Published in final edited form as:

Hum Pathol. 2015 December ; 46(12): 1956–1961. doi:10.1016/j.humpath.2015.08.011.

EBV-associated inflammatory pseudotumor presenting as a colonic mass

Shunyou Gong, MD, PhD¹, Iwona Auer, MD², Rajan Duggal, MD³, Stefania Pittaluga, MD, PhD¹, Mark Raffeld, MD¹, and Elaine S. Jaffe, MD^{1, #}

¹Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, 10 Center Drive, Bethesda, MD 20892

²Division of Hematopathology, Department of Pathology and Laboratory Medicine, University of Calgary & Calgary Laboratory Services, Calgary, AB T2N 2T9, Canada

³Department of Pathology, Medanta The Medicity, Gurgaon 122001, Delhi NCR, India

Abstract

Epstein-Barr virus (EBV) -positive inflammatory pseudotumor (IPT) commonly involves spleen and liver, and has only rarely been reported in the gastrointestinal (GI) tract. The spindle cells may express myofibroblastic or follicular dendritic cell (FDC) markers. We report a challenging case of EBV-positive IPT arising in the ascending colon. The lesion was composed of spindle cells positive for smooth muscle actin but negative for all FDC markers tested, and was associated with an exuberant lymphoid proliferation containing reactive follicles, abundant plasma cells, and small lymphocytes. We further discuss pitfalls for possible misdiagnosis as ALK-positive inflammatory myofibroblastic tumor, IgG4-related disease, and peripheral T cell lymphoma. Our case represents the first EBV-positive inflammatory pseudotumor of the GI tract in the western literature. Awareness of this rare entity in GI tract is essential for correct diagnosis and appropriate patient management.

Keywords

Inflammatory pseudotumor; Epstein-Barr virus; Inflammatory pseudotumor-like follicular dendritic cell tumor; gastrointestinal tract; myofibroblasts

1. Introduction

Inflammatory pseudotumor (IPT) is a term that has been used to describe a diverse group of lesions. Historically, the term has been applied to plasma cell granuloma, inflammatory myofibroblastic tumor (ALK-positive), IgG-4 related disease, and the distinctive EBV-

[#]Correspondence to: Elaine S. Jaffe, MD, Head, Hematopathology Section, Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, 10 Center Drive, Bethesda, MD 20892, Phone: (301) 480-8461, Fax: (301) 480-8089, ejaffe@mail.nih.gov.

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positive spindle cell proliferations most commonly arising in spleen and liver (1). IPTs form benign localized mass-like lesions, usually solitary, and histologically are composed of a matrix of spindle cells and admixed polymorphic inflammatory cells, including abundant polyclonal plasma cells, small lymphocytes and histiocytes. EBV-associated IPT are of mesenchymal origin, and it is likely that the presence of EBV elicits the prominent reactive lymphoid component that may form the majority of the cellular infiltrate. The EBV+ cells often have features of myofibroblasts(1, 2), but virtually identical lesions appear to be derived from follicular dendritic cells (FDC), with similar sites of involvement and histological features(3). Most evidence suggests that IPT derived from FDC and myofibroblasts are related entities.

IPT have been rarely reported in the gastrointestinal (GI) tract, and are a diagnostic challenge. IPTs need to be differentiated from common GI tract malignancies, such as carcinoma, fibrosarcoma, or lymphoma, as well as infectious or inflammatory reactions. Although there are small series and isolated case reports of various GI tract inflammatory mass lesions called “inflammatory pseudotumor” by the authors, the majority of them appear to have clear etiologies, and probably represent non-specific inflammatory responses to diverse irritators, such as bacterial or parasitic infection, trauma, or autoimmunity. Most are rich in plasma cells, and have features resembling what has been termed plasma cell granuloma (4). The etiology of IPT is not well understood, despite various theories proposed, including trauma, infection, and over-production of pro-inflammatory cytokines(1). Arber et al. first reported that the spindle cells in splenic and hepatic IPT were usually positive for EBV, whereas similar lesions in lymph nodes infrequently contained EBV-positive cells, and when present, the EBV-positive cells were lymphoid in nature(1). Similarly, EBV is consistently found in IPT-like FDC tumors (3, 5), further arguing for the concept that EBV+ FDC and myofibroblastic lesions are part of the same spectrum. Although most of these EBV+ spindle cell lesions are cured by local excision, some may be clonal, revealed by EBV genomic analysis (5, 6). We report a unique case of IPT presenting as a pedunculated polypoid mass in the ascending colon. We review the interrelationship and overlap among EBV-positive lesions derived from myofibroblasts and follicular dendritic cells. Additionally, we discuss diagnostic pitfalls in the recognition of several other entities with similar histological features.

2. Materials and Methods

2.1. Case report

A 42-year old female patient underwent appendectomy and was diagnosed with acute gangrenous appendicitis. A follow-up colonoscopy was performed 2 weeks later. She was found to have a polypoid mass with single broad pedunculated stalk, in the ascending colon. The mass was resected uneventfully. Post-surgery CT showed that the mass had been completely removed and the lumen was patent. Grossly, the resected mass measured 4.5 × 2.8 × 2.5 cm. Routine H&E. staining was performed.

She had follow-up colonoscopy in August, 2014, which revealed no abnormalities on the polypectomy site.

2.2. Immunohistochemistry, EBER in situ hybridization, and double labeling

Immunohistochemical stains for CD20, CD3, CD4, CD8, SMA, CD21, CD23, CD35, kappa, lambda, IgG, IgG4, and ALK were performed on formalin-fixed, paraffin-embedded (FFPE) tissue sections following routine procedures, on a Ventana Benchmark automated stainer (Ventana Medical Systems, Tucson, AZ). EBER in situ hybridization was performed with IHC/EBER double labeling according to a published protocol (7)

2.3. T-cell receptor gamma gene rearrangement

DNA was extracted from FFPE tissue and PCR amplified for detection of T-cell receptor (TRG locus) gene rearrangements. A multiplexed PCR reaction was performed following a published protocol (8), using primers that interrogate TRG rearrangements involving all of the known V γ family members, and the J γ 1/2, JP1/2 and JP joining segments. To allow for fluorescence detection, each joining region primer was covalently linked to a unique fluorescent dye. The products were analyzed by capillary electrophoresis on an ABI 3130xl Genetic Analyzer, and electropherograms were analyzed using GeneMapper software version 4.0 (ABI). Duplicate reactions were run for each sample, and the reaction was repeated on independent sections from the lesion, producing four separate assay plots.

3. Results

3.1. Microscopic findings and diagnosis

The H&E sections demonstrated colonic mucosa with surface ulceration and marked lymphohistiocytic infiltrate forming a polypoid, tumor-like lesion (Figure 1). The infiltrate was composed of scattered follicles surrounded by a polymorphous proliferation containing abundant plasma cells, small lymphocytes, and numerous spindle cells with indistinct pale cytoplasm, oval to elongated nuclei, dispersed chromatin and small nucleoli, focally in a storiform pattern. Mitotic activity was low. CD20 revealed scattered well-defined follicles. CD3 showed numerous interfollicular T-cells, which were predominantly small to medium-sized and with no significant cytologic atypia. Kappa/lambda stains revealed polyclonal plasma cells, which were positive for IgG, but only scattered plasma cells (<10%) stained for IgG4. There was strong staining for SMA associated with the spindle cell proliferation, but CD21, CD23 and CD35 were negative, only staining the FDC meshworks associated with the interspersed follicles (Figure 2, A & B). EBER was positive in the spindle cells (Figure 2, C). The findings support a diagnosis of inflammatory pseudotumor, with EBV positivity.

3.2. Smooth muscle actin/EBER double labeling

To determine the specific cell types infected by EBV, we performed double labeling with EBER and both CD20 and SMA. As shown in figure 2D, the majority of EBER+ cells co-expressed SMA, consistent with a myofibroblastic or fibroblastic reticular cell origin, but no co-localization was seen with EBER and CD20.

3.3. TCR γ -chain gene rearrangement study

Sizing control reactions indicated that the quality of the extracted DNA was adequate for all PCR reactions (Figure 3A). TRG PCR revealed several peaks, within a polyclonal background suggestive of a restricted but not clonal TCR gene rearrangement pattern (Figure 3B).

4. Discussion

Our case has several peculiar features worthy of report to the medical community. First, the anatomic site is unusual for inflammatory pseudotumor. The majority of previously reported GI tract IPTs likely represent non-specific inflammatory response to known irritants. We are aware of only a single prior case reported from Taiwan that documents an EBV-positive IPT in the gastrointestinal tract(9). In their report, the colonic polyp was diagnosed as IPT-like FDC tumor, with clinical and morphologic features highly similar to our case, albeit with FDC markers expressed by spindle cells. Our case differs from the former case in that the spindle cells are positive for SMA and negative for all three FDC markers tested. Two additional cases were reported with similar clinical and gross anatomic features, but neither was studied for EBV or the precise cellular lineage by immunophenotypic studies (4, 10). Cheuk et al. in their series reported one case with FDC markers presenting as a peri-pancreatic mass. It apparently was adjacent to the duodenum, but a luminal mass lesion was not identified (3).

The current case was referred to us in consultation. Morphologically, the polymorphous nature of the infiltrate raised concern for diagnosis of peripheral T-cell lymphoma. Additionally, T-cell receptor gene rearrangement studies performed at an outside laboratory reported a “clonal” pattern. Repeat of the TCR gene rearrangement studies in our laboratory showed a restricted pattern, with multiple peaks, not felt to be diagnostic of a clonal process. Although clonal TRG rearrangements are most commonly associated with T-cell lymphoproliferative disorders, abnormal T-cell rearrangement patterns and occasionally clonal peaks may be detected in a variety of non-neoplastic conditions as well, including unusual responses to viral infections, such as EBV(11). Notably, Lee et al. reported that the tumor-infiltrating T cells of a EBV+ gastric adenocarcinoma were oligoclonal and likely immunoresponsive to EBV-encoded peptides, including EBNA1, LMP2, or BARTs(12). A similar situation was reported in a pancreatic inflammatory pseudotumor, which was speculated to be associated with autoimmune pancreatitis. The authors suggested that the oligoclonal T cells could represent autoimmune T cells to pancreatic antigens (13). The reported case contained numerous SMA-positive spindle cells, but was not studied for EBV.

Prior authors have suggested that EBV+ spindle cell lesions, whether they have been called IPT or IPT-like FDC tumor, are part of the same spectrum (14). The earliest reports of splenic IPT identified expression of SMA on the EBV-positive spindle cells, suggesting that they were closely related to myofibroblasts. However, another cell type positive for SMA in lymphoid tissue is the fibroblastic reticular cell (FRC). Both FRC and FDC are of mesenchymal origin, and are thought to be functionally and ontogenetically related, arising from perivascular precursors (15, 16). In one study the FDC markers CD21 and CD23 were upregulated in the paracortical FRC meshworks of angioimmunoblastic T-cell lymphoma,

suggesting plasticity in the immunophenotype of these mesenchymal elements within lymphoid tissue(16).

Some investigators proposed clinical differences between SM!+ and FDC+ IPT. They suggested that IPT positive for SMA are usually cured by local excision, while IPT-like FDC tumors may be real neoplasms, needing a more aggressive approach for successful clinical management (3). The clinically aggressive nature reported by Cheuk et al. may be related to the size of the lesion at diagnosis, and the ease of resection(3). Most of their aggressive cases involved the liver, whereas tumors presenting in the spleen had no recurrences. Notably, the GI case from Taiwan(9) and our case in the colon differed in phenotype (FDC vs. FRC/myofibroblastic markers), but were otherwise similar in terms of morphology and EBV status, further emphasizing the close relationship among these lesions.

Correct diagnosis of inflammatory pseudotumor is challenging, as several other entities morphologically resembling IPT must be considered. ALK-1 positive inflammatory myofibroblastic tumors represent a separate disease entity. Although these two terms have been used interchangeably in the literature, inflammatory myofibroblastic tumor usually defines cases with spindle cells positive for ALK-1, and the *ALK* translocation. These cases are true neoplasms, carrying higher risks of recurrence, and therefore warrant wider excision and closer follow-up. Our case was negative for ALK-1, ruling out inflammatory myofibroblastic tumor. IgG4-related disease is also in the differential diagnosis. IgG4-related disease of GI tract can present with a mass lesion, microscopically composed of abundant plasma cells of predominantly IgG4-type, proliferation of fibroblasts, and marked fibrosis, mimicking the histology of IPT. A very rich plasma cell component was seen in our case, raising a possibility of IgG4-related disease. However, IgG4+ plasma cells only comprised a minority of IgG+ cells in our case, making this diagnosis unlikely.

In summary, we report a novel case of EBV-positive IPT presenting as a colonic mass. Correct diagnosis of EBV+ IPT in rare locations is critical, to avoid misdiagnosis. This can be achieved by carefully reviewing the morphology, appropriate ancillary testing, and appreciation that these novel spindle cell lesions are not restricted to liver and spleen.

Acknowledgments

This work was supported through the Intramural Research Program of the Center for Cancer Research, National Cancer Institute, National Institutes of Health. Intramural NIH funding number: ZIA SC 000550. Dr. Rajan Duggal was supported by a Grant from the *Visitor Training Programme* of the American Society of Hematology.

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Figure 1. Histological and immunohistochemical features of a colonic IPT

A. At low power(20X), the lesion was composed of colonic mucosa with reactive follicles and a marked interfollicular lymphohistiocytic infiltrate forming a polypoid, tumor-like lesion. **B.** At high power (400x), the infiltrate contained abundant plasma cells, small lymphocytes, vascular proliferation, and interspersed spindle cells with bland cytological features. **C.** CD3 showed numerous interfollicular T-cells (100x). **D.** CD20 revealed scattered well-defined follicles (100x). **E.** IgG shows abundant plasma cells (200x), that were negative for igG4 (not shown) **F.** SMA shows rich dendritic pattern of staining associated with the spindle cells (200x).

Figure 2. Characterization of the spindle cell component

A. The spindle cells are positive for SMA, which spares the residual lymphoid follicles (40x). **B.** CD21 stains the FDC meshworks of the follicles but is negative in the remainder of the lesion (40x). **C.** EBER highlights the numerous spindle-shaped cells, which surround residual follicles (200x). Inset shows cells at high power. **D.** Double staining for EBER (black) and SMA (brown) shows co-localization of EBER in spindle cells (400x). No co-localization was seen with EBER and CD20.

Figure 3. T-cell receptor γ -chain (TRG) gene rearrangement studies

DNA extracted from FFPE tissue was subjected to multiplexed PCR amplification of T-cell receptor γ -chain (TRG) gene locus. The products were analyzed by capillary electrophoresis. TRG PCR revealed several moderate peaks, within a polyclonal background, indicating a restricted but not clonal TCR gene rearrangement pattern. Duplicate PCR reactions were performed showing similar results.