



## Case Report

## Recurrent fibrin associated diffuse large B-cell lymphoma: A case report

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## ABSTRACT

Fibrin-associated diffuse large B cell lymphoma (FA-DLBCL) is a rare entity, often incidental finding, categorized under “diffuse large B cell lymphoma associated with chronic inflammation (DLBCL-CI)” in 2017 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues. Here we report a 48-year-old male with FA-DLBCL who experienced recurrence within one year from initial presentation. The patient had a history of an abdominal aortic aneurysm and underwent an endovascular aneurysm repair (EVAR) in 2013. Later in 2019, he was found by CT aortogram to have endoleak of the aneurysm repair. He underwent an open abdominal aortic aneurysm repair with explant of the endovascular stent. The explanted graft was sent to pathology and was found on gross examination to have ample adherent tissue. On microscopic examination this tissue was composed of abundant fibrinous material with several foci of large pleomorphic lymphocytes with enlarged round to polyhedral nuclei, prominent nucleoli, open chromatin, and scanty cytoplasm. Necrosis was also seen in a largest focus of tumor infiltrate. By immunohistochemistry, the atypical, large lymphocytes expressed CD20 and MUM-1; and positive for EBV, by Epstein-Barr virus (EBV) in situ hybridization (EBER-ISH). Together, the diagnosis for FA-DLBCL was made. Further work up by PET scan showed no active disease. The patient re-presented 10 months later with right lower extremity ischemia due to the vascular graft thrombosis. The thrombectomy specimen showed identical findings of his initial FA-DLBCL. Here we discuss the clinicopathologic findings of this entity and the importance of clinical follow up.

## 1. Introduction

Fibrin-associated diffuse large B cell lymphoma (FA-DLBCL) is a rare entity, categorized under DLBCL associated with chronic inflammation (DLBCL-CI) according to 2017 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues. DLBCL-CI is a subtype of mature B cell lymphomas associated with Epstein-Barr virus (EBV) in the setting of long-standing chronic inflammation such as chronic skin ulcers, chronic osteomyelitis, or implants. The most well-known example of DLBCL-CI is pyothorax-associated lymphoma (PAL), an entity which is commonly seen in patients with tuberculosis treated with artificial pneumothorax [1].

While DLBCL-CI is seen in the context of systemic inflammation, FA-DLBCL has been reported in immunocompetent patients as an incidental finding during microscopic examination of specimens collected for other reasons. Specifically, FA-DLBCL is mostly seen in immunologically sequestered sites, such as seen with pseudocysts [2–4], cardiovascular

lesions (prosthesis, thrombi, and grafts) [4,5], implants and chronic subdural hematomas [6]. The lymphoma cells are usually found as small aggregates of atypical lymphocytes embedded within fibrin. The individual tumor cells have large, irregularly folded nuclei with prominent nucleoli. Apoptotic bodies are prominent and mitotic figures are present. The immunophenotype is indicative of activated EBV positive B cell phenotype. Clinically, in contrast to other forms of DLBCL-CI, FA-DLBCL shows a more indolent course and overall favorable prognosis. In a reported series of 12 FA-DLBCL cases, only three patients had recurrent disease all with cardiac/vascular abnormalities, as seen in our patient [4].

## 2. Case presentation

The patient is a 48-year-old male with past medical history of juvenile rheumatoid arthritis, on abatacept, and premature extensive peripheral artery disease necessitating right femoropopliteal bypass for

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popliteal artery aneurysm and infrarenal abdominal aortic aneurysm endovascular repair in 2013. He was noted to have increase in the size of his aneurysm with endoleak of his proximal aneurysm during surveillance imaging in 2019. He therefore had open repair with removal of his old stent-graft and replacement of his vascular graft.

The explanted *endo*-logic band graft was sent to pathology. On gross examination, there was abundant adherent red-brown soft tissue on the outer and inner surfaces of the graft which was submitted for microscopic examination. On microscopic examination, the tissue showed mostly fibrinous material with several foci of large, atypical lymphocytes with enlarged round to polyhedral nuclei, prominent nucleoli, open chromatin, and scanty cytoplasm (Fig. 1A). By immunohistochemistry (IHC), the large, atypical lymphocytes were positive for CD20 (Figs. 1B and 2A), MUM1 (Fig. 2B), dim/partial CD21, partial/dimCD45, and with a Ki67 proliferative index of 60–70%; there was no

expression in the atypical lymphocytes for CD3, CD5, CD10, CD30 (Fig. 2C), cyclin D1, c-MYC, BCL6, BCL2, and HHV8. The immunophenotypic findings were consistent with non-germinal center B-cell phenotype. By Epstein-Barr virus (EBV) Encoded RNA in situ hybridization (EBER-ISH), lymphoma cells were positive for EBV (Fig. 2D). Fluorescent in situ hybridization (FISH) studies for BCL2, BCL6 and MYC rearrangements were performed and all were negative. Based on these findings, including clinical presentation, morphology, immunophenotype, and molecular/FISH results, a diagnosis of FA-DLBCLC was rendered.

He was referred to oncology for follow-up and staging. He did not have fever, night sweats or weight loss and had normal energy level with Eastern Cooperative Oncology Group (ECOG) performance status of 0. He did not have lymphadenopathy on exam. PET-CT did not show any FDG avid lesions or enlarged lymph nodes. There was some increased

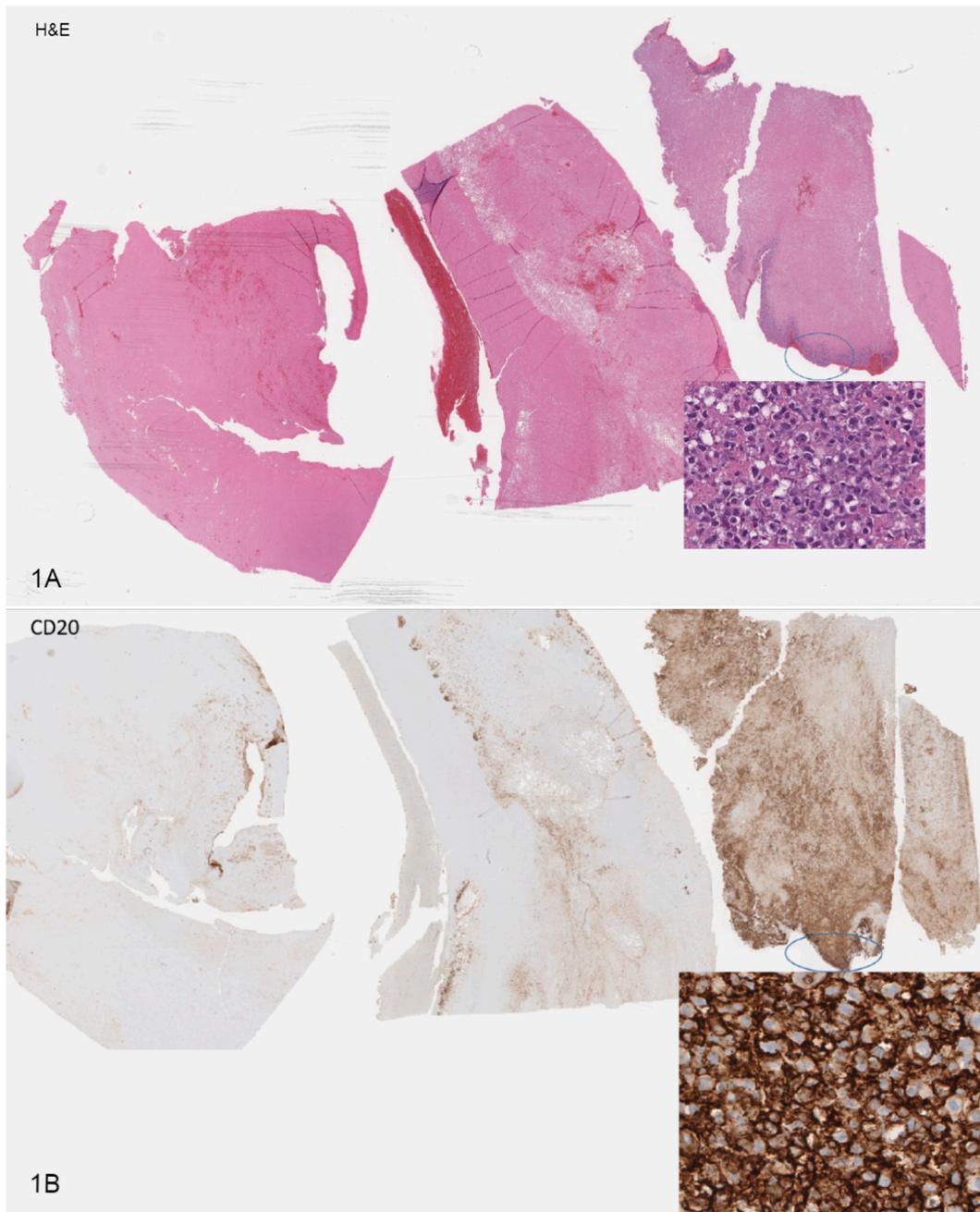
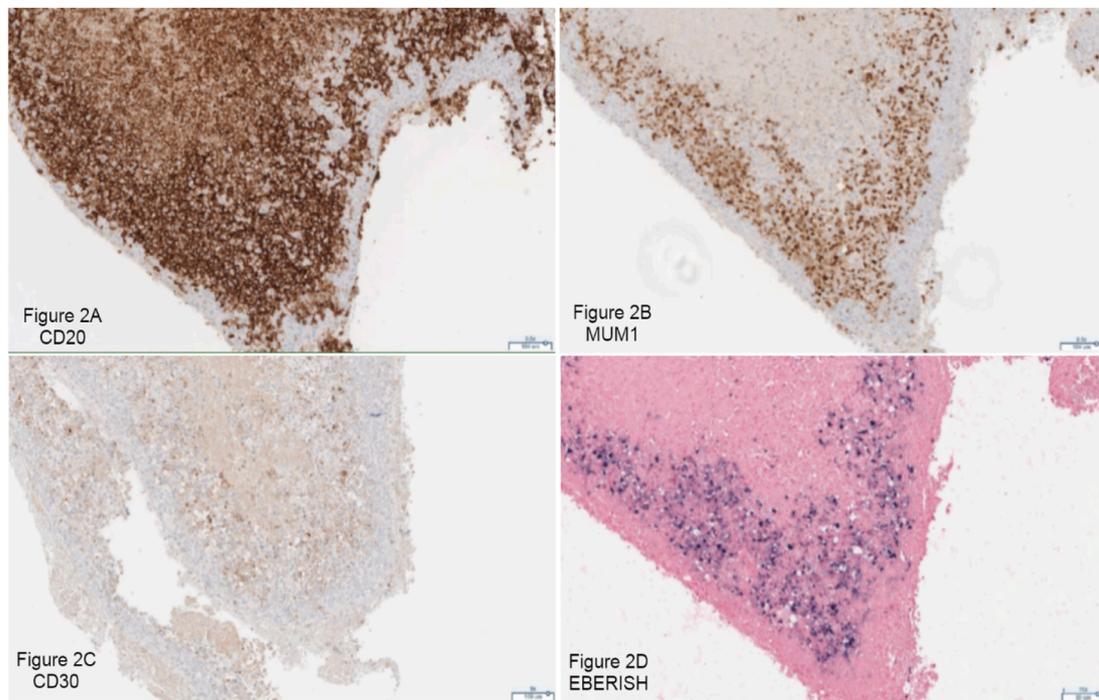


Fig. 1. H&E section (1A) and CD20 IHC (1B) on initial lymphoma diagnostic tissue.



**Fig. 2.** CD20 (2A), MUM1 (2B) and CD30 (2C) IHC stains; and EBER-ISH (2D) on initial lymphoma diagnostic tissue.

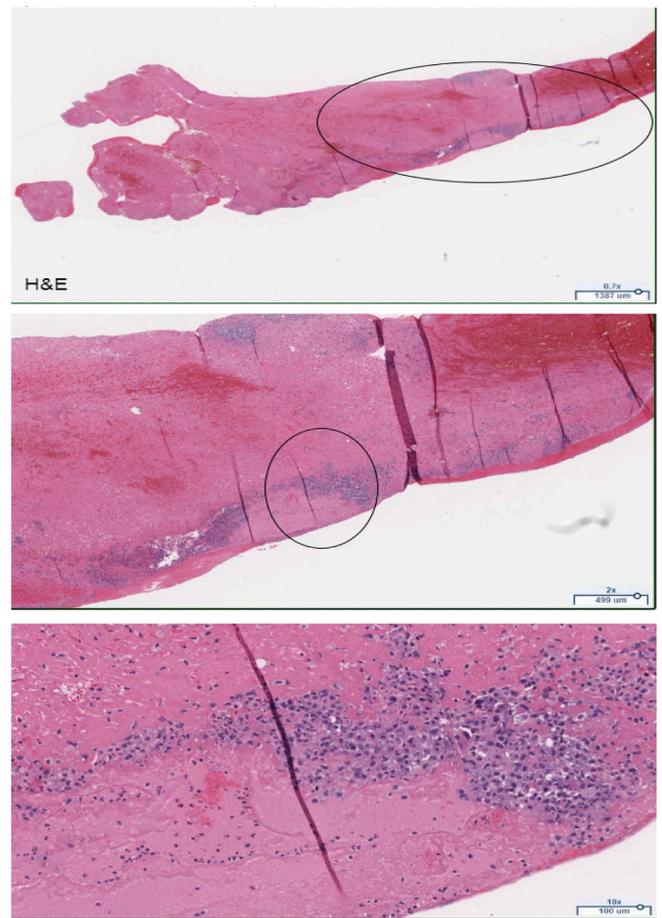
FDG activity of the abdominal aorta and common iliac arteries that was consistent with post-operative inflammation. He was discharged home with close monitoring but without chemotherapy or radiation therapy.

Ten months after discharge, he re-presented to medical care with acute right lower extremity ischemia. A CT angiogram showed a near occlusive intraluminal thrombus of the right common femoral artery. His symptoms improved with anticoagulation and he was discharged home with a plan for subsequent re-vascularization. However, he was readmitted a few days later for acute worsening of his symptoms. He therefore underwent right common femoral artery thrombectomy and bypass. Histologic sections of the graft thrombus again showed clusters of large pleomorphic lymphocytes within the fibrin thrombus (Fig. 3). By immunohistochemistry, the neoplastic lymphocytes showed expression for CD20 (Fig. 4A) and dim Pax5, while negative for CD3. Again, EBV was positive by EBER-ISH (Fig. 4B). Together, the findings supported his disease recurrence in the context of thrombus. He had a restaging PET/CT scan that showed increased FDG activity at the proximal aspect of the graft and a soft tissue attenuation in the region adjacent to the graft raising a concern for residual lymphoma (Deauville 5). There was no other hypermetabolic lymph nodes or vascular lesions. Due to recurrence of disease after surgical resection he was started on treatment with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) and his abatacept was held.

### 3. Discussion

In this report, we present a case of a recurrent FA-DLBCL in the setting of vascular graft. The primary lesion was removed surgically as soft tissue attached to a vascular graft. The following oncological work-up did not reveal active disease in any site and no further treatment was pursued at that time. The patient returned with acute ischemia due to a new common femoral artery thrombus. The retrieved thrombotic material showed recurrent FA-DLBCL.

FA-DLBCL has been reported in case reports and small case series largely seen in association with chronic conditions including pseudocysts (testicle, spleen, liver, adrenal) [2–4], an arachnoid cyst [7], chronic subdural hematoma [6,8] cerebral artery hematoma [9], orthopedic prosthesis [2], vascular grafts and cardiac valve prostheses



**Fig. 3.** HE sections on recurrent lymphoma tissue.

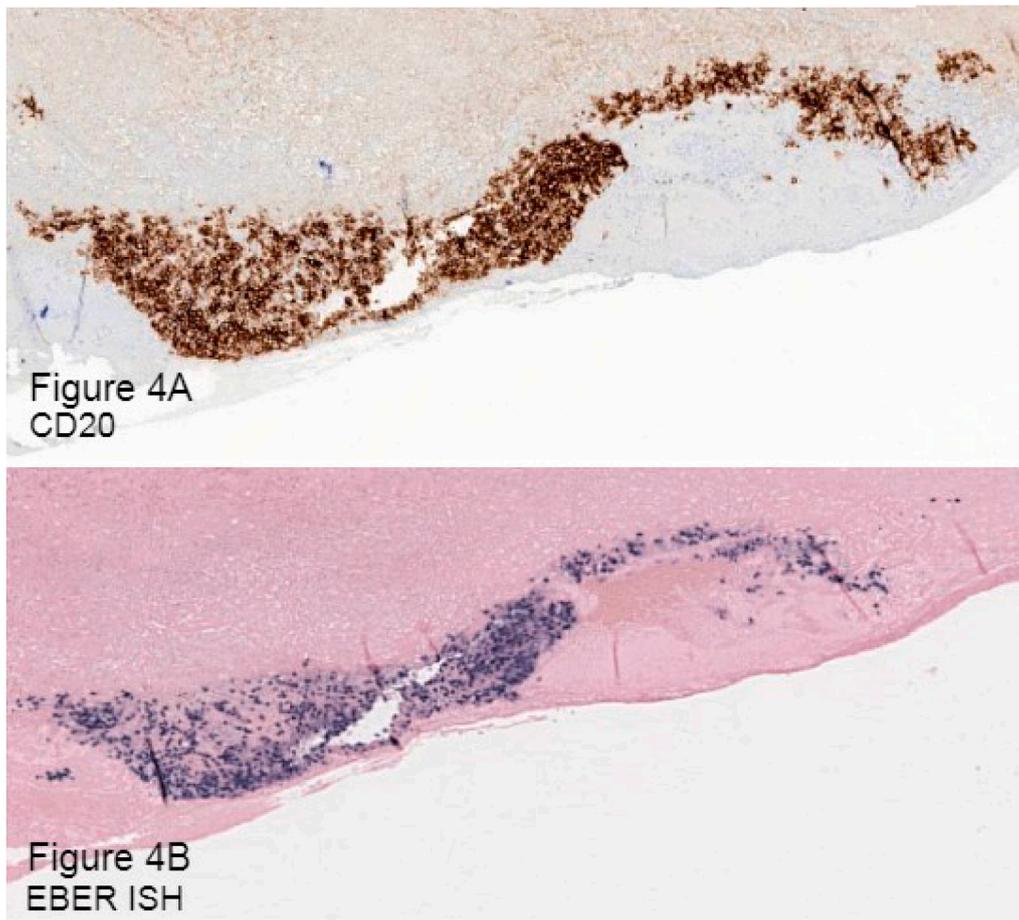


Fig. 4. CD20 IHC (4A) and EBER-ISH (4B) on recurrent lymphoma tissue.

[4,5]. Rare cases of FA-DLBCL have been reported in association with another underlying neoplasm, to include ovarian cystic teratoma [10] and atrial myxoma [4,11,12].

The common features among reported cases include: 1) the incidental finding of the lymphoma, 2) often no mass formation, 3) majority of cases are non-germinal center B-cell phenotype, 4) EBV-positivity associated with latent membrane protein-1 (LMP1) and EBNA2 expression in majority of cases and 5) overall favorable prognosis [11]. A recent literature review of total 50 reported FA-DLBCL cases demonstrated that 74% of reported cases (37 cases) demonstrated non-germinal center B-cells phenotype (non-GCB), while 12% (6 cases) had germinal center B-cell phenotype (GCB) and 14% (7 cases) showed non-definitive findings (11). DLBCL with GCB immunophenotype was reported to have better overall survival compared to DLBCL with non-GCB immunophenotype for nodal lymphoma. However, it is unclear if the outcome of GCB is different from non-GCB in the setting of FA-DLBCL.

Pathogenesis of FA-DLBCL is thought to occur secondary to chronic/latent EBV infection in the setting of chronic inflammatory condition. In normal conditions, EBV infected B cells expressing LMP-1 are subject to be attacked by cytotoxic T cells. However, when there is a chronic inflammatory state, resultant from introduction of a foreign material (surgical mesh, metal implants, etc.), this can be a suitable environment for developing lymphoma, particularly in the setting of latent EBV infection [8]. The oncogenic feature of EBV is proposed to be attributed to EBV latent membrane protein-1 (LMP1) resulting in NF-kappa B activation and expression of Bcl-2 which consequently inhibits EBV infected cell apoptosis [8,12]. In addition, EBV infected B cells produce IL-10, a T cell inhibitor which further suppresses the immune surveillance and provide a local immunosuppressed microenvironment [2,13].

Furthermore, patients with autoimmune diseases have increased risk of developing lymphoma, which mechanistically may be through underlying chronic inflammatory state and/or secondary treatment with immunosuppressant medications [14]. As mentioned above, our patient was on immunosuppressant therapy (abatacept) for juvenile rheumatoid arthritis. Abatacept is a recombinant fusion protein which selectively inhibits T cell activation by binding to CD80 and CD86 [15]. It is well recognized that immunosuppressive therapy is associated with increase the risk of developing lymphoma.

Of the 50 cases of FA-DLBCL in the literature, 4 cases of poor outcomes related to disease have been reported to include persistent disease, recurrence or death due to disease. Three of these cases were associated with cardiovascular prosthetic graft thrombosis of which two died of recurrent thromboembolic events containing EBV positive large B cells and one with persistent disease after surgical resection [4]; in addition to the one patient who experienced death secondary to FA-DLBCL involving chronic subdural hematoma with involvement of the adjacent brain parenchyma [8]. Two prior cases, as well as, the current case have demonstrated recurrence of FA-DLBCL in the setting of cardiovascular prosthetic graft failure [4]. FA-DLBCL may be the cause of endoleak in the aneurism repair for current case.

Given the likelihood of recurrence and/or persistent disease, particularly in the high-risk population with multiple other comorbidities, a thorough microscopic examination of vascular graft associated thrombus is necessary for patient management. Collectively, previously reported cases and our current case, bring a total of five cases of recurrent and/or persistent disease of FA-DLBCL, which perhaps suggests a more aggressive clinical course than initially predicted. Persistent disease even after completing course of chemotherapy may indicate that these locations may also be shielded from chemotherapy. The

optimal approach for managing recurrent disease after incomplete surgical resection is unknown. The risk for thromboembolic disease is high with cardiovascular FA-DLBCL. Further evaluation is required to determine the overall clinical behavior of this disease.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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