**Undifferentiated Pleomorphic Sarcoma Presenting With Cardiac Tamponade: A Case Report and Review**

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**Abstract**

Soft tissue sarcomas (STS) comprise a large group of heterogeneous malignant tumors that form approximately 1% of all adult malignancies. Most sarcomas originate from soft tissue and the rest arise from the bone. Undifferentiated pleomorphic sarcoma (UPS) is an aggressive tumor that usually presents as an asymptomatic subcutaneous mass that exhibits rapid growth with unremarkable skin findings. The diagnosis is usually made with histopathology or immunohistochemistry; once the diagnosis is confirmed, evaluation and workup of the primary tumor, lymph nodes, and metastasis should be made. Treatment is stage-dependent but generally involves en-bloc resection followed by a review of pathology with a discussion of the benefits of adjuvant radiation or chemotherapy. Here, we discuss a case of a 77-year-old patient who presented with a large mass over the right shoulder and echocardiographic findings of cardiac tamponade.

**Keywords**
cardiology, hematology oncology

**Introduction**

Sarcomas in adults are rare, accounting for <1% of cancers. Undifferentiated pleomorphic sarcoma (UPS), previously known as malignant fibrous histiocytoma, is a high-grade soft tissue sarcoma originating from mesenchymal stem cells. They usually present as a rapidly growing, asymptomatic cutaneous or subcutaneous nodule. Undifferentiated pleomorphic sarcoma is characterized by an array of spindled or ovoid mononuclear atypical cells with abundant mitotic figures and occasional giant cells. They are known to be aggressive tumors, and, thus, early detection and treatment of these sarcomas are imperative.

**Case Presentation**

A 77-year-old woman with a medical history of non-insulin-dependent diabetes mellitus, hypertension, and basal cell carcinoma over the right nasal bridge s/p excision presented with a 1-month history of rapidly growing right posterior shoulder mass associated with right shoulder pain. It was not associated with fever, chills, weakness, numbness, or tingling over the upper extremities. Although the patient complained of intermittent dizziness, she denied any symptoms of chest pain, shortness of breath, cough, or wheezing. The patient was tachycardic with a heart rate ranging from 90 to 110 bpm with normal blood pressure. Physical examination revealed a firm, non-tender mass extending over the right shoulder.

Computed tomography (CT) imaging of the right upper extremity as depicted in Figure 1 revealed a large peripherally enhancing mass centered about the right shoulder measuring approximately 11.2 cm × 14.2 cm × 8.8 cm with osseous erosion of the inferior right scapula. Computed tomography of the chest revealed numerous bilateral pulmonary masses/nodules and mediastinal/hilar lymphadenopathy along with a large pericardial effusion. The patient underwent an ultrasound-guided biopsy of the shoulder mass. The following day, the patient started requiring oxygen and an echocardiogram confirmed a large circumferential pericardial effusion with a Doppler suggestive of cardiac tamponade.

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tamponade. A total of 300 mL of sanguineous fluid was extracted by performing a pericardiocentesis. Pericardial fluid analysis revealed a large number of red blood cells (1,884,000 cells/mm³) and a white blood cell count of 4648 cells/mm³ wherein 10% were neutrophils with an elevated lactate dehydrogenase (LDH; 918 U/L) and elevated adenosine deaminase levels (48.1 U/L). Microbiologic cultures were sterile, acid-fast bacillus (AFB) was negative, and cytology was negative for malignancy.

The pathology results of the shoulder mass biopsy revealed a high-grade pleomorphic sarcoma with admixed giant cells, favoring an UPS, high-grade Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC Grade 3 of 3) as depicted in Figures 2 and 3. Histologic sections show an overtly malignant pleomorphic and spindle cell sarcoma with easily identifiable mitotic activity rich in osteoclastic giant cells as depicted in Figure 4. Furthermore, tumor necrosis was identified. Immunohistochemistry was negative for STAT6 (performed in consideration of dedifferentiated solitary fibrous tumor). Additional immunohistochemistry showed focal positive expression of MDM2 (<5% of nuclei of interest) of uncertain significance. Immunohistochemistry stains were also notably negative for multiple keratins, CD30, SOX10, S100, desmin, myogenin, CD34, Thyroid transcription factor (TTF)-1, CD31, BER-EP4, and leukocyte common antigen (LCA). The final diagnosis was metastatic UPS, American Joint Committee on Cancer

**Figure 1.** Computed tomography scan of right upper extremity revealing an 11.2 cm × 14.2 cm × 8.8 cm right shoulder mass with osseous erosion of the inferior right scapula.

**Figure 2.** The low-power view shows a very cellular tumor (Hematoxylin & Eosin stain, original magnification ×200).

**Figure 3.** The high-power view shows malignant tumor cells with large and pleomorphic nuclei, a moderate amount of cytoplasm, prominent nucleoli, and some mitotic figures (arrow). Hematoxylin & Eosin stain, original magnification ×400.

**Figure 4.** The tumor contains several osteoblastic-like multinucleated giant cells (arrows). Hematoxylin & Eosin stain, original magnification ×400.
(AJCC) stage cT3N1M1. After a full discussion, the patient declined aggressive treatment and opted for palliative care.

Discussion

Undifferentiated pleomorphic sarcoma, formerly known as malignant fibrous histiocytoma, is a subtype of soft tissue sarcomas encompassing approximately 1% of all malignancies and an overall incidence of 3 per 100,000.1 Undifferentiated pleomorphic sarcoma as a group comprises up to 20% of all soft tissue sarcomas,2 with an incidence of 0.08 to 1 per 100,000.3 Undifferentiated pleomorphic sarcoma most commonly occurs after the 6th decade of life, with males affected more than females and a slight ethnic predisposition affecting white persons greater than black.7 Although UPS can affect any soft tissue, they most frequently occur in bones and extremities which have the potential to metastasize. Cardiac metastases from any primary tumor are common, with a reported incidence between 2.3% and 18.3%.8

Sarcomas are a group of tumors that primarily originate from the mesenchyme. They have been associated with prior exposure to radiation therapy, carcinogens, certain viruses, and genetic predispositions such as Li-Fraumeni syndrome. The Hippo pathway along with mutations in certain tumor proteins, Dickoff-related protein 1 (DKK1), mutations in tumor protein 53 (TP53), cyclin-dependent kinase inhibitor 2A (CDKN2A), retinoblastoma-associated protein (RB1), and transcriptional regulator ATRX (ATRX) have been implicated in the pathogenesis of UPS.1 The exact mechanism is currently still under research.

A majority of patients present with a painless mass, and another subset presents with pain, edema, or paresthesias secondary to mass effect. Undifferentiated pleomorphic sarcoma is a rapidly growing cutaneous or subcutaneous nodule.9 The most common sites are the extremities, followed by the trunk and retroperitoneum. It is not uncommon to have a delay in diagnosis as they are commonly misdiagnosed to be hematomas or lipomas. Only 4 cases of UPS with cardiac tamponade have been reported to date as described in Table 1. There was a case of primary left heart malignant fibrous histiocytoma presenting with a pericardial effusion without features of cardiac tamponade in 2005 wherein she underwent surgical resection of the cardiac tumor followed by chemotherapy, the patient, unfortunately, died 1 month later.10 Our case represents the fifth case of UPS with a cardiac tamponade reported to date.

Early diagnosis and treatment are crucial to improving the overall prognosis of this disease. The recurrence risk is significantly increased with tumors greater than 5 cm, tumors with subcutaneous fat invasion, and advanced AJCC staging.15 The 5- and 10-year overall survival rates are, respectively, 60% and 48%.2 The classification and differentiation of soft tissue sarcomas have been a challenge due to their rarity and heterogeneous morphology which has made it difficult to accurately diagnose with over a hundred different histological subtypes.

The World Health Organization (WHO) recently published updates in 2020 for the classification of Soft Tissue Tumors and Bone, as they are striving for better standardization of diagnoses. World Health Organization classifies soft tissue sarcomas based on their tissue of origin and morphological features.16 With continued advances in molecular genetics, there is a pivotal role in diagnosing sarcomas and understanding their immunohistochemistry. A prospective study has concluded that molecular genetic testing should be implemented as a standardized diagnostic step to help aid in diagnosis.17

Once pathology has been confirmed with histopathology and immunohistochemistry, it is recommended that the size of the tumor, invasion of visceral structures, and neurovascular involvement be assessed with a contrast-enhanced magnetic resonance imaging (MRI). Undifferentiated pleomorphic sarcoma is staged using AJCC staging with AJCC UICC 8th edition which incorporates TNM staging with AJCC UICC staging. The sarculator nomogram estimates 5- and 10-year overall survival for resected extremity sarcomas (available at https://sarculator.com/). Adjuvant or neoadjuvant external-beam radiotherapy (RT) is used for grade 2 or 3 larger soft tissue sarcomas (>5 cm in greatest dimension) arising from extremities or the body wall. In several randomized controlled trials comparing the efficacy of surgery alone versus surgery plus adjuvant RT, it was found that patients who underwent resection followed by adjuvant RT had decreased local recurrence rates.18-20

Chemotherapy is usually reserved for metastatic disease with regional lymph node metastases or visceral metastases to the liver, lung, or bone.21 Commonly used chemotherapeutic agents include doxorubicin, epirubicin, ifosfamide, gemcitabine, and docetaxel.2,4 In cases of malignant pericardial effusions, treatment includes systemic chemotherapy and local sclerotherapy with tetracyclines hydrochloride or bleomycin sulfate.19-20 Instillation of radionuclides is debatable.20,21 Despite receiving treatment, the presence of a malignant pericardial effusion implies advanced disease.

Sarcomas are well known to be a heterogeneous group of diseases with advancing research reporting that UPS may be preferentially sensitive to novel therapies. Pembrolizumab, an immune checkpoint inhibitor that targets programmed cell death 1 (PD-1), is especially promising in UPS. In a phase II trial, 4 out of 10 patients with progressive UPS responded to this treatment with a 40% response rate, suggesting that it is a novel agent with anti-tumor activity.22 Research into immune biomarkers, such as PD-1 immunohistochemistry, is ongoing and likely to improve patient selection for immunotherapy in the near future.23 Next-generation sequencing (NGS) is a new
Table 1. Cases of Undifferentiated Pleomorphic Sarcoma (UPS), Previously Known as Malignant Fibrous Histiocytoma With Cardiac Tamponade.

| References         | Age (years) | Sex | Diagnosis                                                                 | Immunohistochemistry (IHC)                                                                 | Treatment                                                                 | Outcome                                                                 |
|--------------------|-------------|-----|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Matsukuma, 2008, 646-649.11 | 72          | F   | Primary pericardial malignant fibrous histiocytoma                        | Positive for vimentin while only focally positive for alpha-smooth muscle actins and calretinin Desmins, myoglobin, cytokeratin, CD34, S-100, and carcinoembryonic antigen were all negative | Surgical resection followed by chemotherapy with gemcitabine and doxorubicin for 2 months | Death                                                                   |
| Recchia, 2006, 76-78.12 | 40          | M   | Right thigh malignant fibrous histiocytoma with metastases to the left ventricle | Not reported                                                                              | Open heart surgery followed by 4 courses of chemotherapy with Adriamycin, dexrazoxane, and dacarbazine. Then, followed by a course of chemotherapy with cyclophosphamide, epidoxorubicin, and granulocyte-colony stimulating factor. The patient then had another 3 courses of cisplatin and ifosfamide followed by a high-dose course of chemotherapy with carboplatin, etoposide, and cyclophosphamide. Subsequently, the patient underwent autologous peripheral blood progenitor cell transplantation and prolonged administration of low-dose interleukin-2 and 13-cis-retinoic acid. The patient was later continued on immunotherapy. | Had a 100% performance status following treatment and died 4 years later because of ventricular arrhythmia during exertion |
| Matsumoto, 2021, 1137-1140.13 | 50          | M   | Mediastinal undifferentiated pleomorphic sarcoma (UPS) with pericardial invasion and pleural nodules | Calretinin, D2-40, Wilms’ tumor gene (WT-1), and Heart development protein with EGF like domains 1 (HEG1) were positive while Thyroid transcription factor (TTF)-1, carcinoembryonic antigen (CEA), claudin-4, and desmin were negative | No treatment                                                               | Death                                                                   |
| Yakovlev, 2021, 144-149.14 | 78          | F   | Anterior abdominal wall UPS with left atrium and biventricular masses     | Not reported                                                                              | No treatment                                                               | Death                                                                   |
method of DNA (deoxyribonucleic acid) and RNA (ribonucleic acid) sequencing used in clinical oncology to identify rare mutations and tailor treatment toward the patient’s genomic expression. Most sarcomas are microsatellite stable and exhibit low tumor mutational burden (TMB). Identifying cases with high TMB or high microsatellite instability (MSI-H) will lead to a benefit of immunotherapy. Therefore, NGS is valuable and is recommended, especially in the metastatic or relapsed setting. NTRK gene fusions are important actionable genetic alterations that may be detected in UPS. Genetic testing will typically reveal chromosomal translocations leading to NTRK1, NTRK2, or NTRK3 gene fusions. These driver mutations lead to an activation of tropomyosin receptor kinases (TRK1, TRK2, and TRK3). Larotrectinib is a highly selective TRK inhibitor and in NTRK fusion-positive sarcomas has proven to be effective. Pazopanib, an oral multikinase inhibitor that targets VEGF (vascular endothelial growth factor) receptors, PDGF (platelet-derived growth factor) Receptor A, and PDGF Receptor B along with other receptors, is approved for the treatment of advanced or recurrent/metastatic soft tissue sarcomas following standard chemotherapy. In phase III randomized placebo-controlled trial, pazopanib has demonstrated significant improvement in progression-free survival.

Conclusion
The finding of cardiac tamponade in conjunction with UPS is rare and portends a poor prognosis. Due to the aggressive nature of UPSs, high clinical suspicion must be kept for this rare disease. Next-generation sequencing should be considered and may allow for novel therapies such as immunotherapy or targeted therapy to be considered.

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