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Case Report

Disease Response to Pazopanib in Follicular Dendritic Cell Sarcoma

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Keywords
Follicular dendritic cell sarcoma · Pazopanib · Kinase inhibitors · Pembrolizumab

Abstract
Follicular dendritic cell sarcoma (FDCS) is a rare sarcoma, which commonly presents as a slow-growing, painless mass. There are only a few hundred reported FDCS cases, and the role for adjuvant chemo- or radiation therapy has not been established. Choosing an appropriate therapy in disseminated disease can therefore be challenging. A 26-year-old patient with FDCS was admitted with dyspnea, fever, and night sweats. He was found to have a large right hemothorax with compressive atelectasis on initial imaging. CT of the chest revealed multiple bilateral lung and pleural nodules with associated bilateral hilar adenopathy, a hypodense mass within the right hemithorax, and necrotic right external iliac and inguinal nodes. Inguinal node biopsy diagnosed FDCS. The patient was initially treated with cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. Gemcitabine/Taxotere was given as second-line therapy and pembrolizumab as third-line therapy, with continued disease progression after 2 cycles of both regimens. The patient was switched to fourth-line therapy with pazopanib and had a partial response for 9 months. This case illustrates a successful FDCS treatment with pazopanib. Due to the rarity of FDCS, where large studies comparing treatment approaches are not available, recommendations for optimal treatment are not well defined. This case is in support of growing evidence suggesting that FDCS responds to systemic therapies that are used for soft tissue sarcoma, such as pazopanib.

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Introduction

Follicular dendritic cell sarcoma (FDCS) is an uncommon sarcoma which most commonly presents as a slow-growing, painless mass. FDCS may easily be confused with other solid tumors. This rare sarcoma was first described by Monda's group in 1986 and is now recognized to be a low-grade sarcoma of mesenchymal dendritic cell origin. FDCS originates in antigen-presenting cells of the B-cell follicles of lymph nodes. Dendritic cells play a crucial role in the immune system, contributing to both phagocytosis and antigen processing and presentation to B and T cells [1]. FDCS has been found to have an immunophenotype distinct from other malignant histiocytic tumors. FDCS is associated with widespread chromosomal instability, dysregulation of cell cycle progression, nuclear factor-κB activation, mitogen-activated protein kinase activation, and immune evasion. The mitotic index of FDCS is usually low (0–10), and the Ki-67 is most often less than 25%. FDCS characteristically has a significant infiltrate of B and T cells, including T lymphocytes that express terminal deoxytransferase. The diagnosis of FDCS is based on tissue pathology and presence of immunohistologic markers of dendritic cells (i.e., CD21, CD23, CD35, serglycin, and follicular dendritic cell-secreted protein). FDCS has histologic features of a low-grade sarcoma, with spindle-shaped cells that contain weakly eosinophilic cytoplasm seen in a storiform or whorled pattern [2]. There have only been a few hundred reported cases of FDCS, and most cases seen have presented with localized disease. However, extranodal sites such as tonsils, lung, liver, or spleen have been described. Males and females are affected equally, and the mean age of incidence is in the fifth decade of life, although reported cases have ranged from 9 to 82 years of age [3]. Unfavorable prognostic factors include large tumors (>6 cm), significant cellular atypia, coagulative necrosis seen on pathologic slides, intra-abdominal location, and high mitotic rate (>5 mitoses in 10 high-power field) [4].

Case Presentation

We report a 26-year-old patient with FDCS. The patient was admitted in September of 2018 with dyspnea, fever, and night sweats and was found to have a large right hemothorax with compressive atelectasis on initial imaging. CT chest revealed multiple bilateral lung and pleural nodules with associated bilateral hilar adenopathy, a thick-walled septated centrally hypodense mass within the right hemithorax, and necrotic right external iliac and inguinal nodes. Initial biopsy at our institution was negative for malignancy. Second pathology opinion at tertiary care center diagnosed FDCS. One month later, the patient was admitted for recurrent malignant right pleural effusion and underwent a VATS procedure. The VATS procedure demonstrated significant tumor infiltration and ingrowth within the entire pleural cavity. The patient was initially treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy. After 2 cycles, CT scan showed disease progression. Next generation sequencing did not show any actionable targets. Microsatellite instability was stable, and tumor mutation burden remained low. PD-L1 was negative 2+, 1%. Gemcitabine and Taxotere chemotherapy were given as second-line treatment. After 2 cycles, he once again had disease progression in all anatomic areas. Most concerning was a lytic lesion in the right femur that was a risk for pathologic fracture. He was initiated on radiation therapy to the right femur and pembrolizumab simultaneously. After 2 cycles of pembrolizumab, he had disease progression in all areas of disease except the radiation field (Fig. 1). The patient was switched to fourth-line therapy with pazopanib 800 mg daily. After 1 month of pazopanib, he had significant symptomatic improvement in his cough. He had improved exercise tolerance and decreased oxygen requirements. After 2 months of pazopanib, the patient experienced at

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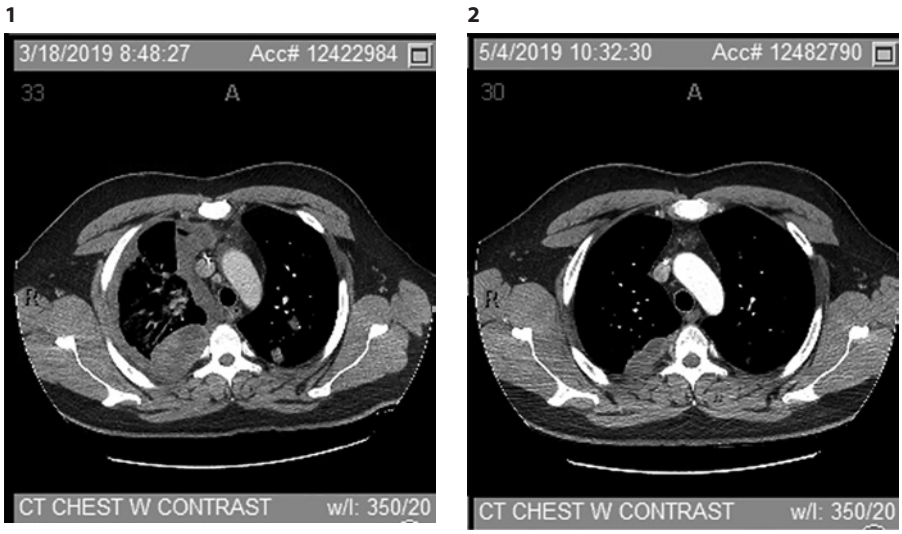

Fig. 1. CT chest with contrast status after pembrolizumab (03/2019), continued disease progression.
Fig. 2. CT chest with contrast status after 2 months of pazopanib (05/2019), significant disease regression.

50–75% partial disease response (Fig. 2). A partial response was sustained for 9 months before disease progression occurred in the lungs. After pazopanib, the patient received sunitinib, ifosfamide/carboplatin/etoposide chemotherapy and cabozantinib with short interval progression on all therapies. At the time of this reporting, hospice discussions are taking place.

Discussion

Due to the rarity of FDCS, large studies comparing treatment approaches are not available, and thus recommendations for optimal treatment are not well defined. The primary treatment of localized FDCS is surgical resection. A role for adjuvant therapy has not been established for either radiation therapy or chemotherapy [5]. FDCS usually has an indolent course, but 50% of patients develop local recurrence. An aggressive course is possible as well, with metastases to the lung, liver, and lymph nodes. Growing evidence suggests that FDCS responds to systemic therapies that are used for soft tissue sarcoma.

Lymphoma regimens such as CHOP and ABVD have been used to treat FDCS with variable outcomes. Other lymphoma-based regimens such as ifosfamide, carboplatin, and etoposide (ICE) have also been employed in cases of FDCS with outcomes similar to CHOP [6]. A case review of 50 cases by Wang et al. [7] showed no recurrence of disease in 80% patients in which CHOP therapy was used after excision of the sarcoma.

Sarcoma-based regimens such as gemcitabine and Taxotere as well as Adriamycin, ifosfamide, and mesna have also been used with success in FDCS. There have been several case reports of FDCS that show that therapy with gemcitabine in combination with a taxane (paclitaxel or docetaxel) have been successful [6]. A study of 46 patients with FDCS in which different chemotherapy agents were used, gemcitabine and Taxotere combination therapy showed the best outcomes. Among patients who received gemcitabine and Taxotere with/without other modalities, 42% (5/12) were complete responders, 41% were partial responders (5/12), and 2 patients were non-responders. In the 10 responders, 6 patients had surgery prior to chemotherapy, 3 had radiotherapy, and 1 had chemotherapy alone [8].

A second study of 66 patients with FDCS who were treated with chemotherapy (gemcitabine and a taxane, CHOP-based, or ifosfamide-based) in non-resectable disease, showed an overall response rate of 80% (including complete response and partial response)

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in gemcitabine + taxane therapy, 100% partial response with ifosfamide-based therapy, and 50% partial response in CHOP-based therapy. The median duration of response with gemcitabine and docetaxel in particular was 13.4 months [9]. This study agreed with other cases that showed favorable outcomes with the combination of gemcitabine and docetaxel. Common factors in the patients who did not respond were bulky and/or intra-abdominal disease, as seen in our patient.

Pembrolizumab is a highly selective anti-programmed cell death-1 humanized monoclonal antibody which inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor on T cells. Anti-PD-1 antibodies (including pembrolizumab) reverse T-cell suppression and induce antitumor responses [10]. In patients with undifferentiated pleomorphic sarcoma, pembrolizumab showed encouraging activity. In a phase 2, two-cohort, single-arm, open-label study, patients with soft tissue sarcoma or bone sarcoma were enrolled. Out of the 40 patients enrolled, 7 (18%) had an objective response including 4 (40%) of 10 patients with undifferentiated pleomorphic sarcoma and 2 (20%) of 10 patients with liposarcoma (LPS). PD-L1 expression was not assessed in this study [11].

Pazopanib is a tyrosine kinase inhibitor that inhibits angiogenesis by inhibiting various cell surface receptors. It has been approved to treat renal cell carcinomas and soft tissue sarcomas, especially in patients who have advanced soft tissue sarcomas (aSTS) and have received prior chemotherapy. Several studies have shown pazopanib to be effective in treating aSTS. In a landmark phase 3 randomized study, the PALETTE trial, pazopanib was compared with placebo in patients with aSTS whose disease had progressed during or following prior chemotherapy. Longer median progression-free survival (mPFS) of 4.6 months (pazopanib) versus 1.6 months (placebo) was observed. The overall response rate was low at 6% for pazopanib versus 0% for placebo [12]. Another prospective single-arm phase 2 study showed further evidence of efficacy of pazopanib in LPS, leiomyosarcomas, synovial sarcomas, and an "other" group of less common sarcomas. Unfortunately, FDCS was not in this less common group. This multicenter study treated patients with intermediate or high-grade LPS with pazopanib and reported an mPFS of 4.4 months and an overall survival of 12.6 months [13]. These findings were consistent with the data for other STS subtypes that were studied in the PALETTE trial. There are ongoing studies to find predictive biomarkers for use in selecting patients with aSTS for pazopanib, but there is no clinically validated data at present. This unfortunately limits the clinical effectiveness and cost-effectiveness of the therapy [14].

In conclusion, there are several therapies that have been proven to be efficacious in treating aSTS. Because of the rarity of FDCS, however, there are still no treatment guidelines, and the data from therapies for aSTS must be extrapolated when treating FDCS. In the case presented above, chemotherapy-based treatments were initially given with progression of disease. Pazopanib, shown in several studies to have significant efficacy in advanced and aggressive soft tissue sarcomas, yielded significant regression of the tumor along with clinical improvement after just a few weeks of therapy. At the time of this writing, the patient had completed 9 months of therapy with pazopanib before showing progression on imaging studies. He was treated with sunitinib, ICE chemotherapy, and cabozantinib, unfortunately showing progression through all therapies. Hospice discussions are ongoing.

Statement of Ethics

The subject of the above case report has given their express permission in the form of written informed consent to publish their case, including publication of images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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No funding sources were used in this case report.

Author Contributions

Pooja Shah – written contribution. Smit Shah – written contribution. Nicole Agostino – access to case file, treatment modalities, written contribution.

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