Breast implant-associated Epstein-Barr virus-positive large B-cell lymphomas: a report of three cases

Breast implant-associated lymphomas have recently been recognized by the World Health Organization as a subgroup of anaplastic lymphoma kinase (ALK)-negative anaplastic large-cell lymphomas (ALCL). The mean age of patients with this condition is 50 years, and the mean interval from implant placement to ALCL diagnosis is 11 years. Tumoral cells are typically large and pleomorphic, including the so-called hallmark cells. Their phenotype is similar to that of triple-negative (*ALK, DUSP22, TP63*) ALCL with strong CD30 expression, presence of pSTAT3 and loss of pan-T-cell antigens. Tumoral cells may be localized within the seroma cavity, involve pericapsular fibrous tissue, loco-regional lymph nodes or, exceptionally, can present with disseminated disease. In general, it is an indolent condition, and most localized cases do not require systemic treatment.[1] In this letter, we describe three patients with a history of breast implants who developed an Epstein-Barr (EBV)-positive large B-cell lymphoma (LBCL) in the capsular wall. These findings thus expand the spectrum of lymphoproliferative disorders associated with breast implants.

The three patients were women, aged 55, 59 and 63 years at diagnosis. One patient underwent cosmetic surgery 15 years earlier and the other two were treated for breast cancer 10 and 20 years earlier, respectively. They presented with clinical symptoms related to local mass effect, with fat necrosis in one patient and hematoma in the other two. In all three cases, local periprosthetic liquid accumulation was detected by imaging. None of the women complained of fever, weight loss, or other systemic symptoms, and none of them showed lymphadenopathies or organomegalies elsewhere at diagnosis. Capsulectomy was performed in all patients and, at the time of writing, two of them are free of disease (median follow-up of 25 months) and the third failed to attend follow-up appointments. Data regarding the type of implant (silicone or saline; textured or smooth) are not available (Table 1).

With respect to histology, two cases showed small clusters of large atypical cells located under the fibrin layers of the inner part of the capsulectomy, or immersed within it. No floating cells were found in the seroma, and no cells were found to have infiltrated the pericapsular soft tissue. In the third case, a tumor mass showing prominent perivascular angiocentric infiltration, with necrosis in a pattern mimicking lymphomatoid granulomatosis or other types of EBV-related B-cell lymphomas were found. Mitotic figures and apoptotic bodies were easily found. In addition, there was a striking population of accompanying mature plasma cells without a light chain restriction, and small, scattered follicles with germinal centers, in the outer part of the capsulectomy specimen. Most neoplastic cells were large, with abundant clear cytoplasm and large, irregular nuclei with prominent nucleoli, but Reed-Sternberg-like cells were occasionally identified. In all cases, a large majority of the neoplastic cells were positive for EBER (ISH), with EBV/LMP1 expression in a smaller proportion of neoplastic cells (Figure 1). EBNA2 was positive in two of the two cases studied. This data are consistent with an EBV latency type III pattern. In two cases, the neoplastic cells were positive for PAX5, CD79a, CD20, MUM1 and CD30 (dim in most of the cells). One of the cases showed expression of CD3, PERFORIN, TIA-1, MUM1, CD30, and CD20, and focally for CD79a, but was negative for CD4, CD8, CD56, TCRBETA, TCRGAMMA, and PAX5. This case was considered a B-cell lymphoma because of the distinct

Table 1. Clinical data and immunohistochemical markers studied in these series of cases.

Case	1	2	3
Sex	Female	Female	Female
Age at Diagnosis	55	59	63
Time to Follow-up	7 months	41 months	2 months
Previous Breast Cancer	No	Yes, 10 years earlier	Yes, 20 years earlier
Immunohistochemical Markers Studied			
CD20	POS	POS	POS
CD79a	POS	POS	POS
PAX5	POS	POS	NEG
MUM1	POS	POS	POS
CD3	NEG	NEG	POS
TIA-1	NEG	NEG	POS
PERFORIN	NEG	POS	POS
GRANZYME-B	NEG	NEG	POS
CD30	POS	POS	POS
P53	NEG	NEG	NEG
MYC	NEG	NEG	NEG
HHV-8	NEG	NEG	NEG
EBV (EBER)	POS	POS	POS
EBV (LMP-1)	POS	POS	POS
EBV (EBNA-2)	POS	NOT DONE	POS

POS: positive; NEG: negative; EBV: Epstein-Barr virus.

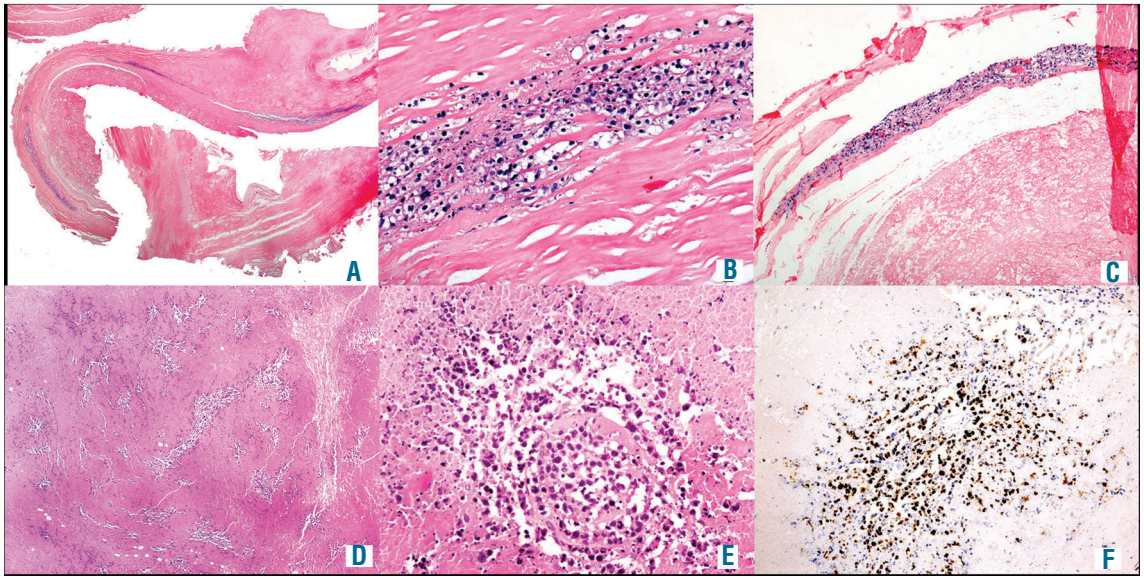

Figure 1. We present here representative images of cases 1 and 3. Representative hematoxylin and eosin staining images of cases 1 (A-C) and 3 (D-F) are shown in low- and high-power views (A and D (10X), B and E (40X), respectively. Epstein-Barr virus (EBV) (EBER) positivity of each case is shown in images (C) (10X) and (F) (20X), respectively.

expression of CD20 and CD79a and the consistency with previous findings describing CD3 aberrant expression in EBV-positive LBCL.[2] HHV8 and p53 were negative in all cases (Table 1). A diagnosis of EBV-positive diffuse large B-cell lymphoma (EBV-DLBCL) associated with breast implant was proposed, taking into account the massive presence of EBV and the clear expression of B-cell markers in all cases.

These cases have some features similar to those of with previously described cases. For example, Geethakumari *et al*. described a tumor classified as a plasmablastic lymphoma,[3] an EBV-positive LBCL developed 40 years after receiving a breast implant. At the recent European Association of Hospital Pharmacists (EAHP) Workshop (Edinburgh 2018), Dr A Wotherspoon illustrated a similar case diagnosed 9 years after placement of breast implants (*https://www.eahp-sh2018.com/*). A case of a LBCL diagnosed in a patient 44 years after placement of a breast implant lacks detail about the presence of EBV,[4] but the non-germinal center (non-GC) immunophenotype is consistent with the presence of EBV.

EBV-positive LBCL has also been reported in relation to other causes of immunosuppression,[5,6] in niches of long-standing chronic inflammation (pyothorax-associated lymphoma, or chronic inflammation [PAL]),[7] or in association with orthopedic metallic implants, where this was suggested as constituting a tumor arising in a setting of chronic inflammation or irritation in a confined body space.[8,9] All these conditions are associated with a poor outcome. Recently, EBV-positive indolent LBCL have been reported, as incidental findings, in atrial myxomas (n=3), thrombi associated with endovascular grafts (n=3), chronic hematomas (n=2), and pseudocyst walls (n=4). A diagnosis of "fibrin-associated EBV-positive LBCL" has been proposed for all these cases.[10] It is unclear whether, at this stage, EBV-positive LBCL associated with breast implants should be grouped with EBV-positive LBCL associated with PAL, or with fibrin-associated EBV-positive LBCL. Taking into account the clinical and social implications of including these cases in any of the above categories, we suggest that these tumors be classified separately until the clinical relevance of this classification has been clarified. Nevertheless, it is reasonable to hypothesize that EBV-positive LBCL developed in the limited space of the breast implant capsule, where chronic inflammation presumably plays a pathogenic role, and that it may have similarities with the EBV-positive LBCL developed in association with metallic orthopedic implants.[8,9]

In conclusion, we describe the morphological and immunohistochemical appearances of three cases of EBV-positive LBCL associated with breast implants, and note an increase in the diversity of the type of lymphomas that may be associated with this condition. More cases like these should be collected in an attempt to establish their etiology, prognosis and appropriate clinical management.

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