimentin is a more sensitive and specific finding for UPS. Immunohistochemistry for our patient also demonstrated negative markers for desmin, myosin, calponin B, DOG-1, CD117, CD34, S100, CD31, pancytokeratin, and CAM 5.2 but Ki-67 revealed a proliferation rate of 60% with numerous mitosis.

The current treatment protocol for UPS is radical surgery/complete resection with wide margins; however, wide margins may be difficult to achieve in intra-abdominal tumors of gastrointestinal origin as UPS usually has exogenous growth that invades the surrounding tissues. Surgical resection with or without intraoperative RT is the treatment of choice in resectable cases while chemotherapy and chemoradiation may be considered in unresectable disease although the benefits of post-surgical RT and chemotherapy for UPS has not been well established unlike UPS of the extremities where utilization is beneficial [2, 3, 6].

In recent years, immunotherapy and targeted therapy have shown remarkable and promising results in many tumors such as Non-Small Cell Lung Cancer (NSCLC), melanoma, Hodgkin’s lymphoma, and advanced squamous cell cancer of the skin, and are currently being studied in other tumors including soft tissue sarcomas including UPS. In a phase II multicenter

clinical trial (SARC 028) with pembrolizumab, patients with UPS irrespective of PD-1 expression had an overall response rate of 40% (4 out of 10 patients); however, pembrolizumab in combination with cyclophosphamide failed to demonstrate good response in the PEMBROSARC trial [7].

Arora and colleagues had demonstrated a good and sustained response to pembrolizumab and pazopanib in a patient with chemotherapy-refractory advanced UPS of the lower extremity, the response observed was remarkable and may guide clinicians in the future if faced with a similar presentation [7]. A similar study by Guram and his colleagues showed a complete response of metastatic UPS of the maxillary sinus following radiation therapy combined with immune checkpoint inhibitor-ipilimumab+nivolumab with stereotactic body radiation therapy (SBRT) as it is believed that RT could alter the tumor microenvironment which eventually potentiates the use of immune checkpoint inhibitors [8].

Undifferentiated pleomorphic sarcoma in the large intestine remains a rare and aggressive malignant tumor with an unclear pathogenesis and a poor prognosis. The 2-year survival rate is 60% with a disease recurrence rate of 44% and a metastatic rate of 44% [2, 3]. Further studies and clinical trials are needed to better understand this disease and guide treatment protocol.

Table 1: Previous documented cases of UPS of the colon

Study	Age	Sex	Size (cm)	Symptoms	Surgery	Adjuvant	Metastasis	Recurrence	Follow-up
Current Patient	68	M	8.5 × 8.0 × 6.0	Abdominal pain and constipation	Yes	Radiation therapy	Lymph nodes	Local	4 months, alive
Waxman et al. [9]	52	F	7.5	Abdominal pain	Yes	No	No	Local	9 months, expired
Levinson et al. [10]	17	M	10.8 × 2.0	Abdominal pain, fever	Yes	No	No		NA
Wang et al. [11]	55	M	6	Abdominal pain	Yes	No	No	Local	5 months, Expired
Bosmans et al. [12]	73	M	3.5	Anemia	Yes	No	No	No recurrence	22 months, expired
Rubbini et al. [13]	60	M	7	Bloody stool	Yes	Chemotherapy	Lymph nodes	Liver	53 months, expired
Waxman et al. [9]	68	M	7.5 × 6.0	Abdominal pain, fever	Yes	No	No	Local	9 months, expired

## CONCLUSION

In conclusion, undifferentiated pleomorphic sarcoma (UPS) of the sigmoid colon is a rare and aggressive malignancy. Abdominal imaging with CT and tissue biopsy with immunohistochemical assay remain the gold standard for diagnosis. The current treatment protocol is radical surgery with wide margins, although the prognosis remains poor, especially in cases with lymph

node involvement and disease recurrence. The limited literature on UPS of the sigmoid colon highlights the need for further research and a better understanding of the molecular and genetic features of this rare malignancy to improve treatment outcomes. Early detection and multidisciplinary management involving surgery, radiation therapy, and chemotherapy are essential in the management of this rare malignancy.

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## Author Contributions

Gogo-Ogute E Ibodeng – 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

Jaime Said – Conception of the work, Design of the work, Acquisition of data, Analysis 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

Marcus Kwon – Conception of the work, Design of the work, Acquisition of data, Analysis 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

Jennifer Ra – Conception of the work, Design of the work, Acquisition 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

Christopher D Johnson – Conception of the work, Design of the work, Acquisition 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

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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.

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