

EBV-associated Diffuse Large B-Cell Lymphoma identified in a breast implant capsule:

A new breast implant-associated lymphoma?

Introduction

Breast augmentation using implants is the most common cosmetic surgical procedure undertaken by women in the UK with 7,745 performed in 2018 ¹. A known rare sequela of textured breast implants is the development of *Breast Implant Associated Anaplastic Large Cell Lymphoma* (BIA-ALCL). The incidence of BIA-ALCL with textured implants is estimated as being between 1 in 3,817 to 1 in 30,000 women according to the FDA (2018) ². BIA-ALCL is a lymphoma which selectively affects T-cells. We report a case of an incidental Epstein Barr Virus (EBV) associated diffuse large B-cell lymphoma in a peri-implant capsule following long standing textured-surface cohesive silicone gel implants in an immunocompromised patient who was undergoing revisional cosmetic breast implant surgery. This is the first documented case in the literature of a B-cell lymphoma occurring in a breast implant capsule whether following cosmetic breast augmentation or postmastectomy reconstruction.

Case description

Presentation

A 51-year old woman presented for revision breast implant surgery having undergone a cosmetic breast augmentation 21 years earlier (in 1998 in the USA) with smooth, round saline-filled implants inserted via infra-mammary incisions. In the interim she had an uneventful exchange of implants 15 years ago (in 2004 in the UK), to textured firm cohesive

silicone gel implants (Allergan style 510 extra-full projection, full height, volume 560cc).

Textured surface implants were selected to reduce the chances of capsular contracture whilst the form-stable prostheses enabled the anatomical shape. Of note in her past medical history was a diagnosis of HIV two years after her breast augmentation (in 2000), for which she has had good control on anti-retrovirals with no detectable virus.

Her presenting complaints were intractable breast pain and marked distortion of the breasts from severe capsular contractures especially on the left side in 2017. (**Figure 1: preoperative photos a, c and e demonstrating the deformed grade 2 ptotic breasts with a “waterfall” appearance prior to surgery and b, d, and f demonstrating the remarkably improved 20-month post-operative appearances**). She was scheduled for bilateral explantation, total capsulectomies and exchange to larger implants, the latter as she declined the recommendation for mastopexy combined with insertion of smaller implants or no implants at all. It was noticed that the peri-implant capsules were severely thickened and contracted with a fleshy, floridly abnormal appearance, worse on the left. Both implants were intact, but notably distorted, with the left malrotated 90 degrees clockwise. The capsules were excised in toto and sent for histopathological examination. The dual-plane implant pockets were adjusted laterally and superiorly by internal sutures and the implants replaced with new soft cohesive gel anatomical implants (Sebbin 665cc, tall height, full projection). The patient had an uneventful recovery and was discharged home on day 3 after removal of the drains.

Histological findings

Histological examination of the left capsule showed surface fibrin deposition with occasional fragments of refractile foreign material. There was a focal chronic inflammatory infiltrate and, between the fibrous and overlying fibrinous layer, there were clusters of large, malignant lymphoid cells with high nucleus to cytoplasmic (N:C) ratios, homogeneous nuclear chromatin and prominent nucleoli. Clusters of these cells showing necrosis were seen within the overlying fibrin. **(Figure 2: histological slide showing the clearly malignant lymphoid cells and a focal chronic inflammatory infiltrate)**. Intra-mammary lymph nodes fortuitously harvested with the florid capsulectomy specimen were unremarkable

The right breast showed sections of dense fibrous connective tissue lined by metaplastic synovial-type cells, consistent with implant capsule. Fragments of refractile foreign material were noted. There was a focal chronic inflammatory infiltrate and a small amount of subjacent skeletal muscle with no evidence of malignancy .

Immunohistochemistry

The malignant cells in the left breast capsule were positive for the cell surface markers CD30, CD45, MUM1, PAX5, CD79a (weak), BCL2 and BCL6 (weak). In-situ hybridisation for EBV encoded RNA (EBER) was positive. The MIB-1 proliferation fraction was approximately 80%. The cells were negative for CD3, CD5, CD10, CD2, CD138, HHV8 and ALK. The right capsule showed no evidence of a malignant CD30 positive cell population.

The histological features and the immunoprofile were consistent with an EBV-positive immunodeficiency-associated lymphoproliferative disorder with features of a diffuse large

B-cell lymphoma. The differential diagnoses were primary effusion lymphoma, which was excluded since its pathognomonic Human Herpes Virus 8 (HHV8) staining was negative, or Diffuse large B-cell lymphoma associated with chronic inflammation. The latter was excluded as there were no signs of mass formation nor marked inflammation in this case.

Work up and further investigation

As a consequence of the above findings she was referred for a staging CT and referred to the Lymphoma MDT which requested a PET-CT. The CT scan showed small volume axillary nodes, whilst the PET-CT showed physiological tracer distribution and uptake in the rest of the body with no concerning findings

It was concluded that she did not require any additional adjuvant treatment since the affected tissue was excised and the implant was removed, so conservative management with further monitoring and scanning was indicated. The MDT recommended prophylactic removal of the implants on account of the diagnosis of a breast-implant associated lymphoma, however the patient declined to have the implants removed. She requested a second opinion with a national lymphoma expert, but she further declined the implant removal advice and is currently well and symptom-free being followed up under the 'watch and wait' protocol.

Discussion

Our patient presented with a rare type of lymphoma which has not previously been associated with breast implants. The diagnosis was of Epstein Barr Virus (EBV) related diffuse large B cell lymphoma. EBV-DLBCL has been reported previously in a small number of cases in relation to other foreign materials, however, not in relation to a breast implant. Two separate cases of implant related EBV+ve DLBCL are documented in the literature; for a chest wall Polyethylene (PET) surgical mesh used after lung and partial thoracic wall resection for squamous cell carcinoma (SCC) with adjuvant radiotherapy³, and in a metallic implant for knee replacement after septic arthritis⁴. In the first case the patient had his initial mesh implanted 20 years prior at the age of 61. He developed a chest wall lymphoma adjacent to the mesh. He was deemed too unwell for further aggressive intervention, subsequently dying 4 months later. The lower limb patient had his initial Shier's prosthesis (cobalt-chromium-molybdenum alloy, *Howmedica Inc*) at the age of 56 with one revision to a similar prosthesis 16 years later due to loosening of the prosthesis. A further 16 years later having presented with severe pain he had exchange of the implant and analysis of abnormal appearing peri-implant material revealed the lymphoma. This was treated with post-operative radiotherapy and two years on he was disease-free and mobilising normally with no adverse effects. Seven cases of EBV associated primary valve-associated B-cell lymphoma after prosthetic cardiac valve replacement have also been documented, with three of them receiving adjuvant chemotherapy^{5, 6}. These cases show that varied foreign bodies may be associated with lymphoma in conjunction with a viral aetiology.

The exact pathophysiology for development of the lymphoma in these cases is unclear however malignant transformation instigated by chronic inflammation is postulated^{4, 3}.

Epstein Barr Virus (EBV) is a very common gamma (γ) - herpes virus which more than 90% of the world's population carry ⁷ and is known to be the cause of infective mononucleosis. It becomes latent in most individuals, where it remains dormant and is largely asymptomatic in the immunocompetent host. Our patient would therefore have previously been infected with this virus with it then becoming latent. However, in the immunocompromised host it can cause both hematopoietic and epithelial derived cancers ⁸. EBV is known to affect different cell types with a predilection for B cells. Although our patient was HIV positive, her condition was stable on antiretrovirals and she had an undetectable viral load, suggesting she had good immunity. During the EBV latent stage different genes are expressed by the virus, which can result in the development of certain cancers and lymphoproliferative disorders such as B- cell lymphoma (BCL) ⁹.

EBV +DLBCL presentation

EBV+DLBCL not otherwise specified (NOS) in younger patients, commonly shows extra-nodal presentations and may have a florid progression which is less responsive to treatment ¹⁰. In our case there were no signs of spread beyond the breast capsule, no nodal presence or generalised metastatic signs of disease and hence no immediate indication for adjuvant treatment. The multi-disciplinary decision not to give adjuvant treatment would also have been based on the limited information on management of women presenting with BIA-ALCL, where implant removal with complete capsulectomy is associated with good outcome ^{11, 12}. More advanced presentations of BIA-ALCL such as presence of nodal disease, tumour mass or distant disease would require chemotherapy or radiotherapy or a combination of both ¹². In the aforementioned case reports there was no clear consensus on

adjuvant management, with some patients receiving either chemotherapy or radiotherapy. Lack of spread beyond the breast capsule implied that this was implant-related as opposed to a primary breast lymphoma (PBL). Whilst The Surveillance, Epidemiology, and End Results (SEER) registry has noted an increase over the last 40 years in PBL of the Lymphoma subtypes: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, marginal zone lymphoma (MZL), and anaplastic large cell lymphoma (ALCL) ¹³, her clinical picture supported implant-associated disease. In addition, her lymphoma was in conjunction with EBV and was most in keeping with a fibrin-associated diffuse large B-cell lymphoma.

We believe this to be the world's first reported case of EBV-positive DLBCL in a breast implant. It may have arisen secondary to her HIV, (albeit being clinically well controlled), or it may also have occurred denovo as a post chronic inflammatory reaction as occurred in the case reports above. The histological findings probably fit best with a fibrin-associated diffuse large B-cell lymphoma (DLBCL) which is an unusual form of DLBCL, associated with chronic inflammation and EBV positivity, which is not mass forming. Within the literature a single case of a non BIA-ALCL is documented of a breast implant related follicular lymphoma in a 56 year old woman presenting with painful capsular contractures and a palpable breast nodule ¹⁴. She had an extra-nodal follicular lymphoma with associated granulomatous response. Whilst this lymphoma appeared to have developed secondary to the breast implant this is a different type of lymphoma to that of our case. Follicular lymphoma has a characteristic nodular pattern, composed of centrocytes and centroblasts whereas in DLBCL clusters of large lymphoid cells with large nucleus-to-cytoplasmic ratios and prominent nucleoli are seen (**Figure 2**). Furthermore differences in cell marker expression will differentiate between these lymphoma types and also identify BIA-ALCL which expresses CD30 and is Alk-1 negative ¹⁵.

The recognised lymphoma associated with breast implants is anaplastic large cell lymphoma (ALCL) which derives from T cells as opposed to B cells as in our case. The literature on BIA-ALCL is increasingly well documented ^{11, 2, 16}. The most common presentations are delayed seroma, followed by presence of a mass ¹², with less common presentations including capsule contracture, nodal disease and metastatic disease. It is postulated that the architecture of predominantly textured implants is the causative factor for disease development, however in a small number of reports smooth implants have been implicated ^{17,16}. In some of these women with smooth implants they have been previous recipients of textured surface implants. The pathogenesis is thought to be due to the larger surface area created by implant shell texturisation which allows adherence of a biofilm that instigates the chain of inflammation and secondary malignant change within the cells of the capsule ^{11, 16}. Such texturisation can be from different methods; imprinting, foam impressions and salt loss technique ¹⁸. From US Manufacturer and User Facility Device Experience (MAUDE) database a few implant manufacturers have had cases of BIA-ALCL arise from their implants ^{17, 19}. In some cases, however, the manufacturer was unknown. This suggests a common implant causal factors for the development of the lymphoma. Our patient initially had smooth implants but had exchange to textured implants which then remained in situ for 18 years. Chronic inflammatory response has also been thought to contribute to the malignant transformation in the previous cases of EBV-DLBCL. Applying the bio-film theory, it may be possible that the presence of textured implants as well as patient related factors resulted in the development of our patient's implant related B-cell lymphoma.

The management of BIA-ALCL requires total capsulectomy and explantation of the implant ²⁰, with postoperative observation for some years. Neoadjuvant or adjuvant

treatment is indicated with advanced disease presentation. Our patient presented with severe capsular contracture but no peri-implant seroma or local breast mass. She underwent capsulectomy and exchange of implants, with removal of the implicated implants. Despite surgical advice she has declined explantation of her new implants.

Conclusion

It is important to document such cases as ours to add to the knowledge about breast implant-related lymphomas as thousands of women globally have implant surgery for both cosmetic and reconstructive reasons. The first case of BIA-ALCL was documented in 1997 as a case report and since then the importance of it has become apparent as many more cases presenting in a similar manner have been reported worldwide, spurring on developments in terms of diagnosis and best management of such patients. Hence this report of this unique case of EBV positive DLBCL, which may represent a fibrin-associated diffuse large B-cell lymphoma, will add to the knowledge available on breast implant associated lymphomas.

References

1. BAAPS Annual Audit Results. Cosmetic surgery stats: number of surgeries remains stable amid calls for greater regulation of quick fix solutions. 20 May 2019. Available at: https://baaps.org.uk/media/press_releases/1708/cosmetic_surgery_stats_number_of_surgeries_remains_stable_amid_calls_for_greater_regulation_of_quick_fix_solutions. Accessed Sept 1, 2019.
2. Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). Available at: www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm . Accessed August 5, 2019.
3. Fujimoto M, Haga H, Okamoto M, et al. EBV-associated diffuse large B-cell lymphoma arising in the chest wall with surgical mesh implant. *Pathol Int*. 2008; 58: 668–671.
4. Cheuk W, Chan AC, Chan JK, Lau GT, Chan VN, Yiu HH. A metallic implant-associated lymphoma. A distinct subgroup of Large B-Cell Lymphoma related to Pyothorax-Associated Lymphoma? *Am J Surg Pathol*. 2005; 29: 832–836.
5. Miller DV, Firchau DJ, McClure RF, Kurtin PJ, Feldman AL. Epstein-Barr Virus-associated diffuse large B-cell lymphoma arising on cardiac prostheses. *Am J Surg Pathol*. 2010; 34:377-384.
6. George S, Gehrs B, Srour SA. *An unusual case of primary cardiac prosthetic valve-associated lymphoma. J Community Support Oncol* .2015; 15: 109-112.
7. Saha A, Robertson ES. Epstein-Barr virus associated B-cell lymphomas: Pathogenesis and Clinical Outcomes. *J Clin Cancer Res* .2011; 17: 3056–3063.
8. Roy SG, Robertson ES, Saha A. Epigenetic impact on EBV associated B-Cell lymphomagenesis. *Biomolecules*. 2016; 6: E46.

9. Grywalska E, Rolinski J. Epstein-Barr Virus–associated lymphomas. *Semin Oncol*, 2015; 42: 291-303.
10. Shannon-Lowe C, Rickinson AB, Bell AI. Epstein–Barr virus-associated lymphomas. *Philos Trans R Soc Lond B Biol Sci*. 2017 Oct 19; 372(1732). pii: 20160271. doi: 10.1098/rstb.2016.0271.
11. Deva AK. Discussion: U.S. Epidemiology of Breast Implant–Associated Anaplastic Large-Cell Lymphoma. *Plast Reconstr Surg*. 2017; 139: 1051-1052.
12. Leberfingher AN , Behar BJ, Williams NC et al. Associated Anaplastic Large Cell Lymphoma: A systematic review. *JAMA Surg*. 2017; 152: 1161-1168.
13. Thomas A, Link BK, Altekruse S, Romitti PA, Schroeder MC. Primary breast lymphoma in the United States: 1975-2013. *J Natl Cancer Inst*; 2017 Jun 1; 109(6). doi: 10.1093/jnci/djw294.
14. Cook PD, Osborne BM, Connor RL, Strauss JF. Follicular lymphoma adjacent to foreign body granulomatous inflammation and fibrosis surrounding silicone breast prosthesis. *Am J Surg Pathol*. 1995; 19: 712–717.
15. Freedman A. Follicular lymphoma: 2018 update on diagnosis and management. *Am J Hematol*. 2018; 93:296-305.
16. Nava MB, Adams WP, Botti G et al. MBN 2016 Aesthetic breast meeting BIA-ALCL consensus conference report. *Plast Reconstr Surg*. 2018; 141: 40-48.
17. Srinivasa DR, Miranda RN, Kaura A, et al. Adverse Event Reports of Breast Implant-Associated ALCL: An International review of 40 Government Authority Databases. *Plast Reconstr Surg*. 2017; 139:1029-1039.

18. Shauly O, Gould DJ, Patel KM. Microtexture and the cell/biomaterial Interface: A systematic review and meta-analysis of capsular contracture and prosthetic breast implants. *Aesthet Surg J*. 2019; 39: 603–614.
19. The FDA Requests Allergan Voluntarily Recall Natrelle BIOCELL Textured Breast Implants and Tissue Expanders from the Market to Protect Patients: FDA Safety Communication. Available at:

<https://www.fda.gov/medical-devices/safety-communications/fda-requests-allergan-voluntarily-recall-natrelle-biocell-textured-breast-implants-and-tissue>

Accessed Nov 10, 2019.
20. Clemens MW, Medeiros LJ, Butler CE, et al. Complete surgical excision is essential for the management of patients with breast implant–associated anaplastic large-cell lymphoma. *J Clin Oncol* 2016; 34:160-8.

Figure 1

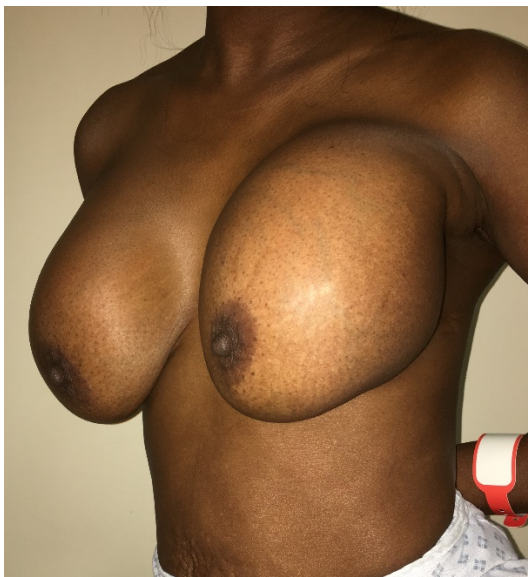
Preoperative photos (a, c, e) of a 51-year old revision surgery patient demonstrating the deformed breasts caused by severe peri-implant capsular contracture prior to surgery. 20-month postoperative images (b, d, f) showing a dramatic improvement in her aesthetic appearances following total capsulectomy and implant exchange to anatomical cohesive gel implants.



a)



d)



b)



e)



c)



f)

Figure 2

Histological slide of left breast capsule showing the clearly malignant cells and a focal chronic inflammatory infiltrate.

