Rare Metastatic Primary Intra-Abdominal Follicular Dendritic Cell Sarcoma Poorly Responsive to Chemotherapy: A Case Report

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Abstract

Background: Follicular dendritic cell sarcoma (FDCS) accounts for about 0.4% of soft tissue sarcomas. Approximately one-third of cases occur in extranodal sites and about 28% of extranodal FDCS may metastasize. Intra-abdominal occurrence is rare and there is limited published data to guide oncologists on how to best treat this malignancy.

Case Presentation: This is a case of a 33-year-old female who came in due to incidental finding of a left supraclavicular mass with 2-year history of early satiety. Neck node biopsy revealed a poorly differentiated malignant tumor with positive staining for CD21, CD23, vimentin and S100 consistent with FDCS. PET-CT revealed an intensely FDG-avid large mass in the left upper abdomen with signs of necrosis and mass effect. The patient was given three different chemotherapy regimens that included (1) gemcitabine/docetaxel, (2) single agent doxorubicin and (3) ifosfamide/etoposide, but she progressed on all these. Off-label use of bendamustine was then offered and after just the first cycle, the patient reportedly regained strength and was able to get up from wheelchair with noted interval decrease in size of the cervical mass. Unfortunately, the patient deteriorated and succumbed to infection and multiple pulmonary embolisms.

Conclusion: Intra-abdominal FDCS is a rare malignancy with heterogenous outcomes with no uniform treatment strategy at present. Molecular tumor board discussion and multi-disciplinary approach in extranodal FDCS is important in the diagnosis and management. Patients with multiple poor prognostic factors are at risk for tumor recurrence, metastasis, and death.

Keywords: follicular dendritic cell sarcoma, abdominal neoplasm, chemotherapy, bendamustine, prognosis, case report

Introduction

Follicular dendritic cell sarcoma is a neoplastic proliferation of spindled ovoid cells with immunophenotype and morphology similar to normal follicular dendritic cells. It was first described by Monda et al in 1986 in a case series of four patients presenting with unilateral cervical adenopathy as a non-lymphomatous primary lymph node malignancy.[1] It may be suspect in asymptomatic patients with gradually enlarging painless lymphadenopathy.[1,2]

Follicular dendritic cells are normally present in both nodal and extranodal lymphoid follicles serving as antigen presenting cells and helps in B-cell migration, proliferation, and differentiation.[1] Sarcoma accounts for less than 1% of all adult solid malignant cancers.[2,3] FDCS accounts for only 0.4% of soft tissue sarcomas.[2,4] About one-third of cases occur in extranodal sites and intraabdominal occurrence is very rare.[3,5] The process by which follicular dendritic cells develop neoplastic potential is still unclear.[2]

The World Health Organization Classification of Tumors places FDCS under histiocytic and dendritic cell neoplasm. It is diagnosed based on pathologic evaluation of involved tissue and demonstration of characteristic immunohistology markers of dendritic cells. Histologically, it should be differentiated from other low-grade sarcoma, histiocytic neoplasms, melanoma, thymoma and other tumors.[1,2]

Given the rarity of this tumor in the intra-abdominal area and the lack of consensus on treatment, documentation of this case is important. Upon review of literature, there are only few case reports on intra-abdominal FDCS worldwide and after an exhaustive search, to our

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knowledge, there is no published data in the Philippines. In this paper, we describe the case of a 33-year-old female with primary intra-abdominal FDCS who presented with incidental finding of left supraclavicular mass.

Case Report

This is a case of a 33-year-old female with an incidental finding of a left supraclavicular mass. She presented with a two-year history of early satiety without associated fever, weight loss, anorexia, and changes in bowel habits. The patient has no known co-morbidities, denies smoking and drinking alcoholic beverages and, no family history of malignancy. Contrast-enhanced computerized tomography (CT) scan of the neck (*Figure 1A*) showed a 2.5cm x 2.2cm x 2.9cm soft tissue mass in the region of the left carotid space.

Chest CT scan showed no lung abnormality but there was an incidental finding of an enlarged soft tissue mass in the left upper quadrant of the abdomen in between the liver and stomach. CT scan of the whole abdomen revealed a heterogeneously enhancing subhepatic mass measuring 11.7cm x 11.5cm x 8.6cm in largest diameter as shown on *Figure 1B*.

The patient underwent excision biopsy of the left supraclavicular mass. *Figure 2* showed the neoplasm involving a lymph node composed of epithelioid and spindle cells arranged in nest and sheets or storiform pattern. The lesion shows focal necrosis and foci with high mitotic count of up to 8 to 10 per high power fields.

Initial histopathologic diagnosis was a poorly differentiated malignant tumor. Immunohistochemistry showed positive staining for CD23 and CD21, vimentin and S100. Tumor was negative for the following IHC stains: CK, CD34, SMA, ALK1, Melan A, ERG, DOG1 and Epstein-Barr encoding region (EBER) in-situ hybridization (*Figure 3*). After holding a molecular tumor board discussion, a final diagnosis of intra-abdominal follicular dendritic cell sarcoma (FDCS) was made.

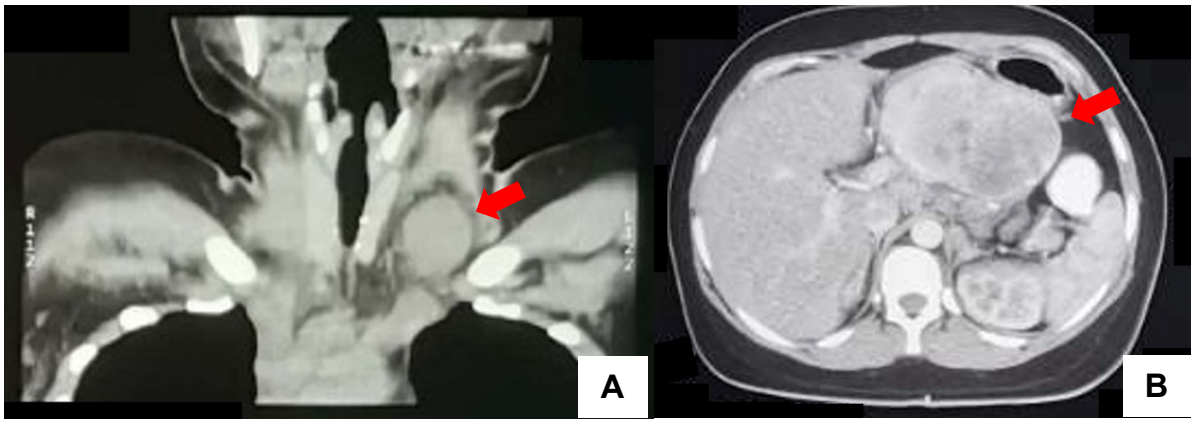


Figure 1. (A) CT scan of neck showed soft tissue mass (red arrow) in the region of the left carotid space with minimal fat stranding. (B) CT scan of the abdomen showed heterogeneously enhancing hypodense focus (red arrow) seen in the left subhepatic area closely adherent to the left lobe, pancreatic body and tail and lesser curvature of the stomach.

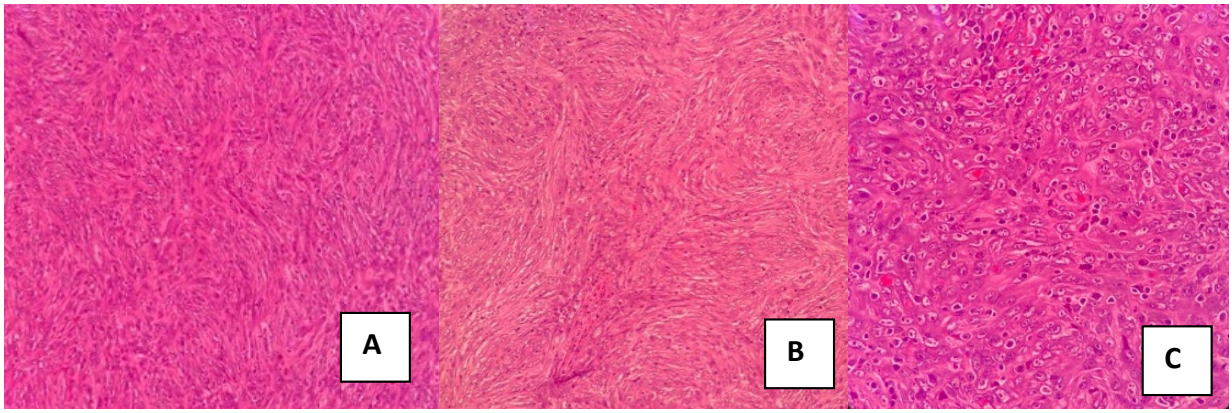


Figure 2. (A) High power magnification using hematoxylin and eosin showing the neoplasm involving a lymph node is composed of spindle cells arranged in storiform pattern: (B) The neoplastic cells show focal whorled or meningioma- like pattern of growth (white arrow); (C) The cells are focally ovoid in shape and have vesicular chromatin, small nucleoli, and moderate amount of cytoplasm with ill-defined cellular borders (white arrow).

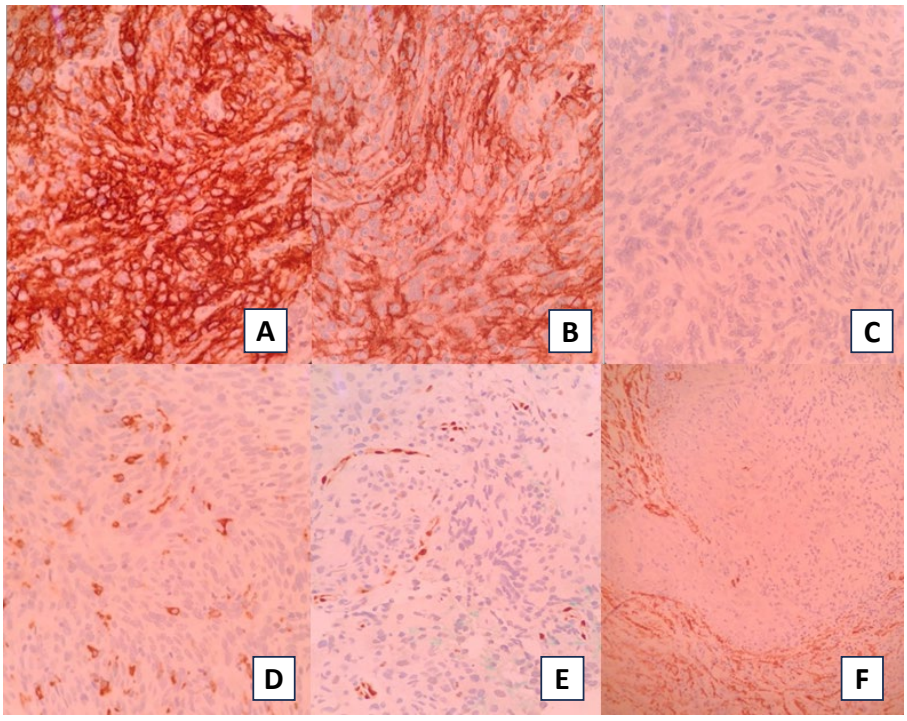
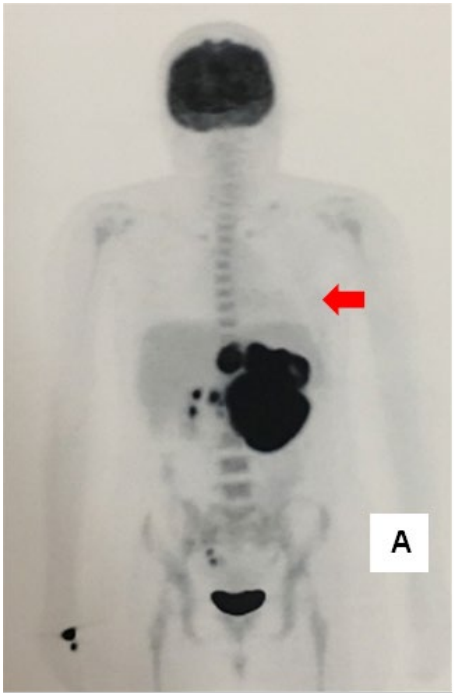


Figure 3. Immunohistochemistry. (A) Vimentin and CD23 stain focally positive; (B) CD21 stain focally positive; S100 positive in entrapped dendritic cells and possibly positive in few tumor cells; (C) Negative stain for ALK1, Melan A, DOG1, EBER in-situ hybridization; (D) CD68 negative in spindle cells, positive in histiocytes; (E) ERG negative in spindle cells, positive in blood vessel endothelial cells (F) SMA negative in spindle cells; positive in fibrous tissue



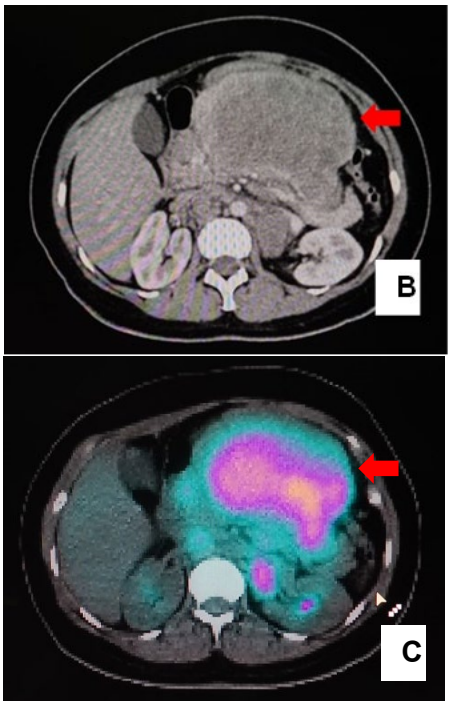


Figure 4. PET-CT scan (A) Coronal section revealed an intensely FDG-avid large mass in the left upper abdomen (red arrow). (B) The mass is heterogeneously enhancing (red arrow) with areas within the mass that have reduced or absent uptake may be due to necrosis. (C) Multiple FDG-avid enlarged nodes perilesionally and along the retroperitoneal region (paraaortic, aortocaval, paracaval). The node which has the most intense uptake (red arrow) is along the left para-aortic region (level of the renal vessels) with SUV max of 12.0 and is also the largest at 2.5x4cm (APxT)

Fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT scan showed an intensely FDG-avid large left upper abdominal mass, approximately 8.5cm x 11.9cm x 12.9cm with standardized uptake value maximum of 15.8 with areas of probable necrosis exerting mass effect, pushing the left hepatic lobe superiorly and gastric body anteriorly. There was no FDG uptake in the left supraclavicular area after the excision biopsy was done (*Figure 4A*).

During the interim the patient reported gradual upper abdominal enlargement accompanied by persistence of early satiety and now with lower back pain (pain score of 4/10). Another tumor board discussion was done including radio-oncology and surgery service with plans to proceed with neoadjuvant chemotherapy for sarcoma

prior to plans of definitive surgical intervention. She was started on gemcitabine 900 mg/m^2 administered on days 1 and 8 while docetaxel 100 mg/m^2 administered day 8 of a 21-day cycle. After 3 cycles of chemotherapy, the patient reported decrease in abdominal girth from 99 to 94 cm, ability to tolerate liquids during each meal and resolution of lower back pain. During the chemotherapy, no significant toxicities were noted and the patient tolerated it well. Alopecia grade 1, anemia and leukopenia grade 1 were managed with erythropoietin and filgrastim administration. The patient tolerated 4 cycles of chemotherapy however repeat imaging noted interval increase in size of intra-abdominal mass.

The patient then received 4 cycles of single agent doxorubicin 60mg/m^2 every 21 days however the patient deteriorated with worsening body weakness associated with enlarging abdominal girth and back pain. Likewise, there were no signs of cardiotoxicity such as chest discomfort, orthopnea, easy fatigability, palpitations or bipedal edema. She was referred to a sarcoma specialist who gave regimen for refractory lymphoma: high dose ifosfamide 3.5 g/m^2 and etoposide 100mg/m^2 daily for 5 days every 21 days. The patient reported persistence of symptoms such as progressive abdominal enlargement, early satiety, decreased appetite and generalized body weakness. No noted severe diarrhea, thrombocytopenia, or bleeding. Progressive disease was noted after the 3rd cycle of chemotherapy.

Off-label use of bendamustine 70mg/m^2 every 28 days was offered to the patient and consented after thorough explanation of possible risks and benefits associated. After the first cycle, the patient reportedly regained strength and was able to get up from wheelchair with note of interval decrease in size of the cervical mass. Unfortunately, the patient deteriorated and succumbed to septic shock from staphylococcal septicemia, multiple pulmonary embolism and cardiac decompensation.

Discussion

Sarcomas are rare and heterogenous group of malignant tumors of mesenchymal origin that comprise less than 1% of all adult malignancies. Approximately 80% of new cases of sarcoma originate from soft tissue.[5] Follicular dendritic cells are cardinal members of primary and secondary lymphoid follicles serving in antigen presentation and humoral responses.[3,6] The process by which follicular dendritic cells develop neoplastic potential is still unclear. Comprehensive genetic analysis has not revealed a universal driver mutation or translocation.[2]

FDCS accounts for only 0.4% of soft tissue sarcomas.[2,3] Extranodal site FDCS is rare and can occur in sites including lung, liver, spleen and gastrointestinal tract.[1] Similar to how the patient presented, FDCS generally present as a slowly growing, painless cervical lymphadenopathy.[6] Approximately one-third of FDCS cases occur in extranodal sites, including skin, mediastinum, tonsil, gastrointestinal tract and soft tissue.[1,4] Among patients with intra-abdominal involvement, they may present with mass effect symptoms such as abdominal pain and distention.[7] This was seen in the patient who reported 2 year history of early satiety relating to mass effect from gradual tumor enlargement.

Imaging studies should include an integrated FDG-PET/CT scan since FDCS is FDG-avid .[1,2] With the scan of the patient, the SUV of the intra-abdominal mass was 6 times higher than that of the liver background indicating significantly high activity in the tumor. A broad differential diagnosis can be developed as this tumor has morphologic features similar to other tumors, hence creating a diagnostic pitfall – but its immunophenotypic profile is quite specific and is diagnostically crucial.[4] Expert pathology review is essential due to the rarity of FDCS and the difficulty in distinguishing it from other entities hence the conducted molecular tumor board discussion for this case.[2]

FDCS appears histologically as spindle-shaped cells organized in a storiform pattern or meningioma-like pattern similar to what was seen in the patient.[3] In addition, the diagnosis of FDCS is through tissue pathologic evaluation and demonstration of characteristic immunohistology markers of dendritic cells such as CD21, CD23, CD35, follicular dendritic cell-secreted protein (FDCSP), clusterin and podoplanin (D2-40).[1,2] Immunohistochemically, the patient's tumor stained positive for CD21, CD23, and vimentin which are characteristic of FDCS.[2,6] Interdigitating dendritic cell sarcoma is S100 positive but negative in CD21 and CD35 hence this was ruled out in this case.[2,3,6] Additionally, the patient's tumor negatively stained for cytokeratin which is commonly seen in spindle cell carcinoma. Iinflammatory pseudotumor variant FDCS, an Epstein-Barr virus-associated neoplasm which typically arises in the liver and spleen was not considered due to negative EBER in-situ hybridization.[2] Malignant melanoma and gastrointestinal stromal tumor (GIST) may also appear histologically similar to FDCS however, they stain positive in Melan-A and DOG1, respectively which were both negative in the patient's neoplasm. Another possible differential diagnosis is inflammatory myofibroblastic tumor which stains positive in smooth muscle actin (SMA) and ALK which however were negative in this case.

Management of FDCS is challenging due to rarity of this condition which is considered as a diagnostic challenge since its clinical presentation is highly variable.[7] Moreover, robust studies comparing various treatment approaches are not available.[4,7] Surgical resection of localized FDCS is the mainstay of treatment. In the local setting, molecular tumor boards impact the clinical management of patients with cancer through multidisciplinary team discussion consulting on multiple cases with experts to discuss the optimal treatment plans.

Combination therapy with surgery, radiotherapy and chemotherapy are the options for treatment strategies. The role of adjuvant therapy in advanced disease such that of this case is undefined. A subset of patients with locally advanced disease may be converted into surgical candidates following initial neoadjuvant chemotherapy.[8]

The systemic therapy for FDCS involved use of regimen commonly given to treat intermediate grade lymphoma such as CHOP therapy due to several early observations linking FDCS with B lymphocytes. Preferred options include gemcitabine plus docetaxel or an anthracycline-based regimen such as that used for other metastatic soft tissue sarcomas.[2,8] A multicenter phase II trial compared gemcitabine with or without docetaxel and the combination produced superior objective response rate, progression-free survival and overall survival.[2,8]

Among patients with metastatic disease, the goal of treatment is ultimately improvement of quality of life and palliation of symptoms.[3] About 20 to 30% single agent response rate was seen among metastatic sarcomas treated with doxorubicin and with a median survival of 7.7 to 12 months. Direct correlation with increase in dosage versus the response rate at 75 to 90 mg/m^2. However, it entails toxicities such as myelosuppression, gastrointestinal side effects, alopecia and cardiotoxicity.[3,7]

The prognosis of patients with FDCS is not well defined due to variable approaches to management and because most data in the medical literature come from small retrospective series and anecdotal case reports.[1,2] In a case analysis of 97 extranodal FDCS, poor prognostic factors include extensive necrosis, a large tumor size (> 6cm), cytologic atypia, an intra-abdominal location, and a high proliferative index (mitotic count > 5 mitoses/10 HPF), all of which increase the likelihood of recurrence, metastasis, and death.[4,6,9] These features were seen in our patient.

Having failed two regimens for sarcoma treatment, the patient was given high dose ifosfamide in combination with etoposide like treatment strategy for relapsed/refractory lymphoma, but this regimen has also been found to be active in sarcomas.[10] In a review done by Proctor et al, this showed 43% over all response to these agents but only 10% for those with primarily refractory disease. In terms of two-year survival, 22% for patients who respond to first-line of treatment and unfortunately 0% for primary refractory patients.[3,10]

In general, the two-year and five-year overall survival rates were 82% and 79%, and their two-year and five-year disease-free survival rates were 57% and 32%, respectively.[5] FDCS lesions were defined as low-, intermediate- and high-risk tumors, and their recurrence rates were 16%, 46% and 73%, and their mortality rates 0%, 4% and 45%, respectively.[4,6]

Bendamustine, which was initially given for low-grade lymphoma, is known to have low cross-resistance with alkylators – desired effect among patients refractory to alkylators.[9,11] In this case, the patient also received bendamustine which may correlate with the positive immunostaining for CD23, a B-cell marker. Sasaki et al discussed a case report on follicular dendritic sarcoma treated with a variety of chemotherapy including bendamustine.[11] Improvement of laboratory data such as alkaline phosphatase and C-reactive protein levels were observed, however side effects such as diarrhea and loss of appetite caused severe complications necessitating discontinuation of treatment. A non-comparative multicenter Phase 2 study of the German Sarcoma Group showed that bendamustine is well tolerated and among patients with refractory soft tissue sarcoma. Partial response rate of 3% was noted among previously treated soft tissue sarcoma while patients with stable disease rate was 31%.[12] Until now, there is no consensus on the treatment strategy for FDCS hence documentation of treatment responses is important.[9,11]

Conclusion

Intra-abdominal FDCS is a rare malignancy with heterogenous outcomes and there is no uniform treatment strategy at present. Molecular tumor board discussion and multidisciplinary approach in extranodal FDCS is important in the diagnosis and management. Patients with multiple poor prognostic factors such as extensive necrosis, large tumor (> 6cm), presence of cytologic atypia, intra-abdominal location, and high-mitotic count (> 5/10 HPF) are at risk for tumor recurrence, metastasis, and death.

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