Breast implant-associated lymphoma: what a radiologist should know.

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Learning objectives

- To provide an overview of the clinical presentation, imaging appearances of breast-implant associated anaplastic large T-cell lymphoma (BI-ALCL) at diagnosis;

- To illustrate a case-based review of this disease with pathology correlation;

- To give tips in terms of imaging for a prompt diagnosis and an adequate follow-up.

Background

Breast implant-associated anaplastic large cell lymphoma (BI-ALCL) is an extremely rare and distinct oncological entity arising within or around the prosthesis previously inserted post-mastectomy, either to treat a carcinoma or after glandular augmentation. It is a T-cell lymphoma composed of large and pleomorphic cells which uniformly express CD30 and are negative for anaplastic lymphoma kinase (ALK) or lack genetic abnormalities involving this enzyme at chromosome 2q23.

Aetiology remains unclear. The neoplasm begins on the luminal surface of the fibrous capsule surrounding the prosthesis and exhibiting varying degrees of infiltration of the capsule, the adjacent soft tissue, or the breast parenchyma.

Usually, it presents as swelling due to effusion around the implant (seroma) or unexpected changes in breast shape; less frequently as a mass. Axillary lymph nodes are not always enlarged. Suspicious peri-prosthetic fluid should be sent to test CD30 immunohistochemistry, cell block cytology, and culture.

Although characterised by good prognosis, this kind of lymphoma is not always promptly diagnosed.

Ultrasound plays a pivotal role in terms of screening symptomatic ladies, demonstrating thickening or fibrous changes of the capsule surrounding the implant or deceptively normal appearances. When present, an adequate amount of fluid should be aspirate for testing. Apart from being positive for CD30, biopsy or resection specimen also express CD4 and CD43, whilst are often negative for antigens like CD3 and CD5.

A separate staging has been proposed for this tumour, which is displayed in table 1 and illustrated in figure 1 and 2.

A key diagnostic distinction is whether the soft tissue mass involves the implant or not. This condition has been newly recognised in clinical practice and, according to the recently published British recommendations, the optimal management is represented by complete surgical excision.

Retrospective data shows that women with lymphoma confined to the fibrous capsule have a better outcome compared to those in whom cancer has spread beyond the capsule. In either case, it is important to perform a radical surgery in the first instance, including breast implant removal and total capsulectomy with complete excision of any

associated mass and negative margins on final pathology assessment. This approach is also recommended for patients who present only with a seroma. An incomplete resection or inadequate local surgical may lead the individual to further unnecessary treatments, considering that BI-ALCL is mostly localised to the breast and chest wall.

The pattern of progression of this cancer is more similar to solid tumours rather than to other non-Hodgkin's lymphoma. Therefore, there does not seem to be a valid role for sentinel lymph node biopsy. However, if nodal dissemination occurs, the axillary lymph nodes are the most likely to be involved; in such a case, excisional biopsy of any suspicious nodal gland should be carried out.

In cases where the lymphoma has spread beyond the capsule, we would generally recommend systemic chemotherapy (the most used regimen consists of cyclophosphamide, doxorubicin, vincristine, and prednisolone), the length of which would depend on the extent of the disease, with or without additional radiotherapy.

Images for this section:

T: tumour extent	
T_1	Confined to effusion or a layer on luminal side of capsule
T_2	Early capsule infiltration
T_3	Cell aggregates or sheets infiltrating the capsule
T_4	Lymphoma infiltrating beyond the capsule

N: lymph nodes	
N_0	Absence of nodal involvement
N_1	One positive regional lymph node
N_2	Multiple positive regional lymph nodes

M: metastases	
M_0	No distant spread
M_1	Spread to other organs/distant sites

STAGE	
IA	$T_1 N_0 M_0$
IB	$T_2 N_0 M_0$
IC	$T_3 N_0 M_0$
IIA	$T_4 N_0 M_0$
IIB	$T_{1-3} N_1 M_0$
III	$T_4 N_{1-2} M_0$
IV	$T_{any} N_{any} M_1$

Table 1: TNM STAGING

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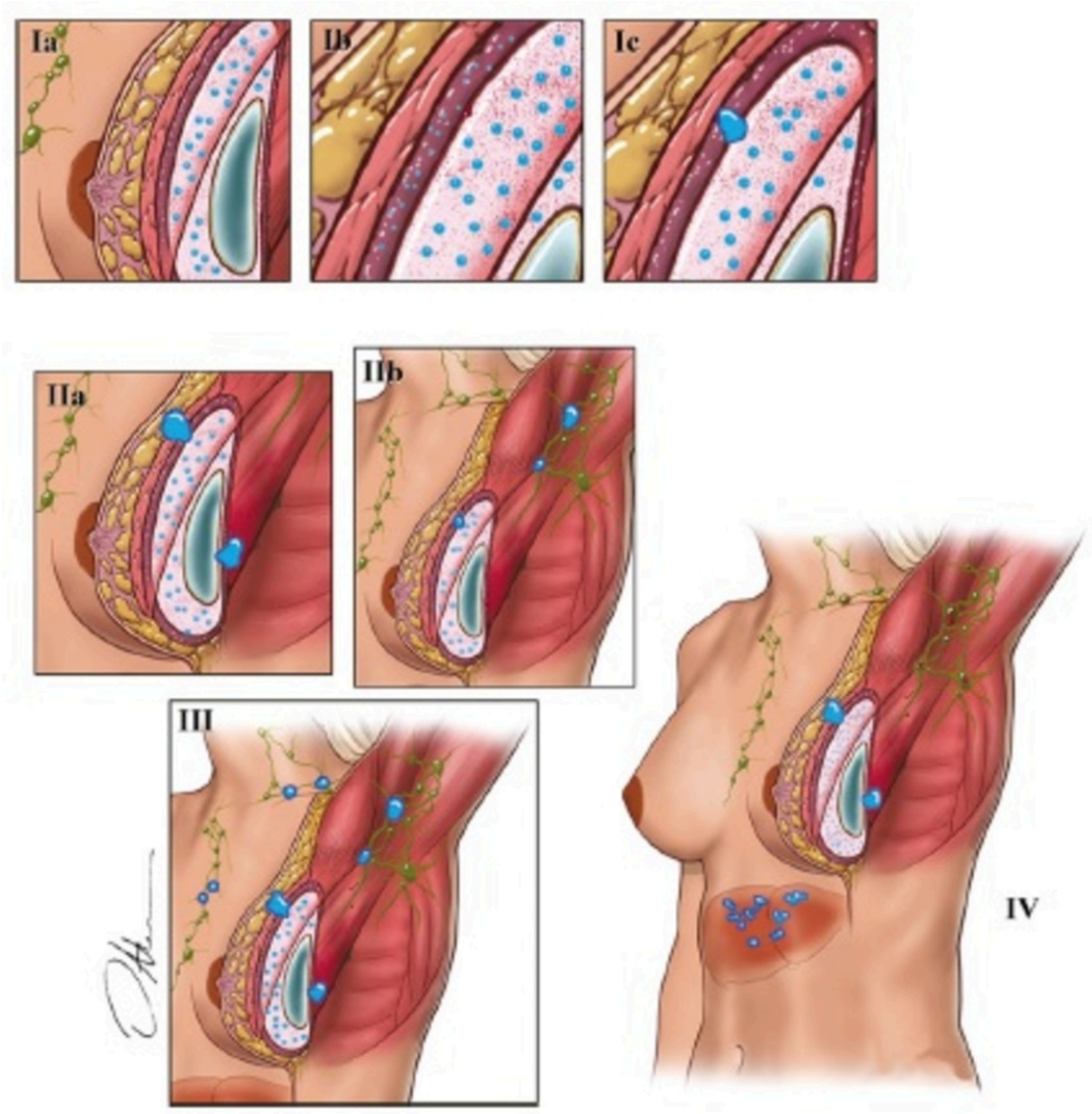

Fig. 1: TNM STAGING for breast implant-associated anaplastic large cell lymphoma.

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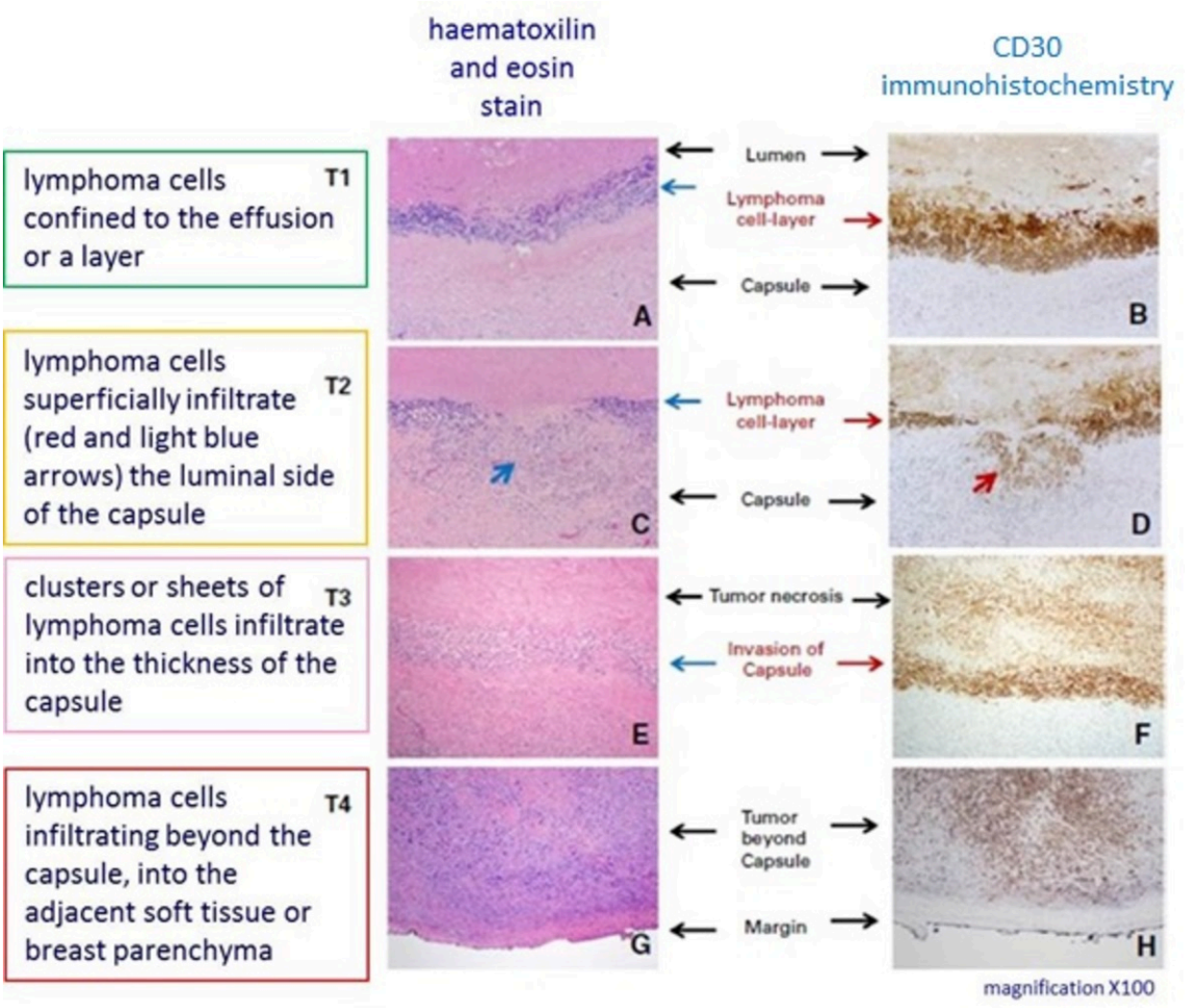

Fig. 2: PATHOLOGICAL TUMOUR STAGING

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Findings and procedure details

At our oncological hospital, 7 women, between 29 and 55 years old, were referred with BI-ALCL between 2015 and 2017. We retrospectively reviewed imaging and pathology of these cases to highlight pathognomonic features.

Furthermore, type and texture of implant along with the onset of the lymphoproliferative disease after surgery were also assessed (table 2).

Hereafter our most explicative and/or challenging cases (1-7) are illustrated.

Images for this section:

	AGE (y)	INDICATION FOR IMPLANT	DIAGNOSIS AFTER IMPLANTATION	TYPE OF IMPLANT	PRESENTATION	STAGE	IMAGING	TREATMENT	FOLLOW-UP	MANAGEMENT	NOTES
pt 1	42	bilateral breast augumentation	14 years	/	seroma around left breast implant; intracapsular rupture	IB = T_2 N_0 M_0	ultrasound	left capsulectomy	PET/CT: 2 x 2 cm nodular residuum	lumpectomy then left mastectomy and 3 cycles of CHOP	
pt 2	29	bilateral breast augmentation	3 years	transform - 520 implants	a 2-cm necrotic mass at the edge of the external capsule, of the right implant alongise a trace of fluid, later the amount of fluid increased and the mass infiltrated the pectoral muscles	IC = T_3 N_0 M_0 at presentation; then IIA = T_4 N_0 M_0	ultrasound & PET/CT	CHOP (3 cycle) but progressive disease so brentuximab, bilateral total capsulectomy and mastopexies; 4 cycles of adjuvant chemotherapy due to a residual soft tissue mass on MRI	PET/CT: complete metabolic response; US-guided biopsy of the residuum which showed no histological malignant features.	1. re-augumentation with smooth implants; 2. autologus augmentation with bilateral deep inferior epigastric perforators flap	
pt 3	50	grade I invasive lobular carcinoma of the right breast	1 year	/	A large seroma predominantly within the outer aspect of the right breast	IA = T_1 N_0 M_0	ultrasound, PET/CT & MRI	removal of implant right capsulectomy and overlying skin.	A fine needle aspiration US-guided of a small prominent node in the left axilla that shows significant cortical thickening but round and of benign sonographic features was performed.		Histology showed no evidence of malignancy
pt 4	49	bilateral breast augmentation	5 years	Poly Implant Prosteheses silicone breast implants	a 3-cm left breast lump	IC = T_3 N_0 M_0	ultrasound & CT	core biopsy of the nodule	A 9-mm non-enhacing nodule in the left breat associated with seroma on CT but non-FDG avid on PET/CT	Bilateral implant excision with total capsulectomy (anterior and posterior) and removal of peri nipple areola complex skin and subcutaneous tissue	Histology showed no evidence of BI-ALCL but intense inflammatory reaction
pt 5	39	BRCA2 mutation carrier so bilateral prophylactic mastectomy with immediate reconstruction	2 years	bilateral Allergan TRF 520 in 2012: recurrent seroma; in 2013 revision of left breast reconstruction with capsulectomy and implant exchange to Polyurethane round polytech 495 g	swelling around left breast implant	IA = T_1 N_0 M_0	ultrasound	removal of both mastectomy flaps and of the right implant alongside bilateral total capsulectomies	PET/CT: inflammatory changes due to recent surgery; no suspicious sites of disease		
pt 6	55	right breast intraductal carcinoma	7 years	/	seroma containg septations around right breast implant; no soft tissue mass	IA = T_1 N_0 M_0	ultrasound & PET/CT	right breast deconstruction of implant and complete capsulectomy			
pt 7	50	left breast intraductal carcinoma	6 years	350 cm^3 polyurethane	large seroma surrounding the left breast implant	IA = T_1 N_0 M_0	PET/CT	Left total capsulectomy with preservation of skin envelope and nipple, completely excised	PET/CT: bilateral internal mammary lymph nodes likely to be reactive and chronic due to treatment and implant presence.	currently waiting for a left breast reconstruction with a tranverse upper gracilis flap, followed by a similar procedure on the right side at a later date	

Table 2: Patients with breast implant associated anaplastic large T-cell lymphoma referred to the The Royal Marsden between 2015 and 2017.

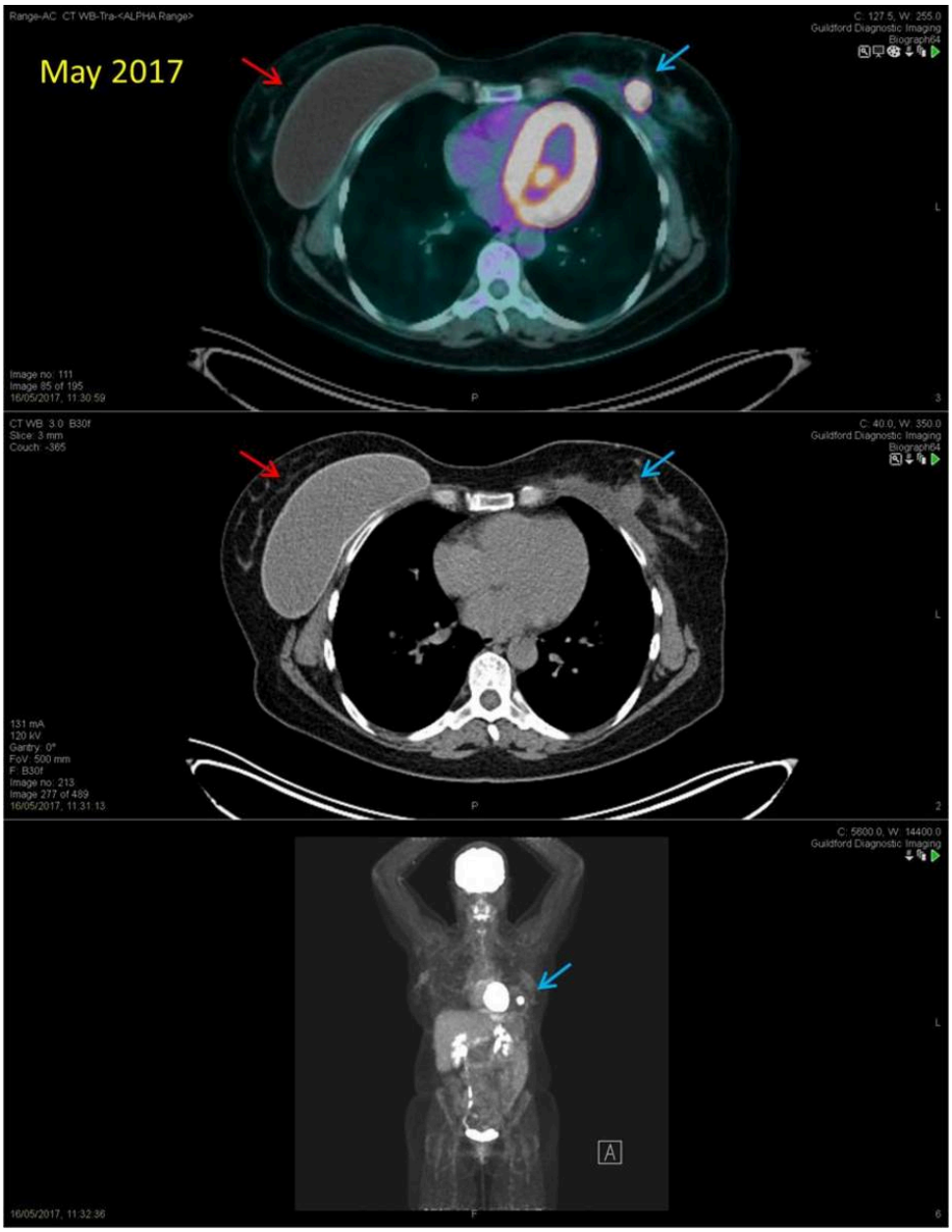

Fig. 3: CASE 1 - 42-year-old woman who had had bilateral breast augmentation in 2003. Previous cervical intra-hepitelial neoplasia grade 3 which was treated. In March 2017 she developed a relatively acute swelling of her left breast. Ultrasound appearances at this point were thought to be consistent with a left intracapsular rupture, due to a seroma detected within the breast around the implant. In view of this, the left breast implant was removed. At the time of surgery, however, irregularities were noted on the surface of the implant capsule hence it was sent for histology. HISTOLOGY: Sections showed a fibrous capsule with some associated fibrofatty tissue. On the inner surface of the capsule there was a fibrinous exudate and within this a cellular proliferation of variable density consisting of large pleomorphic cells with pleomorphic nuclei that contained coarse chromatin and prominent nucleoli. In some areas classical hallmark cells could be seen. The cells stained for CD2 and CD30 and were negative for CD3, ALK1, and cytokeratin.

In one area there appeared to be some infiltration of the capsule but the tumour cells did not penetrate through the full thickness of the dense fibrous tissue that has developed around the implant. The appearances revealed the diagnosis of ALK-NEGATIVE LEFT BREAST IMPLANTED-RELATED ANAPLASTIC LARGE CELL LYMPHOMA (BI-ALCL). In May, following the capsulectomy she had a PET/CT scan to look for residual disease which demonstrated an intensely FDG avid (SUVmax 40) non bulky rounded 19 x 19 mm site of soft tissue change in the inferior left breast, just medial to the midline, being contiguous with the underlying chest wall musculature. The contralateral right breast implant was in situ without evidence of seroma. No evidence of pathological tracer uptake elsewhere. Opinion: solitary malignant focus of disease in the left breast/chest wall. An ultrasound scan at the time showed a 22 x 25 mm hypoechoic area in the left breast. She had a wide large excision of this lump. Histology was consistent with a solid area of ALK-negative ALCL. Although the margins were clear, to maximise the chance of local disease control, a left mastectomy was performed in July. Histology of the gland showed breast tissue with fibrocystic change and no evidence of malignancy. As the residual tumour was external to the capsule, our multidisciplinary team recommendation was to treat this patient with 3 cycles of CHOP (cyclophosphamide, hydroxydaunarubicin, oncovin/vincristine, prednisone) chemotherapy. The role of consolidation radiotherapy in this setting was unclear.

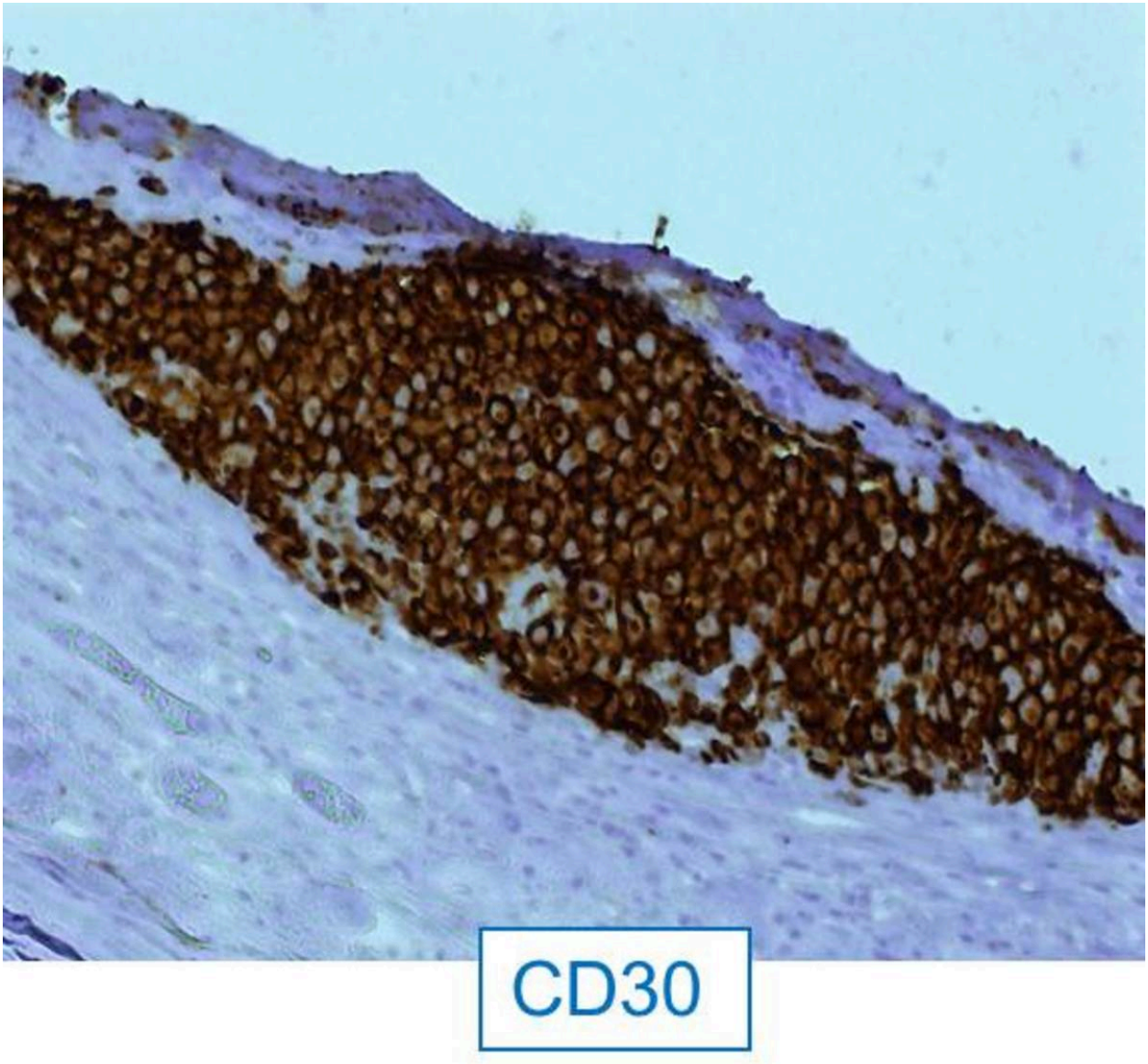

Fig. 4: CASE 1 - IMMUNOHISTOCHEMISTRY: The infiltrate was CD30 positive

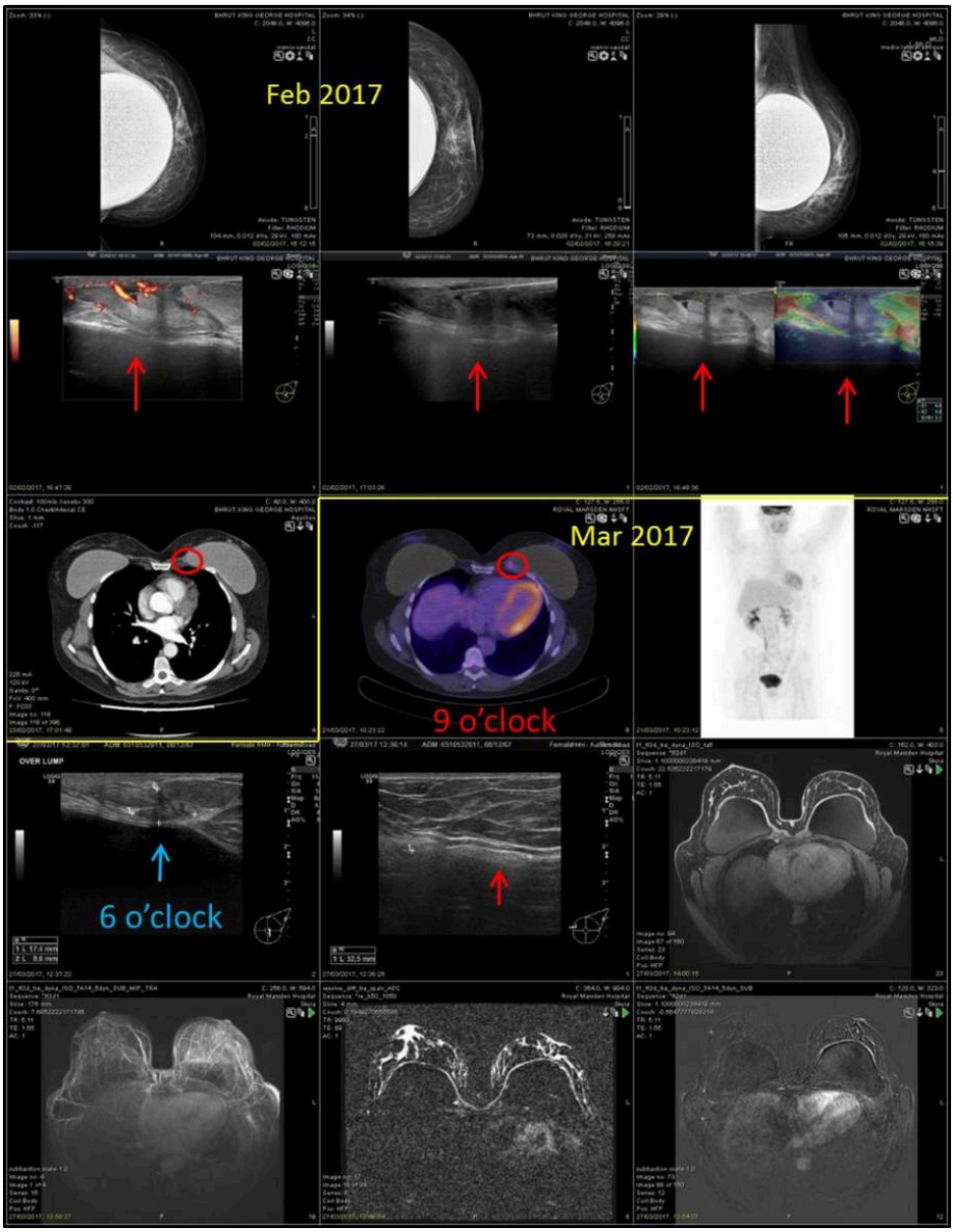

Fig. 5: CASE 2 - 29-year-old woman who had had bilateral breast augmentation (transform - 520 implants) in Apr 2012. In July 2015 a right breast lump upper inner quadrant was palpable. IMAGING: The initial ultrasound images from July demonstrated a 2.3 cm heterogeneous soft tissue mass in the upper inner right breast, lying on the edge of the external capsule of the implant with a gap of approximately 14 mm between the mass and the implant wall. A very small trace of fluid was seen around the implant. A PET/CT study from August displayed an active lesion in the region (right inner quadrant) of the known soft tissue mass with central necrosis. Appearances were in keeping with lymphoma. A follow-up ultrasound exam carried out in October showed progression of the size of the soft tissue mass measuring up to 33 mm in diameter, new central necrosis and infiltration of the pectoral muscle. The MRI study performed in November documented that the mass had markedly increased in size and persistent infiltration of the

pectoral muscles was observed. The mass also lay close to the intercostal muscles and invaginated between the ribs towards the pleura. The peri-implant fluid had increased in volume. The soft tissue mass extended posterior to the implant threatening the overlying skin. There was a new small volume right pleural effusion. Opinion: Aggressive soft tissue mass lying at the upper medial edge of the right sided implant infiltrating the pectoralis major muscle and threatening the intercostal muscles and chest wall. Rapid progression between July and November. Final diagnosis: RIGHT BREAST IMPLANT ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA TREATMENT: 3 cycles of CHOP - initial response but rapid progression prior to final cycle. In November 2015: extensive chest wall involvement with pleural effusion; brentuximab was started with excellent imaging and clinical response. In April 2016: bilateral total capsulectomy and mastopexies. Sentinel lymph node biopsy was negative (0/1) In June 2016: in continuation on surgical review bruising has settled but residual palpable lesion upper inner aspect of right breast Query haematoma. An ultrasound scan demonstrated fat necrosis. On MRI, marked response to treatment by virtue of small residual mildly enhancing soft tissue mass (3 cm) at the site of the previous disease medial to the right upper edge of implant was shown. No evidence of chest wall infiltration. There was evidence of central necrosis and persistent fluid collection around the right implant. The overlying skin was of normal appearances. The left side remained normal. On PECT/CT this medial aspect of the right breast has significantly reduced in size and metabolic activity, measuring approximately 3.2 x 2.5 cm in size (previously 4.2 cm in diameter) with only low grade metabolic activity on the current scan (SUVmax 3.1). No suspicious new lesions detected elsewhere. Impression: good partial response to treatment with interval reduction in size and metabolic activity of the known right breast mass lesion. In January 2016, an MRI study after 4 cycles of chemotherapy documented further response to treatment with only 2.5 cm residual abnormality at the site of original disease. No evidence of residual infiltration of the pectoral muscles and the overlying skin was normal. The small residual abnormality at the medial edge of the implant showed no enhancement and could represent residual scarring only. The implant was of normal appearances. No focal abnormality demonstrated in the overlying breast tissue. No axillary lymphadenopathy. Normal appearances of the left-sided implant and overlying breast tissue. Opinion: a 2.6 cm residual scarring at the site of original disease with no MRI evidence of residual active disease. A PET/CT exam showed ill-defined soft tissue residuum at the right breast site has further regressed since December 2015 demonstrating only background levels of uptake. Impression: complete metabolic response. In March 2016, an ultrasound scan revealed a residual hypoechoic tissue within the upper medial right breast / chest wall lying medial to the implant, measuring approximately 35 x 19 x 7 mm. No internal vascularity demonstrated. It no longer appeared to involve the immediately underlying pectoralis muscle. No further abnormalities identified within the right breast. The implant was intact. Normal appearances of the right axilla. After obtaining informed verbal consent and administrating 5 ml 1% lidocaine, a 3 x 14 gauge biopsy samples was obtained and sent to histology. No immediate complication. Opinion: U6 Histology did not show any evidence of malignancy. No clinical sign of recurrence on the right side and she only had a palpable lymph node in the left axilla. The wounds had healed up nicely

and there was only a slight prominence of the medial aspect of the wise pattern incision on the left side. Surgery to restore her breast volume sits clearly at the more cosmetic end of the reconstructive spectrum. 3 options to consider: - doing nothing and accepting the changes in breast shape and volume, given that overall her aesthetic outcome is pleasing; - re-augmentation, perhaps with smooth implants; - autologous augmentation.

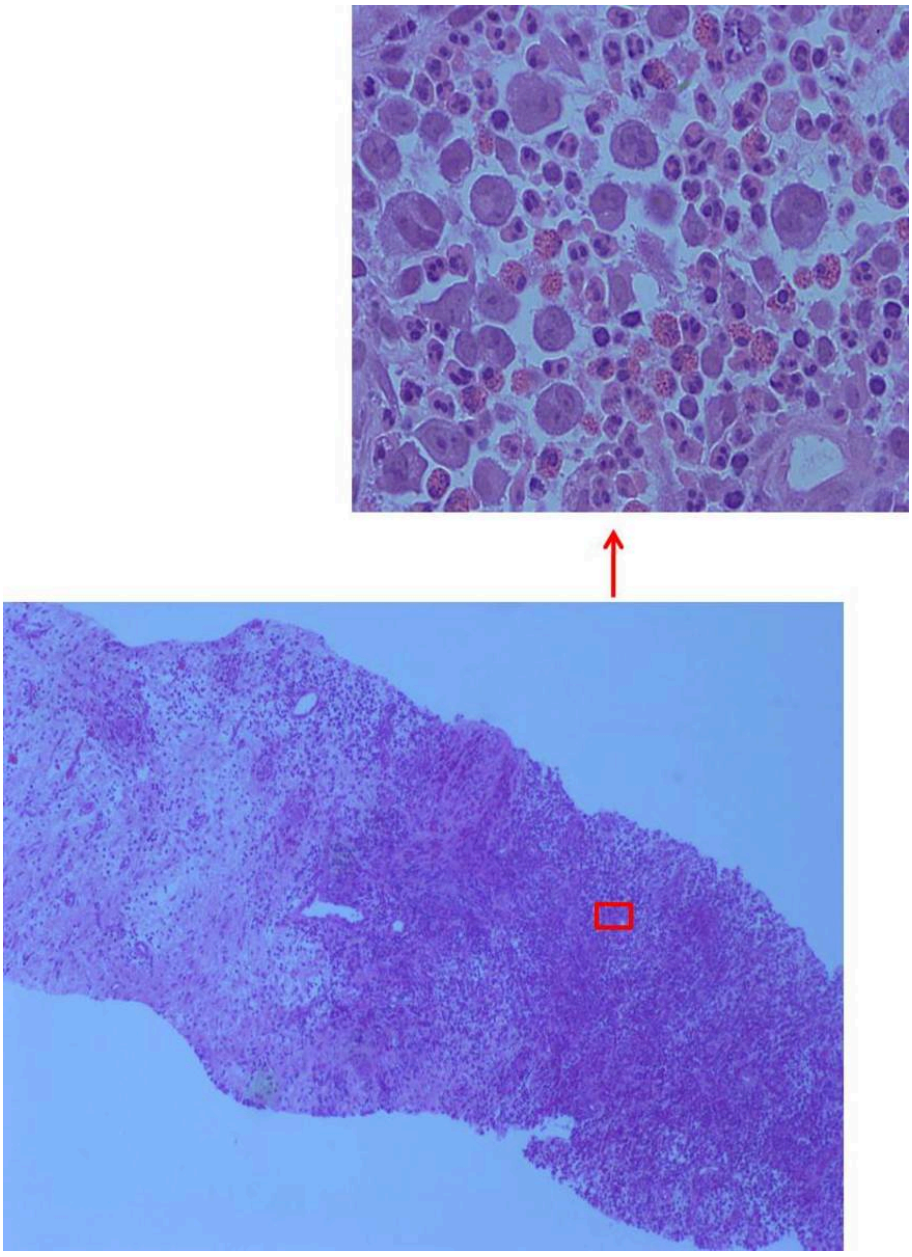

Fig. 6: CASE 2 - HISTOLOGY: The infiltrate of large atypical cells was seen to infiltrate fibrous tissue. High power view (red arrow) showed the large atypical cells, some consistent with Hallmark cells amidst neutrophils and eosinophils.

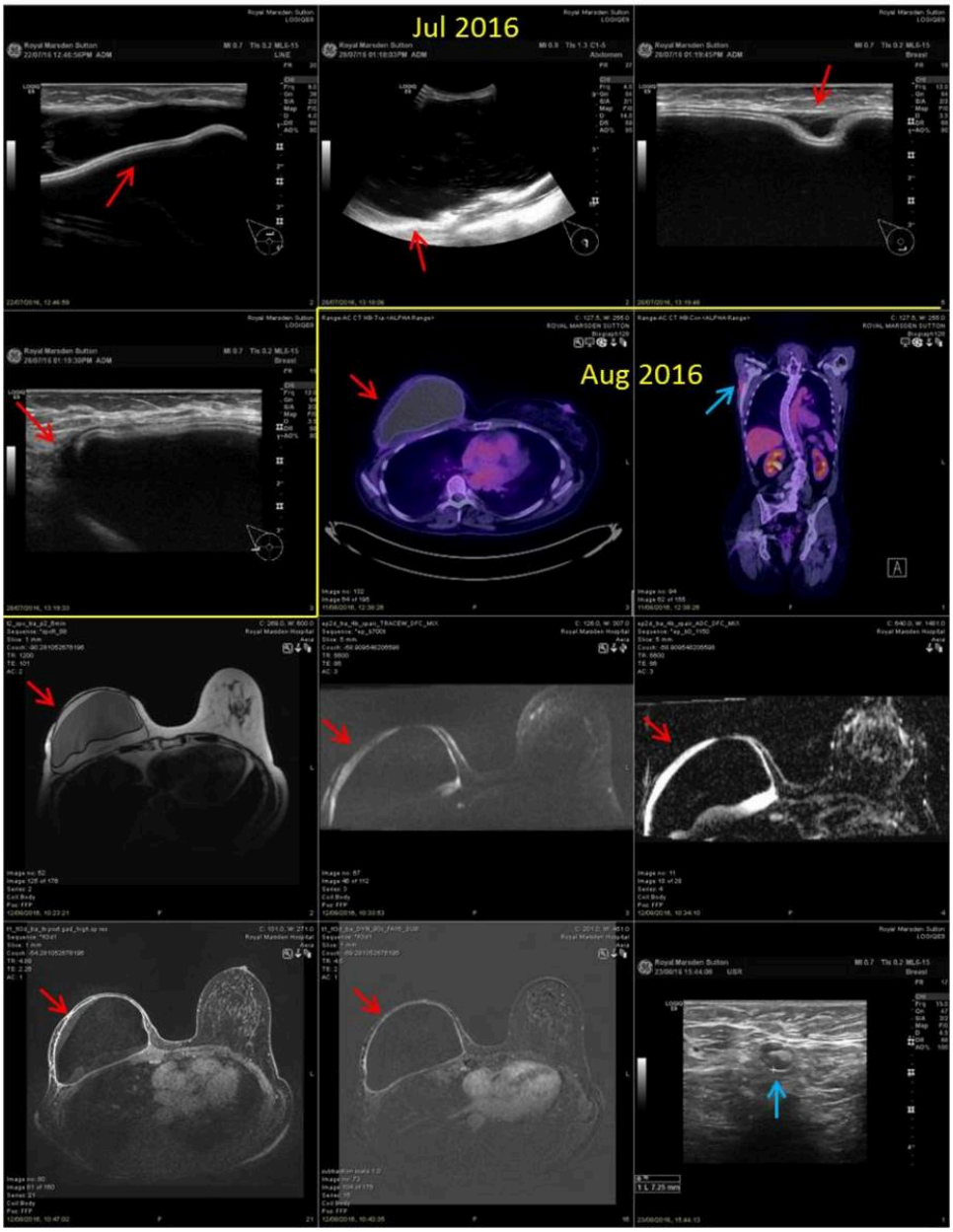

Fig. 7: CASE 3 - 50-year-old lady with right mastectomy and axillary node clearance followed by latissimus dorsi flap and implant reconstruction in May 2005 for a 6 cm, grade l invasive lobular carcinoma, ER7, PR8, HER2 negative, 0/12 lymph nodes. Consequent adjuvant chemotherapy (4 cycles of doxorubicin and cyclophosphamide), radiotherapy 50 Gy, and adjuvant tamoxifen. 3 further reconstructive breast operations, one in 2006 and two in 2015. Furthermore, her past medical history included right hip replacement in April 2016, spinal scoliosis, previous tonsillectomy, endometriosis (two laparoscopies in the past), cervical intraepithelial neoplasia treated with laser. Assisted conception. In 2015 lumpiness along the right lateral breast developed. No B symptoms (fever, night sweats, and weight loss). IMAGING: An ultrasound scan performed in June 2015 showed

right mastectomy with implant reconstruction. A few ripples in the implant membrane in the lateral right breast were observed. No evidence of any leak or rupture demonstrated. Evidence of scar tissue in the right axilla and breast. No obvious focal mass lesion demonstrated along the right lateral breast. In July 2016, scanning of the previous mastectomy site revealed the presence of the postsurgical implant which appeared intact. No evidence of rupture was seen. A large seroma (red arrow) was noted predominately within the outer aspect of the right breast and following verbal consent an aspiration was performed and a total of 330 ml serous aspirate was withdrawn. Due to the site onset and with consideration for BI-ALCL samples were sent for microbiology, cytological and pathological assessment. HISTOLOGY: Sections from both clots showed the presence of partly degenerate large cells with abundant cytoplasm and pleomorphic nuclei. The cells were negative for cytokeratin but expressed CD2, CD3, CD4, CD7 and CD30. There was positive staining for cytotoxic granules. There was no staining for ALK1 or CD20. Final diagnosis: SEROMA (IMPLANT) ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA In August 2016 a PET/CT study did not demonstrate distant disease. The right breast implant had an irregular contour and was surrounded by homogenous FDG-negative fluid which could reflect an earlier rupture. Small-volume, patchy, minimally FDG-avid soft tissue thickening accumulation at the periphery of this collection was non-specific but likely inflammatory. Sub centimetre minimally FDG-avid right internal mammary nodes were non-specific but likely inflammatory and small minimally FDG-avid reactive-appearing left axillary lymph nodes (light blue arrow) are noted. In the same month, an MR study was also performed. The left breast appeared normal. However, there was a small prominent node in the left axilla that shows significant cortical thickening. Ultrasound assessment of this was recommended. In the reconstructed right breast there was expected moderate sized peri-implant seroma within the implant capsule. The capsule itself showed mild enhancement but no mass component was identified. There was no evidence of disease outside the confines of the capsule. No evidence of any associated right-sided adenopathy. Opinion: Reconstructed right breast: MRI 2; Left breast: MRI 1; Left axilla: MRI 3. On ultrasound the two mildly FDG-avid left axillary lymph nodes displayed benign appearances, with short axis measurements of 7 mm, central fatty hilar regions and with ovoid shape. Verbal consent given for fine needle aspiration which was performed with a blue needle, 2 passes; a dry slide sent to cytology. No immediate complications other than some local tenderness. TREATMENT: removal of implant right capsulectomy and overlying skin. HISTOLOGY: breast implant associated anaplastic large cell lymphoma, with focal superficial capsular invasion only; complete excision.

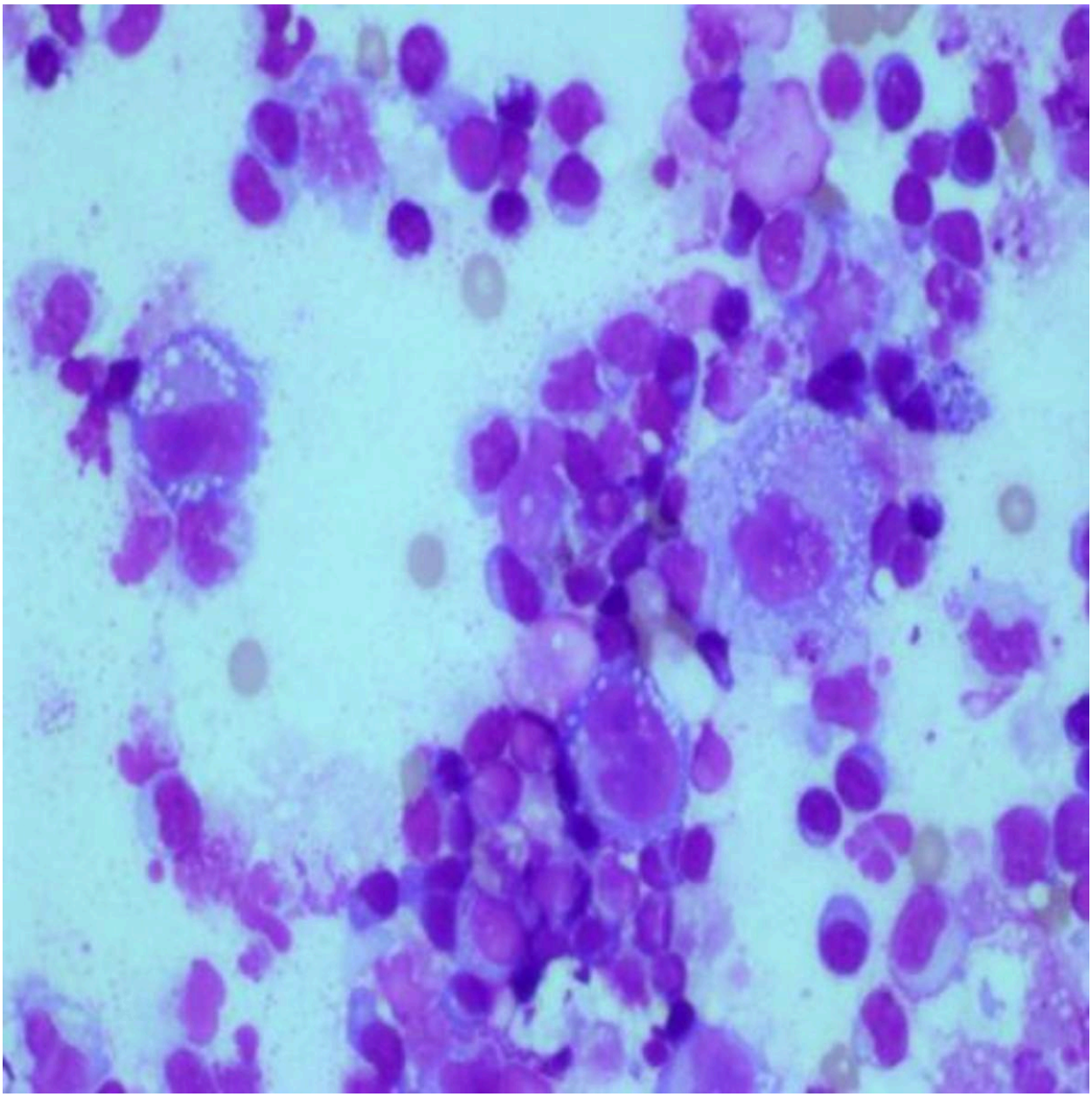

Fig. 8: CASE 3 - HISTOLOGY: Cytology sample of seroma fluid showed large anaplastic lymphoid cells.

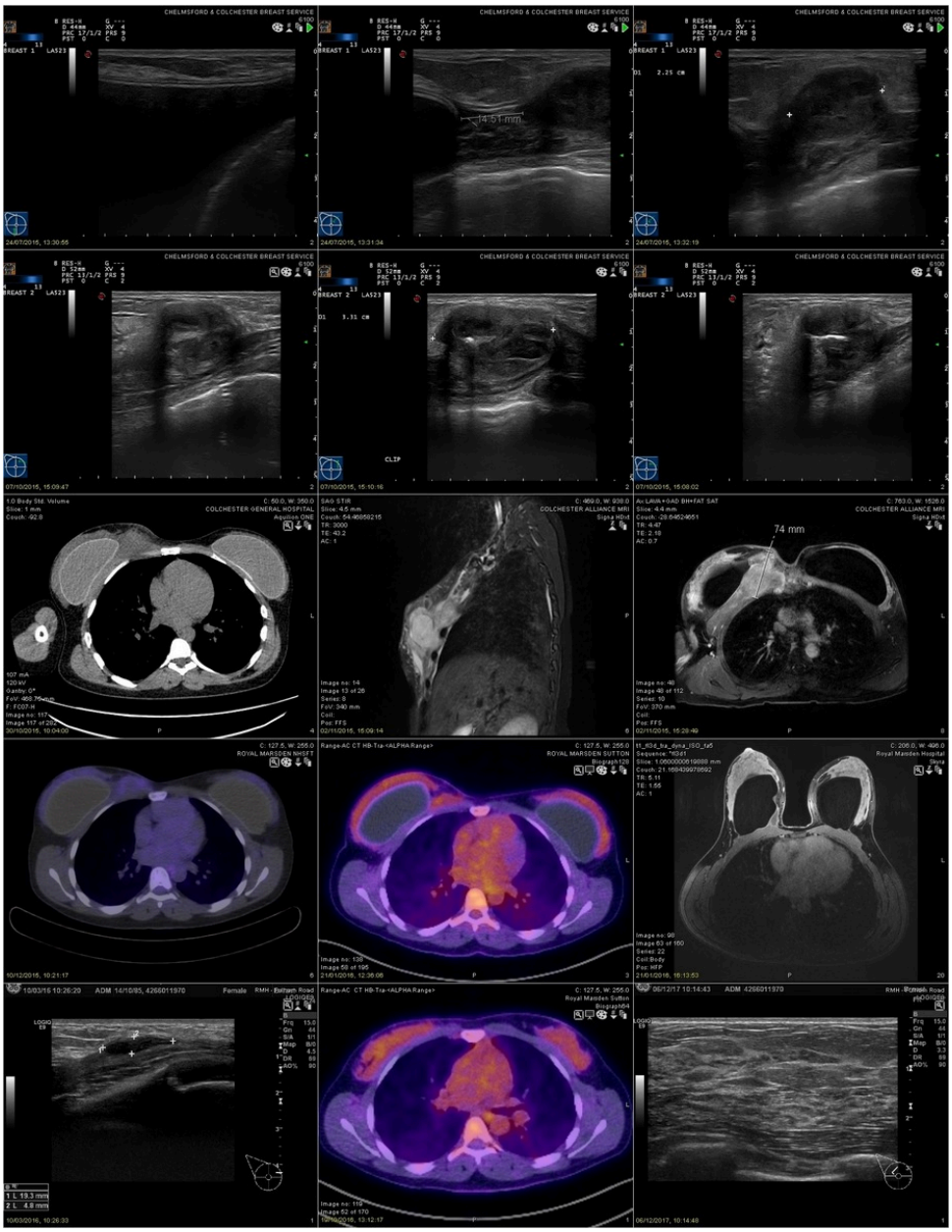

Fig. 9: CASE 4 - 49-year-old woman who had Poly Implant Prostheses silicone breast implants in 2005 in Venezuela; implants had been replaced in 2012 after the report of problems with this kind of implants came out in 2010. A pre-operative ultrasound showed no problems in terms of leakage or rupture of the implants. The surgery lasted approximately 8 hours because of the rupture of the implant whilst she was having the procedure. Initially, she had allergy to the steri strips that she had over the wound, later she required antibiotics intermittently as the wound became infected. In January 2017 she noticed a left breast lump associated with swelling and discomfort on leaning forwards. An ultrasound guided biopsy of a 3 cm lesion corresponding to the palpable lump revealed ALK-NEGATIVE LEFT BREAST IMPLANTED-RELATED ALCL (BIA-ALCL). There was also a hyper-echoic component to this measuring 3 cm extending out to the implant at the 5 o'clock position. The following CT study was unremarkable

in terms of lymphadenopathy or metastatic disease. On clinical examination an irregular swelling measuring approximately 2-3 cm in the lower outer quadrant of the left breast (6 o'clock position) just below the circumareolar wound could be felt. Furthermore, the left gland was more tense than the contralateral. There was no regional or distant lymphadenopathy. HISTOLOGY: fibrofatty connective tissue with a dense irregular diffuse infiltrate of atypical and pleomorphic intermediate sized T lymphoid blasts. Many of the tumour cells had relatively abundant cleared cytoplasm and expressed CD4, CD5, CD30, and BCL2 with a Ki-67 index that was virtually 100%. Final diagnosis: BREAST IMPLANT ASSOCIATED ALK-NEGATIVE ANAPLASTIC LARGE CELL LYMPHOMA HISTOLOGY: core biopsy of a left breast nodule. Sections showed fibrofatty tissue that was infiltrated by a proliferation of large lymphoid cells with abundant pale cytoplasm and pleomorphic nuclei sometimes lobulated. Mitoses were easily found and there were scattered apoptotic cells. In one area the cells appeared to surround and infiltrate a large vessel. Some residual breast epithelial structures were noted. The cells stained for CD2, CD5 and CD30 with expression of TIA1 and granzyme. There was variable staining for CD3 and the cells express CD4 but were negative for CD8, CD7, ALK1, EBER, TdT, CD56, PD1 and for B-cell markers. Opinion: an ALK negative CD30 positive anaplastic large cell proliferation. The differential diagnosis included implant associated anaplastic large cell lymphoma, nodal type anaplastic large cell lymphoma ALK negative and cutaneous anaplastic large cell lymphoma as well as lymphomatoid papillosis. In February, on CT, in relation to the left breast implant, a subtle small site of nonspecific apparent circa 9-mm nodularity appeared to be present related to the inferomedial aspect of the seroma. On PET a little nonspecific activity was documented at the medial aspect of the left implant and could be inflammatory. Objective definite measurable lymphomatous mass lesions not evident in the left breast by PET criteria. On bilateral mammography performed in February a reasonable volume of overlying breast tissue demonstrated fatty change. Mass lesions were not evident. In February, an ultrasound guided core biopsy of a low-volume nodular component of a lesion which immediately contiguous with the overlying cutaneous surface was carried out. A palpable subcutaneous lesion was documented of which a component appeared to be extending down to the implant at 5 o'clock. Opinion: Complex case. The left breast lesion was palpable and appreciable only on ultrasound could reflect either a cutaneous anaplastic large cell lymphoma, or if the soft tissue mass involved the implant itself then this could be an implant associated lymphoma. On a later ultrasound scan, the left implant appeared intact. Corresponding with the site of known disease at the 6 o'clock position close to the areola margin there was an ill-defined density measuring 17 x 6 mm (light blue arrow). No abnormal vascularity. At the 9 o'clock position medial edge of the implant corresponding with the region of increased uptake on the PET scan there was an area (red circle and arrow) of echogenicity measuring approximately 33 mm. This could either represent focal scarring or a localised intracapsular rupture. No discrete mass demonstrated at this site. No peri-implant fluid. No left axillary or supraclavicular adenopathy. Opinion: U6 In March 2017, an MR study demonstrated that both implants were intact. No peri-implant fluid was present. There was faint asymmetric enhancement of the left capsule. This was non-specific and had no specific features to confirm BI-ALCL. Specifically the focal area

of PET uptake showed no enhancement posteromedial to the left implant. There was a mild background uptake pattern within both breasts but neither suspicious focal nor mass-like enhancement on either side. No enlarged nodes in the axillae. The right breast appeared normal. Opinion: No definite mass lesions or evidence of ALCL In May 2017, HISTOLOGY of right breast capsulectomy did not show ductal carcinoma in situ or lymphoma. The left periareolar skin specimen displayed intense inflammatory reaction in relation to previous biopsy but no evidence of residual lymphoma. HISTOLOGY: Right capsule with no evidence of breast implant associated ALCL. On the left side no evidence of breast implant associated ALCL. Intense inflammatory reaction present in relation to previous skin and subcutaneous biopsy site, no evidence of residual lymphoma. Breast multidisciplinary team meeting of 12th May 2017: no residual disease, hence any further action.

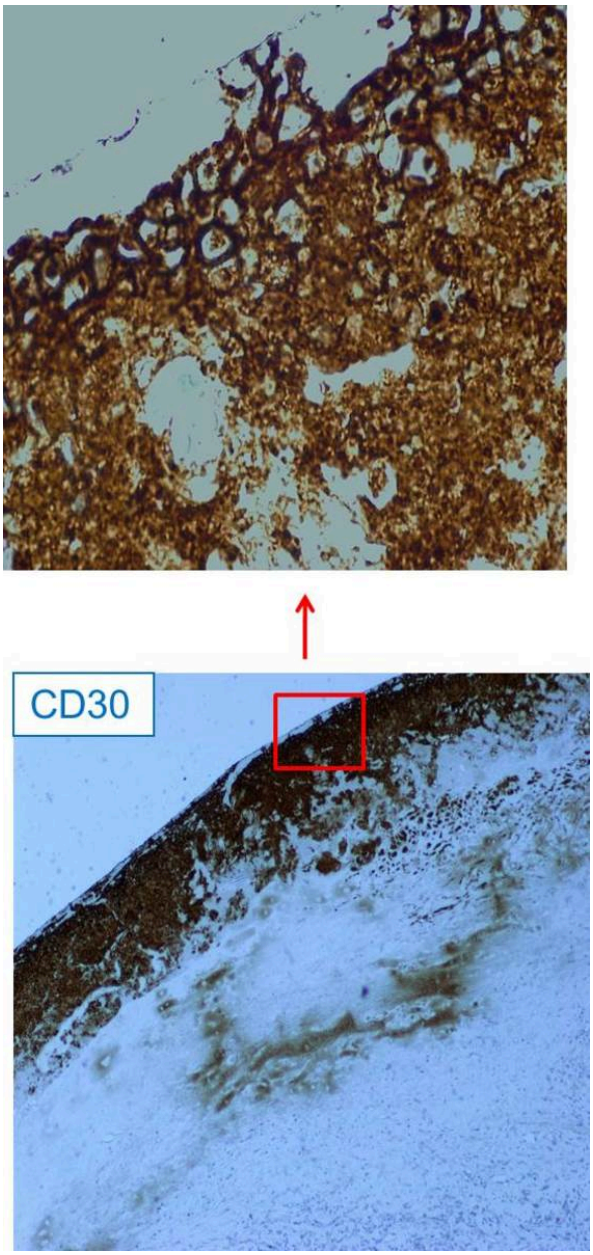

Fig. 10: CASE 4 - IMMUNOHISTOCHEMESTRY: The infiltrate was CD30 positive.

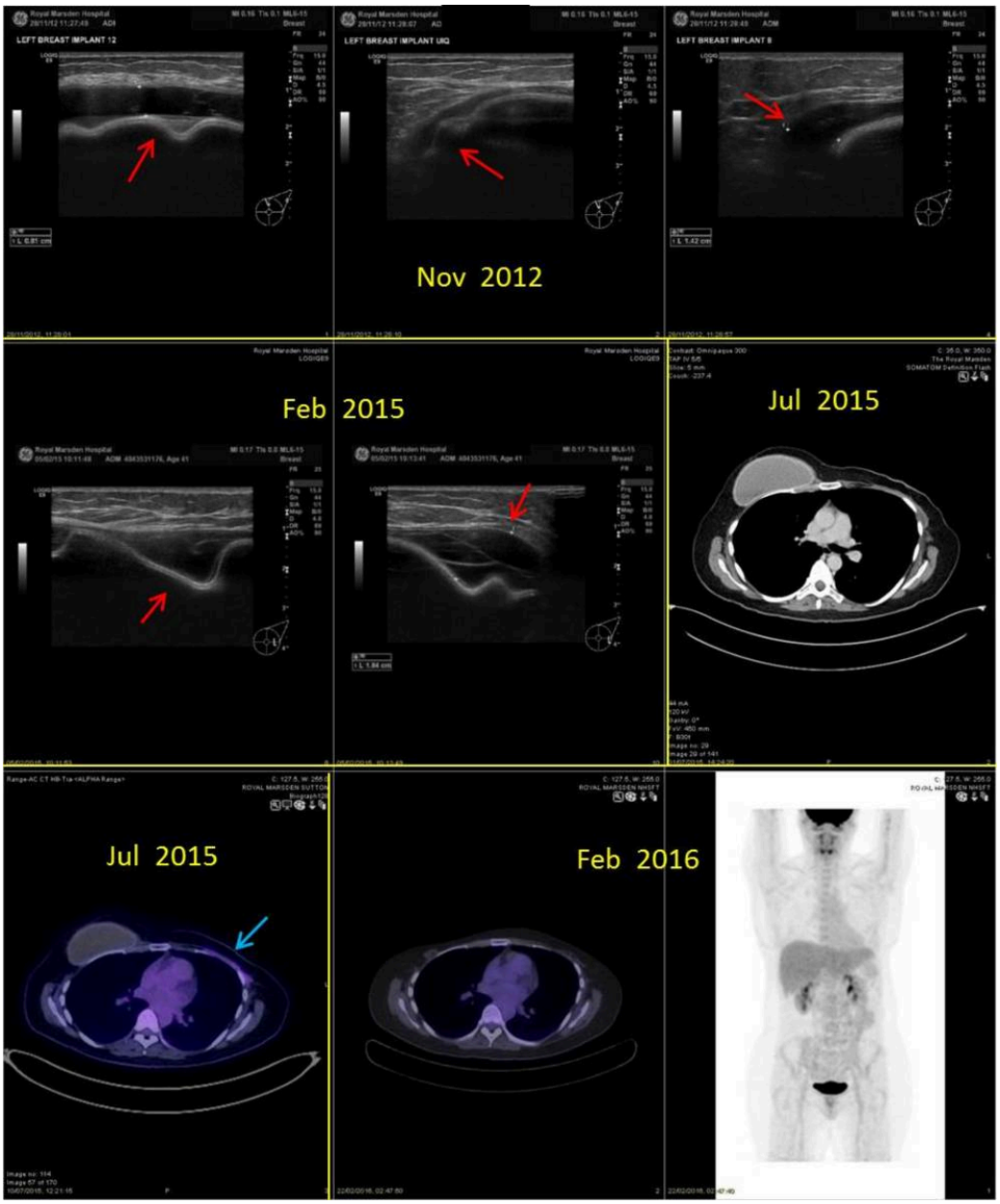

Fig. 11: CASE 5 - 39-year-old lady, BRCA2 mutation carrier. In 2004 she had had bilateral prophylactic/risk-reducing mastectomy with immediate reconstruction. In November 2004 implants were exchanged. Nipple reconstruction and tattooing were performed in August 2005 and in June 2007, respectively. In December 2012: bilateral pocket revision, capsulotomy and exchange of implants (Allergan TRF 520). Problems with recurrent seroma around the left breast reconstruction developed since then. IMAGING: In order to discern between rupture and haematoma, an ultrasound scan was performed. The left breast implant was intact. There was surrounding fluid circumferentially consistent with a seroma (red arrow). Following local anaesthetic to the overlying skin 220 ml of clear yellow fluid was aspirated and sent for urgent microbiology evaluation with no complication. Opinion: seroma surrounding intact left breast implant. Cause unclear. Microbiology awaited. No sinister features are seen throughout. U2. No evidence of

malignancy was found on microbiology. In November 2013: revision of left breast reconstruction with capsulectomy and implant exchange to Polyurethane round polytech 495 g. In 2015 she presented with a swelling around left breast implant. Recurrent seroma leading to removal of left breast implant in May 2015. Left implant pocket revision, drainage of seroma, capsulectomy/capsulotomy and removal of implant HISTOLOGY and IMMUNOCHEMESTRY of the left implant pocket capsule: there was a patchy infiltrate of atypical lymphoid cells confined to the inner aspect of the fibrotic implant capsule adjacent to adherent fibrinous material. This infiltrate, present as dense clusters and cords, was surrounded by an inflammatory reaction and did not infiltrate into the outer aspect of the implant capsule or into the adjacent soft tissue. The atypical cells had moderate to abundant cytoplasm and markedly atypical nuclei, some of which were indented and showing strong and diffuse membrane positivity for CD30. They were also positive for CD4, TIA-1, and perforin. A few atypical cells were positive for granzyme B. They were negative for ALK-1, CD45, CD2, CD3, CD8 and also for CD20, CD79a, and PAX5. The proliferation on Ki 67 stain was very high. Opinion: small area of highly pleomorphic cells including implant capsule diagnosed to be anaplastic large cell lymphoma; capsule completely excised, R0. Final diagnosis: ANAPLASTIC LARGE CELL LYMPHOMA LEFT BREAST (CD30 positive, ALK negative) ASSOCIATED WITH SEROMA (IMPLANT LEFT BREAST) In July 2015, bone marrow was normal. In August 2015, removal of both mastectomy flaps and of the right implant alongside bilateral total capsulectomies were carried out. HISTOLOGY: left focus of CD30 positive staining cells of ALCL, right capsule with inflammation only. Delivery of a baby girl in 2017. In August 2017 the patient underwent to bilateral salpingo-oopherectomy. FOLLOW-UP: A PET-CT scan performed in July 2015 displayed inflammatory changes in the left chest wall (light blue arrow) likely to be consistent with recent surgery. No other sites of suspicious disease. In February 2016, the previously noted residual low grade FDG uptake in the breast tissue showed a marked decrease in intensity of tracer uptake on the right and complete resolution on the left, in keeping with complete metabolic response.

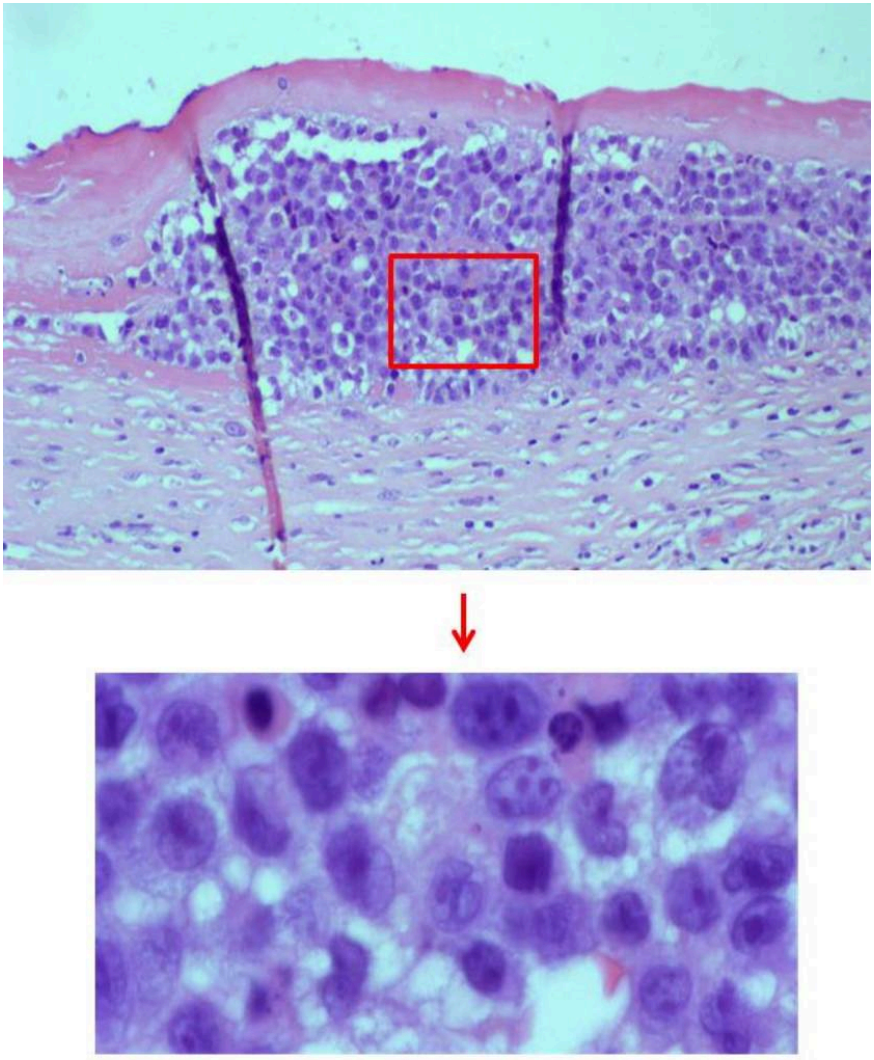

Fig. 12: CASE 5 -HISTOLOGY: The capsulectomy specimen exhibited a dense infiltrate of large atypical lymphoid cells enmeshed in fibrin lining the inner aspect of the capsule with no invasion of it. High power view (red arrow) of the large atypical cells with abundant eosinophilic cytoplasm and pleomorphic at times indented nuclei.

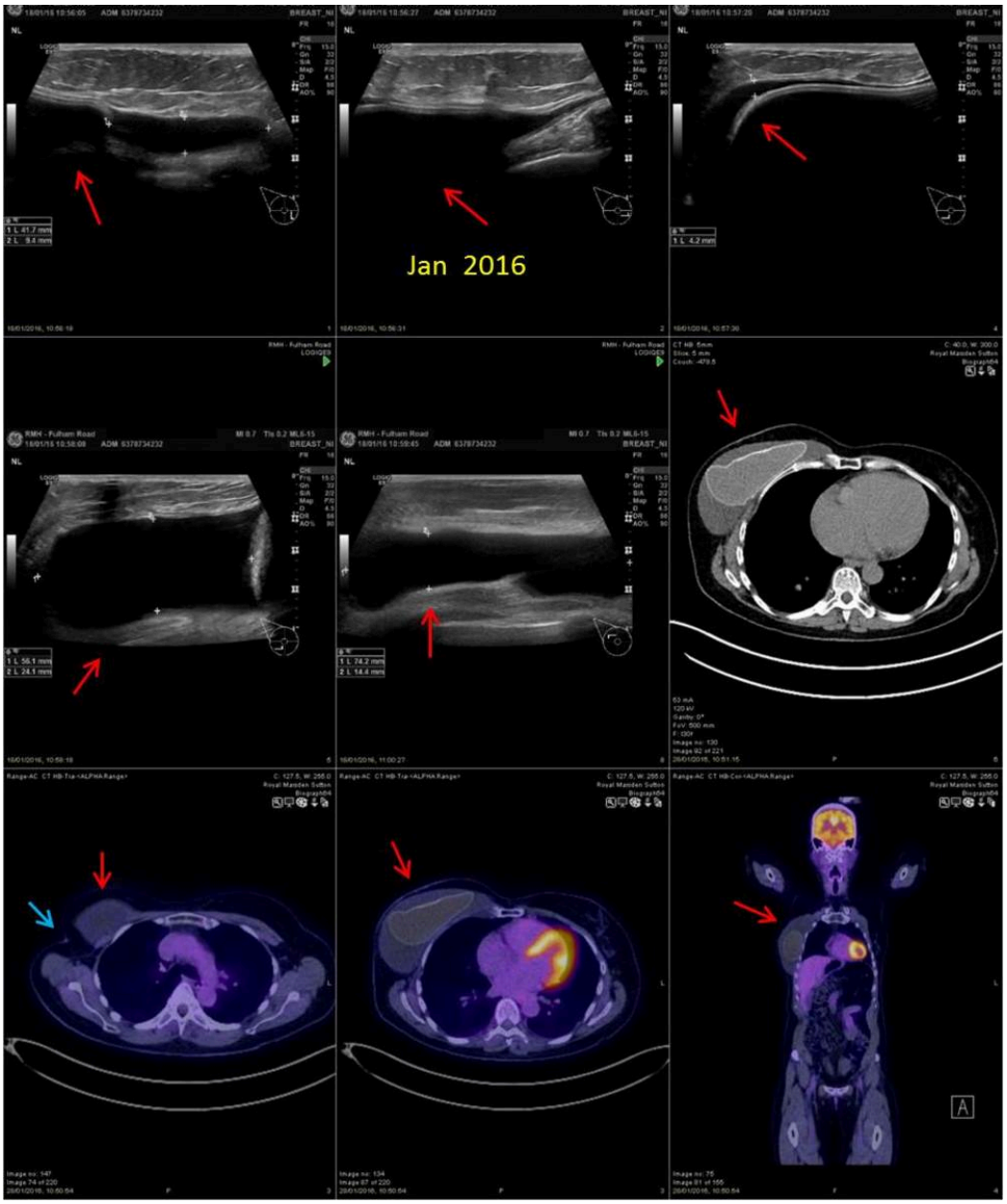

Fig. 13: CASE 6 - 55-year-old lady. In 2000, she was diagnosed a right breast intraductal carcinoma in Stockholm, two lesions of 22 mm and 11 mm, respectively, grade 2, with 5/20 lymph node's extra-capsular spread. ER/PGR were positive. Therefore, right mastectomy associated with axillary nodal dissection was performed, followed by implant reconstruction and 8 cycles of chemotherapy (FEC) alongside radiotherapy to the ipsilateral breast/axilla. Furthermore, tamoxifen (6 years) and goserelin (5 years) were administered. In 2009 the implant was exchanged. In 2016 she had new sudden marked swelling of the right breast. IMAGING: On ultrasound, the implant on the right side appeared intact. There was a large volume of fluid (red arrow) around the prosthesis containing septations. No soft tissue abnormality demonstrated either in relation to the fluid collection or the overlying soft tissues. No evidence of free silicone within the reconstructed right breast or axilla. Diagnostic aspirate obtained from the cloudy

yellow fluid. Opinion: infection of the long standard implant. No evidence of implant rupture or recurrence of disease. U2 PATHOLOGY - MACROSCOPY: cell block from right breast seroma, clot measuring 6 mm in diameter. HISTOLOGY: numerous large atypical lymphoid cells displaying abundant eosinophilic cytoplasm, enlarge atypical nuclei (some multilobated) with coarse chromatin and prominent nucleoli. Some hallmark cells were noted. The large atypical cells expressed CD45, CD30, CD2, CD4, TIA-1, granzyme B, and perforin and were negative for ALK-1, CD3, CD5, CD7, and CD20. Opinion: primary seroma associated anaplastic large cell lymphoma (ALK negative), if clinically compatible. In January 2016, a PET/CT scan demonstrated a large photopenic seroma (red arrow) surrounding the right breast implant. No focal significantly FDG-avid soft tissue or lymphadenopathy present (light blue arrow). TREATMENT: right breast deconstruction of implant and complete capsulectomy. In 2017 the test for BRCA1 and 2 mutations was negative.

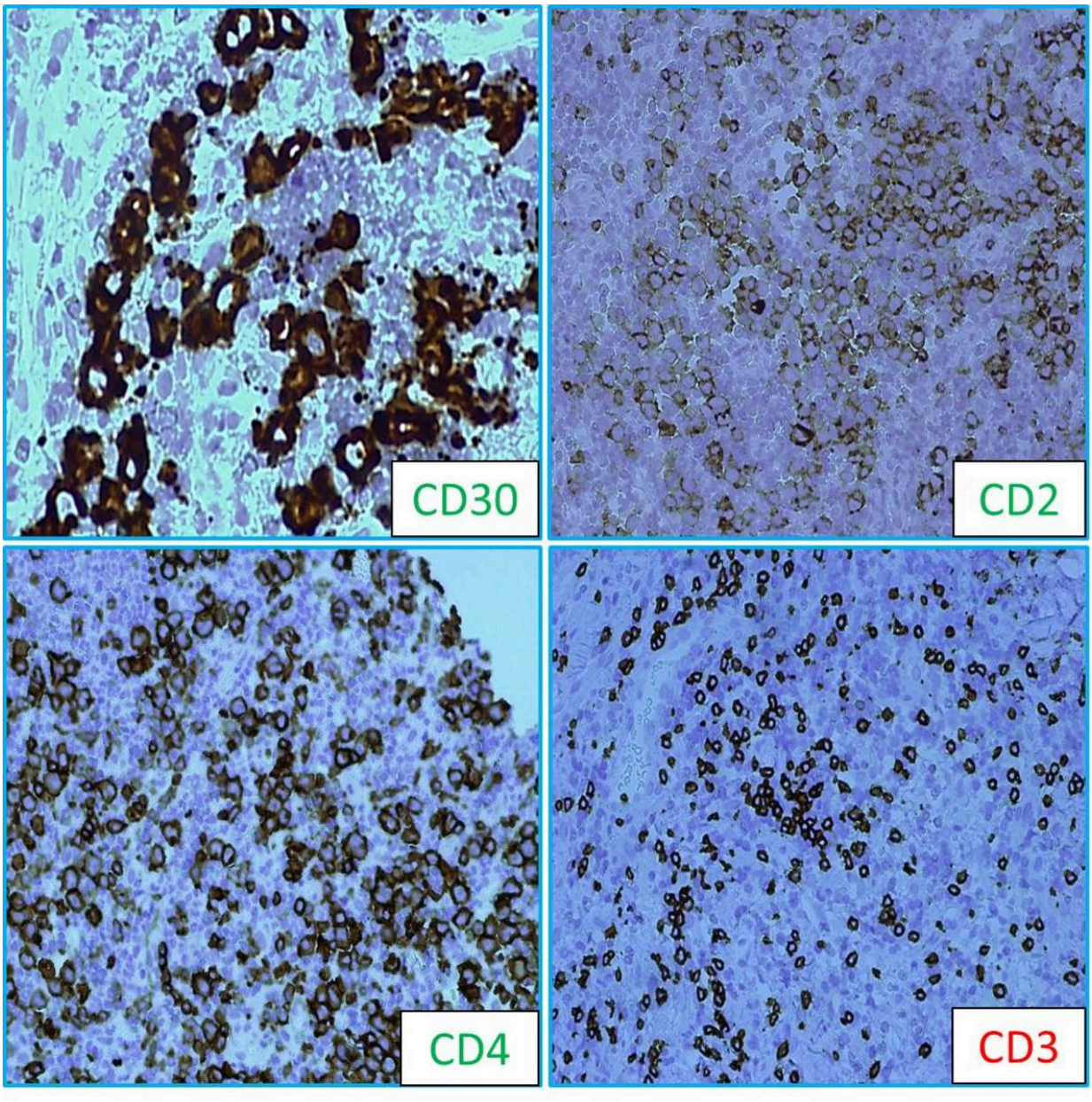

Fig. 14: CASE 6 - IMMUNOHISTOCHEMESTRY: The infiltrate was positive for CD30, CD2. and CD4 but negative for CD3.

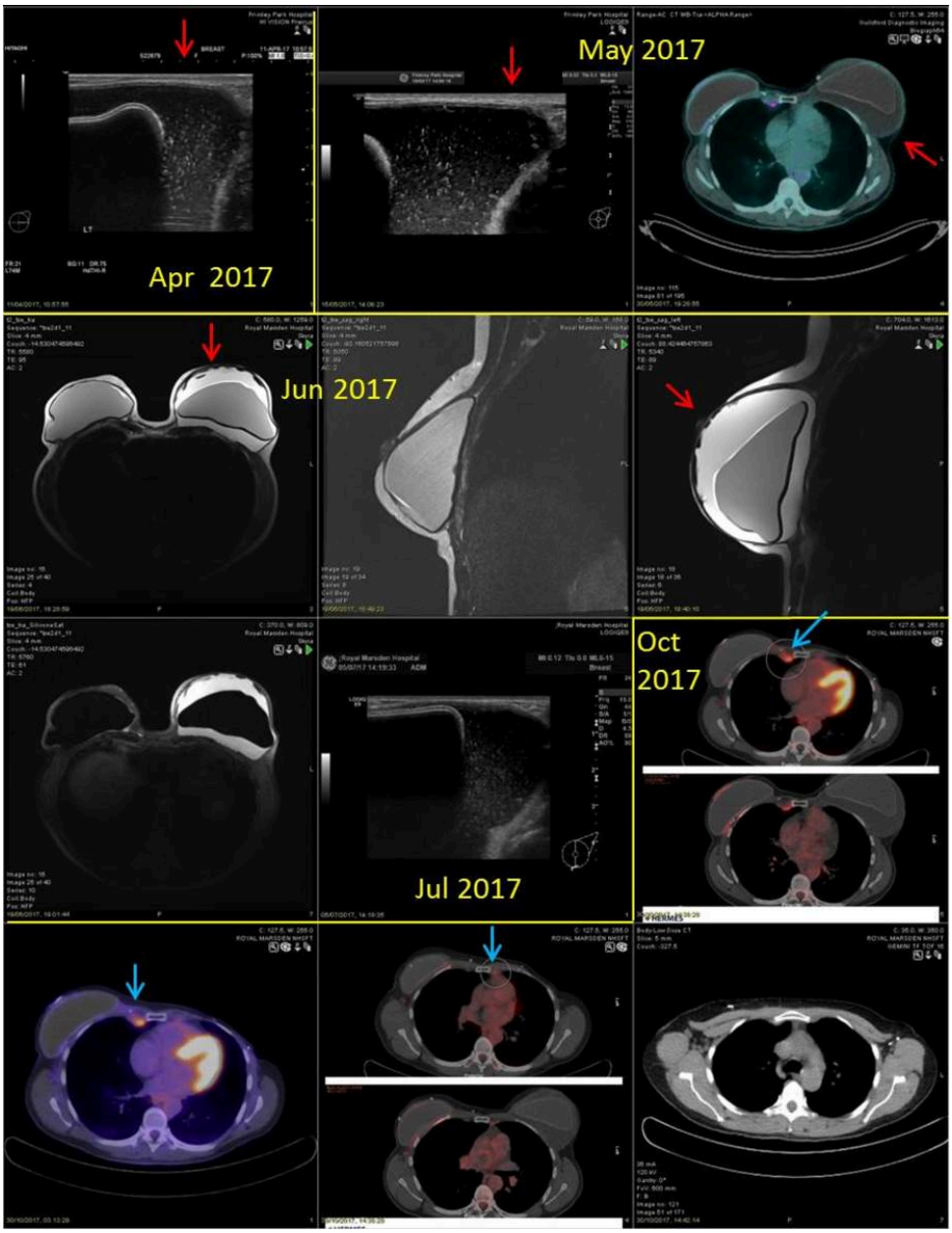

Fig. 15: CASE 7 - 50-year-old lady. In 2010 she had had left breast cancer (HER2 positive, BRCA carrier): a 9-mm nodule of grade 3 intraductal carcinoma, ER8, PR7, and HER2 highly positive alongside a mass of 8 cm intermediate/high grade ductal carcinoma in situ. She was treated with left mastectomy and implant/acellular dermal matrix Mentor 350 cm3 low height high profile. In 2011 she underwent to a right mastectomy with implant/acellular dermal matrix and received multiple revisions due to seroma. The final implant was 350 cm3 polyurethane. In February 2017 she presented with swollen left breast reconstruction and discolouration to lower half skin paddle. IMAGING: In May 2017 an outside PET/CT scan demonstrated a large seroma (red arrow) surrounding the left-sided breast implant. Low-volume right internal mammary chain (light blue arrow) and axillary nodal tissue was documented. However, this was entirely non-specific, considering that small ipsilateral internal mammary chain lymph nodes are often observed

in the context of implants, having a reactive aetiology consequent to the procedure. Clinically correlation and appropriate follow-up recommended. No evidence of systemic disease. In June an MR study exhibited a large seroma surrounding the left sided implant though this appeared intact. There was no right-sided peri-implant effusion or evidence of rupture. Overlying subcutaneous tissues were unremarkable bilaterally with no axillary lymphadenopathy. Slight enlargement (10 mm) of a right internal mammary lymph node of uncertain significance persisted. In July 2017 under ultrasound guidance into the inferior aspect of the left breast peri-implant seroma 250 cm3 of complex fluid was aspirated and the effusion drained to almost dryness. A sample of this was sent for cytological analysis. There were no immediate complications. HISTOLOGY of mucoid material measuring 8 x 8 x 4 mm consisted with ALK-negative implant associated anaplastic large B cell lymphoma. TREATMENT: Left total capsulectomy with preservation of skin envelope and nipple, completely excised. Final diagnosis: ALK-NEGATIVE IMPLANT ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA FOLLOW-UP: In October 2017, a PET-CT exam highlighted a few new tiny mildly FDG-avid bilateral axillary lymph nodes non-specific but felt to be inflammatory within the context of recent surgery (up to SUVmax 2.9). Elsewhere, bilateral internal mammary nodes had increased in size and activity. The larger of these were located on the right side, measuring approximately 10 x 17 mm versus 8 x 14 mm for the node lying between the 3rd and 4th costal cartilages (SUVmax 4.5 versus 3.6). Opinion: within the context of history of lymphoma, worsening internal mammary lymphadenopathy is concerning. Therefore, a biopsy would be recommended. MULTIDISCIPLINARY TEAM MEETING: Internal mammary lymph nodes likely to be reactive and chronic due to treatment and implant presence. No further investigation and continue treatment for lymphoma. She is currently awaiting left breast reconstruction with a tranverse upper gracilis flap, followed by a similar procedure on the right side at a later date, the plastic surgeons may have access to excise some nodes if they are close to the site of micro-vascular anastomosis, however an alternative would be to try and biopsy these nodes percutaneously under image guidance if possible. CT study thorax booked in February 2018 prior to definitive surgery.

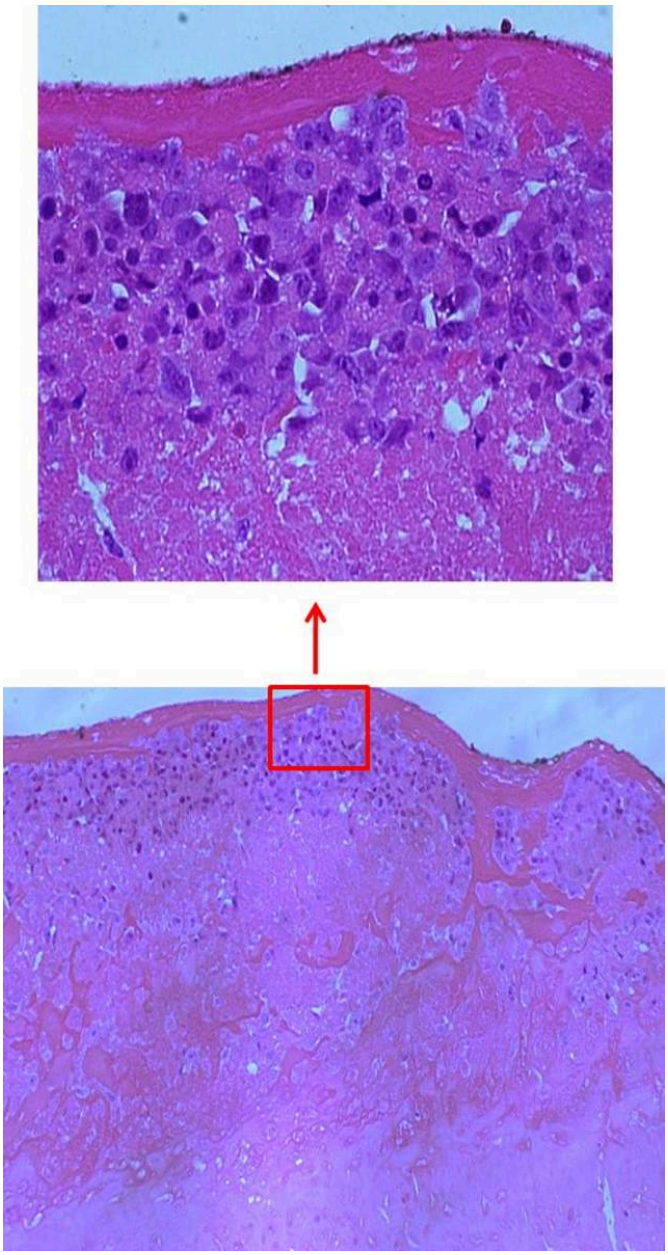

Fig. 16: CASE 7 - HISTOLOGY of capsulectomy specimen displayed a dense infiltrate of large atypical lymphoid cells enmeshed in fibrin lining the inner aspect of the capsule with no invasion of it.

Conclusion

Breast implant-associated anaplastic large T-cell lymphoma is a rare disease, relatively recently increasingly recognised, not well known or understood by clinicians, radiologists or most lymphoma specialists not having experience of this condition.

Establishing its diagnosis is often challenging.

It is crucial to identify the potential for this condition when a patient with breast implant presents with late onset seroma, and for a breast radiologist to perform a diagnostic aspirate which is cytologically analysed for lymphoma cells.

BI-ALCL presenting with seroma only has a good prognosis, surgical management being curative. Mass-forming BI-ALCL has poor outcomes, and requires systemic chemotherapy treatment.

We suggest that surveillance imaging (CT, PET, MRI) should not routinely be performed in BI-ALCL patients: seroma only patients having a good prognosis; clinical follow up being appropriate in mass-forming disease, in line with other lymphomas.

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