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Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL): an overview of presentation and pathogenesis and guidelines for pathological diagnosis and management

J Louise Jones,[1] Andrew M Hanby,[2] Clive Wells,[3] Marie Calaminici,[1] Laura Johnson,[4] Philip Turton,[5] Rahul Deb,[6] Elena Provenzano,[7] Abeer Shaaban,[8] Ian O Ellis,[9] Sarah E Pinder[10] & on behalf of the National Co-ordinating Committee of Breast Pathology

[1]*Barts Cancer Institute, Queen Mary University of London, London,* [2]*Leeds Institute of Cancer and Pathology, University of Leeds, Leeds,* [3]*Department of Histopathology, Rockefeller Building, University College Hospital London NHS Foundation Trust,* [4]*St Bartholomew's Hospital, West Smithfield, London,* [5]*Breast Unit, St James's Hospital, The Leeds Teaching Hospital NHS Trust, Leeds,* [6]*Department of Histopathology, Derby Teaching Hospitals NHS Foundation Trust, Derby,* [7]*Department of Histopathology, Addenbrookes Hospital, Cambridge,* [8]*Department of Pathology, University Hospitals Birmingham NHS Foundation Trust, Birmingham,* [9]*Department of Histopathology, City Hospital Campus, Nottingham University Hospitals, Nottingham, and* [10]*School of Cancer and Pharmaceutical Sciences, King's College London, London, UK*

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Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL): an overview of presentation and pathogenesis and guidelines for pathological diagnosis and management

Aims: Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is an uncommon complication associated largely with textured implants. It is important that the symptoms associated with BIA-ALCL are recognised and that robust pathways are in place to establish the diagnosis. The aim of this paper is to review what is known of the incidence of the disease, current thoughts on pathogenesis, patterns of presentation and pathological features to provide standard guidelines for its diagnosis.

Methods and results: Systematic review of the literature via PubMed covering cases series, modes of presentation, cytological, histological and immunohistochemical features and disease outcome. Since 1997, 518 cases throughout 25 countries have been registered on the American Society of Plastic Surgeons PROFILE registry, with an estimated risk for women with an implant of one to three per million per year. It most frequently presents as a late-onset accumulation of seroma fluid, sometimes as a mass lesion. The neoplastic cells are highly atypical, consistently strongly positive for CD30, with 43–90% also positive for EMA, and all are ALK-negative. Behaviour is best predicted using a staging system for solid tumours.

Conclusion: BIA-ALCL is a rare but important complication of breast implants. While characterised by CD30-positive neoplastic cells this must be interpreted with care, and we provide pathological guidelines for the robust diagnosis of this lesion as well as the most appropriate staging system and management strategies. Finally, in order to generate more accurate data on incidence, we recommend mechanisms for the routine central reporting of all cases.

Keywords: breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), central reporting, diagnostic guidelines, staging

Address for correspondence: J L Jones, Centre for Tumour Biology, John Vane Science Building, Barts Cancer Institute, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK. e-mail: l.j.jones@qmul.ac.uk

Introduction

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) was included as a new entity in the 2016 revised World Health Organisation classification of lymphoid neoplasms, described as a non-invasive disease with excellent outcome.[1] It was first described in 1997;[2] since then, 518 cases throughout 25 countries have been registered on the American Society of Plastic Surgeons Patient Registry and Outcomes for Breast Implants and Anaplastic Large Cell Lymphoma Etiology and Epidemiology (PROFILE) registry.[3] The estimated risk for women with an implant is one to three per million per year,[4] although it has been suggested this may be an underestimate. A recent study reported the cumulative risk of breast ALCL in the general population to be 0.35 per million at age 75 years, while the cumulative risk in women with an implant was 29 per million at age 50, rising to 82 per million at age 70, exceeding previous estimates 10–20-fold.[5] There is, however, inherent difficulty in measuring the absolute risk of development of BIA-ALCL because of the nature by which it has been reported, mainly through case reports and small series, although the move towards central registration of cases should allow accumulation of more accurate data.

BIA-ALCL is distinct from other breast lymphomas, which most frequently are diffuse large B cell lymphomas and extranodal marginal zone lymphomas.[6] It is a non-Hodgkin lymphoma characterised by the presence of a monoclonal population of large anaplastic cells that are uniformly CD30-positive, anaplastic lymphoma kinase (ALK)-negative and variably express T cell markers and EMA.[1,7] While generally considered to be an indolent disease, there is a subset of patients who exhibit more aggressive disease.[8] It is therefore imperative that there is more widespread recognition of this condition, that there is a clear process for its diagnosis and that there is appreciation of the emerging recommendations for diagnosis and treatment. This paper will review patterns of presentation, provide guidelines for an efficient and robust diagnostic pathway, and consider the recommended staging classification and how this relates to recommended treatment. Finally, in order to generate more accurate data on incidence, we recommend routine central reporting of all cases.

Disease presentation

BIA-ALCL is considerably more frequent in women with textured implants, and has been reported in association with both silicone gel and saline implants positioned either for cosmetic or reconstructive purposes.[3,9] It most frequently presents as a late-onset accumulation of seroma fluid between the implant and fibrous capsule in women with no other clear reason for seroma formation, such as infection, implant rupture or trauma, with a mean time to onset of 8–10 years post-implant.[9] Less frequently, it may present as a palpable tumour mass, with malignant cells infiltrating through the capsule and surrounding tissue with potential lymph node and systemic involvement, where there is a significantly poorer prognosis, with reported overall survival of 52.5% at 2 years.[10]

Pathogenesis

The cause of BIA-ALCL is not established; however, it has been proposed that lymphomagenesis may be driven by a chronic inflammatory reaction induced by capsule contents or surface,[11,12] and there is some evidence to support this. A comparison of the bacterial biofilm on breast implant capsules associated with ALCL when compared to that on implant capsules with contracture has revealed a distinct microbiome in BIA-ALCL, with a significantly greater proportion of Gram-negative bacilli of *Ralstonia* spp. compared to the greater predominance of *Staphylococcus* spp. in non-tumour capsule tissue.[12] However, despite the association between BIA-ALCL and *Ralstonia* spp. this does not prove causation, and it has been suggested that this may simply reflect an opportunistic infection.[13] A significantly greater risk has been identified in association with implants with the roughest textured surface compared to those with less prominent texturing.[14] *In-vitro* bacterial attachment studies show a linear relationship between surface area/roughness and bacterial attachment/growth.[15] Chronic inflammation due to repeated antigenic stimulation has been shown to cause T cell activation and is associated with several other T cell malignancies, and it is postulated that more sustained chronic inflammation may be mediated by the higher bacterial load associated with highly textured implants.[16,17] A T helper type 17 (Th17)/Th1 phenotype has been described for the lymphocytes in BIA-ALCL, which further supports the role for chronic inflammation and antigenic stimulation in the pathogenesis.[18] Silicon leachables and particles have also been implicated as the chronic inflammatory stimulus in BIA-ALCL and, interestingly, other prostheses containing silicon also have been associated with

peri-implant lymphoma.[19] However, a definitive causal relationship between silicon and lymphomagenesis has not yet been established. Owing to incomplete evidence on pathogenesis, the majority of implants remain in use. Aberrant Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling has an established role in inflammation-associated cancers,[20] and one of the central drivers of systemic ALCL is activation of STAT-3.[21] A recent study identified overexpression of STAT-3 in BIA-ALCL, and there are several reports of activating mutations resulting in activation of STAT-3,[22,23] further supporting this hypothesis. It is important to note that no clustering of BIA-ALCL cases to particular units has been described, so this association with bacterial infection does not implicate a relationship with surgical practice, but rather it has been suggested that genetic host factors are likely to play a role in susceptibility,[24] further supported by the almost complete absence of cases in Asian countries.

Cytology and histology

BIA-ALCL may be diagnosed on cytological examination of seroma fluid or histological examination of capsulectomy samples. The greatest chance for early diagnosis comes from the cytological analysis of the very first peri-implant seroma aspirate. False negatives are more commonly seen if the analysis is repeated on subsequent aspirates, due presumably to a dilutional effect as the seroma fluid reforms. Direct smears as well as a cytoblock preparation are valuable for diagnosis, facilitating immunocytochemistry when indicated by morphological features on the smear preparations. The variable abundance of neoplastic cells, varied background cell population and highly variable immunophenotype mean it is imperative that morphological examination is integrated with molecular characterisation.

The neoplastic cells of BIA-ALCL comprise medium to large atypical cells with abundant eosinophilic cytoplasm and irregular nuclei with prominent nucleoli. The cells may sometimes have eccentric kidney-shaped nuclei or be multinucleate and resemble Reed–Sternberg cells.[10,25] Usually, neoplastic cells make up ~70% of the total cellularity of the seroma fluid, although some cases with as few as 10% atypical cells have been described[25] (Figure 1).

In tissues, the histological features mirror the clinical presentation. In disease presenting as a seroma, non-cohesive atypical neoplastic cells are confined to the luminal aspect of the capsule embedded in fibrinoid material. Generally, there is a sparse associated inflammatory infiltrate. Identifying areas on the luminal surface of the capsule that appear macroscopically abnormal may aid identification, but the abnormal cells may not be seen at all in capsule tissue in the early phase of BIA-ALCL. In those cases presenting with a mass lesion, sheets of malignant cells infiltrate the capsule and surrounding tissue,

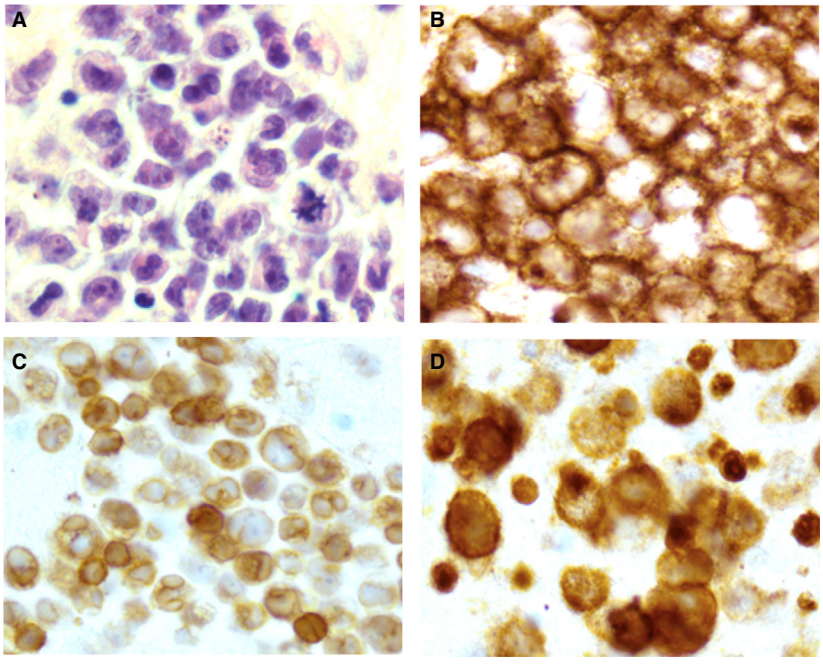

Figure 1. Cytological features of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). **A**, The image shows a clot from seroma fluid indicating the cellular nature, with medium and large atypical cells and a mitotic figure. **B**, Immunohistochemistry indicates strong surface staining for CD30. **C**, The cells show variable staining for CD3 and **D**, are positive for CD7.

often with areas of necrosis and a variable acute inflammatory infiltrate, sometimes with prominent eosinophils[10] (Figure 2).

In contrast, reactive seromas comprise variable proportions of neutrophil polymorphs, small lymphocytes and bland macrophages, sometimes with numerous multinucleate cells in more chronic forms of the condition. Sometimes atypical macrophages can be seen in reactive seroma fluid, and immunophenotyping can be helpful here to distinguish these from BIA-ALCL.[10,25]

Immunophenotype

The neoplastic cells of BIA-ALCL are consistently strongly positive for CD30, with 43–90% of cases also positive for EMA, and all are ALK-negative.[10,25,26] However, CD30 expression needs to be interpreted with care: CD30 has been detected on both activated T and B cells, in some cases shown to be induced by viral infection, as well as on natural killer (NK) cells, monocytes and lymphocytes.[23,27,28] Thus, detection of CD30 expression alone is insufficient to make a diagnosis – expression must be in a cell population with the characteristic cytological features of ALCL, as described above. In a minority of cases, atypical reactive macrophages may be present which are CD30-negative and CD68/CD163-positive, clearly distinguishing them from BIA-ALCL cells (Figure 3).

The neoplastic cells of BIA-ALCL typically display an incomplete T cell phenotype with variable loss of CD3, CD5 and CD7. Most cases retain CD4, although occasionally this is lost.[25] Very rarely, cells exhibit an NK/T cell phenotype with CD56 positivity, but they are Epstein–Barr virus (EBV)-negative and show clonal rearrangement of the T cell receptor gene (TCR), allowing distinction from nodal NK/T lymphoma.[10] Most cases reported show rearrangement of T cell

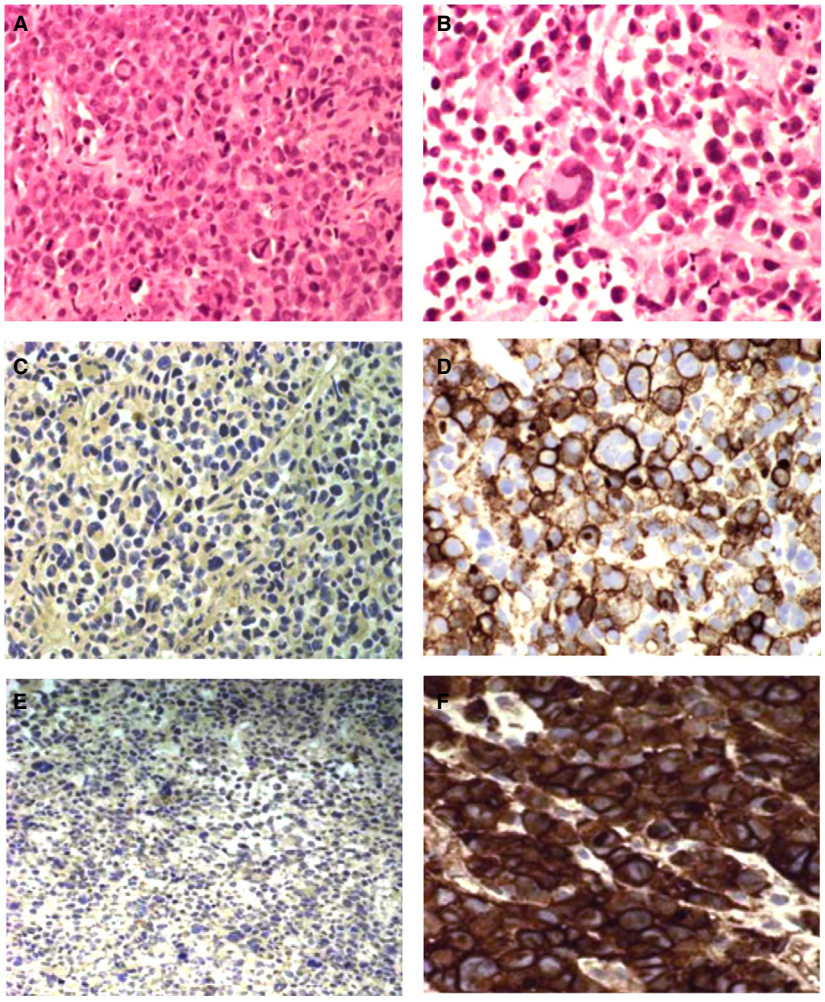

Figure 2. Histological features of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). **A**, An area from a solid capsular mass with cellular infiltrate. **B**, The cells are pleomorphic, with occasional large cells with horseshoe-shaped nuclei. **C**, The cells are uniformly negative for the broad-spectrum cytokeratin MNF116. **D**, The cells are positive for CD45, **E**, uniformly negative for anaplastic lymphoma kinase (ALK) and **F**, strongly positive for CD30.

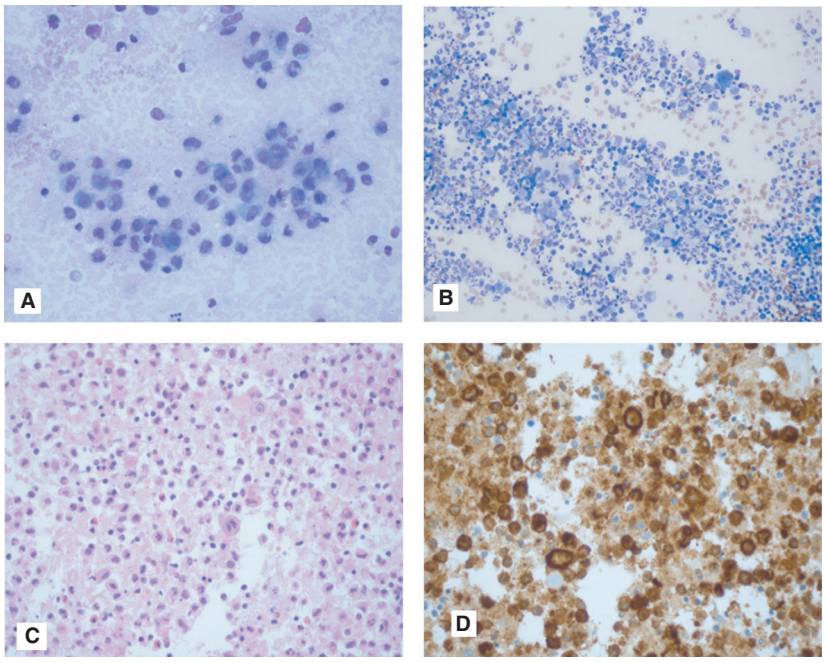

Figure 3. Cytological and immunocytochemistry characteristics of seroma fluid containing atypical macrophages. **A**, May–Grünwald–Giemsa (MGG) smear showing large, atypical cells some with kidney-shaped nuclei and cytoplasmic vacuolation. **B**, MGG stain of cytoblock demonstrating high cellularity with atypical cells on a background of mixed lymphocytes and neutrophils. **C**, Haematoxylin and eosin (H&E) stain of cytoblock showing similar features with some cells exhibiting prominent nucleoli and apparent binucleate cells. **D**, Cell block stained for CD163, showing strong cytoplasmic staining of the large atypical cells. These cells are also positive for CD68 and negative for CD30 (images not shown). [Colour figure can be viewed at wileyonlinelibrary.com]

receptor genes and therefore, in cases with an indeterminate immunocytochemical profile, clonality studies for TCR might be very helpful.[1,23]

Occasional cases have been described as positive for paired box 5 (PAX5) and CD15, leading to misdiagnosis as Hodgkin lymphoma,[10] although TRG rearrangement is a consistent feature.[25] A summary of the typical marker profile is given in Table 1.

By taking an integrated morphological and immunophenotypical assessment it should be possible to avoid the diagnostic pitfalls consequent upon over-reliance on marker profile alone.

Table 1. Summary of immunophenotype of BIA-ALCL neoplastic cells, emphasising the variability of staining profile between cases

Consistent phenotype	Variable phenotype
$CD30^+$	CD2/CD3
ALK^-/EBV^-	CD15
$CD43^+$	IRF4/MUM1
$CD4^+$	PAX5
$CD68^-$	CD8
Cytotoxic granules (TIA1, perforin/granzymeB)$^+$	EMA

BIA-ALCL, breast implant-associated anaplastic large cell lymphoma.

Recommended guidelines for diagnosis

An International Consensus Conference recommended, with 100% agreement, that all late seromas should have cytological assessment, flow cytometry and CD30 immunohistochemistry.[29] This appears to imply that such investigation is required regardless of the initial cytological or tissue examination. We recommend against using CD30 expression – either on flow cytometry or immunocytochemistry – as a screening tool for several reasons, as outlined in Table 2. Recent pathway recommendations have been published by UK breast surgeons,[30] but these focus predominantly on patient management. Here we provide evidence-based guidelines for the cytological and histological assessment of patients presenting with symptoms raising suspicion of BIA-ALCL (Figure 4).

Table 2. Rationale for two-stage assessment process: initial morphological assessment for characteristics neoplastic cells is recommended prior to immunocytochemical or immunohistochemical assessment

Vast majority of seromas, even late-onset, will not be ALCL
CD30 is a non-specific marker: screening on basis of CD30 expression could result in false-positive diagnosis
Highly variable antigenic profile of BIA-ALCL neoplastic cells may give rise to false-negative or false-positive results based on flow-cytometry
Reliance on flow cytometry restricts diagnosis to large centres with impact on timely diagnosis

BIA-ALCL, breast implant-associated anaplastic large cell lymphoma.

We recommend that all patients with implants presenting with late persistent unexplained seroma or peri-implant mass should undergo appropriate imaging (mammogram or ultrasound). Where fluid is present, the entire volume should be aspirated and submitted for cytological examination. The sample should be placed in liquid preservative to facilitate cell-block preparation and adjunct immunocytochemistry studies, rather than made initially as direct smears. It is imperative to include full clinical details on the pathology request form and a clear indication of suspicion of BIA-ALCL.

In the laboratory, we recommend that preparations of May–Grünwald–Giemsa (MGG), Papanicolaou (PAP) or haematoxylin and eosin (H&E)-stained smears (according to local preference) should be made from liquid cytological samples, and additional material made into cytoblocks. The primary analysis will be morphological, and we strongly recommend that cytopathologists or breast pathologists who may initially receive such specimens work closely with haematopathology colleagues. Samples that are acellular or are composed entirely of inflammatory cells

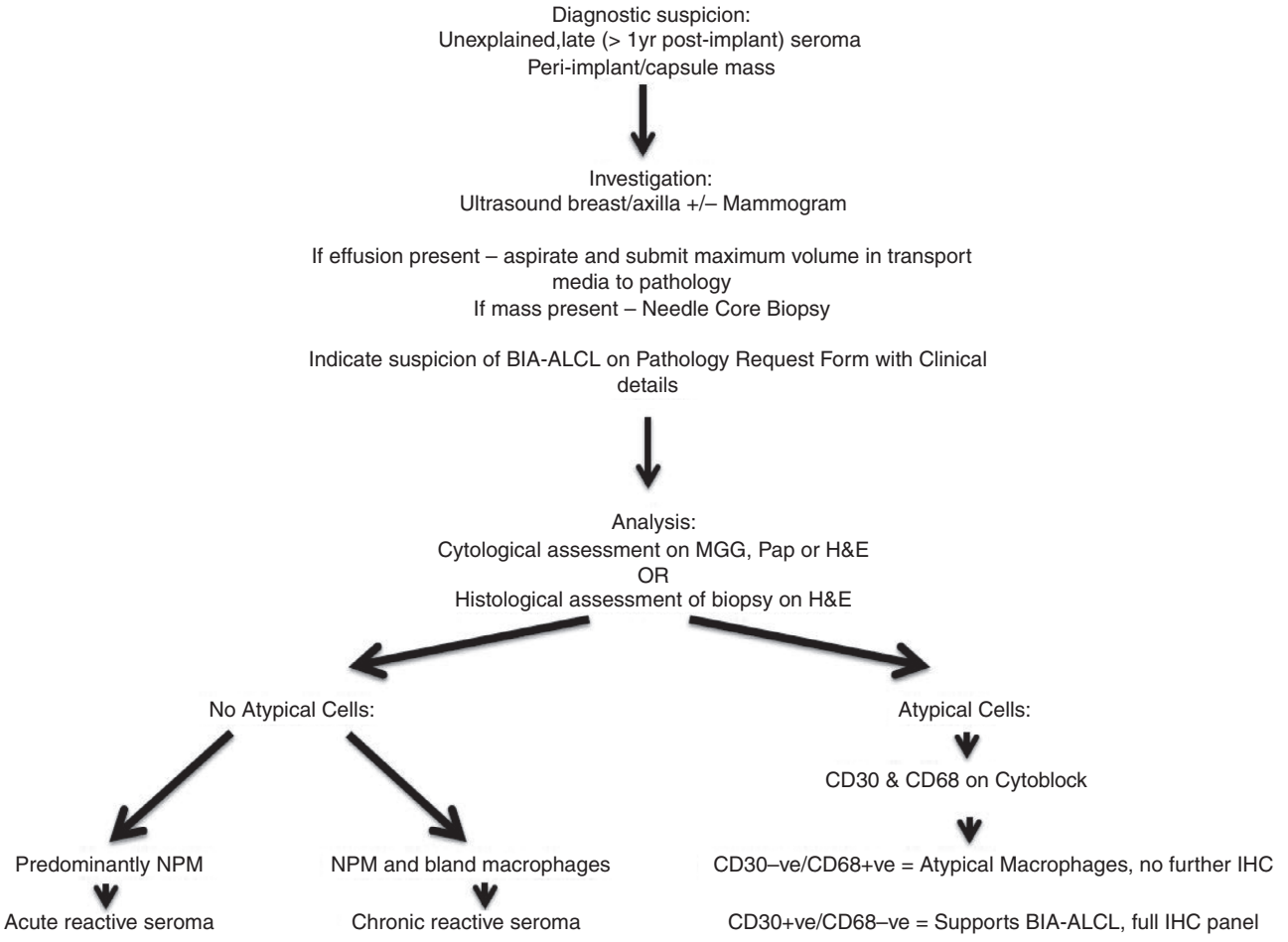

Figure 4. Recommended diagnostic approach.

(neutrophils and 'bland' macrophages) can be reported as negative without further immunohistochemistry. Those samples containing 'atypical' macrophages and/or large atypical lymphoid blasts should have CD30 and CD68/CD163 assessment undertaken. If these atypical cells are CD30-positive and CD68-negative, the remaining panel for ALCL should be requested. Additional T cells markers are essential to confirm the diagnosis of BIA-ALCL. The latter, similarly to ALK-negative ALCL, frequently express CD4 and cytotoxic granules (granzyme B and TIA1) in addition to CD30 and MUM1, while other T cell markers (CD2, CD3, CD5, CD7 and CD8) are often lost or down-regulated. ALK-1 is always negative. EMA and CD15 can be expressed in some cases. The diagnostic panel should always also include B cell markers (CD20, CD79, PAX5) and EBV to exclude other large cell lymphomas [diffuse large B cell lymphoma (DLBCL) and classical Hodgkin lymphoma (cHL)]. A pan-cytokeratin to exclude poorly differentiated carcinoma, and S100 and Melan-A to exclude melanoma, are also essential in this setting.

If CD30 is negative and CD68/CD163 are positive this confirms 'atypical' macrophages; hence, no ALCL panel is required.

Where a mass is present on imaging this should, wherever possible, undergo needle or open biopsy and an integrated morphological and immunophenotyping assessment should be undertaken, as described for cytology samples. Once again, we advise a two-step process whereby histological assessment directs any molecular analysis. As with cytology specimens, the primary analysis will be morphological, and we recommend that pathologists who initially receive such specimens work closely with haematopathology colleagues.

Disease staging

The Ann Arbour staging system is traditionally used for staging of haematological malignancies. When applied to BIA-ALCL, stage IE refers to disease limited to breast involvement only and IIE to disease involving ipsilateral lymph nodes.[31] However, using this system, 80–96% of patients have stage IE disease and 3.6–18.8% stage IIE, with 80% of recurrences occurring in stage I disease, suggesting that this system is of limited prognostic use in BIA-ALCL.[32] Clemens *et al.*[32] suggested that BIA-ALCL behaves more like a solid tumour, and proposed a pathological staging system based on the American Joint Committee on Cancer TNM system (Table 3). This staging system is more discriminatory in terms of event-free survival and more accurately predicts overall survival compared to the Ann Arbour system, and is therefore recommended for use.[32]

Table 3. Recommended staging system, adapted from Clemens *et al.*[32]

TNM stage	Description
Tumour extent	
T1	Confined to effusion or luminal side of capsule
T2	Superficial infiltration luminal aspect of capsule
T3	Sheets or clusters of cells infiltrate thickness of capsule
T4	Cells infiltrate beyond capsule into breast or soft tissues
Lymph node	
N0	No lymph node involvement
N1	One regional lymph node
N2	Multiple regional lymph nodes
Metastasis	
M0	No distant spread
M1	Spread to other organs

Management

There has been a lack of standardised treatment for patients with BIA-ALCL, which makes it difficult to evaluate the most effective approach; however, a comprehensive report by Clemens *et al.*[32] on 87 patients emphasises the importance of complete surgical excision. Of 51 patients who had chemotherapy, six of 11 who did not have complete surgical excision had further recurrence compared to four of 40 who had complete surgical excision. Indeed, for all patients, those who underwent complete surgical excision had improved event-free and overall survival compared to those with limited surgery, chemotherapy or radiotherapy. They therefore recommend removal of the implant, total capsulectomy and removal of any mass with confirmation of negative margins, both for disease limited to the effusion and for infiltrative disease.[32] Furthermore, their observations suggest that capsule fluid can drain into multiple lymph nodes, so advise that there is no place for

routine sentinel lymph node removal but that surgical excision of individual nodes should be performed where there is suspicion of involvement. In the National Comprehensive Cancer Network (NCCN) guidelines[33] and the recent UK management guidelines,[30] complete surgical excision for stage I disease is considered sufficient. Traditional capsulectomy for capsular contraction is often a piecemeal excision of the capsule and the specimen, if sent for histological analysis, is not orientated. This presents significant limitations for useful oncological reporting should BIA-ALCL be found. Surgeons should therefore perform a complete *en-bloc* capsulectomy wherever possible, to ensure that no capsule tissue is left behind, to avoid intraoperative drainage of seroma fluid into the surgical field and to facilitate standard orientation of the specimen. A proposed technique for specimen orientation is to provisionally mark the capsule intraoperatively (e.g. with ink), and after removal and transfer to the bench to complete more formally with orientation sutures, thus providing a fully orientated and intact surgical specimen (Figure 5). The surgeon is required to record the details relating to implant integrity, type and texture. In addition, on the posterior central patch there will usually be details relating to implant size, manufacturer details and a serial number. In the published UK series,[30] one patient treated with implant exchange and standard capsulectomy developed aggressive local recurrence within 6 months. After further review of the original specimen focal penetration through the capsule was seen, but the original specimen was unorientated. If it had been, opportunity for further excision may have been afforded. Surgeons may wish to consider removal of any contralateral implant, as incidental contralateral lymphoma has been reported in up to 4.6% of cases.[32] When complete excision cannot be achieved or there is chest wall invasion, radiotherapy should be considered. Where there is more advanced disease (stage II and above) systemic chemotherapy is warranted; the most frequently used has been a combination anthracycline-based regimen. There has been growing interest in the potential value of brentuximab vedotin, an antibody–drug conjugate with a chimeric CD30 antibody attached to a microtubule inhibitor,[34] in the treatment of BIA-ALCL. Clinical trials in relapsed or refractory CD30-positive systemic lymphoma demonstrate durable response and tumour regression in the majority of patients,[35,36] and its use as frontline therapy in combination with chemotherapy has demonstrated an overall response rate of 86% and complete remission in 57% of patients.[37] Johnson *et al.*[30] provide one of the first reports of the use of brentuximab vedotin in a patient with BIA-ALCL who progressed on chemotherapy, where treatment achieved a complete pathological response, and a recent report further supports clinical efficacy as frontline treatment in BIA-ALCL,[38] suggesting that additional studies for its use in BIA-ALCL are certainly warranted.

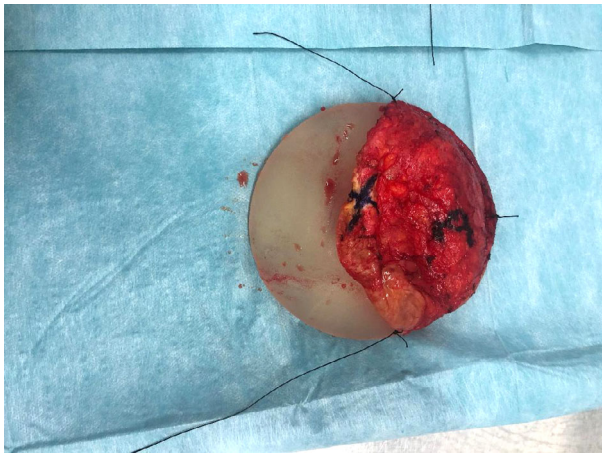

Figure 5. *En-bloc* capsulectomy with suture orientation allowing appropriate assessment of margins. [Colour figure can be viewed at wileyonlinelibrary.com]

Central registration

It is a requirement that all cases of BIA-ALCL in the United Kingdom are reported to the Medicines and Healthcare Products Regulatory Agency (MHRA) via the online Yellow X+Card Scheme (https://yellowcard.mhra.gov.uk). In the United States, the American Society of Plastic Surgeons and the Plastic Surgery Foundation, together with the Food and Drug Administration (FDA), have established the Patient Registry and Outcomes for Breast Implants and Anaplastic Large Cell Lymphoma Etiology and Epidemiology (PROFILE).[3] The aim is to collect both prospective and retrospective data on confirmed cases of primary ALCL in women with implants, and to utilise this information to accurately establish the aetiology, potential risk factors and optimum management of the disease. It is strongly recommended that UK clinicians register their cases and contribute to the global effort to better understand this rare condition.

Conflicts of interest

The authors have no conflicts of interest to declare.

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