A RARE SARCOMA DIAGNOSED ON FINE NEEDLE ASPIRATION IN TWO PATIENTS WITH CASTLEMAN DISEASE

clinical cases with questions for students

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Case 1:

A 38 year old female presented with a 3.6 x 1.8 cm peri-aortic mass and retroperitoneal lymphadenopathy. She initially presented at an outside institution with a large right suprarenal mass seven years prior which was diagnosed on core needle biopsy as hyaline vascular Castleman disease. After receiving chemotherapy of gemcitabine and Taxotere partial remission was achieved. She subsequently underwent surgical excision of the right suprarenal mass and right kidney at MD Anderson Cancer Center. The resected specimen showed large spindle and epithelioid tumor cells in a background of small mature lymphocytes. Many tumor cells had prominent nuclear pseudoinclusions. There were also areas with prominent proliferation of plasma cells, with deposition of amorphous eosinophilic extracellular material. Additionally, focal dystrophic calcification was present. In situ hybridization for kappa and lambda immunoglobulin light-chain showed a polytypic pattern of positivity in plasma cells for kappa and lambda light chains. The spindled and epithelioid tumor cells were positive for CD21, CD35, clusterin and vimentin by immunohistochemistry. The images from the aspirate smears and cell block are shown below **(image 1-3)**.

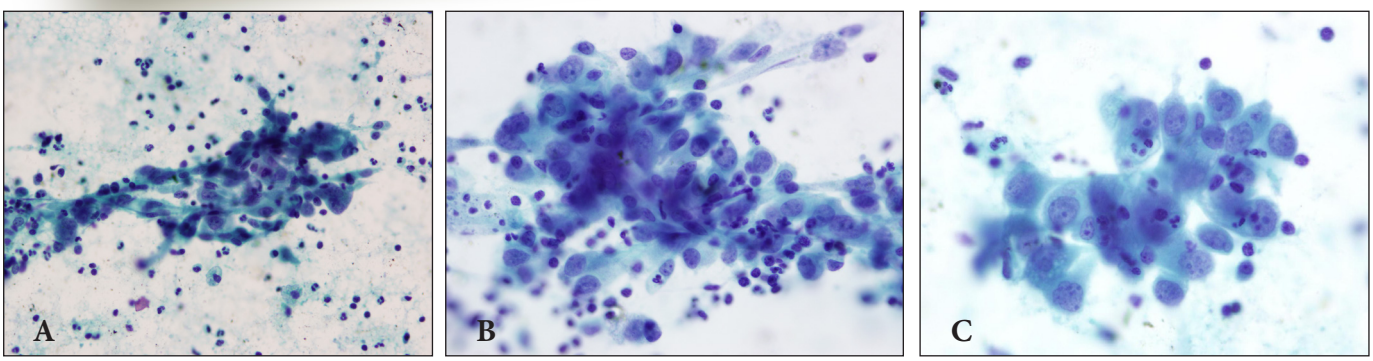


Image 1. Pap stained smear, 20x (A), 40x (B) and 60x (C) magnification.

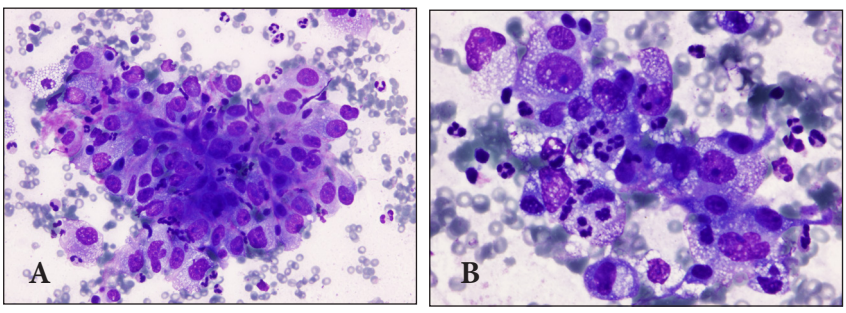


Image 2. Diff-Quik Stain, 20x (A), 40x (B) magnification.

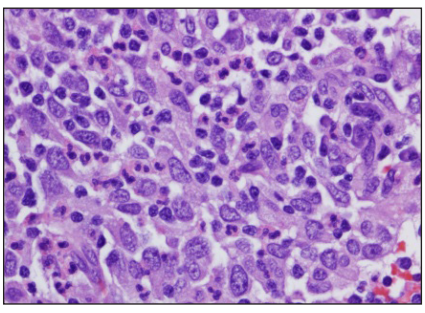
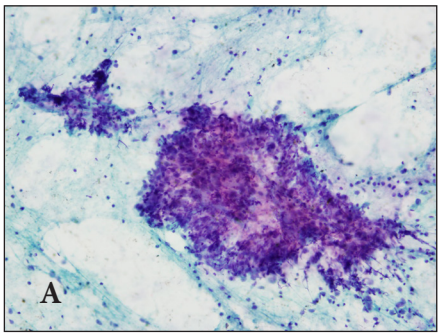


Image 3. Cell block (40x).

Case 2:

A 53 year old male presented with a 6.1 cm, lobulated, well-circumscribed extra-hepatic mass at the level of the porta-hepatis encasing the main portal vein. His initial tumor presented as a peri-gastric soft tissue mass arising in a background of hyaline vascular Castleman disease. At that time, he underwent a partial gastrectomy. The slides from the resected neoplasm were reviewed at MD Anderson Cancer Center and showed both spindle cells and epithelioid areas. The spindle cells were cytologically low-grade and closely related to foci that resembled hyaline vascular Castleman disease. The spindled areas were positive for CD21, CD35, CXCL13, D2-40, fascin, clusterin and vimentin by immunohistochemistry. A subset of epithelioid cells was positive for CD11c and CD68 immunostains. In-situ hybridization for Epstein-Barr virus small encoded RNA (EBER) and immunohistochemical markers for T-cells, B-cells, muscle specific antigens, keratin, CD33 and ALK1 were negative.

A CT guided fine needle aspiration of the recurrent extra-hepatic mass was performed at MD Anderson Cancer Center and the images from the aspirate smears and cell block are shown below **(image 4-6)**. The cytomorphologic and immunhistochemical features were similar to the patient's initial peri-gastric tumor.



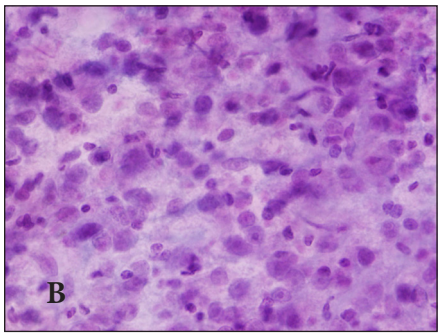


Image 4. Pap stained smear, 20x (A), 40x (B) magnification.

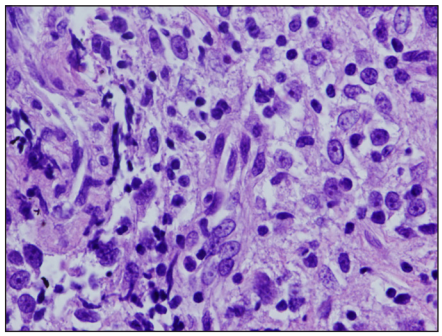
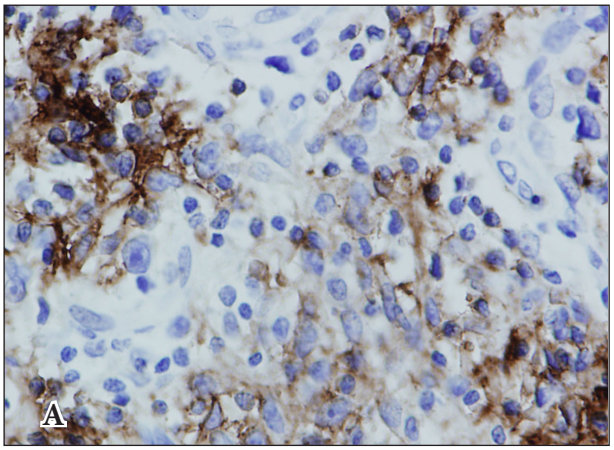


Image 5. Cell block (40x).



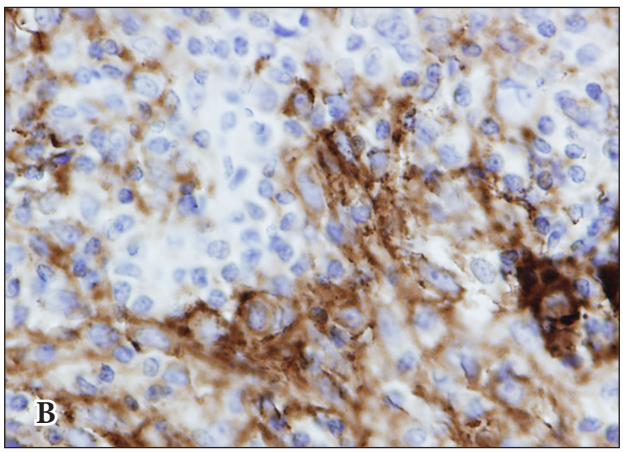


Image 6. Immunostain CD21 (A) and CD35 (B).

Which is the most likely diagnosis?

A. Follicular dendritic cell sarcoma
B. Gastrointestinal stromal tumor (GIST)
C. Leimyosarcoma
D. Malignant fibrous histiocytoma (MFH)
E. Melanoma

The answer is A. **Follicular dendritic cell sarcoma**

Follicular dendritic cell sarcoma (FDCS) was first described by Monda and coworkers in 1986 [1]. It is a rare neoplasm characterized by a dual cell population of malignant large epithelioid and spindled cells in a background of numerous small lymphocytes. The lymphocytes are of T-cell origin [2]. Interestingly, a recent study shows that TdT+ T-lymphoblastic populations may be increased in Castleman disease associated with FDCS [3].

FDCS can present in nodal (cervical or mediastinal) or extranodal (skin, soft tissue, tonsil, GI tract liver and spleen) sites. It is a tumor of young adults usually presenting less than 50 years of age with no gender predilection. There is an association with hyaline-vascular Castleman follicular hyperplasia [4] and Epstein-Barr virus in cases associated with inflammatory pseudo-tumor [5, 6]. Both recurrence and metastasis can occur. Majority of tumor presented as an early disease (85.4%), while 6.4% presented as locally advanced disease, and 8.2% presented with distant metastasis [7]. FDCS is considered a low to intermediate grade tumor with an overall mortality of 17%. When presented as local disease only, median survival is 168 months (range 2–360 months)[7]. The presence of certain histological features such as foci of necrosis and high mitotic activity along with an intra-abdominal location has been correlated with a more aggressive clinical course [8, 9]. Additionally, absence of lymphoplasmacytic response and large tumor size also appears to be associated with poor prognosis [7].

Histologically, the tumor is composed of oval to spindle cells forming fascicles, storiform patterns and whorls. The neoplastic cells have plump, slightly eosinophillic cytoplasm with indistinct cell borders and the nuclei are elongated with vesicular or granular finely dispersed chromatin. Occasional multinucleated giant cells and pseudo-intranuclear inclusions may be seen [4]. The presence of small lymphocytes throughout the tumor is characteristic [10]. The mitotic rate is usually between 0 and 10 per 10 high power fields. Uninvolved residual lymphoid tissue is often present in cases with nodal involvement. This may take the form of residual germinal centers or clusters of small lymphocytes in a perivascular location. These tumors may also contain foci of necrosis [4, 11].

On cytological examination, both the Diff-Quik and Papanicolaou-stained smears in this case showed that the tumor cells were syncytial and discohesive clusters of epithelioid to spindled cells in a mixed inflammatory background similar to previously described cases of FDCS [2, 10-13]. The tumor cells had eosinophillic granular cytoplasm and indistinct cell borders. The nuclei were usually single with small distinct nucleoli. Although marked pleomorphism, atypical mitotic figures and multi-nucleated giant cells have been reported, we did not observe these features in our cases [11, 13]. Intranuclear inclusions and nuclear grooves were present in our cases similar to a previous report [2].

The neoplastic cells in FDCS demonstrate the phenotype of non-neoplastic follicular dendritic cells. They are positive for one or more of the follicular dendritic cell markers, including CD21, CD35 and CD23 [4]. They are also positive for clusterin, desmoplakin, vimentin, fascin, EMA and variably positive for S100 and CD68 [4, 14]. Ki-67 labeling ranges from 1 to 25% [4]. BRAF (V600E) mutations can be detected in 18.5% of FDCS. The significance of this mutation in the pathogenesis of FDCS requires further investigation [15]. Complex cytogenetic abnormalities including losses of multiple chromosomes have been reported in FDCS [16].

The diagnosis can be challenging when cytology is the sole diagnostic modality. The clinical presentation can be variable and the cytomorphological features can overlap with other tumors including sarcomatoid carcinoma, gastrointestinal stomal tumor (GIST), leiomyosarcoma, malignant fibrous histiocytoma (MFH) and melanoma. Distinction from the other tumors is essential because of the low to intermediate grade nature of FDCS. Sarcomatoid carcinoma, also called spindle cell carcinoma, is characterized by anaplastic spindle cells with prominent necrosis and mitotic activity, features usually not seen in FDCS. The carcinoma cells are positive for cytokeratin. GIST is characterized by a prolif-

eration of bland spindle cells with whorls and short intersecting fascicles. The tumor cells in GIST stain with CD117 which is not observed in FDCS. Leiomyosarcoma is characterized by fascicles of spindle cells intersecting at right angles. The cells have cigar-shaped blunt-ended nuclei with variable atypia and will be positive for muscle markers such as desmin and SMA. The cells of MFH are more pleomorphic with bizarre giant cells and increased mitotic activity in a mixed inflammatory background. While melanoma can have a variety of histological features, the cells are usually pleomorphic with prominent nucleoli. Melanomas will be positive for HMB-45 and S100 without staining for CD21 or CD35. In addition, the presence of melanin pigment would aid in the diagnosis of melanoma.

Check your knowledge

1. Which of the following features can be seen in cytology smears of FDCS?

   A. Syncytial clusters and discohesive cells
   B. Spindled and epithelioid morphology
   C. Intranuclear inclusions and nuclear grooves
   D. Lymphocytes and plasma cells
   E. All of the above

   The answer is **E**.

2. Which immunohistochemical markers support a diagnosis of FDCS?

   A. CD21 or CD35
   B. CD117
   C. Vimentin
   D. Cytokeratin

   The answer is **A**.

3. What clinical features are characteristic of FDCS?

   A. The tumor is more common in women than men.
   B. The tumor only presents in elderly patients.
   C. Recurrence and metastasis never occur.
   D. Presentation in both nodal and extranodal sites has been reported.

   The answer is **D**.

4. Which of the following has been associated with FDCS?

   A. Castleman disease
   B. Rheumatoid arthritis
   C. Sjögren's syndrome
   D. Mesothelial hyperplasia
   E. Rhabdomyosarcoma

   The answer is **A**.

5. Which of the following features has been associated with a more aggressive clinical course for FDCS?

   A. Patient age greater than 50 years
   B. Nodal presentation
   C. Intranuclear inclusions
   D. Absence of mitotic activity
   E. Intraabdominal location

   The answer is **E**.

6. Which of the following has been associated with FDCS?

   A. Polyoma Virus
   B. Ebstein Barr Virus
   C. Herpes Virus
   D. Enterovirus
   E. Human Papilloma Virus

   The answser is **B**.

7. The overall mortality rate for FDCS has been reported as:

   A. 90%
   B. 60%
   C. 40%
   D. 17%
   E. 5%

   The answer is **D**.

8. Which of the following statements about FDCS is true?

   A. FDCS does not demonstrate the presence of lymphocytes on cytology smears.
   B. The differential diagnosis is limited to melanoma only.
   C. No cases of FDCS containing multi-nucleated giant cells have been reported.
   D. The neoplastic cells of FDCS can be variably positive for S100.
   E. Ki-67 labeling is usually above 90%.

The answer is **D**.

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