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ORIGINAL RESEARCH

Follicular Dendritic Cell Sarcoma of Gastrointestinal Tract: an Uncommon Lesion, Commonly Missed

Usman Hassan[1,2] · Iftikhar Ali Rana[1] · Sajid Mushtaq[1] · Muhammad Azam[1] · Noreen Akhter[1]

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Abstract

Introduction Follicular dendritic cell sarcoma (FDCS) is a rare neoplasm, accounting for only 0.4% of soft-tissue sarcomas. It shows both nodal and extranodal involvement. Considering the rarity and difficulties in diagnosing this tumor, we consider it very important to share our experience of diagnosing FDCS. Its correct diagnosis cannot be overemphasized as the treatment and prognosis of FDCS are very much different from tumors which come in its differential diagnosis.

Material and Methods We are presenting eight cases of extranodal FDCS in gastrointestinal tract diagnosed at our center in a period of 3 years (Feb 2015 to Feb 2018). Presenting complaints, demographic details, gross description, histologic features, immunostain results, and clinical follow-up were evaluated.

Results Four patients were females and four were males. Tumor ranged in size from 5.5 to 35 cm. In five cases, tumor cells were arranged in storiform and whorling pattern. Lymphocytes were seen sprinkled in between these cells. In one case, lymphocytic infiltrate was extensive. Giant cells and frequent mitoses were noted in two cases. One case showed extensive necrosis. Tumor cells were strongly and diffusely positive for CD21 and CD35. Mean follow up of 11.8 months (range 01 to 24 months) was noted.

Conclusion FDCS is a rare tumor having distinct morphology and phenotype which if known can be correctly diagnosed. Therefore, knowledge of its varied location, morphology, and phenotype is very important to correctly diagnose this tumor and to prevent misdiagnosis and mistreatment.

Keywords Follicular dendritic cell sarcoma · Gastrointestinal tract

Introduction

The existence of follicular dendritic cell tumors was predicted by Lennert [1] in 1978 but follicular dendritic cell sarcoma (FDCS) was first described by Monda et al. in 1986 [2]. Initially, it was considered as nodal disease; however, later studies revealed that this tumor also shows extranodal involvement [3, 4]. This tumor is derived from follicular dendritic cells which are accessory cells of the lymphoid follicles and play important role to maintain the immune system by interacting with B cells [5]. Follicular dendritic cells are found in both nodal and extranodal locations which explain nodal and extranodal involvement by FDCS [6]. Follicular dendritic cell sarcoma can have association with paraneoplastic pemphigus [7, 8] and Castleman disease [9]; however, most FDCS cases occur sporadically [10]. Diagnosis of FDCS in extranodal location is challenging because of its rarity and varied morphology. Moreover, follicular dendritic cell sarcoma immunohistochemical stains are not included in routine

✉ Usman Hassan
drusmanhassan256@gmail.com

Iftikhar Ali Rana
dr.ifti141@gmail.com

Sajid Mushtaq
sajidm@skm.org.pk

Muhammad Azam
mazam98@hotmail.com

Noreen Akhter
noriaakhter@yahoo.com

[1] Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan

[2] Department of Pathology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Johar Town, Lahore, Pakistan

panel. FDCS predominantly comprises of spindle-shaped cells in whorling and storiform pattern with scattered mitoses and lymphocytic infiltrate in background. However, these tumors can show epithelioid morphology in nests and sheets, absence of lymphocytic infiltrate, extensive lymphoid infiltrate, necrosis, and frequent mitoses. Tumor cells usually reveal strong and diffuse positivity for CD21, CD23, and CD35; clusterin; D 2-40; and gamma synculcein [3]; however, patchy positivity can be seen for EMA, S100, and CD68. FDCS shows consistent negative expression for CD34, CD3, CD79a, CD30, HMB-45, desmin, and high-molecular weight cytokeratins.

Although FDCS behaves as an intermediate grade neoplasm [11], unfavorable prognostic factors include young age at diagnosis (≤ 40 years), absence of lymphoplasmacytic infiltrate, large size of tumor (> 6 cm), intraabdominal location, coagulative necrosis, significant cellular atypia, and high mitotic index (≥ 5/10 HPF), with intraabdominal location the single most important unfavorable prognostic factor [12]. Because of its morphology, differential diagnoses of FDCS in gastrointestinal tract include undifferentiated carcinoma, sarcomatoid carcinoma, KIT negative gastrointestinal stromal tumor, lymphoma, peripheral nerve sheath tumor, smooth muscle tumor, and interdigitating dendritic cell sarcoma. Considering the rarity and difficulties in diagnosing this tumor, we consider it very important to share our experience of diagnosing FDCS because there are reports of 30–58% misdiagnosed cases especially when FDCS occur in extranodal sites [10–12]. Moreover, its correct diagnosis cannot be overemphasized as the treatment and prognosis of FDCS are very much different from other tumors which are usually considered in its differential diagnoses.

Materials and Methods

After approval from internal review board (IRB), a total of eight patients diagnosed as extranodal FDCS in gastrointestinal tract from February 2015 to February 2018 at Shaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore, Pakistan, were included in the study. Tumors involving both lymph nodes and gastrointestinal tract were excluded to rule out the possibility of secondary involvement of gastrointestinal tract by lymph node malignancy. Reports, slides, and all clinical data were archived from the database of the hospital. Mean, median, and mode were calculated for quantitative variables like age and tumor size and frequencies and percentages were calculated for immunostain results. Clinical history, presenting complaints, demographic details, gross description, histologic features, and immunostains were reviewed by two consultant histopathologists. Clinical follow-up was also evaluated.

Results

Four patients were females and four were males. Age ranged from 20 to 46 years (mean age 29.2 years). All patients presented with abdominal pain. Three patients also had history of constipation and intestinal obstruction. Tumors were found during radiological work up including ultrasonography and computed tomographic scan. One patient had liver metastasis at the time of presentation. Seven patients are currently alive and one patient has died of disease.

Tumors were located in large intestine in four patients (two in cecum and two in ascending colon), small intestine in three patients (two in ileum and 1 in jejunum) and in stomach and lesser sac in one patient. The mean size of tumor was 13 cm (range 5.5 to 35 cm). In one patient, tumor showed polypoid appearance, rest of the cases revealed solid mass like growth. In seven cases, cut surface of tumor was homogenous, tan white in color with areas of hemorrhage. In one case, extensive necrosis was also seen.

Microscopically, five tumors showed typical morphology exhibiting spindle to epithelioid cells arranged in fascicles, storiform and whorling pattern (Fig. 1a–c). Tumor cells had hyperchromatic to vesicular nuclei and occasional prominent nucleoli (Fig. 1b). In background, sprinkling of lymphocytes was noted in all cases (Fig. 1a–d). In one case, extensive lymphocytic infiltrate was present (Fig. 1d). One case also showed marked necrosis (Fig. 1e). Presence of tumor giant cells was seen in two patients (Fig. 1f). Mitoses were < 5 or equal to 5/10 HPFs in five cases, while three cases showed > 5 mitoses/10HPF (Fig. 1).

In each case, extensive panel of immunohistochemical stains was performed because of rarity of tumor, its odd location and lot of entities had to be excluded before considering FDCS as a possibility. All tumors were diffusely and strongly positive for CD21 and CD35 (Fig. 2a, b), and negative for CK, CAM5.2, EMA LCA, CD30, DOG-1, CD117, CD34, HMB45, and S100.

Patient follow up ranged from 01 to 24 months (median 11.8 months). Seven patients underwent surgical resection only and one patient received adjuvant chemotherapy. The patient who received adjuvant chemotherapy actually had metastasis in liver and peritoneum and this patient died of disease 24 months after diagnosis. Rest of the seven patients are on follow-up and at the moment they are free of disease. Patient who died was a 24-year-old female, with 20-cm tumor in Jejunum. Histology showed epithelioid to spindle-shaped cells, moderate lymphocytic infiltrate and giant cells. Mitotic count was 15/10HPFs. Complete tumor description and clinical features are given in Table 1.

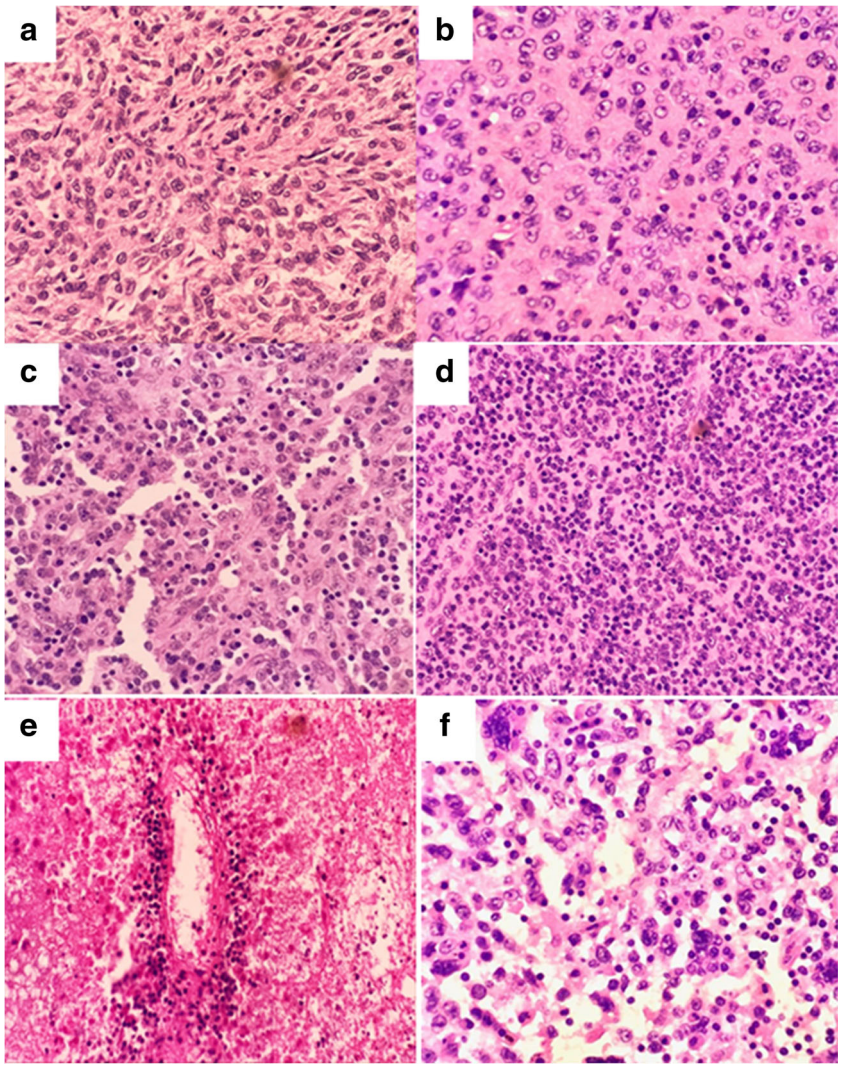

Fig. 1 Histology of follicular dendritic cell sarcoma (FDCS). **a** FDCS showing predominantly spindle cells with mild atypia. **b** Epithelioid cells with vesicular nuclei and prominent nucleoli. **c** FDCS with epithelioid morphology having rounded hyperchromatic nuclei and eosinophilic cytoplasm. Sprinkling of lymphocytes is seen in the background. **d** FDCS with extensive lymphocytic infiltrate in background. **e** FDCS with prominent necrosis and perivascular lymphocytic infiltrate. **f** FDCS with giant cells

Discussion

Follicular dendritic cells are antigen presenting cells of the primary and secondary follicles. These cells are present in germinal centers of B cell follicles [5], which are present in lymph nodes as well as in extranodal locations, either as acquired lymphoid tissue or as part of the organized constitutive lymphoid tissue. Tumor arising from follicular dendritic cells is called follicular dendritic cell sarcoma (FDCS). As follicular dendritic cells are present in both nodal and extranodal locations, FDCS can arise in both nodal and extranodal locations. These tumors are rare in lymph nodes and even rarer in extranodal sites. Apart from lymph nodes, FDCS have been reported in tonsil, palate, pharynx, spleen, mediastinum, liver, thyroid, lung, thigh soft tissue, and gastrointestinal tract [13–21].

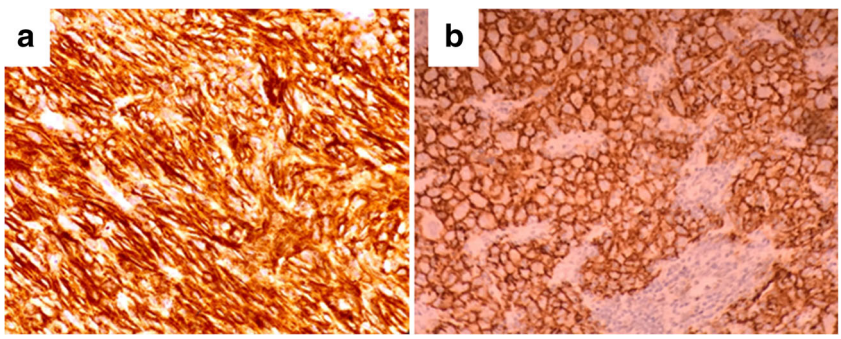

Fig. 2 Immunohistochemical staining showing cytoplasmic and membranous positivity positive for CD21 (**a**) and CD35 (**b**)

Table 1 Clinical features and tumor description

Case no.	Age (year)/sex	Presentation	Site of involvement	Morphology	Tumor size	Mitotic count
1	24/female	Abdominal pain and weight loss	Jejunum	Epithelioid to spindle-shaped cells, moderate lymphocytic infiltrate, and giant cells	20 cm × 15 cm	15 mitoses/10 HPF
2	35/female	Abdominal pain and weight loss	Ascending colon	Epithelioid cell and mild lymphocytic infiltrate in background and giant cells	5.5 cm × 4.3 cm	03 mitoses/10 HPF
3	22/male	Abdominal pain and constipation	Ascending colon	Epithelioid to spindle-shaped cells in short fascicles and severe lymphocytic infiltrate	10 cm × 8 cm	09 mitoses/10 HPF
4	20/male	Abdominal pain and constipation	Distal ileum	Spindle-shaped cell in fascicles and perivascular lymphocytic infiltrate	07 cm × 05 cm	04 mitoses/10 HPF
5	46/female	Abdominal pain	ileum	Epithelioid to spindle-shaped cells and lymphocytic infiltrate	09 cm × 09 cm	03 mitoses/10 HPF
6	25/male	Abdominal pain	Cecum	Epithelioid to spindle-shaped cells	08 cm × 06 cm	04 mitoses/10 HPF
7	40/male	Abdominal pain and constipation	Cecum	Spindle to ovoid cells and necrosis	35 cm × 25 cm	05 mitoses/10 HPF
8	22/female	Epigastric pain	Lesser sac and stomach	Spindle-shaped cells in fascicles, and necrosis	09 cm × 08 cm	07 mitoses/10 HPF

FDCS behaves as an intermediate grade neoplasm which can show recurrence and metastasis [12]. Most common metastatic sites are the liver and lung followed by lymph node and bone. Young age at diagnosis (≤ 40 years), absence of lymphoplasmacytic infiltrate, large size of tumor (> 6 cm), intraabdominal location, coagulative necrosis, significant cellular atypia and high mitotic index (≥ 5/10 HPF) are considered poor prognostic factors [22].

In the recent years, FDCS are being diagnosed in different locations and oncologists are facing difficulties in treating this tumor as there are no definite guidelines for its management. However, role of surgery is considered pivotal in treatment of FDCS as prior studies showed better overall survival after surgery when compared with other treatment modalities. Role of neoadjuvant and adjuvant chemotherapy with surgery has shown different results with some studies showing benefit and some showing no added advantage when compared with surgery alone [23]. Our seven patients underwent surgical resection only and are still surviving without any evidence of disease. One patient received adjuvant chemotherapy. This patient had metastasis in liver and peritoneum and died of disease 24 months after diagnosis.

FDCS have distinct morphology regardless of their location. Most of the tumors are composed of plump spindle cells arranged in fascicular, storiform and whorling patterns with lymphocytic sprinkling in background. Variation in morphological features include epithelioid appearance, nested and sheet like arrangement of tumor cells, areas of marked atypia, frequent mitoses, extensive lymphoid infiltrate, scanty lymphoid infiltrate and necrotic foci. These tumors stain diffusely with follicular dendritic cell markers (CD21, CD35, and CD23). CD21 and CD35 are most commonly used markers. Clusterin and podoplanin (D2–40) are other markers which also have high sensitivity for FDCS [24, 25].

Saygen et al. reported 02 cases of FDCS and analyzed all reported cases of FDCS in English literature from 1986 to 2012 [23]. This study demonstrated that 31.5% patients had nodal disease, 58% patients with isolated extranodal involvement and 10.5% patients with both nodal and extranodal involvement. The most common extranodal site was liver followed by lung, tonsil, spleen, soft tissue, mediastinum, gastrointestinal tract, retroperitoneum and mesentery. Males and females were equally affected with no gender predilection. Median age of patients was 50 years (range 9 to 90 years). Eighteen cases of FDCS were reported in gastrointestinal tract. Wang et al. reported 6 cases of FDCS and reviewed all 44 cases of FDCS published in Chinese literature from 1993 to 2009 and found out that 44% patients showed nodal disease while 54% had extranodal disease [26]. Males were affected more than females (males to female ratio, 3:2). Patient's age ranged from 7 to 75 years (median age 44 years). The most common extranodal site was the liver. About five patients had FDCS in gastrointestinal tract. In our study, we have eight cases of FDCS diagnosed in gastrointestinal tract; three cases were diagnosed in small intestine (two in ileum and one in jejunum, four in large intestine (two in cecum and two in ascending colon) and one in stomach and lesser sac, with equal distribution in males and females. The mean age of patients in our study was 29.2 years (range 20 to 46 years).

Studies discussed above and others [6, 26, 27] revealed that FDCS exhibits nests, fascicles, and storiform pattern with sprinkling of lymphocytes in background. Tumor cells show spindle to epithelioid cell morphology. Variations in morphological features include epithelioid morphology, presence of

coagulative necrosis, giant cells, and areas harboring marked atypia. In our study, five cases showed typical morphology with tumors composed of spindle to epithelioid cells arranged in storiform and whorling patterns. Lymphocytes were seen in the background. No definite atypia, frequent mitoses and necrosis were noted in these five cases. One case was received for second opinion diagnosed as diffuse large B cell lymphoma from an outside lab. This was an ascending colon mass and histologically, it showed extensive lymphoid infiltrate but on closer look on other sections, typical areas of FDCS could also be seen and the areas with extensive infiltrate had mixed B and T cell immunophenotype. One case showed extensive necrosis and this case and one other case also showed tumor giant cells. So these morphological variations should be known to a pathologist. Extensive sampling is of utmost importance as we noticed that the tumors which showed necrosis, tumor giant cells and extensive lymphoid infiltrate, additional sectioning revealed typical areas of FDCS. The most consistent immunohistochemical stains that were positive in tumor cells were CD21 and CD35. Other immunostains CK, CAM5.2, CD30, DOG-1, CD117, CD34, HMB45, desmin, and synaptophysin were negative. One important observation was that most of the tumors showed variable and focal staining for S100, CD68, and EMA. In our experience, FDCS in extranodal sites are missed either due to lack of knowledge of this tumor or this tumor is not routinely considered in differential diagnoses of spindle and epithelioid tumors in GIT tract. Important differential diagnoses in GIT are sarcomatoid and undifferentiated carcinoma, KIT negative GIST, lymphoma, neural tumors, smooth muscle tumors, and undifferentiated sarcomas. For instance, if FDCS is not in the differential and if it shows variable staining for S100, CD68, and EMA and is negative for other markers, depending upon the morphology (epithelioid or spindle), it can be misdiagnosed as neural tumor, undifferentiated sarcoma and sarcomatoid and undifferentiated carcinoma respectively. On the other hand, if FDCS is considered in the differential and pathologist is well aware of all its morphological variations and knows that CD21 and CD35 are consistently positive in FDCS, then all above-mentioned entities can be easily differentiated from FDCS. Some FDCS show extensive lymphoid infiltrate and unfortunately these lymphoid cells can show aberrant B or T cell immunophenotype. In such cases, extensive sampling to look for typical areas and knowledge of immunoprofile of FDCS are important. KIT negative GIST and smooth muscle tumors are also negative for CD21 and CD35. We have to admit that in most of the case we diagnosed, FDCS was not considered in the initial list of differential diagnoses and CD21 and CD35 were not applied in the initial panel of immunostains. However, when the usual markers started giving negative results, FDCS was included in the differential list and these cases showed very promising results with CD21 and CD35.

Conclusion

FDCS is a very rare tumor presenting in both nodal and extranodal locations. These tumors have distinct morphology and immunophenotype. Pathologists should know the usual morphological and immunophenotypical features and also the morphological variations which this tumor can show. This is very important for correct diagnosis and to prevent misdiagnosis and mistreatment.

Compliance with Ethical Standards

Conflict of Interest The authors declare that there is no conflict of interest.

References

1. Meyer RL. Malignant lymphomas other than Hodgkin's disease: histology, cytology, ultrastructure, immunology. JAMA. 1979;242(2):193.
2. Monda LA, Warnke RO, Rosai JU. A primary lymph node malignancy with features suggestive of dendritic reticulum cell differentiation. A report of 4 cases. Am J Pathol. 1986;122(3):562.
3. Hollowood K, Stamp G, Zouvani L, Fletcher CD. Extranodal follicular dendritic cell sarcoma of the gastrointestinal tract: morphologic, immunohistochemical and uhrastructural analysis of two cases. Am J Clin Pathol. 1995;103(1):90–7.
4. Li J, Geng ZJ, Xie CM, Zhang XK, Chen RY, Cai PQ, et al. Computer tomography imaging findings of abdominal follicular dendritic cell sarcoma: a report of 5 cases. Medicine. 2016;95(1): e2404.
5. Tew JG, Wu J, Qin D, Helm S, Burton GF, Szakal AK. Follicular dendritic cells and presentation of antigen and costimulatory signals to B cells. Immunol Rev. 1997;156(1):39–52.
6. Chan JK, Fletcher CD, Nayler SJ, Cooper K. Follicular dendritic cell sarcoma. Cancer. 1997;79(2):294–313.
7. Su Z, Liu G, Liu J, Fang T, Zeng Y, Zhang H, et al. Paraneoplastic pemphigus associated with follicular dendritic cell sarcoma: report of a case and review of literature. Int J Clin Exp Pathol. 2015;8(10): 11983.
8. Chow SC, Yeung EC, Ng CS, Wong RH, Fai To K, Wan IY. Mediastinal follicular dendritic cell sarcoma with paraneoplastic pemphigus. Asian Cardiovasc Thorac Ann. 2015;23(6):732–4.
9. Cakir E, Aydin NE, Samdanci E, Karadag N, Sayin S, Kizilay A. Follicular dendritic cell sarcoma associated with hyaline-vascular Castleman's disease. J Pak Med Assoc. 2013;63(3):393–5.
10. Gounder M, Desai V, Kuk D, Agaram N, Arcila M, Durham B, et al. Impact of surgery, radiation and systemic therapy on the outcomes of patients with dendritic cell and histiocytic sarcomas. Eur J Cancer. 2015;51(16):2413–22.
11. Li L, Shi YH, Guo ZJ, Qiu T, Guo L, Yang HY, et al. Clinicopathological features and prognosis assessment of extranodal follicular dendritic cell sarcoma. World J Gastroenterol: WJG. 2010;16(20):2504.
12. Chen T, Gopal P. Follicular dendritic cell sarcoma. Arch Pathol Lab Med. 2017;141(4):596–9.
13. Chan JK, Tsang WY, Ng CS. Follicular dendritic cell tumor and vascular neoplasm complicating hyaline-vascular Castleman's disease. Am J Surg Pathol. 1994;18(5):517–25.
14. Biddle DA, Ro JY, Yoon GS, Yong YW, Ayala AG, Ordonez NG. Extranodal follicular dendritic cell sarcoma of the head and neck

region: three new cases, with a review of the literature. Mod Pathol. 2002;15(1):50.
15. Soriano AO, Thompson MA, Admirand JH, Fayad LE, Rodriguez AM, Romaguera JE, et al. Follicular dendritic cell sarcoma: a report of 14 cases and a review of the literature. Am J Hematol. 2007;82(8):725–8.
16. Kröber SM, Marx A, Aebert H, Dohmen BM, Kaiserling E. Sarcoma of follicular dendritic cells in the dorsal mediastinum. Hum Pathol. 2004;35(2):259–63.
17. Khalid T, Folman R. Symptoms in cancer patients and an unusual tumor: case 3. Follicular dendritic cell sarcoma. J Clin Oncol. 2005;23(36):9425–6.
18. Galati LT, Barnes EL, Myers EN. Dendritic cell sarcoma of the thyroid. Head Neck. 1999;21(3):273–5.
19. Romero-Guadarrama MB, Reyes-Posada O, Hernández-González MM, Durán-Padilla MA. Follicular dendritic cell sarcoma/tumor: 2 cases of a rare tumor of difficult clinical and pathological diagnosis. Ann Diagn Pathol. 2009;13(4):257–62.
20. Geerts A, Lagae E, Dhaene K, Peeters M, Waeytens A, Demetter P, et al. Metastatic follicular dendritic cell sarcoma of the stomach: a case report and review of the literature. Acta Gastro-Enterol Belg. 2004;67(2):223–7.
21. Granados R, Aramburu JA, Rodríguez JM, Nieto MA. Cytopathology of a primary follicular dendritic cell sarcoma of the liver of the inflammatory pseudotumor-like type. Diagn Cytopathol. 2008;36(1):42–6.
22. Urun Y, Kankaya D, Koral L, Yalcin B, Karabork A, Ceyhan K, et al. Intraabdominal follicular dendritic cell sarcoma: a report of three cases and review of the literature. Tumori. 2013;99(2):e65–9.
23. Saygin C, Uzunaslan D, Ozguroglu M, Senocak M, Tuzuner N. Dendritic cell sarcoma: a pooled analysis including 462 cases with presentation of our case series. Crit Rev Oncol Hematol. 2013;88(2):253–71.
24. Grogg KL, Macon WR, Kurtin PJ. Nascimento AG. A survey of clusterin and fascin expression in sarcomas and spindle cell neoplasms: strong clusterin immunostaining is highly specific for follicular dendritic cell tumor. Mod Pathol. 2005;18(2):260.
25. Yu H, Gibson JA, Pinkus GS, Hornick JL. Podoplanin (D2-40) is a novel marker for follicular dendritic cell tumors. Am J Clin Pathol. 2007;128(5):776–82.
26. Lima FE, Jorge IF, Kauffman J, Gerson G, Beco MD, Cavalcante JM, et al. Follicular dendritic cell sarcoma: report of two cases and literature review. Jornal Brasileiro de Patologia e Medicina Laboratorial. 2015;51(4):258–64.
27. Fonseca R, Tefferi A, Strickler JG. Follicular dendritic cell sarcoma mimicking diffuse large cell lymphoma: a case report. Am J Hematol. 1997;55(3):148–55.