CASE REPORT

Mesenteric Follicular Dendritic Cell Sarcoma Presenting as Paraneoplastic Pemphigus

A. Marinis[1], M. Voultsos[2], I. Siannis[1], V. Georgilaki[1], A. Zarafidou[1], F. Kyramargios[1], N. Kouzakos[1], N. Vlahakos[1]

[1]Third Department of Surgery, Tzaneio General Hospital, Piraeus, Greece and [2]Consultant General, Laparoscopic and Colorectal Surgery, Royal Free NHS Foundation Trust, Barnet and Chase Farm Hospitals

ABSTRACT

Follicular Dendritic Cell Sarcoma (FDCS) is a rare neoplasm defined by neoplastic proliferation of follicular dendritic cells (FDCs) which are localized in B-cell areas in primary and secondary lymphoid follicles. We herein present a 64-years-old female patient with a prior history of oral pemphigus who was admitted for management of a large abdominal mass. The intra-abdominal lesion was located in the small bowel mesentery. Immunohistochemical staining of the neoplastic cells demonstrated strong and diffuse positive staining of follicular dendritic cell markers CD21, CD23, CD35 and vimentin. The patient followed an uneventful postoperative course and was subsequently referred to an oncologist for adjuvant chemotherapy which consisted of cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone (CHOP regimen).

Keywords: Follicular dendritic cell sarcoma, mesentery, paraneoplastic pemphigus

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INTRODUCTION

Follicular Dendritic Cell Sarcoma (FDCS) is a rare neoplasm defined by neoplastic proliferation of follicular dendritic cells (FDCs) which are localized in B-cell areas in primary and secondary lymphoid follicles. Its existence was predicted by Lennert in 1978 but it was not until 1986 that Monda *et al* characterized it as a unique form of sarcoma [1, 2]. Fewer than 200 cases have been reported in medical literature worldwide. Its etiology is unknown but a small subset of cases are associated with Castleman's disease and Epstein-Barr virus (EBV). It presents as a slow-growing, painless mass in lymph nodes (cervical, axillary, mediastinal, mesenteric and retroperitoneal) and about 30% is found in extranodal sites such as tonsil, oral cavity, gastrointestinal tract, soft tissues, skin, thyroid, breast, mediastinum, liver and spleen. Most cases behave like low-to-intermediate grade soft tissue sarcoma but recur frequently and are generally insensitive to chemotherapy with a subset of cases being clinically aggressive. The differential diagnosis includes interdigitating dendritic cell sarcoma,

inflamamatory myofibroblastic tumor, lymph node inflammatory pseudotumor, diffuse large B-cell lymphoma, Hodgkin lymphoma, spindle cell carcinoma, melanoma and Kaposi's sarcoma. This fact along with the rarity of these neoplasms makes diagnosis cumbersome. Aiming to deepen the understanding of this disease entity and to add to the existing literature on FDCS we present a case of a Caucasian female who presented with a paraneoplastic pemphigus and an underlying FDCS.

CASE REPORT

A 64-year-old Caucasian female patient was admitted to our hospital for investigation of a newly diagnosed abdominal mass. The patient was under therapy for oral mucosa pemphigus during the past 6 months (appeared roughly one year ago) (Figure 1) when she mentioned to her General Practitioner a change in her bowel habits along with a palpable mass in her left abdomen for approximately 3 months.

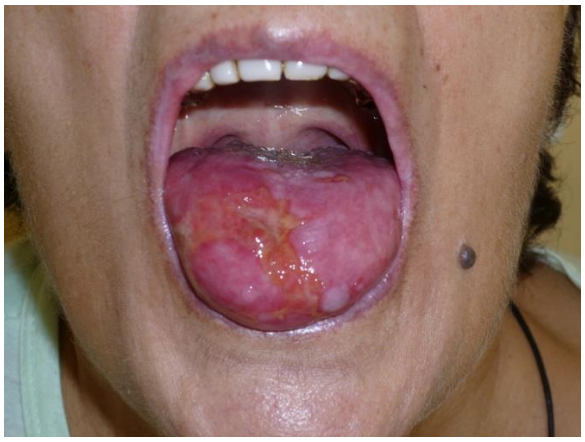


Figure 1. Paraneoplastic pemphigus exhibiting painful sores in the oral cavity mucosa (Endoscopy did not reveal additional esophageal lesions).

Prior personal history was unremarkable except for a mild autoimmune hemolytic anemia (positive direct Coombs reaction). Physical examination revealed a large movable, painless, palpable tumor mass located in her left abdomen without evidence of lymphadenopathy (inguinal, axillary, neck). Pulmonary function tests were within physiologic parameters.

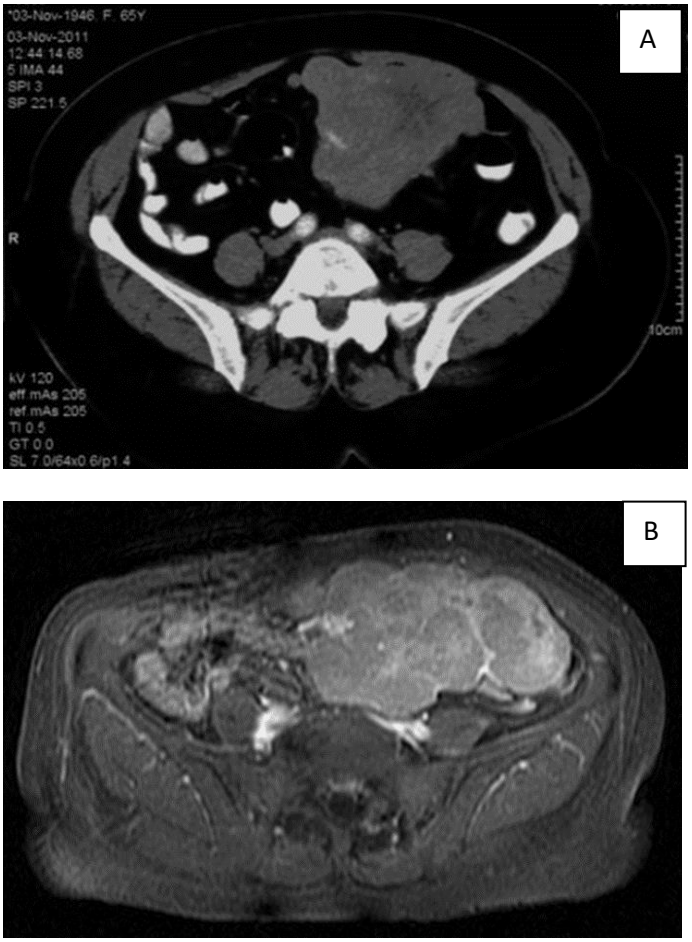


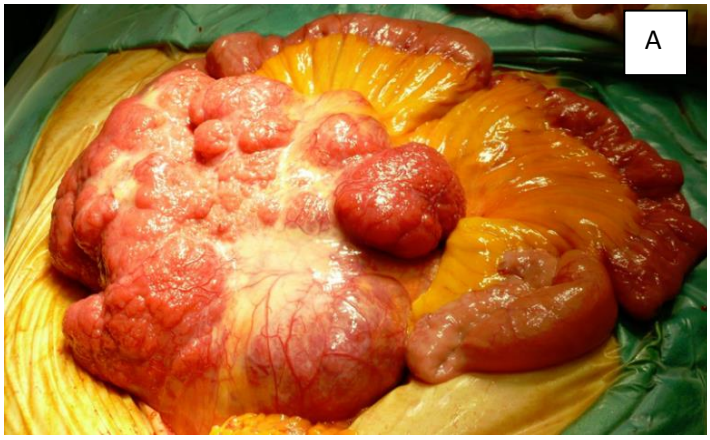
Figure 2. Radiological characteristics of extranodal FDCS (A) Contrast-enhanced CT scan revealed a large inhomogeneous mass with central areas of necrosis (B) MRI scan revealed a large multilobulated abdominal mass with areas of focal necrosis and peripheral hemorrhagic foci in contact with the anterior abdominal wall.

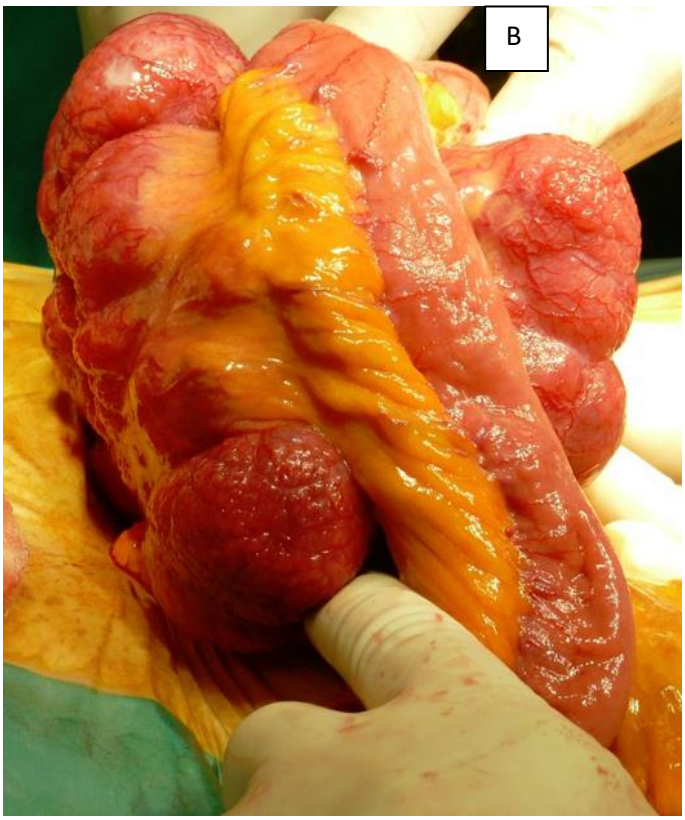
Laboratory examination revealed that all parameters were within normal levels with the exception of two mildly elevated tumor markers [carcinoembryonic antigen (CEA) of 65.87 U/ml (normal <25); CA125 52.09 U/ml (normal <35)].

Contrast - enhanced computed tomography (CT) and magnetic resonance imaging (MRI) scans showed a large multilobulated abdominal mass with areas of focal necrosis and peripheral hemorrhagic foci in contact with the anterior abdominal wall. The lesion showed a mass effect on adjacent abdominal organs but without evidence of direct invasion (Figure 2).

Intraoperative findings revealed a large well-defined intra-abdominal mass with a gross diameter of 17cm located in the small intestinal mesentery (Figure 3). Further abdominal exploration did not reveal any additional findings and a radical resection of the tumor was successfully performed.

Gross examination of the tumor revealed a multilobulated, encapsulated mass with heterogeneous appearance on cut surface with focal hemorrhagic changes and central necrotic areas.





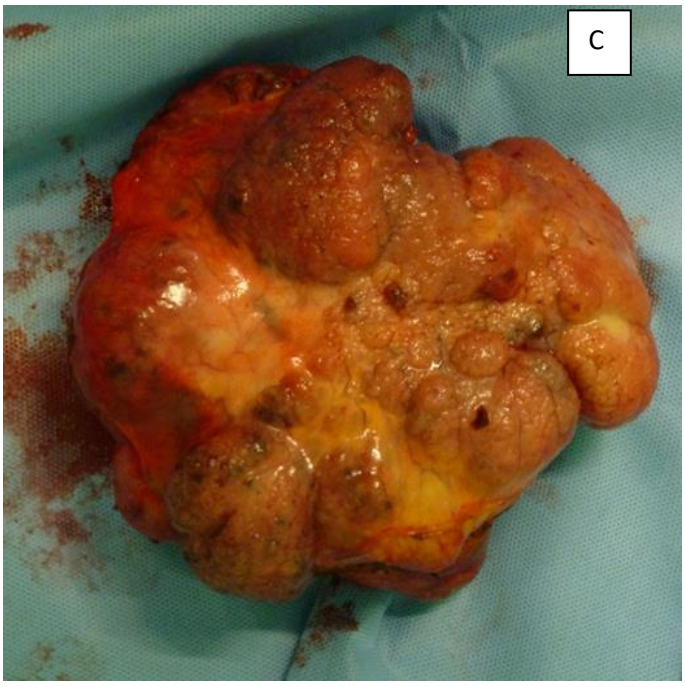


Figure 3. (A) Intraoperative macroscopic tumor view. (B) Tumor arising from the small intestinal mesentery. (C) The resected tumor specimen was multilobulated and was surrounded by a fibrous capsule.

Histologically the tumor showed predominantly low-grade cytologic features consisting of proliferation of spindle and ovoid cells with mild nuclear atypia and low mitotic rate in a variety of growth patterns including whorled, storiform, fascicular and vaguely nodular associated with lymphocyte-rich stroma. Focal higher-grade features included mild cellular pleomorphism with occasional binucleated and multinucleated cells, more diffuse growth pattern, areas of necrosis and fewer stromal lymphocytes. Immunohistochemical staining of the neoplastic cells demonstrated strong and diffuse positive staining of follicular dendritic cell markers CD21, CD23, CD35 and vimentin. CD68 and S100 staining was positive for a limited number of tumor cells. Ki67 index ranged from 0 to 20% (focally). Negatively stained markers included CD20, CD79a, UCHL1, CD3, CD5, CD30, CD15, MPO, ALK, LMP1, Pankeratin (AE1/AE3), EMA, SMA, desmin, CD117, CD34, CD31, FVIII, HMB45, MelanA, HHV8. EGFR staining was inconclusive.

The patient followed an uneventful postoperative course and was subsequently referred to an oncologist for adjuvant chemotherapy which consisted of cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone (CHOP regimen).

DISCUSSION

FDCs are localized in B-cell areas in primary and secondary lymphoid follicles and play a pivotal role in antigen presentation to B-cells. They are closely related to bone marrow stromal progenitors and share some features of myofibroblasts. Neoplastic proliferation of FDCs is typically seen arising from lymph nodes but extranodal involvement in small intestine and its mesentery as in our case has been reported [3]. Extranodal FDCS (30% of all FDCS) was first reported by Chan et al in 1994 [4]. Reported extranodal sites include tonsils, oral cavity, gastrointestinal tract, soft tissues, skin, thyroid, breast, mediastinum, liver and spleen [5-16]. Its etiology remains elusive even though a small subset of cases is associated with hyaline-vascular type Castleman disease and EBV infection, particularly the hepatic and splenic lesions [17-29]. A possible role of the p53 tumor suppressor gene in the tumorigenesis has been proposed [30, 31].

Regarding the clinical characteristics, FDCS show no gender or ethnic preference with a median presentation age ranging from 40-50 years even though older ages have been reported [6,] which coincide with our patient's age. It usually presents as a slow-growing painless mass with minimal or absent systemic symptoms, although patients with abdominal disease may present with mild abdominal pain [32]. Paraneoplastic syndromes, though rare, include pemphigus and neurologic diseases, such as Myasthenia gravis, suggesting the possibility that FDC sarcomas may be capable of mediating aberrant immune activation leading to autoimmune diseases which might become clinically evident even after radical tumor excision [33-39].

The diagnosis of FDCS is based on histology morphological findings and immunohistochemistry. The histological features tend to be stereotypical, as in our

patient and include spindled to ovoid cells forming fascicles, storiform arrays, whorls, diffuse sheets or nodules often admixed with small lymphocyte aggregates around blood vessels. Significant cytologic atypia and high mitotic figures are associated with high-grade FDCS [40]. FDCS cells generally share the immunophenotye of non-neoplastic FDCs, with CD21, CD35 and/or CD23 being the most specific diagnostic markers. Other positive markers include vimentin, fascin, HLA-DR and EMA. Some tumors are also positive for S-100, CD68, CD45 and CD20, whereas others are not [6, 32, 41]. FDCS typically lacks expression of CD1a, desmin and CD45, which allows their differential diagnosis with interdigitating dendritic cell tumors, Langherhans cell tumors, histiocytic and lymphoid neoplasias [42].

The differential diagnosis includes interdigitating dendritic cell sarcoma, Langerhans cell Histiocytosis/sarcoma, inflammatory myofibroblastic tumor, inflammatory pseudotumor of lymph nodes, diffuse large B-cell lymphoma, melanoma, Kaposi sarcoma, classical Hodgkin lymphoma. Moreover, in case of intestinal FDCS, the major differential diagnosis includes gastrointestinal stromal tumor (GIST) and primary intestinal lymphomas. In this case, GIST was easily excluded by a lack of expression of CD34 in tumor cells [41-43].

In our case the tumor markers CEA and CA125 were mildly elevated and returned within normal levels postoperatively. Even though increased CA125 has been reported [44], the values of both elevated markers for FDCS remains to be determined.

FDCS is generally regarded as having an indolent nature behaving like a low-to-intermediate grade sarcoma and associated with a low risk of metastasis but with a tendency of local recurrence [40, 45-46]. Lymph nodes, lung, and liver are the most common sites for metastasis [42]. The reported 5-year disease-free survival rates range from 27-32%, whereas 5-year overall survival is around 80% [40, 47]. Potential predictors of an unfavorable outcome include intra-abdominal involvement, a high mitotic count (≥5/10HPF), coagulative necrosis, marked cellular atypia and large tumor size (≥5cm in diameter). The latter seems to be the most important concerning a negative clinical outcome [40, 48]. A model for recurrence risk assessment has been proposed based on tumor size, mitotic activity and histological grade [40]. By this model, FDC sarcomas were classified into low-, intermediate- and high-risk groups. Recurrence rates in the three groups were 16%, 46% and 73%, and the mortality rates were 0%, 4% and 45%, respectively.

Based on the fact that no prospective data exists regarding FDCS treatment since most of the published data are retrospective analyses, no recommendations exist and the optimal therapeutical approach to these patients still remains to be defined. Therefore, reported treatment is based on radical resection and adjuvant chemotherapy and radiation with the former being the mainstay of therapy as with other sarcomas [47]. However, even though the role of adjuvant therapy is targeted towards lowering the recurrence risk, its role in improving overall survival still remains to be defined. The present case suggested that FDCS can be

effectively treated with surgery and adjuvant chemotherapy.

CONCLUSION

Extranodal follicular dendritic cell sarcoma is only rarely encountered by physicians and most data are based on single case reports and small case series. To our knowledge, this is the second case presentation through a paraneoplastic pemphigus and based on the patient's aberrant immune system may provide further clues regarding its pathogenesis. Many FDCS cases remain under-recognized even though immunohistochemistry has added a lot to its diagnosis. Nevertheless, further investigation is required to bring insight to its biology, pathogenesis and behavior and to provide the pathologist with independent genetic markers so that our therapeutical efforts would be better aimed against this scarce disease entity.

ΒΙΒΛΙΟΓΡΑΦΙΑ

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Συγγραφέας αλληλογραφίας: **Athanasios Marinis,** E-mail: drmarinis@gmail.com