

Intra-muscular follicular dendritic cell sarcoma in the thigh

A case report

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Abstract

Rationale: Follicular dendritic cell sarcoma (FDCS) is an intermediate-grade malignancy originating from follicular dendritic cells. Nodal FDCS is the most common type, meaning that the extranodal type may not be recognized and could be easily misdiagnosed. Reported extranodal sites include the head and neck, retroperitoneum, spleen, liver, and gastrointestinal tract. FDCS in the soft tissue is extremely rare.

Patient concerns: A 75-year-old male presented with complaints of a localized swelling and intra-muscular soft tissue mass in the left upper thigh.

Diagnosis: The present tumor consisted of fascicular or vague storiform-arranged spindle cells with less pleomorphism and many lymphoid aggregates. Tumor cells were positive for CD21, CD35, CD68, vimentin, and EGFR. Intra-muscular FDCS was confirmed by immunohistochemical studies.

Interventions: The patient received a wide marginal excision, followed by adjuvant radiotherapy.

Outcomes: Symptomatic improvements were achieved and no subsequent relapses were observed.

Lessons: If the tumor arises in the extranodal sites, especially in the soft tissue, it is difficult to include FDCS in the differential diagnosis. When the immunoprofile is not consistent with that of common spindle cell tumors, immunostaining for follicular dendritic cell markers such as CD21, CD23, and CD35, as well as further immunohistochemistry for D2-40, CD68, EGFR, Epstein-Barr virus, and BRAF can be helpful for the diagnosis and subtyping of FDCS. To the best of our knowledge, the present case is the first case of intramuscular FDCS.

Abbreviations: EBV = Epstein-Barr virus, FDCS = follicular dendritic cell sarcoma, IPT = inflammatory pseudotumor.

Keywords: extranodal, follicular dendritic cell sarcoma, intra-muscular, soft tissue, thigh

1. Introduction

Follicular dendritic cell sarcoma (FDCS) is an extremely rare intermediate-grade malignancy originating from follicular dendritic cells (FDCs), which are essential for the formation of lymphoid follicles comprising B cells. Accordingly, FDCS

involves lymph nodes and constitutive lymphoid tissue, as well as acquired lymphoid tissue. Although most lymphoid-associated dendritic cells are of myeloid origin, FDCs are regarded to be of mesenchymal origin.^[1,2] Since its discovery in 1986, FDCS has been reported to generally occur in lymph nodes, with less than one-third cases of FDCS having been described in extranodal sites.^[3,4] The most common extranodal sites are the intra-abdominal organs, followed by the head and neck; however, involvement of the thorax, thyroid, skin, and breast has also been reported. Although FDCS usually exhibits indolent behavior, intra-abdominal cases show more aggressive clinical behavior.^[1,5,6] As an extremely rare tumor, FDCS occurring in extranodal sites has occasionally been misdiagnosed, as it is rarely considered in the differential diagnosis. FDCS occurs in all age groups, but is most frequently observed in young to middle-aged adults, with no sex predilection.^[1,7]

In the English literature, 1 case of FDCS has been reported in the extremities, with a tumor found in the thigh of a 6-year-old female. Although further detailed information on clinical presentation, including the specific location within the thigh, was missing, considering the histologic pattern described as “interlacing fascicles of spindle cells with sprinkling of lymphocytes” and the referring pathologist’s diagnosis reported as spindle cell sarcoma, this case seems to be classic type FDCS.^[6]

Here, we report the case of a tumor consisting of vague storiform and fascicular arrangement of plump spindle cells, presenting as an intra- and inter-muscular lesion of the thigh,

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which was diagnosed as FDCCS based on the positive immunoreactivity for the FDC markers CD21 and CD35. In addition, mature lymphocytes sprinkled throughout the tumor or forming dispersed aggregates were reminiscent of inflammatory pseudotumor (IPT), leading to the differential diagnosis of IPT-like FDCCS. In light of its rarity and unusual clinical presentation, we report the first case of FDCCS presenting as an intra-muscular lesion in the extremity, in addition to a review of the relevant literature.

2. Case report

This study was approved by the institutional review board of the Chosun University Hospital (Permission number: CHOSUN 2021-02-006). Informed written consents were obtained from the patients for publication of this case report and accompanying images.

A 75-year-old male presented with complaints of a localized swelling and mass in the left upper thigh. Although the lesion had been recognized about 11 months prior, treatment was not administered until the patient visited a local clinic 3 months ago, owing to gradual growth of the lesion. A 5 × 5 cm mass was detected upon ultrasonography, and the patient was subsequently advised to visit our hospital. No history of trauma or inflammation was reported, and the patient complained of no specific pain except discomfort when sitting down. Past medical history included hypertension for 15 years, diabetes for 20 years, and benign prostatic hyperplasia. The patient had received surgery for lumbar vertebral disc herniation 12 years ago and total knee arthroplasty on both knee joints 6 years ago. No significant weight change, fever, or fatigue were noted.

Magnetic resonance images showed a 12.5 × 6 × 3.5 cm sized irregular abnormal signal intensity and vividly enhanced space indicating a soft tissue mass in the left posterior thigh, surrounded by the semimembranosus muscle and semitendinosus muscle. This inter- and intra-muscular lesion had invaded the superficial investing fascia and adjacent sciatic neurovascular bundle (Fig. 1). The clinical impression was soft tissue sarcoma, and a wide marginal excision was performed. After surgery, the size of the mass invading the adjacent skeletal muscle was found to be 4.5 × 4.5 cm; The larger size observed upon magnetic resonance image may be attributed to fibrosis and the change in muscle fibers induced by tumor invasion. To obtain safety margins, mass resection including the adjacent normal skeletal muscle was performed. However, since the tumor encircled the sciatic nerve and adhered to the nerve sheath, complete surgical resection was impossible, and a residual lesion was therefore left in the region abutting the sciatic nerve.

Upon histopathologic examination, the mass was found to be unencapsulated and showed an infiltrative growth into the adjacent skeletal muscle (Fig. 2). The tumor was composed of an admixture of chronic inflammatory cells and spindle cells. The spindle cells were haphazardly distributed or arranged in vague fascicles or a storiform pattern. The chronic inflammatory cells mostly consisted of mature lymphocytes and plasma cells, and the main cellular component was spindle cells with sprinkled lymphocytes (Fig. 3A), with lymphocytes distributed in aggregates (Fig. 3B). This growth pattern was considered similar to that of IPT. At high power, the spindle cells showed an indistinct cell membrane and were found to be eosinophilic with slightly fibrillar cytoplasm. The nuclei were elongated and vesicular, and some were irregularly twisted. Although cellular pleomorphism

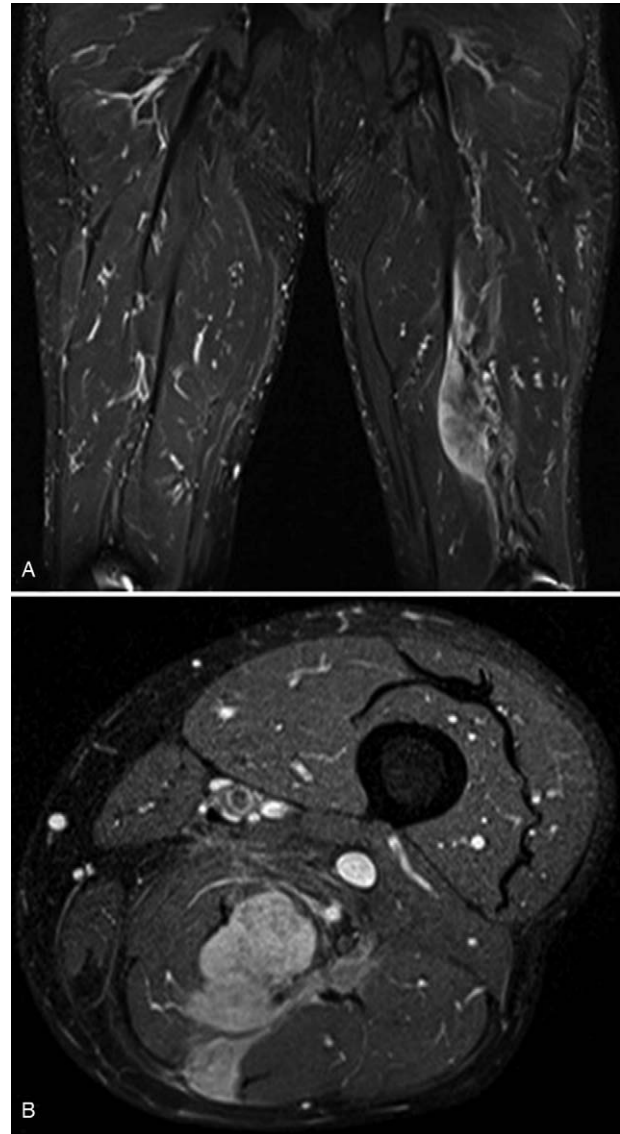


Figure 1. MRI showed a 12.5 × 6 × 3.5 cm sized irregular abnormal signal intensity with a vivid, enhancing soft tissue mass in the left posterior thigh, along the semimembranosus and semitendinosus muscle. MRI = magnetic resonance image.

was minimal, based on small nucleoli, cytologic atypia, and occasional atypical mitoses (averaged 2/10 high power fields), spindle cell sarcoma was considered (Fig. 3C). No necrosis was observed. Immunohistochemically, the spindle cells showed diffuse positivity for CD21, CD35, CD68, vimentin, and EGFR (Fig. 4 A, B), and focal positivity for D2-40 (podoplanin) and EMA. The spindle cells were negative for α -smooth muscle actin, ALK, CD23, CD34, BRAF, Epstein-Barr virus (EBV) Epstein-Barr virus-encoded small RNAs (EBER), and S-100 protein and had a Ki-67 labelling index of 43% (Fig. 4C). The background lymphocytes were mainly CD3-positive, sometimes CD20-positive, and EBV-negative. Presence of the BRAF V600E mutation was investigated via real-time polymerase chain reaction of the paraffin-embedded tissue block; however, no mutation was detected. In addition, the presence of mutations in EGFR on chromosome 7p11.2 was examined using polymerase chain reaction and pyrosequencing; no mutations were identified

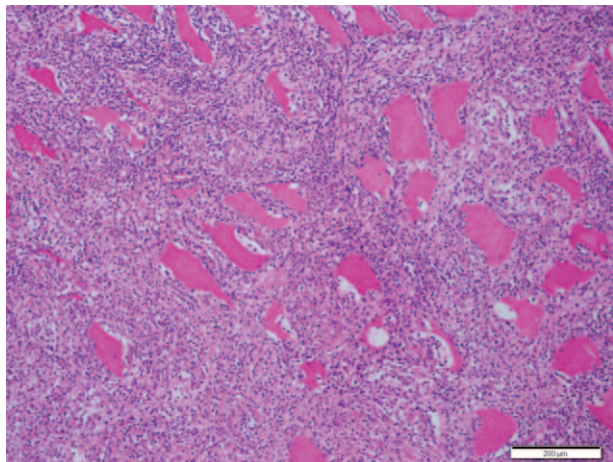


Figure 2. Histopathological findings of intra-muscular mass. It was found to be unencapsulated and showed an infiltrative growth into the adjacent skeletal muscle. Scale bar measures 200 μm.

in exons 18, 19, 20, and 21. Taken together, the final diagnosis was extranodal FDCC, showing an extremely rare clinical presentation.

The patient received adjuvant radiotherapy at 3.5 weeks after surgery. The radiation dose was 180 to 200 cGy daily in 5 fractions/week, resulting in a total dose of 66 to 70 Gy/7 weeks. As of now, no signs of recurrence have been observed after 14 months of surgery.

3. Discussion

FDCC, the most common histologic subtype of dendritic cell tumors, is an intermediate-grade sarcoma with a propensity for local recurrence (28.1%) and distant metastasis (27.2%). Similar to that in other soft tissue sarcomas, it is known that tumor size of ≥ 6 cm, the presence of tumor necrosis, high mitotic count (≥5/10 high-power fields), and cytologic atypia are associated with poor prognosis,^[8,9] although 1 prior study reported that tumor necrosis has no association with prognosis.^[10]

According to histological morphology, FDCC can be classified into the classic type and the IPT-like type. IPT-like FDCC is much rarer than classic FDCC and has distinctive features. IPT-like FDCC occurs mainly in the liver and spleen, has a marked female predilection (F:M=2.2:1), and rarely recurs or metastasizes.^[7,11,12] Regarding the aspects of histological morphology and biological behavior, IPT-like FDCC is considered to be completely different from the classic type and is consistently associated with EBV, and present in monoclonal episomal state.^[7,11-13] Present case showed EBV negativity by EBER, so IPT-like FDCC could be ruled out. Moreover, the lymphoid infiltrate in this case did not appear heavy, only sprinkling with occasional aggregates. Such a lymphoplasmacytic infiltrate is typically seen in classic FDCC. No significant eosinophilic infiltrate is noted either. If the tumor has a heavy lymphoplasmacytic infiltrate with or without eosinophils, obscuring the neoplastic FDCCs and really mimicking ‘inflammatory pseudotumor’, IPT-like FDCC could be considered as a differential diagnosis.

It is difficult to diagnose FDCC in cases where the tumor consists of bland spindle cells with no nuclear atypia admixed with chronic inflammatory infiltrates and is present in extranodal

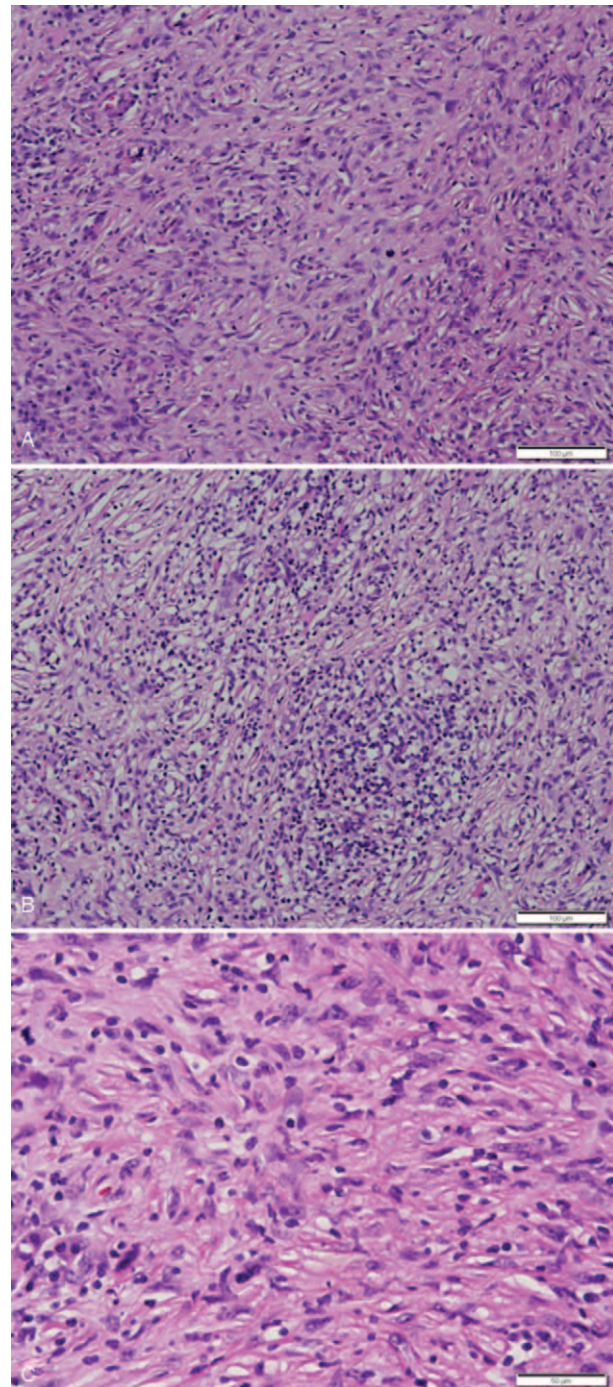


Figure 3. Histopathological findings of follicular dendritic cell sarcoma. (A) The tumor consisted of spindle cells forming short storiform and vague interlacing fascicles with sprinkled lymphocytes. (B) The tumor showed less cellularity with lymphoid aggregates. (C) A high-power view of the area in A shows spindle cells composed of elongated, vesicular, sometimes irregularly twisted, nuclei with small nucleoli and occasional atypical mitosis. Scale bars measure 100 μm (A, B) and 50 μm (C).

sites. In the present case, the tumor consisted of spindle cells, forming vague fascicles and storiform patterns, and lymphoplasmacytic cells, which were reminiscent of IPT, thus indicative of an inflammatory myofibroblastic tumor. However, the results of immunohistochemical staining showed α-smooth muscle actin negativity, based on which other tumors should be considered in

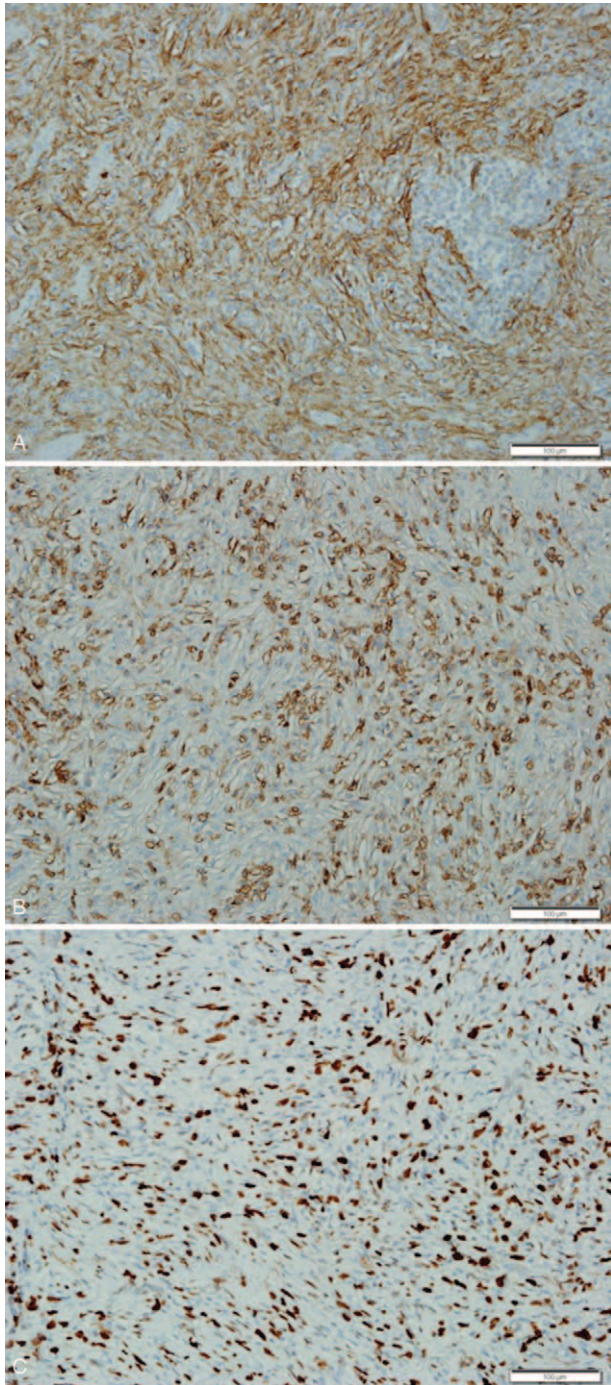


Figure 4. Immunohistochemical findings. (A) Spindle cells showed positivity for CD21, but not in the lymphoid aggregates. (B) Spindle cells showed positivity for CD35. (C) Ki-67 labelling index showed expression in 43% of the tumor cells. Scale bars indicate 100 μ m.

the differential diagnosis. Despite minimal cellular pleomorphism, the cytologic atypia and occasional atypical mitoses (averaged 2/10 high-power fields) warranted the consideration of a malignant spindle cell tumor. Since additional immunohistochemical staining showed negativity for S-100 protein and positivity for vimentin, FDCS was considered despite its rarity. Based on the strong reactivity for CD21, CD35 and CD68, and EBV negativity by EBER in spindle cells, a diagnosis of FDCS was

made. Likewise, discordant diagnoses are common in the initial evaluation of IPT-like FDCS, which have been misdiagnosed as Hodgkin lymphoma,^[14] malignant fibrous histiocytoma,^[15] and myofibroblastic tumor.^[11,16] Therefore, when an unusual immunoprofile is observed upon the immunohistochemical examination of a malignant spindle cell tumor, additional immunostaining for CD21, CD23, CD35 could be helpful to rule out FDCS, although this tumor is rare. In addition, 1 study reported that the spindle cells of FDCS show strong, diffuse immunoreactivity for D2-40, with a membranous and cytoplasmic staining pattern, suggesting D2-40 as a highly sensitive marker^[17]; in the present case, D2-40 showed a focal positivity.

Although BRAF mutations can be found in both the classic and IPT-like types (18.5%), it was reported that the mutation is markedly observed in the IPT-like type (40%) and, accordingly, could be helpful to distinguish between the 2 types.^[18] BRAF mutation was not detected in the present case. It has been reported that the spindle cells in FDCS are positive for CD68^[8,19] and EGFR^[4,20] on immunohistochemical staining; additionally, the key role played by EGFR in the tumorigenesis of FDCS by driving the survival and proliferation of tumor cells has been previously verified.^[20] In the present case, immunohistochemical staining revealed positivity for CD68 and EGFR, although no EGFR mutation was found.

Extranodal FDCS is extremely rare and generally affects the intra-abdominal organs and the head and neck. In addition, there have been scattered reports on its occurrence in the retroperitoneum, paratracheal region, lung, mesentery, thyroid, parotid, paravertebral region, orbit, nasopharynx, and mediastinum. Moreover, FDCS occurs more rarely in the soft tissue, and only 1 case has been reported in the extremities, which affected the thigh of a 6-year-old girl.^[6] However, since the specific site was not described in this report, the present case seems to be the first intra-muscular FDCS reported in the English literature.

The established treatment protocol for patients with FDCS is not present due to the low incidence and the variable clinical courses. However, main treatment for FDCS is surgical resection in majority of early local cases. Chemotherapy and/or radiotherapy can be applied in advanced cases or incompletely resected tumors.

According to the research report,^[21] 11/23 (48%) patients underwent either adjuvant radiation (9/11, 82%) or neo-adjuvant chemotherapy with doxorubicin and ifosfamide-based regimens (2/11, 18%). The 5-year overall survival for patients who received adjuvant or neo-adjuvant therapies (n=11) and those who were observed (n=12) were 39% and 69%, respectively; however, this difference was not statistically significant ($P=.58$).

In the present case, since the tumor encircled the sciatic nerve and adhered to the nerve sheath, it was impractical to carry out complete removal, and further radiotherapy was performed. This tumor generally has a low recurrence rate and a favorable long-term outcome^[22]; in line with this, the present case has shown no evidence of disease for 14 months after surgery.

4. Conclusion

To the best of our knowledge, only 1 case of FDCS in the thigh has been reported to date. The present case seems to be the first report of intra-muscular FDCS. Regardless of its subtypes, FDCS is an extremely rare tumor, with no characteristic clinical or imaging features. Thus, if the tumor arises in the extranodal sites,

especially in the soft tissue, it is difficult to include FDCC in the differential diagnosis, potentially leading to misdiagnosis. When the immunoprofile is not consistent with that of common spindle cell tumors, immunostaining for FDC markers such as CD21, CD23, and CD35, as well as further immunohistochemistry for D2-40, CD68, EGFR, EBV, and BRAF can be helpful for the diagnosis and subtyping of FDCC.

Author contributions

Data curation: Yong Jin Cho, Song-Iy Han.

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Supervision: Sung-Chul Lim.

Validation: Sung-Chul Lim.

Writing – original draft: Yong Jin Cho.

Writing – review & editing: Song-Iy Han, Sung-Chul Lim.

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