High grade sarcoma presenting as multifocal recurrent seromas after inguinal hernia repair: A case report

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Abstract

In this report, we describe a 54-year-old male with cystic retroperitoneal sarcoma extending through the inguinal canal. Patient initially underwent inguinal hernia repair with mesh placement for suspected cord lipoma, after which he developed recurrent loculated retroperitoneal fluid collections refractory to multiple attempts at drain placement and laparotomy. Twenty-nine months after initial surgery, patient was referred to our institution on suspicion of malignancy. Pathology of resections taken during subsequent laparotomy showed foci of malignant cells interspersed throughout reactive proliferations. Follow-up immunohistochemistry confirmed high-grade sarcoma, likely atypical liposarcoma, but was unable to definitively establish subtype. Despite en bloc resection and gemcitabine/docetaxel chemotherapy, local progression continued, and patient was enrolled in clinical trials of doxorubicin with dual immune checkpoint blockade. This case suggests that sarcoma should be considered as a differential diagnosis of retroperitoneal or inguinal mass unresponsive to treatment; and highlights the difficulty of subtyping and managing cystic retroperitoneal sarcoma.

Introduction

Sarcomas are a rare and heterogeneous group of soft tissue and bone cancers that arise from mesenchymal tissue. Collectively, over 100 histologic subtypes account for <1% of adult cancers.[1] According to SEER, the estimated new cases and deaths from soft tissue sarcoma in the United States in 2020 is 13,130 and 5350, respectively. The median age of diagnosis for soft tissue tumors is 61 and the median age at death is 66. The current 5-year relative survival is 64.7% according to SEER.[2]

While sarcomas can present anywhere from head to toe, the most common symptom is a palpable and growing lump or mass, most commonly in an extremity location. Sarcomas occurring in body cavities, such as the peritoneum, may not cause clinical symptoms until they are extremely large. Because of the rarity and lack of awareness, sarcomas are often diagnosed late in the treatment course, and can be mistaken for more common entities, such as cysts, infections, or benign alternatives such as lipomas.

While pathologist expertise and immunohistochemical staining are the mainstays for diagnosis of sarcoma subtypes, genetic and molecular testing is also helping to improve diagnostic accuracy. A recent study of more than 5700 sarcoma patients who underwent next generation sequencing revealed that the pathologic diagnosis was changed or refined in 8% of patients.[3] Importantly, different

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subtypes of sarcomas may have dramatically different therapies and prognoses. Even with modern techniques, some sarcomas still cannot be definitively subtyped and are categorized as undifferentiated sarcomas in the 2018 World Health Organization (WHO) classification of tumors. With the wide genetic heterogeneity in this subtype, further efforts are required to better identify subsets of tumors, and to identify effective therapies.

In this case report, we present a case of high-grade undifferentiated sarcoma that exemplifies mimicry and diagnostic challenges clinically, pathologically, and molecularly.

Case report

The patient is a 54-year-old Caucasian male with a past medical history significant for chronic lower back pain for 15 years and basal cell carcinoma, who initially presented with a left sided inguinal mass associated with mild discomfort (Figure 1(a)). The patient was diagnosed with an indirect inguinal hernia which was repaired robotically using Progrip mesh at an outside community hospital. Intraoperatively, the surgeon noted what appeared to be a large cord "lipoma," as well as hematoma that was attributed to attempted reduction, and incarcerated sigmoid colon through the defect. The mass was not sent for pathology and was assumed to be a simple lipoma. At 4.5 months postoperatively, the patient returned with a left sided groin fluid collection (Figure 1(b)).

Ascribing this to postoperative seroma, a 15 French Blake drain was placed with removal of 1 L of serosanguinous fluid without evidence of infection. This fluid was not sent to pathology. Drain placement was complicated by cellulitis 1 week later which resolved with IV antibiotics. Two weeks following drain placement it was removed as the fluid had resolved. At 7 months postoperatively, the patient again noted recurrent fluid collection in the left inguinal site. A follow up CT scan of the abdomen/pelvis with contrast demonstrated a large left sided retroperitoneal seroma with fluid that extended into the left inguinal canal in addition to a new retroperitoneal fluid collection (Figure 1(c) and (d)). Additionally, a new right sided retroperitoneal fluid collection was noted well away from the original postoperative bed. Bilateral drains were again placed with evacuation of 1140 mL of hematoma. Cytology of the fluid revealed mononuclear mesothelial, monocytic, and histiocytic cells and culture was negative for microbial organisms.

The treating medical team felt that the patient's symptoms were most consistent with mesh complications, and the patient underwent explantation of the mesh. Intraoperatively, fluid was noted to extend below the mesh into the scrotum. A small portion of the mesh was left behind because it was adherent to the iliac vessels. Follow up CT scan unfortunately showed reaccumulation of bilateral retroperitoneal fluid collections, so repeated attempts were made at drain placement without benefit. Eleven months out from the initial surgery, follow up CT scan revealed a cystic mass-like collection at the site of the retained mesh. Additionally, at this time, a culture from one of the drains showed Klebsiella. Thus, the patient underwent open laparotomy with removal of the residual mesh, and found to have purulent material in the retroperitoneum. After washout and recovery with IV antibiotics, the patient continued to have persistent and recurrent fluid collections and underwent two additional laparotomies to break up what were thought to be loculated fluid collections. Approximately 29 months after the original surgery, the patient again had progressive pain and mass in the left inguinal region and was referred to the University of Colorado. CT scans of the abdomen/pelvis were reviewed by a urologist with experience in sarcomas, and interpreted as being suspicious for a malignant cystic mass (Figure 1(e)–(g)). He underwent a third laparotomy, and intraoperatively, multiple cystic, hemorrhagic masses were removed along with the left testicle which was completely surrounded by the mass (Figure 1(e)–(g)).

The pathology was reviewed by expert bone and soft tissue pathologists, and arriving at a diagnosis was challenging. The majority of the resected specimens was dominated by reactive-appearing changes, including fibrosis, hemorrhage, dense hemosiderin deposition, and stromal proliferations. Throughout the masses however there were pockets of neoplastic cells. Some foci demonstrated frankly malignant cells that were compatible with pleomorphic sarcoma (Figure 2(a)–(c)). The following immunohistochemical (IHC) studies were performed: ERG, CD31, CD34, D2-40, calretinin, S100, SOX10, pancytokeratin (AE1/AE3), muscle-specific actin (MSA), smooth muscle actin (SMA), ALK1, STAT6, HMGA2, CD43, CD45, CD3, CD20, CD30, CD1a, and CD23. All of these markers were negative on the malignant cells. The initial histologic differential diagnosis included angiosarcoma, based on the hemorrhage and slightly vascular-like growth pattern, but based on the negative IHC results this was ruled out. Additionally, mesothelioma was considered given the anatomic location and areas of apparent surface growth of the tumor, but was also ruled out using IHC. The remainder of the IHC did not show a definitive line of differentiation. Resected lymph nodes were negative for malignancy. Conferring expert soft tissue pathologists ultimately concurred on a diagnosis of a high grade undifferentiated sarcoma. Figure 2 shows different sections of the mass for comparison.

In order to help determine the subtype of sarcoma, whole genome sequencing was performed on the tissue sample using Foundation One Heme/Sarcoma panel. The tumor was microsatellite stable with a low tumor mutational burden (1 Mut/Mb). Additional genomic findings included MDM2 amplification, BCL7A rearrangement, FRS2 amplification, and NCOR2 rearrangement. Considering the MDM2 amplification, clinical appearance, and the originating site of an inguinal hernia, the most likely diagnosis was an atypical, highly cystic, dedifferentiated liposarcoma. The
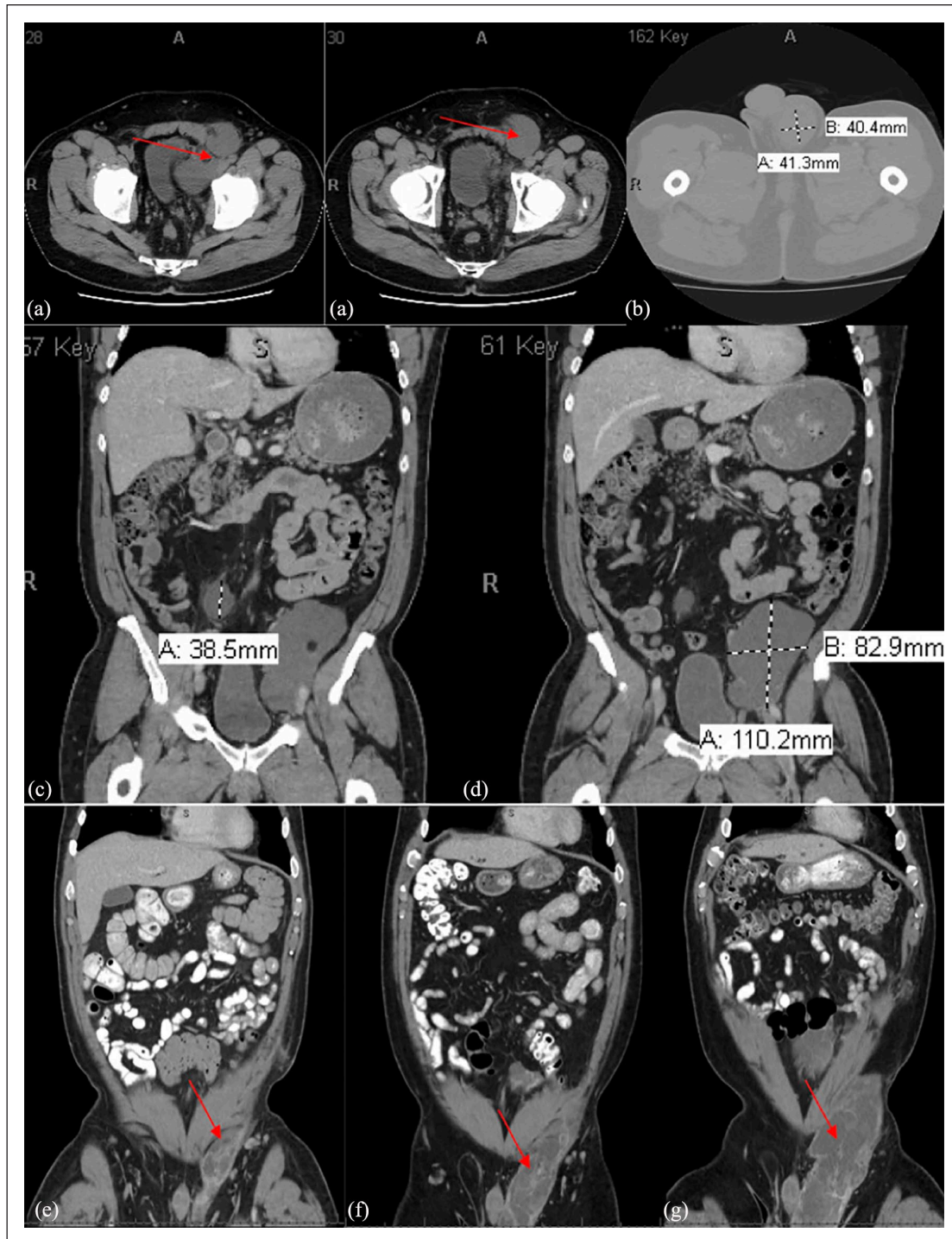
Figure 1. Imaging assessments. (a) CT abdomen/pelvis w/o contrast demonstrating hernia. (b) Left sided inguinal fluid collection. (c and d) Right and left sided fluid collection shown in CT abdomen/pelvis with contrast. (e) CT abdomen/pelvis with contrast 13 months after original surgery. (f) CT abdomen/pelvis with contrast 21 months after original surgery. (g) CT abdomen/pelvis with contrast 27 months after original surgery.

patient was monitored with serial CT scans of the abdomen/ pelvis as per National Comprehensive Cancer Network (NCCN) guidelines for resected retroperitoneal sarcomas.[4]

He did well until 4 months after surgery, when CT scan again showed local progression of disease. Notably, at no time did the patient develop distant metastases to lungs or
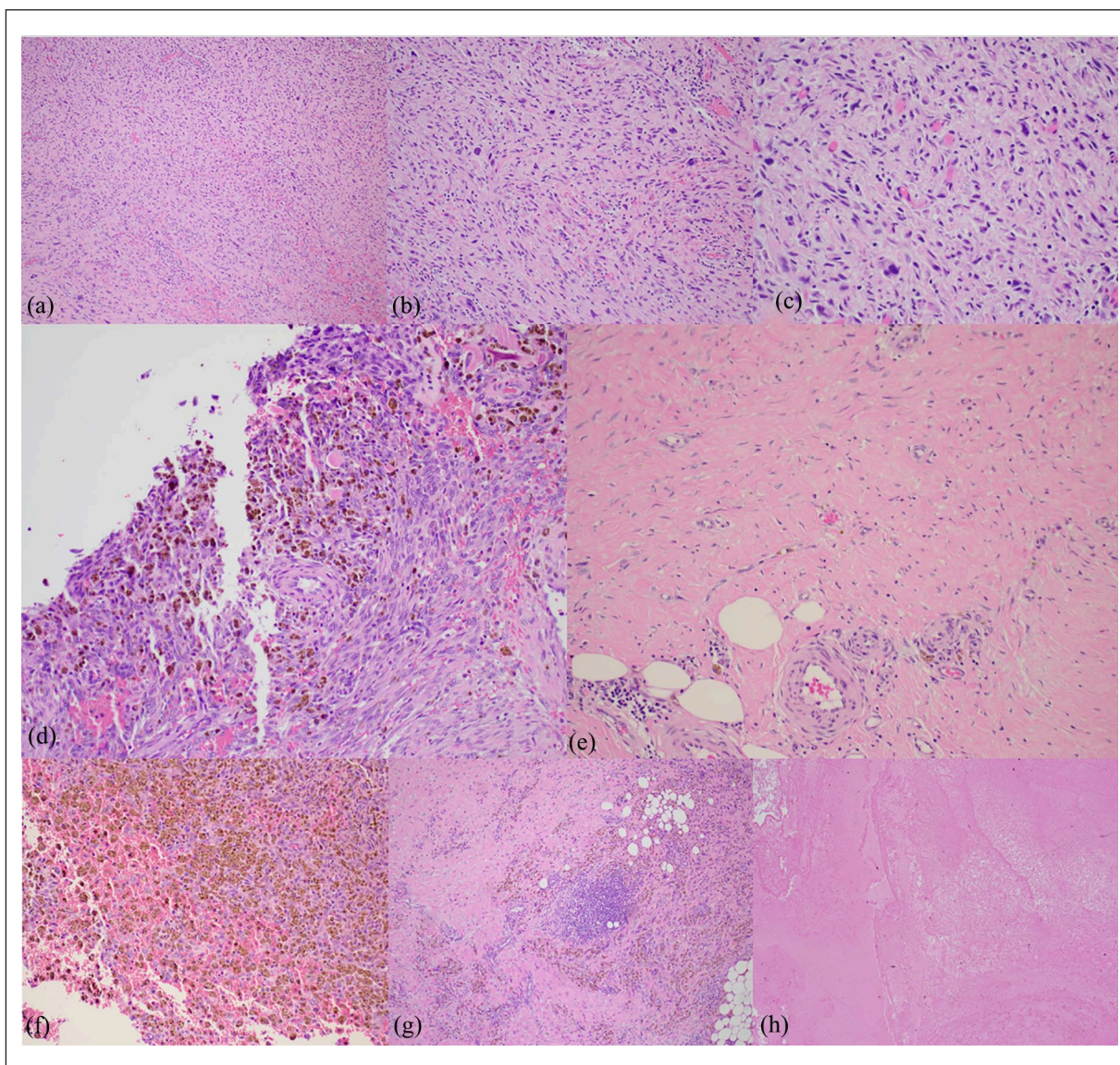
Figure 2. Immunohistochemistry analysis. (a–c) 100X, 200X, and 400X, respectively of most atypical areas with histologic and IHC results consistent with undifferentiated pleomorphic sarcoma (UPS). Less than 5% of the reviewed tumor looked like UPS. These areas feature scattered large, bizarre, frankly malignant pleomorphic cells, present in a background of moderately atypical spindled to epithelioid sarcoma cells, with some admixed collagen deposition. (d) Besides the areas of UPS (a–c), other areas were also compatible with sarcoma; these areas were often present along the apparent "surfaces" of the tissue, where it presumably bordered cystic spaces. These areas consisted of hypercellular proliferations of mildly to moderately atypical spindle cells with a "streaming" growth pattern. The results of IHC studies of these areas also showed no definite line of differentiation (undifferentiated). These areas accounted for 5–10% of reviewed tumor area. As these areas were usually located along the apparent surfaces of cystic spaces, which were often bloody spaces, they often had admixed hemorrhage and hemosiderin deposition. (e) The majority of the solid tissue within the specimen appeared benign and reactive – as shown in this picture. These areas often consisted of reactive-appearing collagenous fibrosis, with some focal entrapped fat, and with foci of chronic inflammation. (f) Similar to (d), showing the second (spindled) pattern of malignant cells along an apparent surface of a hemorrhagic cystic space. (g) The majority of the solid areas of this specimen showed reactive-appearing collagenous fibrosis, with hemosiderin deposition, with foci of chronic inflammation, and with foci of entrapped fat. (h) Also present within the specimen, admixed with the benign-appearing fibrotic areas and the few areas appearing consistent with sarcoma, were areas of organized hemorrhage/hematoma.

bones. He was initiated on gemcitabine/docetaxel chemotherapy for three cycles with best response of stable disease, however eventually developed progression of disease. At that time the patient was enrolled on a clinical trial combining doxorubicin with dual immune checkpoint blockade (NCT04028063).

Discussion

Inguinal hernia is a common clinical finding that is often managed surgically. A recent study showed no change in management resulting from pathologic evaluation of hernia specimens, and recommended against this practice routinely,[5] suggesting exceptionally low likelihood of malignancy related to herniation. Similarly, the finding of post-operative fluid accumulation in this patient was minimally concerning for malignancy, as various sources have demonstrated seroma formation rates between 1.9% and 22.9%.[6] In contrast, retroperitoneal liposarcoma with hernial extension was only documented in 10 cases between 1987 and 2017[7] and the multicystic liposarcomatous retroperitoneal tissue ultimately removed from the patient was only described in four prior cases,[8] to our knowledge. Given the disparity in the likelihood of these diagnoses, this case exemplifies the difficulty in early detection of rare conditions which mimic common pathology.

CT scans are commonly used in the evaluation of abdominal/pelvic processes due to the ability of CT to discern infiltration of organs and involvement of neurovascular structures.[9] However, MRI with gadolinium can add additional detail by showing enhancing soft tissue with areas of cystic or necrotic material. Even for cases where retroperitoneal sarcoma is already suspected, NCCN guidelines recommend CT with or without MRI in the initial workup of retroperitoneal sarcomas.[4] It is worth considering whether the use of MRI with gadolinium in this patient's case may have revealed solid components within the cystic areas that could have raised the concern for a malignancy in the setting of his recurrent abdominal masses.

Arriving at a sarcoma diagnosis was further delayed by the confusing histologic features of the case. The neoplastic foci interspersed throughout reactive inflammatory changes seen on pathology could easily have been overlooked on analysis of a smaller cytologic or core needle biopsy sample and suggest the need for full pathology review in cases such as this. The persistence of this patient's condition despite numerous attempts at surgical resection further highlights the importance of early diagnosis and initial en bloc resection to avoid continuous seeding of neoplastic cells. It has been shown in multiple studies that early referral to centers with sarcoma expertise for surgical intervention and expert pathology review improves outcomes with favorable local relapse free survival and overall survival.[10,11] Thus, improving awareness of sarcoma as a differential diagnosis in atypical peritoneal masses is paramount.

This case also highlights the difficulty of definitively subtyping and treating sarcomas. The most common retroperitoneal sarcoma subtypes are well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), undifferentiated pleomorphic sarcoma (UPS), and leiomyosarcoma (LMS).[12] Optimal therapy is impacted by the histologic subtype; for example well-differentiated/dedifferentiated liposarcomas are best managed surgically if at all possible, where LMS and UPS may benefit from neoadjuvant chemotherapy to downstage the lesion prior to surgery. While the IHC results and expert pathology review confirmed a high grade sarcoma, further subtyping was not possible, leading to the use of whole genome sequencing to gain additional insight. The MDM2 amplification found in this patient's sarcoma is seen in 27%–33% of all sarcomas and 90% of liposarcomas,[13] but the BCL7A mutation found in this patient is present in <1% of sarcomas.[14] Based on this profiling, along with the location and appearance on imaging, the best diagnostic hypothesis is dedifferentiated liposarcoma.

A major challenge with liposarcomas is the limited response to systemic chemotherapy. Standard approved sarcoma regimens used for dedifferentiated liposarcomas include anthracycline based regimens including doxorubicin with or without ifosfamide,[15] gemcitabine plus docetaxel,[16] trabectedin,[17] and eribulin.[18] However, response rates are only 10%–15% with these regimens, and median progression-free survival ranges between 3 and 6 months.[19] However, recently completed studies of targeted agents have shown promise in treating liposarcomas. CDK4 is generally amplified along with MDM2 based on the amplification of chromosome 12q13-15, and clinical trials of the CDK4 inhibitors palbociclib and abemaciclib in liposarcomas showed a median PFS of 17.9 weeks and 30.4 weeks, respectively.[20,21] Additionally, small molecule inhibitors of MDM2 have shown promising activity, including a recently reported trial of milademetan which showed a median progression-free survival of 6.3 months in liposarcoma patients.[22] A nuclear export protein inhibitor, selinexor, is currently being studied in an international Phase 3 trial for liposarcomas (NCT02606461); early results from the Phase 2 portion of the study showed a median PFS of 5.6 months compared to 1.8 months with placebo.[23] Finally, immune checkpoint inhibitors have shown early promising results in a subset of dedifferentiated liposarcomas, with response rates of about 10% and median progression-free survival as high as 5.5 months with combination ipilimumab/nivolumab.[24] Based on the MDM2 amplification in the patient's case, CDK4 inhibitors or MDM2 inhibitors in clinical trials may be additional treatment options should he progress on his current therapy.

Conclusion

Sarcomas remain a diagnostic challenge due to the rarity and heterogeneity of clinical presentations, and the potential for mimicry of more common entities. Improving awareness of these rare neoplasms, with prompt referral to tertiary sarcoma centers for expert pathology review, molecular diagnostics, and multidisciplinary treatment planning including consideration of standard and clinical

trial treatment options is critical to avoid diagnostic delay and subsequent negative impact on patient outcomes.

Author contributions

Lorne Muir and Breelyn Wilky wrote the manuscript. All authors reviewed, edited, and approved the final version of the manuscript.

Ethical approval

Ethical approval to report this case does not require ethical approval for reporting individual cases.

Declaration of conflicting interests

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