Epstein-Barr virus–associated Inflammatory Pseudotumor–like Follicular Dendritic Cell Tumor in the Spleen of a Patient with Diffuse Large B Cell Lymphoma: A Case Report and Review of the Literature

We report a case of an Epstein-Barr virus (EBV)-associated inflammatory pseudotumor-like follicular dendritic cell tumor (IPT-like FDC tumor). The tumor occurred in the spleen of a 64-year-old woman with a history of a diffuse large B-cell lymphoma (DLBCL) of neck nodes that presented four years ago. The splenectomy specimen revealed a 5 cm-sized, tan-colored and well-circumscribed mass. Histologically, spindle or ovoid cells with large vesicular nuclei were admixed with abundant inflammatory cells. Immunohistochemically, spindle cells were positive for FDC marker CD35, but negative for CD20, CD30 and ALK. EBV was detected almost exclusively in spindle cells by EBER in situ hybridization. IPT-like FDC tumors are rare, and are recognized as a distinctive clinicopathologic variant of FDC tumors. Among only 18 similar cases reported in the English language literature, the present case is the first case of a patient with a history of DLBCL.

Key Words: Inflammatory pseudotumor; Follicular dendritic cell tumor; Spleen; Neoplasm; Epstein-Barr virus

A follicular dendritic cell tumor is uncommon and arises in the lymph nodes or various extranodal sites.1,2 Histologically, follicular dendritic cell (FDC) tumors display syncytial, storiform, fascicular, and diffuse growth of spindle or ovoid cells that are immunoreactive to at least one of the following FDC markers; CD21, CD35, CD23, and CAN.42. FDC tumors mainly affect young to middle-aged patients with no gender predilection. The tumor shows a generally indolent behavior, but intra-abdominal cases can exhibit an aggressive clinical course.1,3

A few cases of FDC tumor have been reported to be associated with the presence of Epstein-Barr virus (EBV), and almost all reported cases of EBV-positive FDC tumors have occurred in the liver or spleen, and have characteristically demonstrated a conventional inflammatory pseudotumor (IPT)-like histology.1,3–7 Based on several reports, it has been postulated that a tumor showing definite nuclear atypia and positivity for both EBV and FDC markers at least in a proportion of proliferating spindle cells, and demonstrating so-called IPT-like histology should be defined as an ‘IPT-like FDC tumor’.7 However, the clinicopathologic nature of this entity remains controversial.

To the best of our knowledge, only 18 cases of IPT-like FDC tumors have been described in the English language literature, and six of these cases arose in the spleen. Here, we present an additional case of a splenic IPT-like FDC tumor occurring in a patient with a history of diffuse large B-cell lymphoma with a review of the literature.

CASE REPORT

A 64-year-old woman had been previously diagnosed with a diffuse large B-cell lymphoma of Ann Arbor stage IIA involving the cervical lymph nodes and palatine tonsils. After completing CHOP-based chemotherapy and radiation therapy, the patient...
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was disease free for a period of four years. At this time, a solid mass was detected in the spleen by a routine ultrasonographic examination. A CT scan of the abdomen performed 19 months later revealed a 4 cm-sized solid enhancing mass in the normal-

![Image](image-url)

**Fig. 1.** Enhanced computed tomograph (A) shows an enhancing solid mass in normal-sized spleen. In the cut surface (B), the mass is 5.5 cm-sized, well circumscribed, and white to tan-colored.

![Image](image-url)

**Fig. 2.** Microscopic feature of the splenic mass. Neoplastic spindle or ovoid cells are admixed with chronic inflammatory cells. Spindle cell nuclei are large and vesicular, sometimes twisted, and contained centrally located small but distinct nucleoli. Binucleated cells are occasionally observed (A, B). Spindle cells stain positively for CD35 (C). EBV is detected almost exclusively in spindle cells, whereas background lymphoid cells are negative by in situ hybridization for EBER (D).
ly sized spleen, and the mass increased in size to 5.1 cm over the next 5 months (Fig. 1A). Repeat needle biopsies at this time showed mixed infiltration of lymphocytes and plasma cells without atypism and the presence of a few spindle cells. Scattered EBV-encoded RNA (EBER)-positive cells of indefinable nature were detected in both biopsies, and the patient was diagnosed with an EBV-associated lymphoproliferative disorder—not further specified. No other clinical or radiological evidence of relapse of the previous lymphoma was present, and no remarkable systemic symptoms developed. A total splenectomy was performed without complication.

Grossly, a 5.5 cm-sized solitary, round well-circumscribed mass with a pushing border and a fleshy texture was observed. Its cut surface was white to tan in color and was interspersed with multiple small foci of hemorrhage and necrosis (Fig. 1B). Histologically, the tumor was composed of intermixed dense infiltrates of chronic inflammatory cells and vaguely fasciculated spindle or ovoid cells. The nuclei of the spindle cells were large and vesicular, sometimes irregularly twisted with occasional binucleation, and contained centrally located small but distinct nucleoli. The cytoplasm was eosinophilic and slightly fibrillary, and the cytoplasmic membrane was indistinct. Delicate cell processes were occasionally seen (Fig. 2A, B), and mitotic figures were rare, at up to one per ten high power fields. Background inflammatory cells seen were mainly mature lymphocytes and plasma cells, and some histiocytes; a few immunoblasts and eosinophils were also present.

Immunohistochemical analysis demonstrated that the spindle or ovoid cells were positive for CD35 (Fig. 2C), and focally positive for CD21 and CD23, with a weaker intensity than for non-neoplastic follicular dendritic cells. Spindle cells were also focally positive for smooth muscle actin, S-100 protein, and CD68, but were negative for CD20, CD3, CD30 (Ki-1) and ALK. The bizarre binucleated cells were also negative for CD30. In the inflammatory background admixed with spindle cells, CD3 (+) T cells were more predominant than CD20 (+) or CD79a (+) B cells, and were diffusely distributed within the lesion; the ratio of CD4 (+) and CD8 (+) T cell populations were equal. However, B cells were seen in multifocal aggregates. EBER in situ hybridization detected EBV almost exclusively in spindle or ovoid cells displaying immunoreactivity for follicular dendritic cell markers, namely CD35, CD23, or CD21 (Fig. 2D). Lymphoid cells in tumor and non-neoplastic splenic tissue backgrounds were negative for EBV. T-cell receptor and IgH gene rearrangement studies revealed no monoclonality of T- or B-cells.

### Table 1. Clinical features of IPT-like FDC tumors

<table>
<thead>
<tr>
<th>Site</th>
<th>Spleen</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other sites</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Size</td>
<td>Mean (Range)</td>
<td>11.7 cm (3.5-22)</td>
</tr>
<tr>
<td>Age</td>
<td>Mean (Range)</td>
<td>48.1 years (19-77)</td>
</tr>
<tr>
<td>Sex</td>
<td>Female:Male</td>
<td>16:3</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Asymptomatic</td>
<td>6</td>
</tr>
<tr>
<td>Fever, weight loss, malaise</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Recurrence</td>
<td>3</td>
</tr>
<tr>
<td>Metastasis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Expire</td>
<td>None</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>Immunohistochemistry</th>
<th>CD21 or CD35</th>
<th>CD23</th>
<th>LMP1</th>
<th>ALK1</th>
<th>CD30</th>
<th>SMA</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>12/15 (80%)</td>
<td>6/13 (46.2%)</td>
<td>3/14 (21.4%)</td>
<td>0/11</td>
<td>0/9</td>
<td>2/12 (16.7%)</td>
</tr>
</tbody>
</table>

The digit is the number of cases; ‘; Present case is included; ‘; Subtle involvement of FDC marker-positive, EBV-positive tumor cells in portal hepatic lymph node was found in this case; ‘. Majority of data (11 out of 16 cases) were from the report of Cheuk et al. In that study they used CD21/CD35 cocktail antibodies. So in this review, we assigned the results of CD21 or CD35 to the one category.

### DISCUSSION

An IPT-like FDC tumor is defined as a lesion that shows positivity for both FDC markers and EBV in at least a proportion of the proliferating spindle cells, and also demonstrates a so-called IPT histology. This entity is extremely rare, and the pathogenesis and the clinicopathologic nature are still debated. The clinicopathologic features of reported IPT-like FDC tumors, including the present tumor, are summarized in Table 1. IPT-like FDC tumors exhibit some characteristic clinicopathologic features that distinguish them from conventional FDC tumors. IPT-like FDC tumors are exclusively intra-abdominally located, especially in the liver and spleen whereas conventional FDC tumors involve lymph nodes and various anatomical sites. IPT-like FDC tumors show marked female predilection, whereas FDC tumors lack gender predilection. IPT-like FDC tumors are also commonly accompanied by systemic symptoms such as weight loss, malaise, and fever, which rarely accompany conventional FDC tumors. In particular, all IPT-like FDC tumors have been associated with the presence of EBV, which is rare for a conventional FDC tumor. The biologic course followed by conventional FDC tumors is generally indolent, but intra-abdominal cases can be aggressive and may metastasize and lead to patient death. IPT-like FDC tumors show a more indolent course and are associated with longer survival than conventional FDC tumors.
Before IPT-like FDC tumors were recognized as a separate disease entity, reports concerning inflammatory pseudotumors (IPTs) associated with EBV continued. Interestingly, EBV was more frequently detected in extranodal, especially splenic and hepatic IPTs, than in nodal cases. Subsequent reports suggested that many splenic and hepatic ‘IPTs with EBV-positive spindle cells’ were in fact FDC tumors with an IPT-like histology. This suggestion was based on the expression of at least one FDC marker in EBV-positive spindle cells.

According to previously published reports containing immunohistochemical data (Table 1), CD21 and/or CD35-positive spindle cells occur in 80% (12/15), CD23 in 46.2% (6/13), and SMA in 16.7% (2/12) of IPT-like FDC tumors. As IPT-like FDC tumors often show only focal or weak FDC marker immunostaining, in situ hybridization for EBER is recommended as a first-line investigatory modality for suspected IPT-like FDC tumors. However, a case of splenic inflammatory pseudotumor associated with a clonal EBV infection without FDC marker expression has also been described. A meticulous examination for an immunophenotype is needed for an interpretation of IPT-like tumors with EBV-positive spindle cells, especially in the liver and spleen.

To explain the overlapping histologic and immunohistochemical features of IPTs and IPT-like FDC tumors, it has been hypothesized that hepatic and splenic IPT-like tumors arose from a common mesenchymal cell and differentiated along different pathways. This process occurred, mostly via a myofibroblastic lineage with vimentin and SMA expression, rarely via an FDC lineage expressing CD21, CD35, and CD23, or via another lineage displaying only mesenchymal and histiocyte markers like vimentin and CD68. All reported IPT-like FDC tumors have shown the presence of spindle cells with EBV positivity, but no ALK positivity, which has been demonstrated by some inflammatory myofibroblastic tumors. Because CD21 expressed in FDC is a well-known EBV receptor, and functionally active EBV-transformed FDC cell lines have been successfully established and clonal EBV infection in some IPT-like FDC tumors has been demonstrated, it has been suggested that EBV might be involved in the pathogenesis of IPT-like FDC tumors.

Rare FDC tumors have been associated with hyaline-vascular Castleman’s disease, but no such association has been reported for IPT-like FDC tumors, although an IPT-like FDC tumor was reported in a patient with stable monoclonal gammopathy of undetermined significance. However, to the best of our knowledge, no IPT-like FDC tumors complicating hematolymphoid malignancies have been encountered. In the present case, the IPT-like FDC tumor occurred four years after DLBCL that had been successfully treated without any evidence of relapse. Although possible relationships between IPT-like FDC tumors and malignant lymphoma should be resolved with additional examples, it is tempting to speculate that impaired host immunity might have predisposed the development of EBV-associated IPT-like FDC tumor in the described case.

In summary, we have present a case of an IPT-like FDC tumor in the spleen of patient with a history of DLBCL. This tumor showed the characteristic histologic features of IPT-like FDC tumors including an extensive inflammatory background and the proliferation of spindle and ovoid cells with positivity for FDC markers and EBV.

REFERENCES

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