PATHOLOGICA 2024;116:242-248**;**
DOI: 10.32074/1591-951X-944

Case report

Fibrin associated large B-cell lymphoma accidentally identified in a breast implant capsule: a molecular report of a rare entity

Cristian Scatena[1,2,*], Antonio Giuseppe Naccarato[1,2,*], Margherita Vannucchi[4], Maria Chiara Siciliano[4], Angelo Giovanni Bonadio[2], Livio Colizzi[3], Matteo Ghilli[3], Arianna Di Napoli[5], Giuseppe Nicolò Fanelli[1,2,#], Stefano Lazzi[4,#]

[1] Division of Pathology, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy; [2] Department of Oncology, Pisa University Hospital, Pisa, Italy; [3] Breast Centre AOUP, University Hospital of Pisa, Pisa, Italy; [4] Anatomic Pathology Unit, Department of Medical Biotechnology, University of Siena, Siena, Italy; [5] Department of Clinical and Molecular Medicine, Sant'Andrea University Hospital, Sapienza University of Rome, Rome, Italy
[*] These authors contributed equally as first authors; [#] These authors contributed equally as senior authors

Summary
Breast implant-associated (BIA) lymphoma is a rare malignancy, typically originating from T-cells; however, few cases of diffuse large B-cell lymphoma (LBCL) have been recently described. These cases share major features: Epstein-Barr virus positivity and a favorable prognosis with surgical intervention alone, hinting at a potential link to fibrin-associated LBCL (FA-LBCL). This study presents the first case of BIA-FA-LBCL in Italy and one of the few assessed from a molecular standpoint so far. We identified two pathogenic mutations in DNMT3A and a variant of uncertain significance (VUS) in JAK2. These findings suggest that dysfunctional epigenetic mechanisms and constitutive activation of the JAK-STAT pathway may underpin BIA-FA-LBCL lymphomagenesis. Finally, we summarized all the previously reported cases in alignment with the updated WHO-HAEM5 classification, shedding further light on the nature of this new entity. This report highlights the rarity of BIA-FA-LBCL and underscores the importance of comprehensive capsule sampling and reporting to national databases for accurate characterization and management of these lymphomas. The study supports the classification of BIA-FA-LBCL within the spectrum of FA-LBCL, emphasizing the need for further research to elucidate its molecular underpinnings and improve clinical outcomes.

Key words: breast implant associated lymphoma, non-Hodgkin lymphoma, fibrin associated-large B cell lymphoma

Received: February 12, 2024
Accepted: April 15, 2024

Correspondence
Cristian Scatena
E-mail: cristian.scatena@unipi.it

How to cite this article: Scatena C Naccarato AG, Vannucchi M, et al. Fibrin associated large B-cell lymphoma accidentally identified in a breast implant capsule: a molecular report of a rare entity. Pathologica 2024;116:242-248. https://doi.org/10.32074/1591-951X-944

Introduction

Breast implant-associated (BIA) lymphomas are rare and are mostly of T-cell origin; however, a few reports of diffuse large B-cell lymphoma (DLBCL) cases related to breast implants have been described since 2019 [1]. All these cases had common features such as positivity for Epstein-Barr virus (EBV) and an unusual, good prognosis with surgical management only. Since the first reports, it was hypothesized that they could be a new presentation of fibrin-associated LBCL (FA-LBCL), because of the same pathological characteristics and similar indolent behavior [2]. Thus, in our report, we will refer to these EBV+ BIA-DLBCLs as BIA-FA-LBCLs. Here we describe the first case of BIA-FA-LBCL in Italy, its clinical presentation, pathological and molecular findings, and the multi-disciplinary meeting (MDM) approach following the literature published until early 2023.

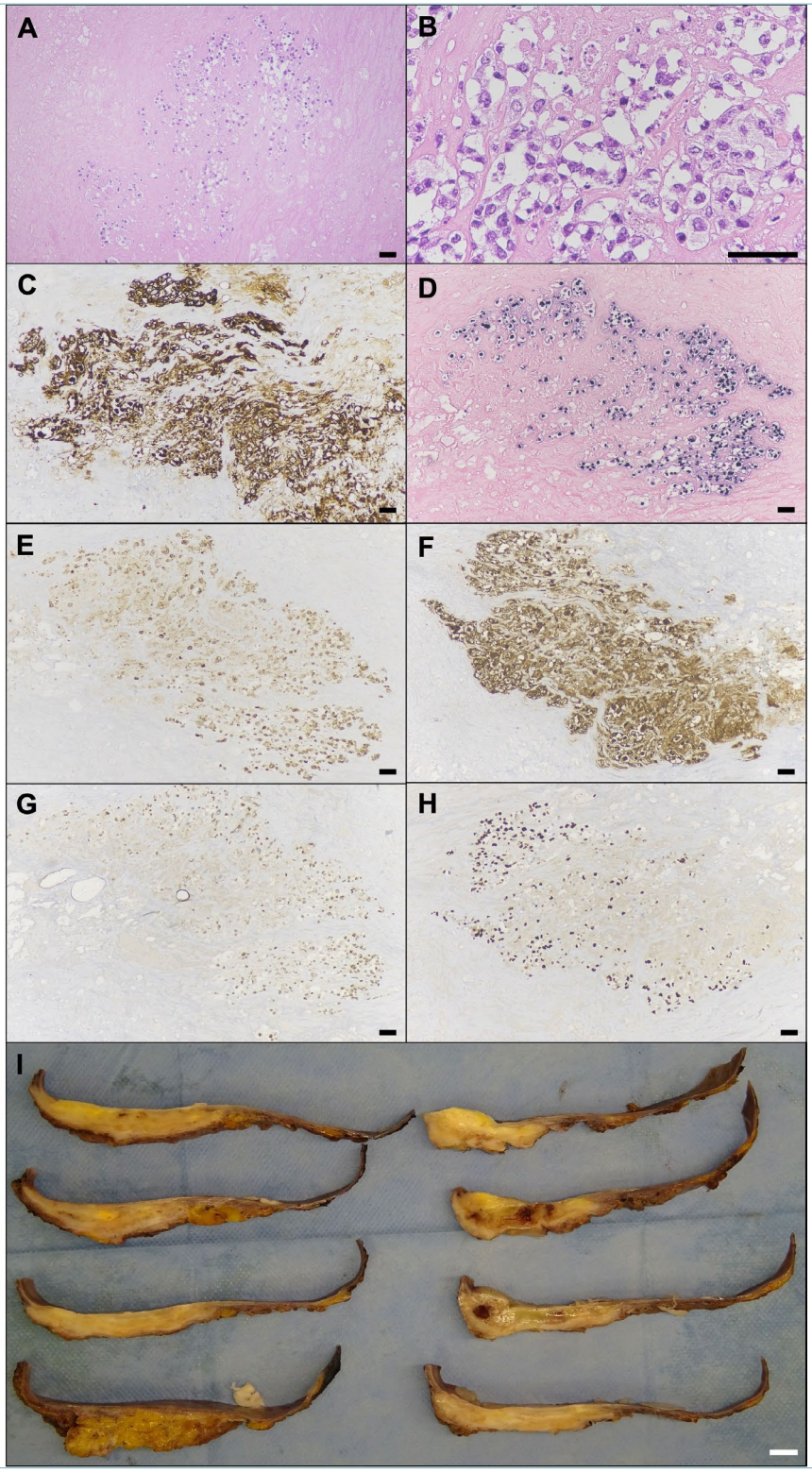

Figure 1. Schematic representation of the morphological and immunophenotypical features of the current case. (A-B) Small clusters of large, atypical, and pleomorphic lymphocytes with prominent nucleoli distributed within the capsule and associated with fibrin deposits and necrosis (A-B hematoxylin & eosin). Immunoreactivity for CD20 (C), EBER-ISH (D), BCL2 (E), CD30 (F), MUM1 (G). Proliferation index (Ki-67): 90% (H). A gross investigation of the total capsulectomy showed areas of hemorrhage and myxoid necrosis, and a smooth and pale surface, without fluid content and/or tumor mass (I). Magnification of A, C-H: 100X. Magnification of B: 40X. Scalebar of A-H: 100 µm. Scalebar of I: 1 cm.

Case presentation

A healthy, immunocompetent, 77-year-old woman had a right skin-sparing mastectomy and implant-based reconstruction performed for multicentric lobular carcinoma in 2009 at the Breast Center of the University Hospital of Pisa. Thirteen years later, she developed pain in the right breast and was diagnosed with capsular contracture, grade III. In September 2022 she had surgical partial capsulectomy with implant replacement at the same Institution. The capsule was sent for analysis to the Laboratory of Pathology of the Breast Center in Pisa. Histologic evaluation revealed small clusters of large, atypical, and pleomorphic lymphocytes with prominent nucleoli distributed within the capsule and associated with fibrin deposits and necrosis (Fig. 1A, B).

By immunohistochemistry, the atypical cells were positive for CD20, CD30, BCL2, and MUM1 (Figure 1C, 1E-G), and negative for CD3, CD15, CD10, ALK, or CD138 (not showed). The Ki-67 proliferation index was high (> 90%) (Fig. 1H). In situ hybridization for EBV-encoded small RNA (EBER-ISH) was positive (Fig. 1D), with a type III latency pattern.

A targeted next generation sequencing (tNGS) analysis was performed using Illumina DNA Prep with Enrichment solution (Illumina MiSeq sequencing platform) with a custom panel of 83 genes, covering the most frequently mutated genes in T and B cell lymphoma. Sequencing analysis revealed two pathogenic mutations in *DNMT3A* (p.K754E) and (p.R577G) with variant allele frequencies (VAF) of 15% and 5% respectively. Furthermore, a variant of unknown significance (VUS) was detected in exon 10 of *JAK2* gene (p.G417S, VAF 38%) (Fig. 2).

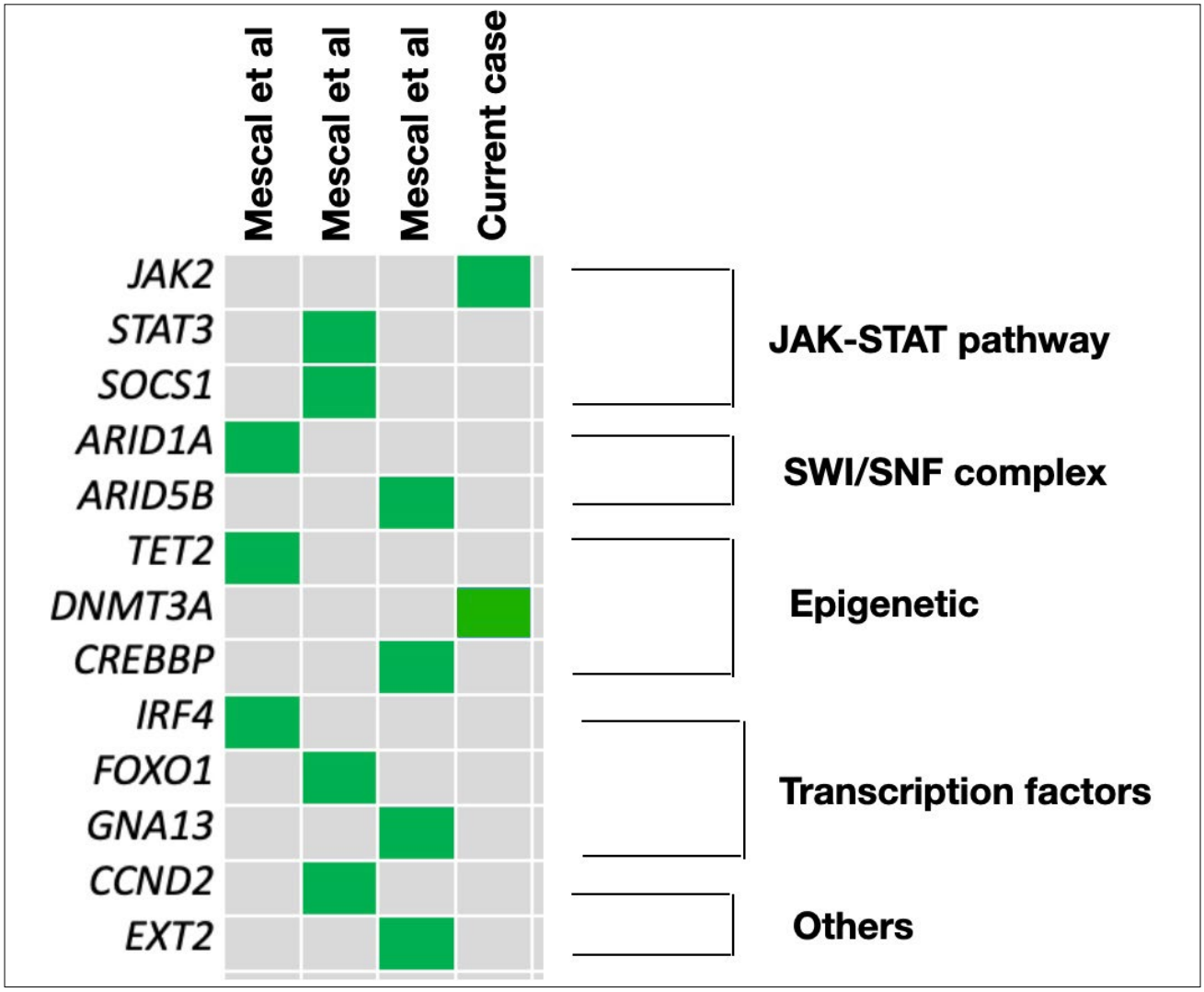

Figure 2. Oncoplot summarizing the major molecular features of the current case compared to literature.

These findings led to the diagnosis of BIA-FA-LBCL. The case was discussed within the MDM and systemic examination by laboratory tests and a positron emission tomography scan was recommended. All the exams ruled out the presence of systemic disease. Due to the indolent nature of this rare condition based on the literature at that time, the MDM decided for total capsulectomy with prophylactic removal of the new implant, performed in February 2023, and subsequent active surveillance.

Gross examination of the surgical specimen showed a capsule up to 15 mm thick with areas of hemorrhage and myxoid necrosis, and a smooth and pale surface, without fluid content (Fig. 1I). No mass formations were found. Histologically, small and diffuse fields of lymphoma within the luminal surface of the capsule were evident without signs of infiltration of the capsule and the adjacent tissues. The patient is currently under follow-up, and after almost 10 months she has no evidence of disease recurrence.

Discussion

Fibrin-associated large B cell lymphoma (FA-LBCL), considered in the WHO-HAEM4 and International Consensus Classification (ICC) as a subtype of DLBCL-associated with chronic inflammation (CI-DLBCL), is now upgraded to a distinct entity in the WHO-HAEM5 [3].

FA-LBCL consists of a large B cell proliferation incidentally found at sites of chronic fibrin deposition in confined natural or acquired anatomic spaces (cardiac myxoma, chronic hematomas, endovascular prostheses, or cysts) [3].

To date, 18 cases of FA-LBCL arising at the breast implant site (BIA-FA-LBCL) have been described, including the current one. Clinical and pathological data, molecular features, treatment strategies, and outcomes of all 18 cases are summarized in Table I.

Based on this evidence, the space associated with the breast capsule is now considered another potential site for FA-LBCL development [2,3].

Molecular features by tNGS analysis have been investigated in 5 cases. Of these, 3 cases harbored mutations in various genes associated with DLBCL as *CREBBP*, *GNA13*, and *IRF4,* and others involving the JAK-STAT pathway as *STAT3* and *SOCS1* also reported in breast implant associated-anaplastic large cell lymphoma (BIA-ALCL)[4]. Instead, rearrangement or extra copies of *MYC* gene have been detected in 3 out of 7 cases [1,2,4-6].

Here we describe the first BIA-FA-LBCL occurred in Italy so far, in which target sequencing analysis revealed two pathogenic mutations in the epigenetic modifier *DNMT3A* and a likely pathogenic alteration in the *JAK2* gene.

Interestingly, at least a proportion of BIA-FA-LBCL shares the same molecular alterations with BIA-ALCL. These similarities may be related to the unique microenvironment in which they arise, characterized by chronic inflammation elicited by the breast implant and by the low oxygen levels of the peri-implant cavity, which in turn can favor the accumulation of mutations of epigenetic modifiers and key players of the JAK-STAT3 pathway [7,8] and the activation of hypoxia signalling with expression of CA9 by tumor cells [2].

Moreover, interleukins related to a long-standing inflamed micro-environment (IL-6, IL-13, IL-10) and PD-L1 expression by either EBV infection or gene amplification can favor immune evasion of both BIA-FA-LBCL and BIA-ALCL [2,9,10].

Although these similarities BIA-FA-LBCL and BIA-ALCL show a different cell of origin suggesting that a distinctive combination of these mechanisms might be involved in their pathogenesis.

Conclusions

Large B cell lymphoma associated with fibrin deposition arising at breast implant site are rare entities with only 18 cases reported to date. The published literature, including the current case, supports the decision of the 5th edition of the WHO classification of Tumours of Hematopoietic and Lymphoid Tissues to classify the BIA-FA-LBCLs as FA-LBCL since they share the same histopathological features and indolent behavior.

The molecular data available are even more rare. Here we describe the first Italian case of BIA-FA-LBCL, adding important genetic data represented by two pathogenic mutations in *DNMT3A* and a VUS in *JAK2*. These data suggest that impaired epigenetic mechanisms and constitutive activation of the JAK-STAT pathway may play an important role not only for BIA-ALCL, but also for BIA-FA-LBCL lymphomagenesis. Further studies are needed to elucidate the pathogenetic mechanisms that differentiate these two entities.

Finally, we highlight the importance of extensive breast capsule sampling according to the same guideline used for BIA-ALCL, also in the case of BIA-FA-LBCL, and the necessity to report these rare cases to National databases in order to better define their real incidence.

Conflicts of interest statement

C.S. has received honoraria for consulting, adviso-

Table I. Clinico-pathological data and molecular features of all cases described in the literature, including the current one.

Patients	Sex	Age at diagnosis	Reasons for implant	Implant Type	Lymphoma Location	Clinical Presentation	Latency time	First Diagnosis	EBV status (Latency pattern)	Clonality	Cytogenetic and Molecular Features	Clinical Stage	Treatment Strategy	Outcome	Reference
1	F	66	Prophylactic mastectomy	Textured silicone	N/A	Bilateral capsular contracture	12 years	DLBCL	EBER+ (ND)	N/A	N/A	Early-stage (IE)	Surgery (complete capsulectomy)	Complete remission	Goodwins *et al.* [11]
1	F	55	Cosmetic	N/A	Limited to the capsule (no further specified)	Haematoma	15 years	DLBCL	EBER+ (type III)	N/A	N/A	Early-stage (IE)	Surgery (complete capsulectomy)	Complete remission	Rodríguez Pinilla *et al.* [12]
1	F	59	Cancer	N/A	Limited to the capsule (no further specified)	Haematoma	10 years	DLBCL	EBER+ (type III)	N/A	N/A	Early-stage (IE)	Surgery (complete capsulectomy)	Complete remission	Rodríguez Pinilla *et al.* [12]
1	F	63	Cancer	N/A	N/A	Tumour mass	20 years	DLBCL	EBER+ (type III)	N/A	N/A	Early-stage (IE)	Surgery (complete capsulectomy)	N/A	Rodríguez Pinilla *et al.* [12]
1	F	72	Cancer	Macrotextured silicone	Limited to the capsule (no further specified)	No symptoms	8 years	CI-DLBCL	EBER+ (type III)	Monoclonal Ig rearrangement	FISH: no rearrangement of *BCL2, BCL6, MYC*. aCGH: no detectable aberration tNGS: *IRF4* (p.L24F; VAF 10.4%), *ARID1A* (p.H684Y; VAF 3.37%), *TET2* (p.R1465§; VAF 4.5%)	Early-stage (IE)	Surgery (complete capsulectomy)	Complete remission	Mescam *et al.* [4]
1	F	61	Cancer	Macrotextured silicone	Limited to the capsule (no further specified)	No symptoms	13 years	CI-DLBCL	EBER+ (type I)	Monoclonal Ig rearrangement	FISH: *IGH-MYC* translocation, no rearrangement of *BCL2* or *BCL6*. aCGH: X monosomy, 7q deletion, 13q deletion involving RB1) and 14q deletion (involving IGH) tNGS: *STAT3* (pG1618R; VAF 48%), *SOCS1* (p.Y203N; VAF 46%), *FOXO1* (pS205R; VAF 45%), *CCND2* (pV284G, VAF 43%)	Early-stage (IE)	Surgery (complete capsulectomy)	Complete remission	Mescam *et al.* [4]
1	F	69	Cosmetic	Macrotextured silicone	Limited to the capsule (no further specified)	No symptoms	9 years	CI-DLBCL	EBER+ (type III)	Monoclonal Ig rearrangement	FISH: no rearrangement of *BCL2, BCL6, MYC*. aCGH: no detectable aberration tNGS: *ARID5B* (p.P79T, VAF 12%), *EXT2* (p.S270L, VAF 10%), *CREBBP* (p.M721I, VAF 8.5%), *GNA13* (p.P6L, VAF 5.1%)	Early-stage (IE)	Surgery (complete capsulectomy) + Chemotherapy (3 R-CHOP cycles)	Complete remission	Mescam *et al.* [4]
1	F	70	Cancer	Macrotextured silicone	Limited to the capsule (no further specified)	Right capsular contracture	9 years	FA-DLBCL	EBER+ (ND)	Monoclonal Ig rearrangement	No *MYC* rearrangement, copy number variation or amplification	Early-stage (IE)	Surgery (complete capsulectomy)	Complete remission	Khoo *et al.* [5]
1	F	51	Cosmetic	Smooth Textured silicone (previous smooth-saline)	Limited to the capsule (no further specified)	Left capsular contracture (HIV well controlled)	15 years (21 years from saline implants)	DLBCL	EBER+ (ND)	N/A	N/A	Early-stage (IE)	None	Complete remission	Malata *et al.* [13]
1	F	48	N/A	Silicone (surface N/A)	Capsule e parenchyma	Invasive mass	21 years	DLBCL	EBER+ (type II)	N/A	N/A	Early-stage (IE)	Surgery (complete capsulectomy) + Chemotherapy (4 R-CHOP, 2 BEACOPP + RT, 1 ICE + ASCT)	Complete remission (after 2 relapses)	Medeiros *et al.* [14]
1	F	69	Cancer	Macrotextured silicone	Limited to the capsule (no further specified)	Right capsular contracture	12 years	DLBCL	EBER+ (ND)	Monoclonal Ig rearrangement (IGH and IGK)	N/A	Early-stage (IE)	Surgery (complete capsulectomy)	Complete remission	Morgan *et al.* [6]
1	F	53	N/A	Macrotextured silicone	Limited to the capsule (no further specified)	Bilateral capsular contracture	9 years	FA-DLBCL	EBER+ (ND)	N/A	FISH: *MYC* rearrangement	Early-stage (IE)	Surgery (complete capsulectomy) + Chemotherapy (4 R-CHOP)	Complete remission	Morgan *et al.* [6]
1	F	46	N/A	Textured silicone	Limited to the capsule (confined at the inner surface)	Bilateral capsular contracture	8 years	FA-DLBCL	EBER+ (type III)	Monoclonal rearrangement V-J(FR2) IGK polyclonal	N/A	Early-stage (IE)	Surgery (complete capsulectomy)	Complete remission	Mansy *et al.* [15]
1	F	42	Cosmetic	Textured silicone	Limited to the capsule (no further specified)	Bilateral capsular contracture	7 years	BIA-DLBCL	EBER+ (ND)	N/A	FISH: no *BCL-2, BCL-6* and *MYC* rearrangements.	Early-stage (IE)	Surgery (complete capsulectomy)	Complete remission	de Bustamante *et al.* [1]
1	F	63	N/A	N/A	Limited to the capsule (no further specified)	Capsular contracture	10 years	FA-DLBCL	EBER+ (ND)	N/A	FISH: *MYC*/*BCL2*/*BCL6* rearrangements (*MYC* extra copies) tNGS (64 genes): No mutations	N/A	Surgery (complete capsulectomy)	Complete remission	R. Leguit, Utrecht, Netherland in Di Napoli *et al.* [2]
1	F	56	Cancer	Microtextured silicone	Limited to the capsule (no further specified)	N/A	26 years	FA-DLBCL	EBER+ (type III)	Monoclonal Ig rearrangement (IGH)	tNGS (36 genes): no mutations	N/A	N/A	N/A	E. Poullot, Créteil, France in Di Napoli *et al.* [2]
1	F	45	Cosmetic	N/A	Limited to the capsule (confined at the inner surface) and seroma	Seroma HIV+ (under control with therapy);	9 years	FA-DLBCL	EBER+ (type III)	N/A	N/A	N/A	N/A	N/A	T. Tousseyn, Leuven, Belgium in Di Napoli *et al.* [2]
1	F	77	Cancer	N/A	Limited to the capsule (confined at the inner surface)	Right capsular contracture	13 years	BIA-FA-LBCL	EBER+ (type III)	N/A	tNGS (83 genes): *DNMT3A* (p.K754E; VAF 15% and p.R577G; VAF 5%), *JAK2* (p.G417S; 38% VAF)	Early-stage (IE)	Surgery (complete capsulectomy)	Complete remission	Current case

DLBCL: diffuse large B-cell lymphoma; CI-DLBCL: diffuse large B-cell lymphoma associated with chronic inflammation; FA-LBCL: fibrin-associated large B-cell lymphoma; HIV: human immunodeficiency virus; R-CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; BEACOPP: Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone; RT: radiation therapy; ICE: Ifosfamide, Carboplatin, Etoposide; ASCT: autologous stem cell transplant; EBER, EBV-encoded small RNA; FISH, fluorescence in situ hybridization; Ig, immunoglobulin; VAF, variant allele frequency; tNGS, targeted Next Generation Sequencing; FISH: Fluorescent *in situ* hybridization; aCGH: Array-Comparative genomic hybridization; IGH, Immunoglobulin heavy chain constant region IGK, Immunoglobulin Kappa Locus, N/A: data not available; ND: not done; §Stop codon.

ry role, speaker bureau and/or research grants from Bristol Myers Squibb, Astra Zeneca, Daiichi-Sankyo, Gilead, Roche SPA and Novartis. A.D.N. has received honoraria for consulting from Novartis, Menarini, Incyte, EusaPharma and research grants from the Italian Ministry of Health. G.N.F has received honoraria for advisory role from Astra Zeneca.

Funding

This research received no external funding.

Authors' contributions

C.S, A.G.N, G.N.F, and S.L. conceived the study; C.S. and A.G.N. wrote the manuscript; M.V. and M.C.S. analysed molecular data, C.S, A.G.B. A.D.N, and S.L. analysed the histological data; L.C. and M.G. analysed the clinical data; G.N.F. edited manuscript and created images and table. G.N.F. and S.L. supervised the study. All the authors have read and approved the manuscript.

Ethical consideration

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from the patient for study participation and data publication.

References

1 Martin de Bustamante JM, Mendoza A, Lopez-Munoz S, et al. A New Face of Fibrin-Associated Large B-Cell Lymphoma: Epstein-Barr Virus-Positive Breast Implant-Associated Diffuse Large B-Cell Lymphoma. J Clin Med 2023;12:3614 https://doi.org:10.3390/jcm12113614

2 Di Napoli A, Soma L, Quintanilla-Martinez L, et al. Cavity-based lymphomas: challenges and novel concepts. A report of the 2022 EA4HP/SH lymphoma workshop. Virchows Arch 2023;483:299-316. https://doi.org:10.1007/s00428-023-03599-2

3 WHO Classification of Tumours Editorial Board. Haematolymphoid tumours 5th edition, https://tumourclassification.iarc.who.int/chapters/63/150 Lyon, France: International Agency for Research on Cancer, 2022.

4 Mescam L, Camus V, Schiano JM, et al. EBV+ diffuse large B-cell lymphoma associated with chronic inflammation expands the spectrum of breast implant-related lymphomas. Blood 2020;135:2004-2009. https://doi.org:10.1182/blood.2019003408

5 Khoo C, McTigue C, Hunter-Smith DJ, et al. EBV positive fibrin/chronic inflammation associated diffuse large B-cell lymphoma: an incidental finding associated with a breast implant. Pathology 2021;53:673-675. https://doi.org:10.1016/j.pathol.2020.09.022

6 Morgan S, Tremblay-LeMay R, Lipa JE, et al. Breast implant-associated EBV-positive diffuse large B-cell lymphoma: Two case reports and literature review. Pathol Res Pract 2021;226:153589. https://doi.org:10.1016/j.prp.2021.153589

7 DeCoster RC, Clemens MW, Di Napoli A, et al. Cellular and Molecular Mechanisms of Breast Implant-Associated Anaplastic Large Cell Lymphoma. Plast Reconstr Surg 2021;147:30e-41e. https://doi.org:10.1097/PRS.0000000000007423

8 Di Napoli A, Jain P, Duranti E, et al. Targeted next generation sequencing of breast implant-associated anaplastic large cell lymphoma reveals mutations in JAK/STAT signalling pathway genes, TP53 and DNMT3A. Br J Haematol 2018;180:741-744. https://doi.org:10.1111/bjh.14431

9 Di Napoli A, Greco D, Scafetta G, et al. IL-10, IL-13, Eotaxin and IL-10/IL-6 ratio distinguish breast implant-associated anaplastic large-cell lymphoma from all types of benign late seromas. Cancer Immunol Immunother 2021;70:1379-1392. https://doi.org:10.1007/s00262-020-02778-3

10 Tabanelli V, Corsini C, Fiori S, et al. Recurrent PDL1 expression and PDL1 (CD274) copy number alterations in breast implant-associated anaplastic large cell lymphomas. Hum Pathol 2019;90:60-69. https://doi.org:10.1016/j.humpath.2019.05.007

11 Goodwins LK, Prowse PM, Miliauska JR. Breast Implant-associated Lymphoma: What Is the True Incidence and Clinical Relevance? Plast Reconstr Surg Glob Open 2019;7:e2571. https://doi.org:10.1097/GOX.0000000000002571

12 Rodriguez-Pinilla SM, Garcia FJS, Balague O, et al. Breast implant-associated Epstein-Barr virus-positive large B-cell lymphomas: a report of three cases. Haematologica 2020;105:e412-e414. https://doi.org:10.3324/haematol.2019.232355

13 Malata CM, Madada-Nyakauru RN, Follows G, et al. Epstein-Barr Virus-associated Diffuse Large B-cell Lymphoma Identified in a Breast Implant Capsule: A New Breast Implant-Associated Lymphoma? Ann Plast Surg 2021;86:383-386. https://doi.org:10.1097/SAP.0000000000002537

14 Medeiros LJ, Marques-Piubelli ML, Sangiorgio VFI, et al. Epstein-Barr-virus-positive large B-cell lymphoma associated with breast implants: an analysis of eight patients suggesting a possible pathogenetic relationship. Mod Pathol 2021;34:2154-2167. https://doi.org:10.1038/s41379-021-00863-1

15 Mansy M, Wotherspoon AC, El-Sharkawi D, et al. Fibrin-associated diffuse large B-cell lymphoma misdiagnosed as breast implant-associated anaplastic large-cell lymphoma. Histopathology 2021;79:269-271. https://doi.org:10.1111/his.14372