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Follicular dendritic cell sarcoma: report of two cases and literature review

Sarcoma de células dendríticas foliculares: relato de dois casos e revisão da literatura

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ABSTRACT

Follicular dendritic cell sarcoma is a rare neoplasm, first described in 1986 by Monda. Case 1: A female patient, 50-year-old performed abdominal computed tomography scan that detected a tumor lesion of 8.0 cm in the mesentery. She underwent resection of the lesion. Microscopic examination revealed epithelioid neoplasm, interspersed with lymphocytes, and positive immunohistochemical staining for CD21 and CD35. The patient underwent adjuvant chemotherapy. Case 2: A male patient, 21-year-old presented right-sided neck mass measuring 7.0 cm. The biopsy revealed proliferation of spindle cells, interspersed with inflammatory infiltrate and storiform arrangement, and positive immunohistochemical staining for CD21 and CD23. The patient underwent neoadjuvant radiotherapy and surgical resection.

Key words: follicular dendritic cell; dendritic cell neoplasm; follicular dendritic cell sarcoma; pathology.

INTRODUCTION

Follicular dendritic cells (FDC) are accessory cells of the lymphoid system. Their main function is to trap and present antigens to B cells and immune complexes. Tumor arising from this cell is very rare, and is named follicular dendritic cell sarcoma (FDCS), which was first reported by Monda *et al*. in 1986[2]. Since then, more than 343 cases have been described in the literature, approximately 31% cases had only nodal disease, 58% isolated extranodal involvement, and 11% combined nodal and extranodal disease[3]. The predominant site of tumor was cervical lymph nodes. Recently, the diagnosis accuracy has been significantly improved, thanks to the aid of immunohistochemistry analysis and to more reliable FDC markers CD21 and CD35. Once FDCS is suspected, histologically, immunohistochemical stains for follicular dendritic cell differentiation should be performed to avoid misdiagnosis[4]. Diagnosis of dendritic cell sarcoma (DCS) is a challenge, even for experts of hematopathology, and we still do not have a well-designed treatment protocol for this unique tumor. The role of adjuvant therapy remains unclear[3]. The aim of this case report is to discuss the histopathological, clinical and therapeutic aspects of retroperitoneal FDCS.

CASE 1

A 50 year-old asymptomatic woman was submitted to follow up abdominal computed tomography (CT) scanning, in June 2012, which revealed a 8.0 × 6.2 cm oval-shaped mesenteric mass, with well-defined limits and mild to moderate heterogeneous enhancement (**Figure 1**). Routine biochemical and hematological tests were within normal limits. There was a past medical history, in June 2008, of bowel obstruction due to colorectal adenocarcinoma, treated with left hemicolectomy, radiotherapy and chemotherapy. She underwent surgical resection of the mesenteric mass. Surgical exploration revealed a mass measuring 8.4 cm, adjacent to the transverse colon. No associated lymphadenopathy was observed. Cut sections revealed a tan, homogeneous solid mass with rough surface and some areas of necrosis. Multiple sections were taken from different areas of the tumor. Microscopic examination revealed that the tumor consisted of sheets of epithelioid cells, with oval nuclei, some with prominent nucleoli, eosinophilic cytoplasm and poorly defined cell outlines (**Figure 2**). Numerous small lymphocytes were interspersed between the tumor cells (**Figure 3**). The tumor exhibited necrosis, cellular

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atypia, and high mitotic index (22 per 10 high-power fields) (**Figure 4**). Furthermore, the tumor cells exhibited positive immunohistochemical staining for vimentin, fascin, CD21 and CD35, focally positive for S100, CD68 and CD56, as well as negative staining for cytokeratin, CD45, CD117, epithelial membrane antigen, melan-A, and HMB-45 (**Figures 4** and **5**). Based on these histopathological and immunohistochemical findings, the patient was diagnosed with retroperitoneal FDCS. She received postoperative sequential chemotherapy with eight cycles of standard dose of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), which initiated in May 2013. To evaluate the efficacy of adjuvant therapy, an abdominal CT scan was performed and resulted normal. She is in remission until today.

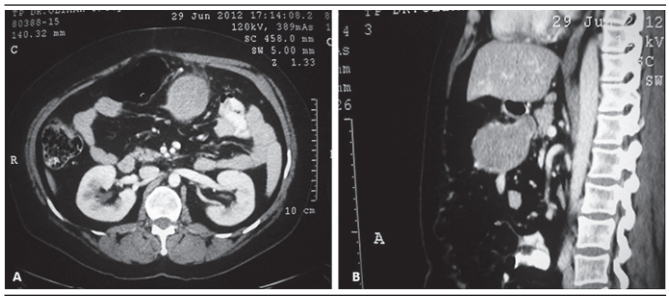

FIGURE 1 – *Abdominal CT scan*

A) post contrast axial CT image shows a well defined mass near the transverse colon measuring approximately 8.0 cm; B) post contrast sagittal CT scan with mild to moderate heterogeneous enhancement.

CT: computed tomography.

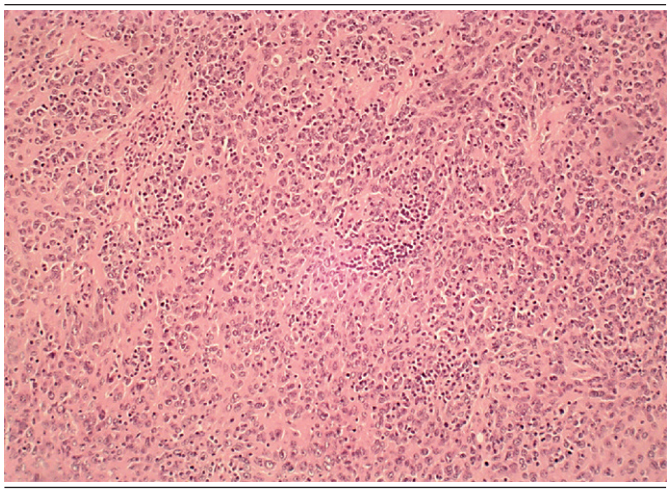

FIGURE 2 – *FDCS*

Sheets of epithelioid cells with eosinophilic cytoplasm.

FDCS: follicular dendritic cell sarcoma.

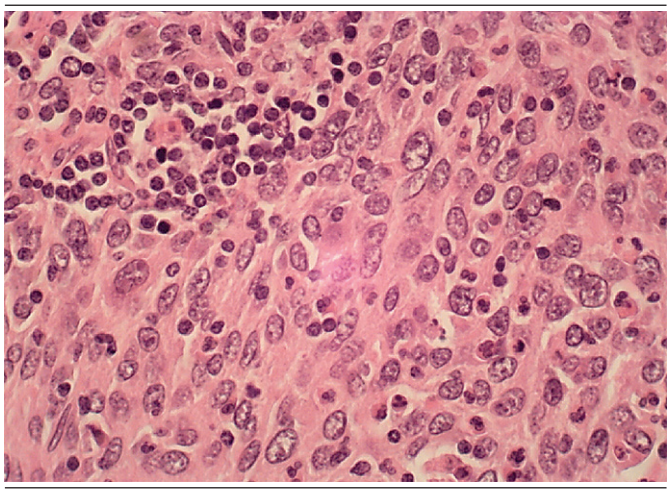

FIGURE 3 – *FDCS*

High magnification shows that the neoplastic cells are epithelioid with ovoid to elongated bland nuclei, distinct nucleolus and eosinophilic cytoplasm. There are numerous small lymphocytes interspersed between tumor cells.

FDCS: follicular dendritic cell sarcoma.

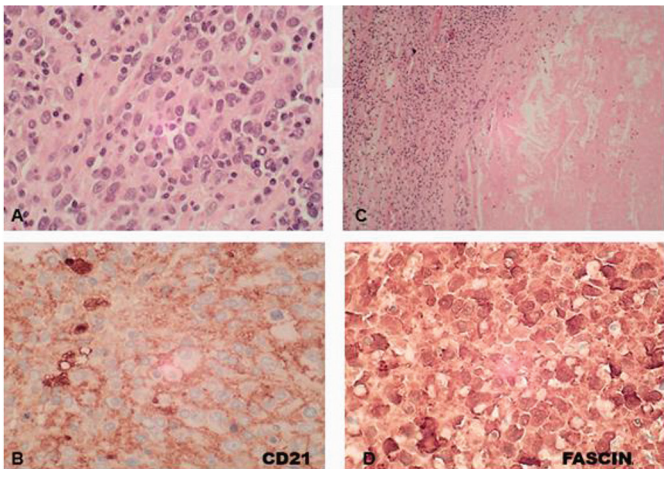

FIGURE 4 – *FDCS*

A) the tumor has numerous mitoses, some atypical; B) areas of necrosis; C) and D) immunohistochemical staining shows that this neoplasm is positive for CD21 (C) and for fascin (D).

FDCS: follicular dendritic cell sarcoma; CD21:

CASE 2

A male patient 21 year-old presented a 4-month history of right-sided level III neck mass. He has no fever, weight loss, malaise, nor night sweats. His medical history was described

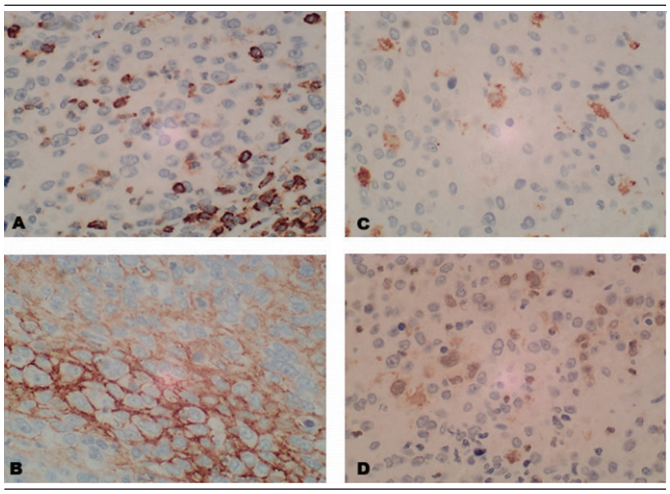

FIGURE 5 – *FDCS*

Immunohistochemical staining show that this neoplasm is focal positive for CD45 (A), D2-40 (B), CD68 (C), and S100 (D).

FDCS: follicular dendritic cell sarcoma; CD45: ; D2-40: ; CD68: ; S100: .

by his mother as unremarkable. Physical examination revealed a right-sided 5.8 × 4.4 cm, elastic hard, painless, fixed mass in the neck. The skin covering the neck swelling was normal with no evidence of ulceration. There was increase in the right amygdala and bulge in the soft palate. No other lesions were found in his head and neck examination. During the diagnose process, a CT scan was performed revealing multiple nodes level II and III on the right side extending to the soft palate (**Figure 6**). A biopsy was performed and revealed a tumor composed of oval to spindle-shaped cells arranged in sheets, fascicles, concentric whorls, and storiform patterns, with oval nuclei, some prominent nucleoli, eosinophilic cytoplasm, and poorly defined cell outlines (**Figure 7**). Numerous small lymphocytes are interspersed between the tumor cells (**Figure 8**). There was no necrosis and the mitotic index was 5 per 10 high-power fields. Immunohistochemically, the tumor cells were positive for CD21, CD23 (**Figure 9**) and CD45 but negative for cytokeratin, CD3, CD20, and CD68. Together, these results support the diagnosis of FDCS. In May 2012, the preoperative interdisciplinary tumor board conference decided to submit the patient to neoadjuvant radiotherapy. After significant reduction in mass volume to 3.0 cm and disappearance of changes in palate and amygdala, he was submitted to complete resection of the mass combined with a right selective neck dissection (level III). He received postoperative sequential chemotherapy with ifosfamida e epirrubicina. In January 2014 the patient had a recurrence in the oropharynx and underwent rescue surgery. He remains in remission until his last consultation.

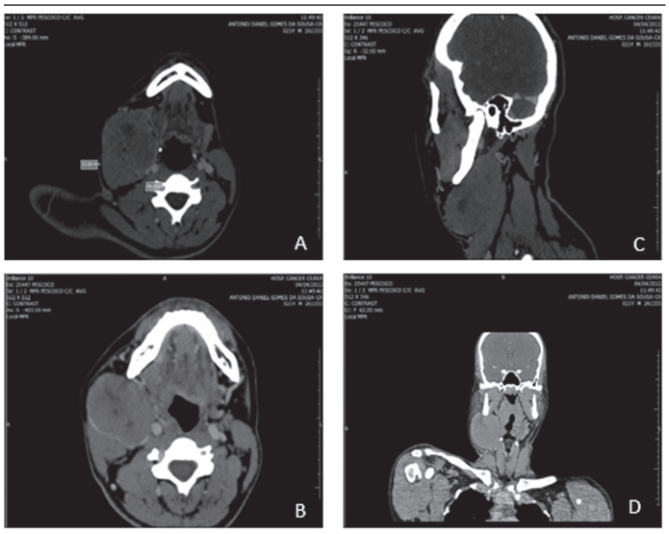

FIGURE 6 – *Head and neck CT images*

Post contrast CT images show a well-defined cervical mass stage II and III on the right side extending to the soft palate measuring approximately 6.0 cm, with moderate heterogeneous enhancement.
A) and B) axial CT image; C) sagittal CT image; D) coronal CT image.

CT: computed tomography.

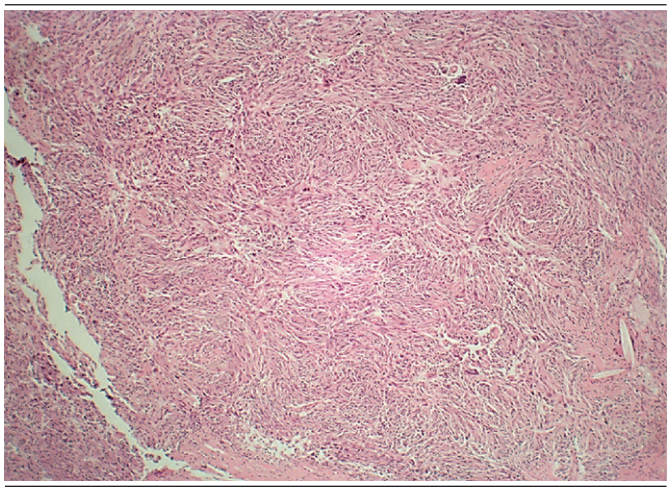

FIGURE 7 – *FDCS*

Whorling bundles and fascicles of tumor cells are admixed with adjacent lymphoid infiltrates.

FDCS: follicular dendritic cell sarcoma.

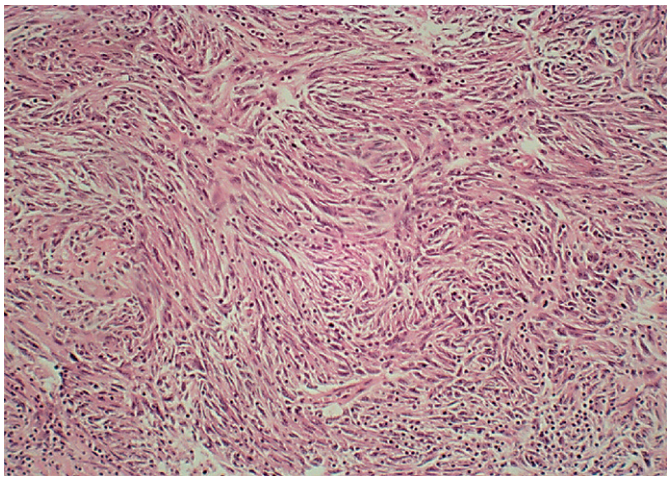

FIGURE 8 – *FDCS*

Spindle tumor cells are admixed with numerous lymphocytes.

FDCS: follicular dendritic cell sarcoma.

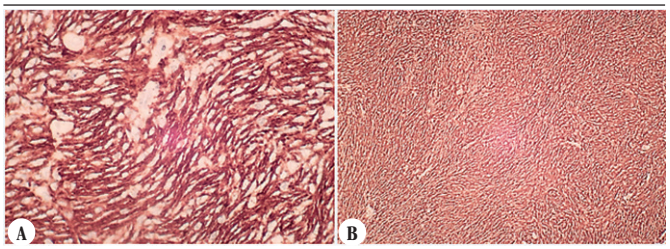

FIGURE 9 – *FDCS*

Immunohistochemical staining shows that this neoplasm is positive for CD21 (A) and CD23 (B).

FDCS: follicular dendritic cell sarcoma; CD21: ; CD23: .

DISCUSSION

FDC are accessory cells of the lymphoid system. Their main function is to trap and present antigens to B cells and immune complexes[1, 2]. Tumor arising from this cell is very rare, and is named FDCS, which was first reported by Monda *et al*.[3]. The origin of FDC has been subject of heavy debates and speculations and remains unclear. In the past, it was believed that they had hematopoietic origin, however the ultrastructure, cytology, and immunophenotype of FDC do not support an hematopoietic origin, but favor a mesenchymal origin and raise the issue of whether they arise from further differentiation of local fibroblastic reticular cell[5] or from migration of mesenchymal cell, probably from the bone marrow[5] or from vascular mural cells[6].

At present, 31% of patient had only nodal disease, 58% cases of isolated extranodal, and 11% had both nodal and extranodal involvement. In addition, the disease has been reported in a huge number of extranodal sites. Cervical lymph nodes were the most frequently affected nodal sites. Only 13 cases were described in the mesentery[7].

Most patients with FDCS present slowly enlarging, painless, asymptomatic mass[6]. Approximately 10% of patients present fever or weight loss[8]. Abdominal pain was the most common symptom for most patients with abdominal involvement, followed by systemic symptoms (i.e., fever, weight loss, fatigue, intestinal obstruction, rectal bleeding, and dyspepsia). We can highlight that 11 patients with abdominal disease were asymptomatic and almost always incidentally diagnosed[3].

The initial diagnosis of FDCS is based on clinical examination, imaging, and pathological assessment. Imaging investigation provides delineation of the extent of the mass and staging. Ultrasound and CT are usually the initial imaging modalities of choice used in the evaluation of patients. CT shows smaller relatively homogeneous masses; however, heterogeneity as a result of necrosis or hemorrhagic areas has been reported in more than 80% cases[9].

Etiopathogenesis of FDCS remains unclear. Castleman disease, which is a benign lymphoproliferative disorder, has been suggested as a precursor lesion for this tumor. As in the hyperplasia-dysplasia-neoplasia sequence proposed for development of some epithelial neoplasms, FDCS may occur in lymph nodes harboring dysplastic FDC in Castleman disease. Additionally, some studies have reported clonal expansion of FDC in Castleman disease[10]. Epestein-Barr virus is involved in pathogenesis of a small subset of FDCS cases, but most of them were reported as "inflammatory pseudotumor-like follicular dendritic cell sarcoma"[11]. It is a variant of FDCS with different clinical and pathologic features. Due to the rarity of EBV infection associated with classical FDCS[12], the pathogenesis of this variant may be different. There are many reports suggesting an association between FDCS and autoimmunity.

Pathological diagnosis is challenging[12] and may require a combination of morphological, immunophenotypical, cytochemical, and electron microscopic analyses[8, 13]. On gross pathology, FDCSs are well-circumscribed with a tan cut surface and areas of necrosis and cystic change in larger tumors. On microscopy, plump spindled to ovoid cells with eosinophilic cytoplasm and distinct cell borders are arranged in a fascicular, whorled or storiform pattern, typically infiltrated by scattered

small lymphocytes[10]. Saygin *et al*.[5] describe morphological features of 16 cases available for analysis. Among them, 75% cases demonstrated classical features with whorls, fascicular or storiform pattern. One case with this pattern presented nuclear pseudoinclusions which is far more common in FDCS. Fiveteen from the 16 patients had lymphoplasmacytic infiltration, epithelioid cells were observed in 18.7% cases (3 from 16). Giant cells were present in 25% cases (4 from 16).

IHC (immunohistochemistry) is required to confirm the diagnosis. FDCS usually show reactivity for CD21, CD23 and CD35[13]. However, diagnosis may be difficult, mainly because follicular dendritic cell markers are not included in a routine IHC panel and, it may require pathology expert review[8]. They are identified by positive immunohistochemical staining for CD21 (C3d receptor), CD23, CD35 (C3b receptor), R4/23, Ki-M4, Ki-M4p, and Ki-FDC1p[14]. To summarize the literature, CD21 and CD35 are the most widely markers used. Other useful markers are vimetin, CD23, CD68, S100 protein, fascin, Ki-M4p and Ki-FDC1p; however, these are unspecific. FDCS typically lacks expression of CD1a, desmin and CD45, which allows their differential diagnosis from interdigitating dendritic cell sarcoma, langerhans cell tumors, histiocytic and lymphoid neoplasias. Therefore, the expression of non-typical FDCS markers should be taken into account in the differential diagnosis from other neoplasms. The diagnosis of FDC tumor is established based on morphology and IHC findings. Ultrastructural studies may be helpful, but are not indispensable for accurate diagnosis. All neoplams in the differential diagnosis lack follicular dendritic cell differentiation and are easily excluded if FDCS is considered and IHC staining with FDC marker is applied[15].

Detailed review of all cases indicated that at least 18.6% of patients (64 from 343) were erroneously diagnosed at the presentation. Entities most commonly confused with FDCS included undifferentiated carcinoma, lymphoma, malignant fibrous histiocytoma, peripheral nerve sheath tumor, ectopic meningioma, inflammatory pseudotumor, granulomatous inflammation, gastrointestinal stromal tumor, and unclassified sarcoma[16].

Local recurrence and/or distant metastasis occurred in 44.6% of patients after initial treatment. Sxty-three patients (28.1%) experienced local recurrence at a median time of 15 months, and 61 cases (27.2%) developed distant metastasis at a median time of 18.5 months. Twenty-four patients had local and distant recurrence at the same time. Common sites of metastasis were lung (9.4%), lymph nodes (8.9%), liver (9.4%), and bone (3%)[17]. Similar to other soft tissue sarcomas, large tumor size (≥ 6 cm), presence of coagulative necrosis, high mitotic counts (≥ 5 per 10 high-power fields), and significant cytologic atypia were shown to be associated with poor prognosis[18]. Younger age, abdominal involvement, sparse inflammatory infiltrate are also poor prognostic factors[19].

In recent years, dendritic cell tumors have been increasingly recognized by pathologists with a difficult management for oncologists. Some treat FDS with an aggressive lymphoma regimen, which often includes chemotherapy, whereas others treat FDS as a soft tissue sarcoma, with wide resection and adjuvant radiotherapy[18]. Surgery should be the mainstay of treatment for early FDCS cases, since patients treated with surgery had better overall survival when compared to other treatment modalities. However, adjuvant radiotherapy did not have a significant influence on overall survival. Prior studies have also demonstrated that adjuvant treatments had no significant effect on disease-free survival after a radical surgical resection[20]. Therefore, meticulous examination of excised specimens for surgical margins and extra-capsular infiltration is highly recommended. On the other hand, the number of patients with locally advanced and distant metastatic disease was low and the treatment received varied. In most of these cases, surgery was performed to reduce tumor burden. The role of surgery in late disease is not clear, only 2 from 23 patients who received combined adjuvant chemotherapy and radiotherapy succumbed to the disease (both had metastatic disease at onset). This highlights the importance of adjuvant therapies in advanced FDCS patients[20].

In conclusion, FDCS is a rare entity that can clinically mimic other tumors. Identification of a different pattern of histopathological features requires further analysis with immunohistochemical stains for follicular dendritic cells. Proper characterization and treatment planning are mandatory due to their recurrent and metastatic potential. Wide local surgical resection is the primary treatment. The role of adjuvant therapy has not yet been clearly defined in the treatment of this neoplasm, but has been indicated in cases showing adverse pathological features and for recurrent or unresectable lesions. Longer and larger studies or additional case reports are needed in order to overcome the difficulties in diagnosis and treatment of such rare tumors.

RESUMO

Sarcoma de células dendríticas foliculares é uma neoplasia rara, descrita pela primeira vez em 1986 por Monda. Caso 1: Paciente do sexo feminino, 50 anos, realizou tomografia computadorizada de abdômen que detectou lesão tumoral de 8,0 cm em mesentério. Foi submetida à ressecção da lesão. A microscopia revelou neoplasia epitelioide, com linfócitos de permeio e expressão imuno-histoquímica de CD21 e CD35. A paciente foi submetida à quimioterapia adjuvante. Caso 2: Paciente do sexo masculino, 21 anos, com massa cervical direita medindo 7,0 cm. A biópsia evidenciou proliferação de células fusiformes, com infiltrado inflamatório de permeio e arranjo estoriforme, com expressão imuno-histoquímica de CD21 e CD23. O paciente foi submetido a radioterapia neoadjuvante e ressecção cirúrgica.

Unitermos: *células dendríticas foliculares; neoplasias de células dendríticas; sarcoma de células dendríticas foliculares; patologia.*

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