



Case studies

# Classic follicular dendritic reticulum cell tumor of the lymph node developing in a patient with a previous inflammatory pseudotumor–like proliferation

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## Keywords:

Follicular dendritic reticulum cell tumor;  
Inflammatory pseudotumor;  
Lymph node

**Summary** Inflammatory pseudotumor (IPT) and follicular dendritic reticulum cell tumor (FDRCT) are rare entities of the lymph node characterized by spindle-cell proliferation. We report a case of a 31-year-old woman, who was admitted for biopsy of a lymph node in the left submandibular area. The microscopic examination revealed a proliferation of spindle cells, partially replacing the normal lymph node architecture, suggestive of an IPT. The preserved peripheral portion showed follicular hyperplasia with Castleman-like appearance. Six years later she presented with a new enlargement in the same submandibular area. The nodule was removed, and a diagnosis of a classic FDRCT of the lymph node was made. The present case is remarkable, and clinicopathological data show that IPT-like proliferations could be in some case an early presentation of FDRCT.

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## 1. Introduction

Follicular dendritic reticulum cell tumor (FDRCT) of the lymph node is a malignant neoplasm made up of cells immunophenotypically and ultrastructurally consistent with follicular dendritic reticulum cells (FDRCs) normally

present in the B areas of the lymph node [1]. It was described in 1986 by Monda et al [2], and as far as we know only a limited number of cases have been reported at the moment, and little is known on its early histological phases and the clinical context of the development of this tumor [3,4]. We report a case of FDRCT showing an unusual presentation that could help to identify its early phases and histological precursors.

## 2. Case report

The patient, a 31-year-old woman, first presented with a 5-month history of progressive, submandibular lymph node

*Abbreviations:* IPT, inflammatory pseudotumor; FDRCT, follicular dendritic reticulum cell tumor; FDRCs, follicular dendritic reticulum cells; IHC, immunohistochemistry; EM, electron microscopy; PR, progesterone receptor; ER, estrogen receptor.

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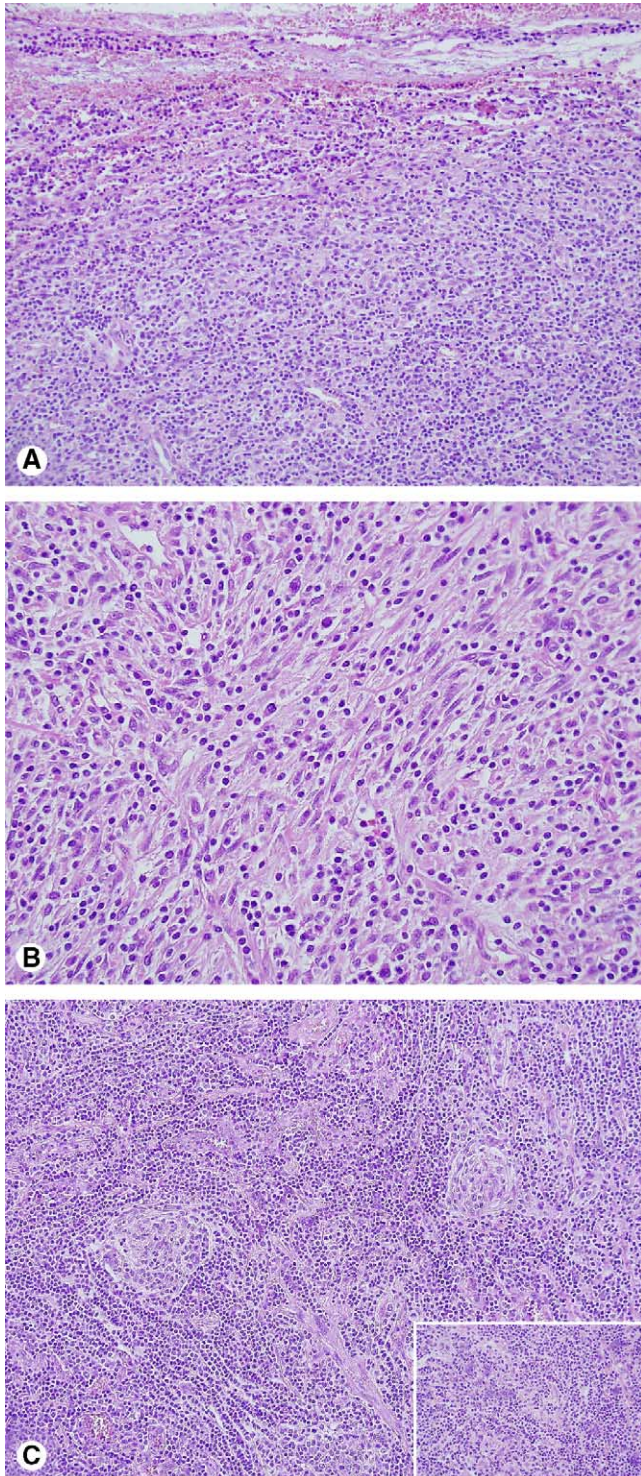
enlargement. At that time she was in the eighth month of pregnancy. On admission, no constitutional symptoms were found. Laboratory investigations were within the normal limits except for mild anemia. The lymph node was excised and the specimen consisted of a solid, capsulated lump, 5 cm in diameter. Microscopically, the enlarged lymph node had been extensively replaced by spindle-cell proliferation; the subcapsular sinus was focally recognizable and the

capsule was not infiltrated (Fig. 1A). The spindle cells were intermingled with mature lymphocytes, immunoblasts, and a few plasma cells. The proliferating cells formed bundles arranged in parallel or storiform patterns, and showed abundant, spindle eosinophilic cytoplasm, elongated nuclei, and occasional small nucleoli (Fig. 1B). A prominent proliferation of small vessels was also appreciable. On immunohistochemistry (IHC), the spindle cells proved to be diffusely positive only for vimentin. In addition, groups of irregularly and loosely arranged CD21-positive cells as well as numerous cells positive for S-100 protein, MAC 387, and CD68 were scattered in between. The lymphocytes were both of the B- or T-cell type.

A small lymph node adjacent to the first one showed a well-preserved architecture with sinuses and lymphoid follicles. The follicles were uniformly oval or round, with prominent germinal centers centered by small vessels and with mantle zone lymphocytes arranged in a targetoid pattern (Fig. 1C). Germinal center cells showed some atypia and multinucleated cells with irregularly clumping chromatin, and prominent nucleoli were scattered in perfollicular areas (Fig. 1C, inset). A florid proliferation of postcapillary venules was also appreciable. Immunohistochemistry revealed an intense proliferation of CD21-positive FDRCS in follicles.

On the basis of the morphology and the IHC results, and in view of the absence of capsular infiltration and the lack of “phlebitis,” a descriptive diagnosis of inflammatory pseudotumor (IPT)–like condition of the lymph node associated with a Castleman-like reaction in an adjacent lymph node was made.

A bone marrow biopsy was interpreted as normal, and the patient did not receive any therapy but a careful follow-up was scheduled. After a normal delivery, the patient was submitted to extensive clinical, x-ray, and computerized tomography scan investigations, which did not disclose any lesions in other sites. She remained in good health for 6 years until she developed a lump in the cervical area of the previous excision that rapidly grew to 3 cm in diameter. She was in the second month of a new pregnancy. A lymph node was removed, and, histologically, it showed a diffuse replacement of the normal architecture by a neoplastic proliferation of spindle or epithelioid-like cells arranged in sheets or fascicles, occasionally whorling. The



**Fig. 1** Typical histological features of IPT. (A) Proliferation of spindle cells diffusely involving the lymph node with a relative sparing of the subcapsular sinus. (B) High-power view showing spindle cells diffusely sprinkled with small lymphocytes and plasma cells. Proliferating cells have a moderate amount of eosinophilic cytoplasm with elongated nuclei and inconspicuous nucleoli. (C) Castleman-like histological features in a lymph node contiguous to that involving IPT. Two germinal centers with a perfollicular cuffing of small lymphocytes and (inset) multinucleated cells with prominent nucleoli scattered in perfollicular areas. (Hematoxylin and eosin).



capsule was infiltrated and the subcapsular sinus was totally obliterated. The cells were uniformly large, closely packed, and showed a moderately abundant cytoplasm occasionally with granular inclusions (Fig. 2A). The nuclei were plump, oval, with prominent nucleoli and dispersed clumps of chromatin, and showed frequent invaginations, pseudoinclusions, and numerous mitoses ( $20 \times 10$  HPF) (Fig. 2B). A lymphoid and plasma cell infiltrate was present in the tumor.

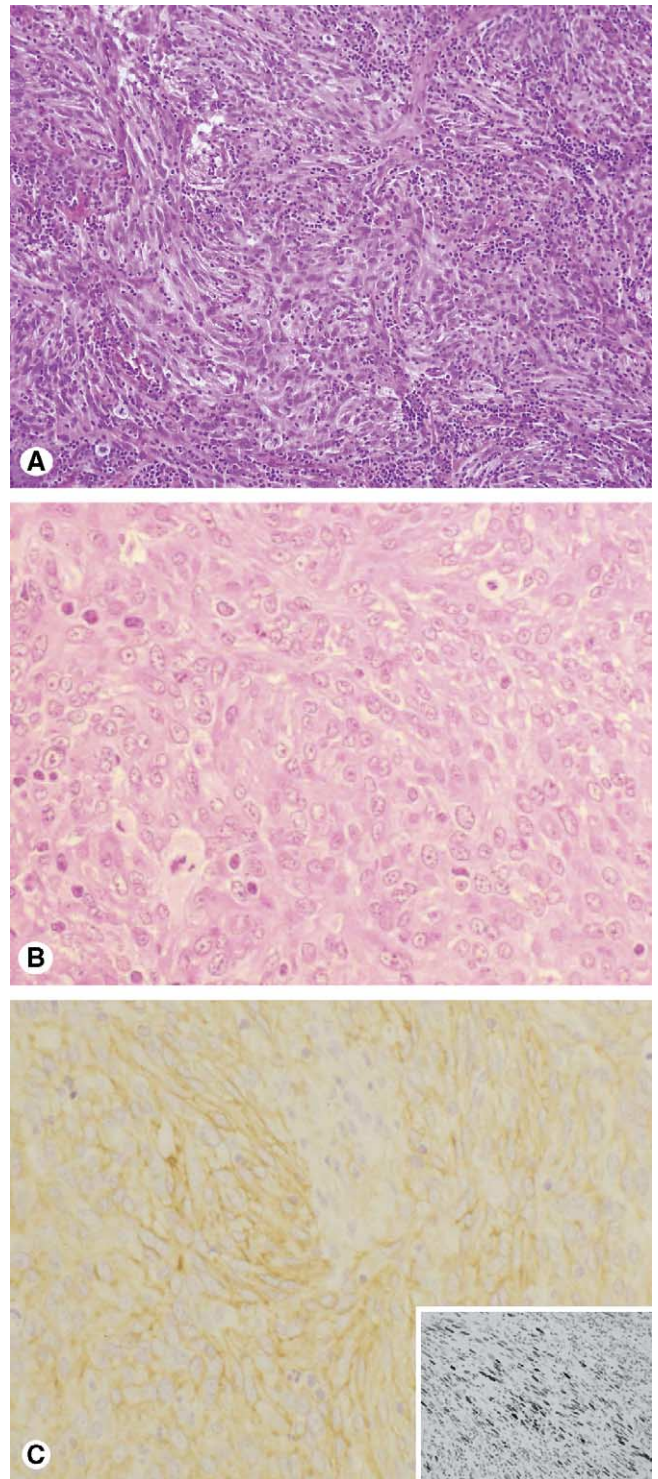
Immunostaining showed the proliferating cells to be strongly positive for CD21 (Fig. 2C), CD35, and smooth muscle actin, but negative for cytokeratins, S-100 protein, CD45, and epithelial membrane antigen. Also, there was a diffuse nuclear positivity for progesterone receptor (PR) antibody (Fig. 2C, inset); estrogen receptor (ER) antibody was negative.

On electron microscopy (EM), the cells showed plump, oval nuclei, smoothly contoured with finely dispersed heterochromatin and prominent nucleoli. The cytoplasm contained scattered ribosomes and polyribosomes, poorly developed rough endoplasmic reticulum, rare mitochondria, and inconspicuous Golgi complex. The most striking feature of the tumor cells was the presence of long cytoplasmic projections that formed an intricate interdigitate complex (Fig. 3). Most of these interdigitations were connected to each other by numerous cell junctions (desmosome type) (Fig. 3, inset). Other peculiar findings were the presence of large amounts of finely granular material often in a perinuclear position and the occurrence of labyrinth-like structures as often seen in active normal FDRCs. Basal lamina, tonofilaments, dense core, secretory granules, and melanosomes were not identified.

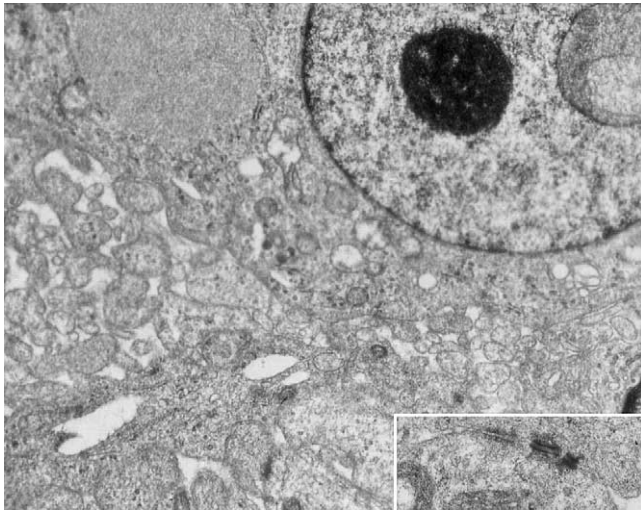
On the basis of light microscopy, IHC, and EM, a diagnosis of FDRCT was confidently made. A review of the slides of the first specimens induced to perform an EM investigation on the paraffin-embedded material. These studies showed that although the spindle proliferating cells were badly preserved some desmosomes were recognizable in a few of such cells.

In situ hybridization with Epstein-Barr virus-encoded RNA (EBER) oligonucleotides was used to test the presence of EBV in formalin-fixed, paraffin-embedded specimens of both lesions, but no positive signals were identified.

She underwent voluntary abortion and after exclusion of bone marrow and other nodal involvement was treated with local radiotherapy (5040 cGy). Two years later, a chest x-ray and computed tomography revealed the presence of multiple nodular opacities in both lungs; furthermore, an osteolytic lesion of the frontal bone was disclosed. A surgical removal of the frontal mass and a diagnosis of dendritic cell sarcoma were made. She underwent polychemotherapy and radiotherapy (5000 cGy) of the frontal area. Two months later, a surgical removal of the lung metastases was performed and histological examination confirmed the clinical diagnosis. After 6 months, she



**Fig. 2** Follicular dendritic reticulum cell tumor disclosing (A) proliferation of plump ovoid cells disposed in short fascicles with a vague storiform pattern and (B) neoplastic spindle cells with remarkable nuclear irregular foldings and distinct nucleoli; mitotic figures are also visible (hematoxylin and eosin). (C) Immunohistochemical staining for CD21 and (inset) PR shows positivity of the proliferating spindle cells in FDRCT. (Immunoperoxidase).



**Fig. 3** Ultrastructure of FDRCT. The spindle cells show an evident small nucleolus, scattered intracytoplasmic organelles, and (inset) cell membrane with well-formed desmosomes. (Electron micrograph).

developed a metastasis in the right sacrum-iliac joint that was treated with local radiotherapy (4500 cGy). Two months later, the follow-up showed other metastatic pulmonary lesions and she underwent high dose chemotherapy and mediastinal radiotherapy (5000 cGy). After 1 year, bone metastases at L2 and left femur level were evidenced, the patient's condition progressed rapidly and she died, 4 years after the diagnosis of FDRCT and 10 years after the IPT-like lesion.

### 3. Discussion

Follicular dendritic reticulum cell tumor is a rare tumor included in the World Health Organization classification of hematopoietic and lymphoid tissue among the histiocytic and dendritic cell neoplasms [5,6]. This entity has been described in 1986 [2], and, subsequently, only about 60 well-documented cases have been reported, primarily in lymph node but also in extranodal sites [7].

In the current case the relationship between the first lesion and FDRCT appears to be of interest. Follicular dendritic reticulum cell tumor appeared 6 years later, in the same site of the first biopsy and with the same clinical pathological context, thus suggesting a recurrence of the lesion having an IPT-like appearance. Actually, both these conditions share the proliferation of spindle cells intermingled with mature lymphocytes and some plasma cells [2,8-10]. However, the cytology of the 2 conditions is very different; in fact, IPT is a benign-appearing disease with inconspicuous nuclei and nucleoli; on the contrary, FDRCT is a neoplastic lesion characterized by atypical proliferating cells, although it is well known that great variability of the atypicity is described

in FDRCT [2]. The immunohistochemistry of the first lump shows only small and loose aggregates of CD21-positive cells, whereas in the typical appearance of FDRCT the positivity for CD21 and CD35 is diffuse. The EM findings of both specimens show desmosomes between the proliferating cells.

In 1994, FDRCT associated to Castleman-like reaction in the same lymph node was reported by Chan et al [11]; they suggested that the dysplastic dendritic cells occurring in Castleman-type proliferation can form the background from which FDRCT can originate. In our case, in the lymph node adjacent to the IPT-like lesion a Castleman type of proliferation was present.

In conclusion, the clinical-pathological presentation and EM findings of our case suggest that IPT-like appearance associated with Castleman-type disorder could be a very early presentation of FDRCT. On the other hand, an inflammatory pseudotumor-like FDRCT has been already reported in the liver and peripancreatic region [12], and Shek et al [13] described an FDRCT of the liver that was previously misdiagnosed as an IPT. All these observations suggest that IPT- and IPT-like proliferations of the lymph node should be carefully followed up for a long time, because it could hide a very early presentation of FDRCT.

It is of some interest that in our patient both lesions presented and quickly developed during pregnancy. Such an occurrence appears to be more than coincidental and suggests that hormonal factors could play some role in the development and growth of these tumors. We investigated for ER and PR expression and found positivity for PR in the proliferating cells of the second specimen. The role exerted by the sex steroids on the development of IPT and FDRCT should be further investigated also in the light of the recent observation that ER  $\alpha$  is a novel marker expressed by FDRCs [14].

The clinical behavior of FDRCT is variable and difficult to predict, and optimal therapies have not yet been identified. The vast majority of patients have been treated with surgery, usually followed by radiotherapy and eventually chemotherapy. Our patient showed some benefit with radiotherapy and chemotherapy but subsequently had progressive worsening and died of the disease 4 years after the second diagnosis. Due to the limited number of cases reported survival statistics are inadequate; however, the best treatment for these tumors seems to be surgical resection; the role of adjuvant therapy remains controversial, but because of the high recurrence rates and metastatic potential of the tumor we believe that radiotherapy and eventually chemotherapy should follow the surgical resection. Interestingly, recently a consistent expression of epidermal growth factor receptor has been demonstrated in FDRCT [15]; this finding could open the possibility to use antibodies and inhibitors targeting epidermal growth factor receptor as treatments for FDRCT refractory to the usual therapies.



## Acknowledgments

Histological diagnosis of inflammatory pseudotumor was kindly confirmed by Dr. Glauco Frizzera. We are grateful to Dr. Juan Rosai for having reviewed the follicular dendritic reticulum cell tumor.

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