Undifferentiated Pleomorphic Sarcoma after Pirfenidone Use: A Case Report

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ABSTRACT

Introduction: Pirfenidone was approved in 2014 for the treatment of idiopathic pulmonary fibrosis. Pirfenidone inhibits several factors such as tissue growth factor-β and platelet-derived growth factor, leading to decreased epithelial and fibroblast proliferation and collagen synthesis. The drug improves progression-free survival and is well tolerated, with minimal side effects. However, data on its long-term effects are lacking.

Case Presentation: We present a rare case in which an undifferentiated pleomorphic sarcoma developed in a 59-year-old man with idiopathic pulmonary fibrosis who was treated with pirfenidone for more than a year.

Discussion: Undifferentiated pleomorphic sarcoma, also known as malignant fibrous histiocytoma, is a soft-tissue sarcoma arising from fibroblasts. The disease presents in the extremities and the trunk of elderly patients, and rarely in the retroperitoneum. Surgical excision is the mainstay of treatment; however, recurrence is common in the form of lung and lymph node metastases. In this report we review this rare malignancy and highlight the need for postmarketing longitudinal studies to determine additional adverse effects in patients with idiopathic pulmonary fibrosis who are on pirfenidone therapy.

INTRODUCTION

Undifferentiated pleomorphic sarcoma is a rare soft-tissue malignancy caused by abnormal fibroblast proliferation. Our article discusses this malignancy occurring in a patient after long-term therapy with pirfenidone, a fibroblast inhibitor, for idiopathic pulmonary fibrosis.

CASE PRESENTATION

Presenting Concerns

A 59-year-old white man was admitted to the hospital from his primary care physician's office with 6 weeks of progressive weakness, intermittent right upper quadrant abdominal pain, and 9-kg (20-lb) weight loss. His medical history included idiopathic pulmonary fibrosis, for which his pulmonary specialist had prescribed pirfenidone (Esbriet, Genentech, South San Francisco, CA) 14 months earlier, after several rounds of oral prednisone therapy had failed. His medical history also included hypertension, obstructive sleep apnea requiring positive pressure ventilation, phlebotomy-dependent secondary polycythemia, and insulin-dependent diabetes mellitus. The patient had no surgical history. He was a former smoker (quit 5 years before this presentation) and reported no use of alcohol or illicit drugs. His family history was notable for coronary artery disease.

On examination, our patient appeared uncomfortable and had tachycardia. Lung auscultation revealed bibasilar crackles and diffuse diminished breath sounds. Palpation found a tender, 15-cm mass in the right upper and lower quadrants that displaced other organs. Muscle strength was 3 of 5 in upper and lower extremities bilaterally.

Abnormal results of biochemical and hematologic investigations included chloride, 94 mmol/L (reference range, 98-107 mmol/L); creatinine, 0.4 mg/dL (0.9-1.9 mg/dL); glucose, 168 mg/dL (70-99 mg/dL); total protein, 5.5 mg/dL (6.4-8.3 mg/dL); albumin, 2.6 mg/dL (3.5-5.2 mg/dL); alkaline phosphatase, 152 IU/L (34-104 IU/L); white blood cells, 36.6 × 10^3/L (3.5-10.5 × 10^3/L); polymorphonuclear lymphocytes, 93% (45%-75%); hemoglobin, 7.7 mg/dL (13.5-17.5 mg/dL); hematocrit, 27.5% (38%-50%), mean corpuscular volume, 78.3 fL (80-100 fL); and platelet count, 812 × 10^9/L (150-450 × 10^9/L). Results of a peripheral blood film demonstrated mature morphologic appearance without dysplastic change or circulating immature precursors, including blast cells.

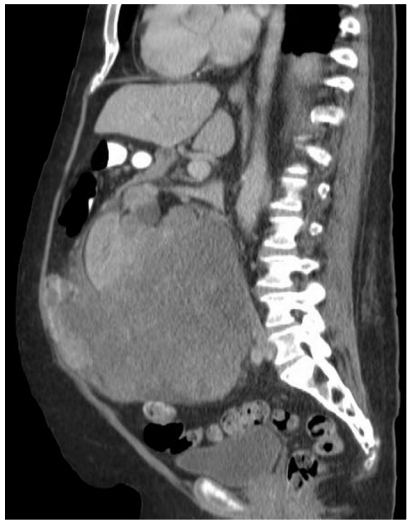

Figure 1. Saggital-view computed tomography scan of the patient's abdomen without contrast enhancement. A large (14.4 cm × 27.1 cm × 21.6 cm) necrotic mass can be seen rising from the inferior pole of the right kidney, with limited invasion of the surrounding structures. This mass compresses the right ureter and causes moderate hydronephrosis.

Computed tomography of the abdomen without contrast enhancement revealed a large retroperitoneal mass (14.4 cm × 27.1 cm × 21.6 cm) superimposed on the right kidney, compressing the right ureter and causing moderate hydronephrosis (Figure 1). No other masses were found.

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Therapeutic Intervention and Treatment

The patient's fatigue stabilized after he received blood transfusions for anemia, and his leukocytosis improved with intravenous antibiotic therapy. He was discharged to a skilled nursing facility after five days of therapy. Two weeks after hospital discharge, he underwent open right nephrectomy and partial small-bowel resection with anastomosis.

Analysis of gross pathology revealed a well-circumscribed tumor pushing into the inferior pole of the right kidney and encasing the right ureter. The cut surface was yellow with pink areas of focal cystic change. Histologic results demonstrated malignant spindle cell neoplasm with marked pleomorphism and vague epithelioid features without lymph node or neurovascular involvement (Figures 2 and 3). Immunohistochemical staining was negative for S100, CD31, MSA, desmin, CAM5.2, epithelial membrane antigen, renal cell carcinoma, keratin 5/6, and keratin 34 beta E12 but was positive for CD34, vimentin, CD10, and keratin AE1/3. Molecular studies were negative for *MDM2* gene amplification.

The differential diagnosis of undifferentiated pleomorphic sarcoma was made for this sarcomatoid malignancy. We favored this differential diagnosis over sarcomatoid carcinoma or dedifferentiated liposarcoma because aberrant expression for keratin and epithelioid features are present in a subset of high-grade sarcomas, and the lack of renal parenchymal involvement argued against sarcomatoid carcinoma.[1] Although some undifferentiated pleomorphic sarcomas represent dedifferentiated liposarcomas, the absence of *MDM2* amplification argued against a liposarcoma diagnosis.[1]

Cancer staging demonstrated Stage 3 (pT2bN0M0 with Grade 3) unresectable disease.

Follow-up and Outcomes

Pirfenidone therapy was discontinued after cancer staging. The patient was referred to the Hematology and Medical Oncology Department for outpatient chemotherapy. Eight cycles of doxorubicin and olaratumab were planned (Table 1 shows a timeline of the case). As of this writing, he has completed four of eight cycles.

DISCUSSION

Undifferentiated pleomorphic sarcoma, also known as malignant fibrous histiocytoma or pleomorphic spindle cell sarcoma, is a bulky, soft-tissue sarcoma arising from fibroblasts and was first described by O'Brien and Stout[2] in 1964. It occurs in patients between the sixth and eighth decades and is more common in men.[3,4] Retroperitoneal cases are rare—fewer than 100 cases have been reported.[5] The malignancy is more common in the extremities and trunk.[6]

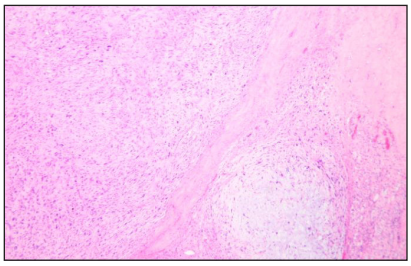

Figure 2. Histologic analysis of the soft-tissue mass near the right kidney (magnification x4) with hematoxylin and eosin stain shows a malignant spindle cell neoplasm that spares the kidney microscopically.

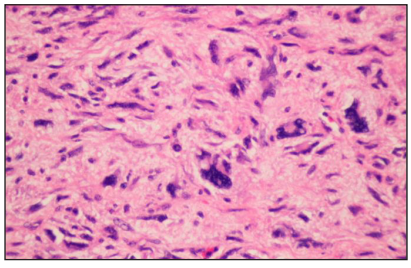

Figure 3. Histologic analysis of the soft-tissue mass near the right kidney (magnification x40) with hematoxylin and eosin stain shows a malignant spindle cell neoplasm with marked pleomorphism and focal vague epithelioid features.

Imaging demonstrates a well-differentiated soft-tissue mass with nonhomogeneous enhancement greater than skeletal

Table 1. Case timeline.

Date	Presenting symptoms	Work-up (findings)	Treatment	Outcomes
January 2015 to March 2015	Chronic cough and dyspnea on exertion	CT of chest (emphysematous and interstitial disease)	6 wks high-dose prednisone	Symptoms improved
July 2015 to September 2015	Worsening of symptoms	Repeated CT chest (idiopathic pulmonary fibrosis)	6 wks high-dose prednisone	Symptoms improved
October 2015 to December 2015	Worsening of symptoms	Bronchoscopy (idiopathic pulmonary fibrosis)	Pirfenidone (Esbriet[a])	Symptoms resolved
November 2016	Intermittent right upper quadrant pain, weakness, and weight loss	None	Conservative	Symptoms progressed
January 2017	Worsening of symptoms, hematologic abnormalities	CT of abdomen/pelvis (large retroperitoneal mass involving right kidney and ureter)	Admission to hospital for intravenous antibiotics and transfusions, discharge to skilled nursing facility for rehabilitation	Symptoms improved
February 2017	None (admitted to hospital for resection of mass)	Open right nephrectomy and bowel resection	Cancer staging (stage 3 undifferentiated pleomorphic sarcoma) and Medical Oncology Department referral	Symptoms stabilized
April 2017 to July 2017	None (Medical Oncology Department referral)	None (staging done previously)	Discontinued pirfenidone, started chemotherapy (doxorubicin and olaratumab)	Symptom stabilization, had completed 4 of 8 cycles at follow-up

[a] Manufactured by Genentech, South San Francisco, CA.
CT = computed tomography.

muscle and poor attenuation in areas of cystic degeneration, hemorrhage, myxomatous tissue, and necrosis.[5] Weiss and Enzinger[7] described five major classes on the basis of histologic findings: Storiform-pleomorphic (most common), myxoid, giant cell, angiomatoid, and inflammatory (least common and worst prognosis).

Primary treatment is resection, which can prolong survival.[8] Despite therapy, it is an aggressive tumor with high recurrence in more than half of cases and frequently metastasizes to the lungs and lymph nodes.[7,9] Prognostic factors are size, depth of involvement, and inflammatory component.[10] Chemotherapy with anthracycline-based regimens is an option for patients with unresectable or metastatic disease.[11] Patients with platelet-derived growth factor (PDGF-α) receptor mutation have increased overall survival with concurrent use of targeted therapy such as olaratumab.[11]

Pirfenidone was approved for the treatment of idiopathic pulmonary fibrosis in October 2014.[12] It inhibits epithelial and fibroblast proliferation and collagen synthesis by inhibiting several growth factors, including platelet-derived growth factor and tissue growth factor-β. In clinical trials, pirfenidone improved progression-free survival and decreased risk of death.[13-15] The drug is well tolerated; common side effects are dermatologic (photosensitivity, rash), gastrointestinal (nausea, vomiting, dyspepsia, anorexia), and hepatic (elevation of alanine and aspartate aminotransferase levels). Data on effects of long-term pirfenidone treatment are lacking.

To our knowledge, there have been no previously published reports of pleomorphic undifferentiated sarcoma associated with pirfenidone treatment. The abnormal inflammatory response leading to idiopathic pulmonary fibrosis, as in our case, may cause upregulation of similar pathways in other tissues.[16] This effect contributes to the increased risk of malignancies such as lung cancer in patients with idiopathic pulmonary fibrosis.[17] We hypothesize that pirfenidone deactivated fibrotic pathways in the lung tissue but further activated fibrotic pathways in the soft tissue, leading to our patient's tumor. Future studies may reveal additional malignancies associated with prolonged use of pirfenidone. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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How to Cite this Article

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Art: Science

The old art cannot possibly be replaced by, but must be absorbed in, the new science.

— William Osler, MD, 1849-1919, physician, pathologist, teacher, diagnostician, bibliophile, historian, classicist, essayist, conservationalist, organizer, manager, and author