BREAST IMPLANT ASSOCIATED-ANAPLASTIC LARGE CELL LYMPHOMA

WHAT IS BIA-ALCL?
Breast Implant Associated-Anaplastic Large Cell Lymphoma (BIA-ALCL) is a rare sub-type of T-cell non-Hodgkin lymphoma (NHL). It is one of four sub-types of ALCL which has been found in association with breast implants in a small number of cases worldwide. This sub-type is always both CD30 positive and ALK negative.

The aetiology is unknown but one of the most plausible current theories on causation of BIA-ALCL is that it is related to the biofilm. A biofilm is where bacteria are attached to an implant surface and surrounded by a protective layer of glycoprotein. They are difficult to treat and can lay dormant for years. It is theorised that BIA-ALCL tumour cells might be derived from a sustained T-cell immune response to the bacterial antigens in biofilm, but as yet there is no substantive evidence this is the case.

If BIA-ALCL is caught early treatment is usually surgical and curative, by complete removal of the capsule and implant.

HOW COMMON IS BIA-ALCL?
The first case of BIA-ALCL was reported as recently as 1997 and was discovered in association with a saline filled breast implant. The most reliable frequency of occurrence of BIA-ALCL is estimated at 1 in 300,000 breast implants or an annual incidence of 0.1 to 0.3 per 100,000 women with implants but with growing awareness and reporting of this rare disease the true incidence may be higher.

Although the first case of BIA-ALCL was in association with a saline implant, it has been shown to occur independently of the filler material and has been more commonly associated with textured implants (including micro-polyurethane) with no cases to date reported with the sole use of smooth implants. However, uncertainty exists as most of the ALCL cases reported in breast implant patients failed to include information about the texture of the shell.

In whatever circumstance a breast implant is being used, either for breast reconstruction or augmentation, there is now a need to provide patients with adequate information, and a discussion of BIA-ALCL must be included as part of the consent process and documented in the patient's medical record. Implants are still regarded as safe for use in augmentation and reconstruction operations and the MHRA does not suggest a change in practice with the current data available.

PRESENTING SYMPTOMS AND SIGNS
The most common presenting symptom for BIA-ALCL is a swollen breast caused by the formation of a delayed (>1 year since implant placement) unilateral idiopathic seroma occurring between the implant surface and the capsule. It is occasionally associated with localised capsule thickening or a mass, however more commonly the capsule may look entirely normal except for the seroma, which often contains free floating debris that is best appreciated on ultrasound. A very small number of cases have been reported in the absence of a peri-prosthetic fluid collection in association with a severe capsular contraction, a mass or as a cutaneous nodule. BIA-ALCL may also occur bilaterally, although this is even more rare.
The differential diagnosis of late seroma includes infection, trauma, haematoma, implant rupture, double capsule, synovial metaplasia, breast cancer and idiopathic causes. These causes greatly outweigh the occurrence of a BIA-ALCL seroma and need to be considered and differentiated. Patients without a clear attributable cause or who have a non-resolving peri-prosthetic fluid collection should be further evaluated and BIA-ALCL needs to be considered. A negative aspiration cytology with strong clinical suspicion of BIA-ALCL requires a breast MRI for further evaluation and referral to a breast multidisciplinary team (MDT) with experience of this disease.

Where ALCL is associated with breast implants, CD30-positive cytokeratin-negative, ALK negative malignant cells are found infiltrating the luminal side of the peri-prosthetic capsule on histological analysis, or in the aspirated fluid collection surrounding the implant.

INVESTIGATION
Establishing the diagnosis of BIA-ALCL can be challenging and a multidisciplinary approach is essential. It is of primary importance that all healthcare professionals caring for patients with breast implants have a working knowledge of BIA-ALCL to make a timely diagnosis and avoid over treatment of capsular contained early stage disease.

Ultrasound guided aspiration of a seroma of adequate volume is essential to be able to make the diagnosis of BIA-ALCL and to exclude other causes. It is paramount that the cytology and pathology request forms state for the exclusion of BIA-ALCL so that specific staining and haematopathology review is performed. If surgical exploration has been carried out, fresh seroma fluid and the capsule should be sent for cytology and histopathology to rule out BIA-ALCL. It should be remembered that the appearance of the capsule is often quite normal to the naked eye, with the exception of the copious seroma, so alone should not be a discriminator if the diagnosis is suspected.

Diagnostic evaluation of seroma fluid should also include standard culture and cytological evaluation. The pathologist must be made aware of the suspicion of BIA-ALCL so that, where appropriate, Wright Giemsa staining and cell block immunohistochemistry testing for CD30 and Anaplastic Lymphoma Kinase (ALK) markers will be performed. BIA-ALCL can only be confirmed if it is found in association with the implant capsule or within the effusion and is confirmed on immuno-histochemistry as being CD30 positive and ALK negative.

Any abnormal breast mass associated with an implant should be biopsied and in addition to standard pathological assessment be additionally assessed for BIA-ALCL which is now a provisional distinct entity in the World Health Organisation classification of lymphoid neoplasms.

Any patient diagnosed with BIA-ALCL should have a PET-CT to exclude regional or systemic spread. If an abnormal lymph node is found in the axilla it is recommended that it be excised whole for histology at the time of surgery, as fine needle aspiration cytology is inaccurate.

Vigilance is required especially where a late peri-prosthetic seroma occurs, as early treatment with complete capsulectomy and implant removal is associated with an excellent prognosis based on follow up data we have to date.

TREATMENT
For most patients the disease is confined to the capsule and will be classified as Stage I disease according to the new, as yet un-adopted classification by Clemens et al. Treatment will include complete capsulectomy and implant removal alone, adjuvant treatment is often not required. Whether the contralateral implant and capsule should be removed remains unanswered, as do questions about when implants should be replaced, with what type of implant and if they should be replaced at all.

The overall survival rate for patients diagnosed with BIA-ALCL is 89% at five years. This rate is significantly higher for patients with Stage I disease who undergo complete capsulectomy and implant removal.

Patients with Stage II+ disease (extends beyond the confines of the capsule) requires more aggressive systemic treatment. In some cases the standard chemotherapy regime for systemic ALCL (CHOP or CHOP-like) appears not to control locally invasive BIA-ALCL disease and patients can demonstrate disease progression through such treatments. The author (LJ) has presented the use of Brentuximab Vedotin in the neoadjuvant setting achieving
complete pathological response in a case of advanced CHOP-resistant BIA-ALCL. Brentuximab Vedotin is a monoclonal antibody drug-conjugate directed to the protein CD30, which appears to have a pertinent role in the management of locally advanced BIA-ALCL and is recommended as part of a trial for such patients with advanced disease.

REPORTING CASES OF BIA-ALCL
There is a strong need for more robust and prospectively collected data to enable better understanding of the incidence, pathogenesis and outcomes for patients diagnosed with BIA-ALCL. Any new cases of BIA-ALCL should be discussed at a Breast MDT and Haematology MDT. They must be reported to the MHRA as per their ALCL alert in 2011.

In the UK the recently launched Breast and Cosmetic Implant Registry (BIR) also affords opportunities for registering cases of BIA-ALCL. The BIR was primarily designed to record the details of any individual who has breast implant surgery for any reason so that they can be traced in the event of a product recall or other safety concern relating to a specific type of implant, and requires explicit patient consent.

You may also wish to register your case with the Patient Registry and Outcomes for Breast Implants and Anaplastic Large Cell Lymphoma Etiology and Epidemiology (PROFILE), a registry launched in the U.S. several years ago in conjunction with the FDA.

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REFERENCES AND FURTHER INFORMATION:

You can also find useful information on the Australian Government’s website: https://www.tga.gov.au/alert/breast-implants