EBV-negative fibrin-associated large B-cell lymphoma arising in thyroid hyperplastic nodule
Report of a case and literature review

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Introduction

Fibrin-associated large B-cell lymphoma (FA-LBCL) is a newly defined lymphoma entity, characterized by a non-mass-forming, microscopic-sized, large B-cell lymphoma (LBCL) found within fibrinous materials, and frequently associated with Epstein-Barr virus (EBV). It has been separated out from the category of diffuse LBCL associated with chronic inflammation, in view of the highly favorable outcome with or without adjuvant treatment. FA-LBCL has been described in a wide variety of anatomic locations, unified by the presence of a milieu of fibrinous materials or necrotic debris. We report herein an unusual case arising within a thyroid hyperplastic nodule and lacking EBV association, and review the literature on this rare entity.

Case report

A 76-year-old Chinese woman presented with long-standing non-toxic goiter. Ultrasonography showed multinodular goiter with a dominant 8.6 x 5.5 x 5.2 cm solid-cystic nodule in the left lobe showing retrosternal extension. Ultrasound-guided fine needle aspiration of the dominant nodule showed benign follicular nodule. Left hemithyroidectomy was performed.

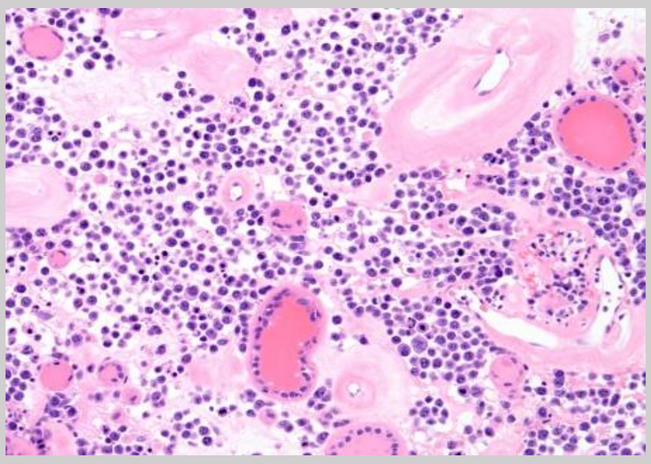
Pathological findings

The hemithyroidectomy specimen showed a 7.5 x 5.0 x 4.0 cm well circumscribed, partially encapsulated nodule, as well as multiple variably circumscribed nodules in the background. The index nodule was composed of variable-sized colloid-rich follicles lined by cuboidal cells with uniform round nuclei; nuclear features of papillary thyroid carcinoma were not present. Prominent edema, hemorrhage and fibrin exudation was noted in the stroma. Many tiny loose clusters of atypical lymphoid cells were seen among the fibrinous materials, being entirely confined within the hyperplastic nodule. The lymphoid cells were large, with round to irregularly folded nuclei, vesicular chromatin, single or multiple prominent nucleoli and amphophilic cytoplasm. Mitotic figures were readily identified.

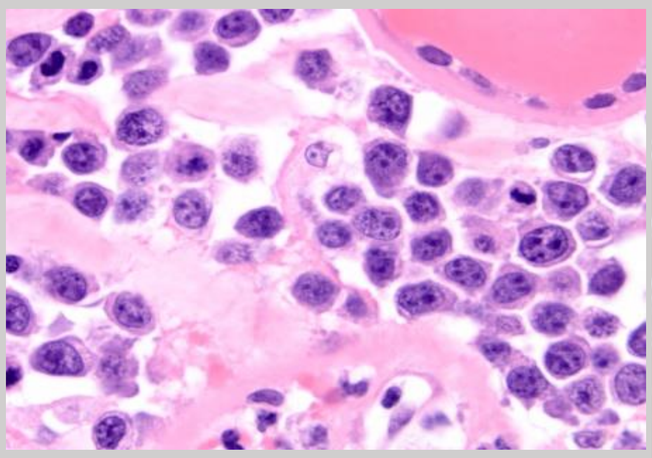
Immunostaining showed that the atypical lymphoid cells were CD20+, PAX5+, CD3-, CD10-, BCL6+, BCL2+, CD30-, MUM1+, MYC+ and HHV8-. The Ki67% proliferation index was over 95%. The PD-L1 expression was low. Immunostaining for EBNA2 and in-situ hybridization for EBV-encoded RNA (EBER) were negative. Fluorescence in-situ hybridization (FISH) study showed no evidence of *MYC* rearrangement using break-apart FISH probes (Vysis). The overall features were consistent with a diagnosis of FA-LBCL.

Clinical outcome

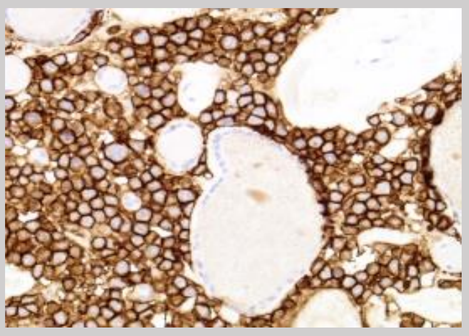
Staging CT and PET- CT showed no suspicious hypermetabolic lesion, and bilateral bone marrow examination showed no lymphoma involvement. The patient was given three cycles of R-CHOP, and was disease-free 55 months from diagnosis.



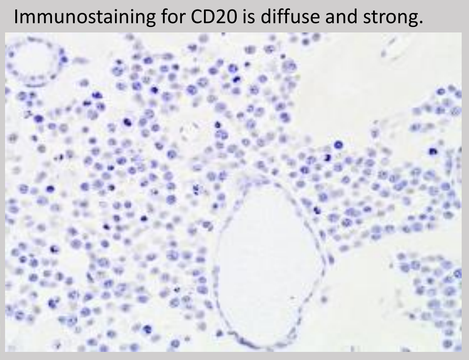
The thyroid nodule is a hyperplastic nodule with colloid-rich follicles lined by cuboidal cells. Prominent edema and fibrin exudation is noted in the interstitium, within which loose aggregates of atypical lymphoid cells are found.



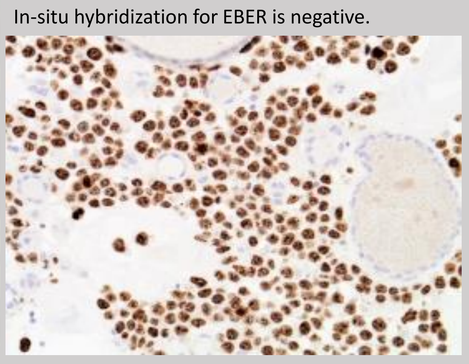
The lymphoma cells are large with vesicular chromatin, prominent nucleoli and amphophilic cytoplasm.



Immunostaining for CD20 is diffuse and strong.



In-situ hybridization for EBER is negative.



The Ki67% proliferation index is over 95%

Literature review and discussion

We report a case of FA-LBCL arising within the thyroid, only the second case reported in this location. This case is further unusual in that EBV is negative, only the fourth such case in the literature.

Eighty-seven cases of FA-LBCL (including the current one) are identified in the English literature through Pubmed search. A male predominance was observed (n = 47, 54%), and the age ranged from 25 to 96 years (median 61 years). Clinical presentation was variable, being mostly related to the site of involvement or underlying pathologic condition. The majority of reported cases arose in atrial myxoma (n = 22, 25%). A significant number of cases were associated with foreign materials (n = 29, 33%), with the duration of implant ranging from 1 – 32 years (median 10 years). Seventeen cases arose in cystic lesions, including degenerative pseudocysts and epithelium-lined cysts of various locations, as well as cystic tumors. These findings confirm that rather than being specific to a particular anatomic location, FA-LBCL can potentially develop in any anatomical site, provided that the appropriate fibrin-rich microenvironment is present. More cases occurring in various anatomic locations are expected to be described in the future as the awareness of this entity increases.

Among the cases with systemic workup and staging, all but one case showed no evidence of systemic disease. The latter case was a 68-year-old man who presented with distal limb embolism 7 years after an aortic graft implant. FA-LBCL was identified within the emboli, and subsequent PET-CT showed a hypermetabolic adrenal mass, biopsy of which showed rare EBV-positive large B-cells. Follow up information was available for 69 cases (range 1 – 240 months, median 14 months). The majority of patients (n = 58, 84%) were alive with no evidence of lymphoma. Residual or recurrent disease was documented in only 4 cases (5%), 2 of which arose in association with aortic graft and 1 from atrial myxoma; these findings suggest that FA-LBCL occurring in the cardiovascular system may develop recurrence due to difficulties in complete removal of the lesion or possible transport of tumor cells elsewhere through the circulation. The remaining case presented with chronic subdural hematoma, who developed disease progression, systemic dissemination, and died after 3 months. However, the presence of brain invasion suggests that this case may not be a “pure” example of FA-LBCL.

Histologically, all cases show microscopic aggregates of large atypical lymphoid cells. They are non-mass-forming and are found within a background of fibrin or degenerative debris. The lymphoid cells often show large pleomorphic nuclei, irregular nuclear membrane, single or multiple nucleoli and high mitotic activity. Immunohistochemically, they show expression of B-cell markers. Phenotyping by Hans algorithm shows 74 of 79 (93%) cases exhibiting a non-germinal center B-cell phenotype. Testing for EBV by in-situ hybridization for EBER shows positive labeling in 82 of 86 (95%) cases. Immunostaining for EBNA2 performed in 39 of the EBER-positive cases is positive in 36 cases (92%), indicating EBV type III latency.

This is only the fourth reported case of EBV-negative FA-LBCL in the literature. These four cases affected two males and two females with a median age of 68.5 years. Two cases arose in atrial myxoma, 1 arose in a native myxomatous mitral valve, and 1 in a thyroid hyperplastic nodule. Three cases showed non-germinal center B-cell phenotype and one germinal center B-cell phenotype. All cases were alive without evidence of lymphoma, with only two cases receiving adjuvant chemotherapy. Hence, no significant differences in clinicopathologic features are found between EBV-associated and EBV-negative FA-LBCL based on the currently available cases, and EBV status does not appear to affect the clinical outcome.

Given the microscopic nature of FA-LBCL, it is not surprising that most patients do well after surgical excision alone, even without adjuvant treatment. Local persistence or recurrence of disease has rarely been documented, and is probably related to incomplete removal, in particular for those examples located in the cardiovascular system. There is no conclusive evidence that FA-LBCL can progress to systemic disease and cause morbidity or mortality. Awareness of the indolent behavior of this rare entity is important so as to avoid unnecessary aggressive therapy.

Table 1. Summary of FA-LBCL as reported in the literature

Localization	No. of case	Sex/ Age	Scenario	Cell-of-origin	EBV+	Outcome
Cardiovascular: cardiac myxoma	22	M:F=11:11 Age: 44-81 (median 54)	/	Non-GCB: 16/21 GCB: 4/21 Plasmacytic: 1/21	18/20	Well at 1-240 months (n=16, including 12 without adjuvant therapy); Local lymphoma recurrence at 25 months and dying 1 month later from embolic stroke (n=1); Died of unrelated disease (n=2)
Cardiovascular: others	15	M:F=13:2 Age: 29-91 (median 68)	Aortic graft (n=7); atrial thrombus (n =3); aneurysm (n=2); myxomatous valve (n=1), bioprosthetic valve (n=1); aortic thrombus (n=1)	Non-GCB: 13/13 GCB: 0/13	14/15	Well at 6-54 months (n=9, including 3 without adjuvant therapy); Recurrence or residual disease at 24-31 months (n=2, one with adjuvant therapy); Died from operative complication or unrelated disease (n=3)
Breast implant	19	M:F=0:19 Age: 47-71 (median 65)	/	Non-GCB: 16/17 GCB: 1/17	19/19	Well at 1-96 months (n=14, including 11 without adjuvant therapy)
Cystic lesions	17	M:F=12:5 Age: 27-88 (median 57)	Pseudocyst and cysts (n=15, including adrenal, renal, paratesticular, retroperitoneal, splenic, pancreatic, old surgical site); ovarian mature cystic teratoma (n=2)	Non-GCB: 16/16 GCB: 0/16	17/17	Well at 4-84 months (n = 11, including 3 without adjuvant therapy)
Central nervous system	8	M:F=6:2 Age: 25-96 (median 69)	Subdural hematoma (n=4); epidermoid or arachnoid cyst (n=3); cerebral artery aneurysm (n=1)	Non-GCB: 6/6 GCB: 0/6	8/8	Well at 3-48 months (n=4, including 4 without adjuvant therapy); Died from tumor dissemination at 3 months (n=1)
Miscellaneous	6	M:F=5:1 Age: 66-79 (median 76.5)	Knee prosthesis (n=2); thyroid goiter (n=2); adrenal mass (n=1); testicular hematoma (n=1)	Non-GCB: 6/6 GCB: 0/6	5/6	Well at 12-84 months (n=4, including 1 without adjuvant therapy); Died of unrelated disease (n=2)

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This study had been submitted to The International Journal of Surgical Pathology and is currently under review.