Lymphoma Network of New Zealand

Breast Implant Associated Anaplastic Large Cell Lymphoma Protocol (BIA ALCL)

Summary of Recommendation

- **Diagnosis and Staging:**
  - Requires high index of suspicion from the GP and surgical team
    - Ultrasound evaluation
    - Histopathological/ cytological assessment
  - Initial work up includes standard lymphoma investigations
  - Staging system
    - Solid tumour staging for BIA-ALCL divide patient in to two subtype
      - In-situ
      - Infiltrative

- **Treatment:**
  - Surgery is the main treatment approach.
  - Adjuvant and systemic treatment should be considered in a selected group.

Sub Topics

Introduction

Breast implant associated anaplastic large cell lymphoma (BIA-ALCL) is a recently recognised and distinct malignancy of T lymphocytes exclusively associated with *textured* breast implants used for both aesthetic and reconstructive surgery.

The pathognomic histological response to breast implant insertion is benign capsule formation. Smooth surface implants are associated with higher rates of benign capsular contracture, because they predispose to a planar arrangement of fibroblasts with organised collagen deposition around implants. By contrast, textured implants typically have grooves larger than the diameter of a fibroblast, disrupting the planar arrangement of cells and reducing the risk of capsular contracture, that same mechanism, increases the risk of the development of lymphoma.

Epidemiology:

BIA-ALCL is a CD30+, ALK negative lymphoma with a typically indolent progression. An accurate estimation of the incidence and prevalence of BIA-ALCL is confounded by under-reporting, poor characterisation and follow up of patients exposed to breast implants and unconfirmed pathology. Initial studies did not differentiate between exposures to smooth or textured implants, which also impacted on estimations of incidence in these cohorts.

Although more than 500 cases of BIA-ALCL have been confirmed worldwide to date, no cases have been reported in women exposed to smooth implants only. Analysing documented cases of BIA-ALCL in the US (1996-2015); Doren et al.[16] reported that the lifetime prevalence of BIA-ALCL was approximately 1 in 30,000 for women with textured breast implants. Loch-Wilkinson et al.[17] investigated implant specific risk of BIA-ALCL in Australia and New Zealand (2007-2016). The reported risk was 1:3817 for Biocell, 6:7788 for polyurethane and 1:60,631 for Siltex-textured implants.

Pathogenesis:

The exact pathogenic mechanisms surrounding BIA-ALCL are unclear. Despite the reduction of capsular contracture rates with implant texturisation, their greater surface area and rough interface enhances bacterial adhesion and biofilm burden. Prevailing theories recognise the role of the breast microbiome and textured implants, which potentially trigger malignant transformation in the milieu of sustained antigen-driven inflammation.

Bacteria attach to the biofilm surface of the implant causing chronic antigenic stimulus that drives T cell proliferation. Textured implants have 30 times more biofilm formation than smooth implants. This is attributed to their greater surface area and the enhanced bacterial adhesion on rough surfaces. ***Ralstonia*** species are gram negative bacteria that predominate on BIA-ALCL surfaces. This parallels the link between *H. pylori* and gastric MALT lymphomas.

Genetic factors may also play a role.

Diagnosis and Staging

Clinical Presentation:

Delayed seromas greater than a year after implantation occur in approximately 0.1-0.2% of patients following implantation of textured implants[15]. BIA-ALCL has been estimated to occur in 9-13% of such cases. Patients with BIA-ALCL most commonly present with either a rapid onset of a spontaneous fluid collection (60-90%), capsular mass (10-40%) or both, at an average of 8-10 years after textured implantation.

Establishing Diagnosis:

- **Diagnosis requires high index of suspicion from the GP and surgical teams.**

Ultrasound evaluation is performed to define the extent of the seroma, identify any capsular masses or regional lymphadenopathy and to guide seroma aspiration. Suspicious masses require a tissue biopsy.

Histopathologic assessment must involve cytological examination of seroma fluid and tissue histology.

- Requires a minimum of a flow cytometry panel and tissue immunohistochemistry
- The diagnosis of BIA-ALCL is confirmed by the presence of large anaplastic cells with uniform *expression of CD30* and the absence of ALK protein expression.
- T cell receptor rearrangemet molecular studies if the above tests are negative and high index of suspicion still exists might be warranted.

Staging:

Initial staging investigations should include routine blood test as per lymphoma guidelines, staging CT or CT-PET scan to exclude distant disease and a bone marrow biopsy.

Two distinct clinicopathologic forms of BIA-ALCL have emerged[14,15,63,69] (Table 1).

- The **"in-situ" subtype (T1-3)** is characterised by anaplastic proliferation of cells confined to the capsule itself and is invariably associated with a seroma.
    - T1-T3 disease is considered curable with complete capsulectomy/ removal of the impants.
    - Fortunately, according to several large reported studies, 59-87% of BIA-ALCL cases, fit into this subset of disease (T1-3).

- The **"infiltrative" subtype (T4)** demonstrates varying degree of infiltration of the capsule, surrounding soft tissue or the breast parenchyma with a tumour mass.
    - Patients, who have disease extending beyond the capsule or metastatic disease, need to be considered for adjuvant/ systemic therapy.

Tumour (T)	T1	Effusion only OR confined to a layer on luminal side of capsule		
	T2	Early capsule infiltration		
	T3	Cell aggregates or sheets infiltrating the capsule		
	T4	Lymphoma infiltrates beyond the capsule		
Lymph node (N)	N0	No lymph node involvement		
	N1	1 regional node involved		
	N2	>1 regional node involved		
Metastasis (M)	M0	No distant spread		
	M1	Spread to other organs/distant sites		
STAGE	IA – T1N0M0	IIA – T4N0M0	III – T4N1-2M0	IV – TanyNanyM1
	IB – T2N0M0	IIB – T1-3N1M0		
	IC – T3N0M0			

Table 1: Solid tumour staging for BIA-ALCL

Treatment

Surgical:

Disease localised to the capsule is adequately treated with surgical removal of the implants alone in the majority of cases. T1 - T3 disease is considered curable with surgery alone . At present, there is no role for radical mastectomy, sentinel lymph node biopsy or elective axillary dissection. The timing and type of secondary breast reconstruction in ALCL cases remains controversial. Secondary prosthetic reconstruction should utilise smooth implants given the association between texturing and tumourigenesis.

Table 2: Surgical goals in management of BIA-ALCL

Total capsulectomy AND excision of any associated capsular mass with negative surgical margins	Strict oncologic technique (specimen orientation sutures, change of instruments if performing contralateral explantation) The capsule may be thickened and fibrous or deceptively normal in appearance Complete posterior capsulectomy may be technically challenging with subpectoral or dual-plane implants.
Explantation of the breast implant	Consider removal of the contralateral implant, as approximately 4.5% of cases to date have demonstrated incidental ALCL in the contralateral breast.
Excisional biopsy of suspicious lymph nodes	Given the focal localisation of lymphoma in most cases with lymph node involvement, fine-needle aspiration may yield false negative results. Excisional biopsy of suspected lymph nodes should be performed.

Adjuvant Treatment:

Patients with incomplete margins, locoregional spread or disseminated disease should receive CHOEP chemotherapy or equivalent.

In relapse/refractory disease consider

- Brentuximab (NPPA required)
- Radiation to the chest wall

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