<https://helda.helsinki.fi>

Breast implant-associated anaplastic large cell lymphoma - From diagnosis to treatment

Kaartinen, I.

2017-08

Kaartinen , I , Sunela , K , Alanko , J , Hukkinen , K , Karjalainen-Lindsberg , M -L & Svarvar , C 2017 , ' Breast implant-associated anaplastic large cell lymphoma - From diagnosis to treatment ' , European Journal of Surgical Oncology , vol. 43 , no. 8 , pp. 1385-1392 . <https://doi.org/10.1016/j.ejso.2017.05.021>

<http://hdl.handle.net/10138/297933>

<https://doi.org/10.1016/j.ejso.2017.05.021>

publishedVersion

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.

Review

Breast implant-associated anaplastic large cell lymphoma — From diagnosis to treatment

I. Kaartinen ^{a,*}, K. Sunela ^b, J. Alanko ^c, K. Hukkinen ^d,
M.-L. Karjalainen-Lindsberg ^e, C. Svarvar ^f

^a Tampere University Hospital, Department of Musculoskeletal Surgery and Diseases, Tampere, Finland

^b Department of Oncology, Tampere University Hospital, Tampere, Finland

^c Medical Imaging Center, Tampere University Hospital, Tampere, Finland

^d HUS Medical Imaging Center, Radiology, University of Helsinki, Helsinki University Hospital, Finland

^e Department of Pathology, University of Helsinki, HUSLAB, Helsinki University Central Hospital, Helsinki, Finland

^f Department of Plastic Surgery, and Breast Surgery Unit, Comprehensive Cancer Center, Helsinki University Hospital, University of Helsinki, Helsinki, Finland

Accepted 30 May 2017

Available online 7 June 2017

Abstract

Breast lymphomas comprise a rare group of malignant breast tumors. Among these, a new entity has emerged as a potentially under-diagnosed disease. Breast implant-associated anaplastic large cell lymphoma (BI-ALCL) most often manifests as a late periprosthetic effusion between 1 and 10 years after the implantation of silicone or saline-filled breast prostheses. BI-ALCL is an anaplastic lymphoma kinase-negative T-cell lymphoma that has a distinctively different clinical course than other breast lymphomas or ALCLs. Diagnosis is based on aspiration of the effusion around the implant and CD30 positivity of the sample. Every periprosthetic effusion after breast augmentation or reconstruction using implants should be considered as potential BI-ALCL until proven otherwise. The majority of cases at diagnosis are in the *in situ* stage, i.e., confined to the lumen around the prosthesis. Most patients have an excellent prognosis when complete removal of the capsule and prosthesis with negative margins is achieved surgically. Some patients, however, develop infiltrative disease with a potentially life-threatening clinical course. Treatment planning regarding the extent of surgery and role of adjuvant therapy, especially in advanced cases, requires further investigation.

© 2017 Elsevier Ltd, BASO ~ The Association for Cancer Surgery, and the European Society of Surgical Oncology. All rights reserved.

Keywords: ALCL; BI-ALCL; ALK-negative lymphoma; Breast implants; Seroma; Cytotoxic c-cell

Introduction

Anaplastic large cell lymphoma (ALCL) and its subtypes

Anaplastic lymphoma kinase (ALK)-negative ALCL is a rare CD30-positive lymphoma, accounting for only 2%–3% of non-Hodgkin lymphomas and 12% of T-cell lymphomas. ALK-negative disease comprises 15%–50% of

all ALCL cases. Morphologically, it is similar to ALK-positive ALCL, except for the anaplastic lymphoma kinase staining. This entity, when not connected with breast implants, is usually diagnosed in patients 55–60 years of age and more often in males, usually in stage III–IV, with B-symptoms, a high International Prognostic Index (IPI) score, and an aggressive course.¹ Systemic ALK-negative ALCL is more common in Europe than in North America or Asia.² The overall prognosis in these cases is poor, with a 5-year overall survival of 30%–49% despite a standard CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy regimen. The addition of

* Corresponding author. Teiskontie 35, 33521, Tampere, Finland.

E-mail address: ilkka.kaartinen@pshp.fi (I. Kaartinen).

etoposide to the CHOP regimen (CHOEP) has improved the outcome.¹ Although the risk factors of this disease are not clear, autoimmune disorders, celiac disease, and psoriasis are associated with an increased risk.³

Primary lymphomas of the breast

Breast lymphomas are very rare.^{4–6} The incidence of breast lymphoma is 0.04%–0.5% of all breast malignancies and approximately 1.7% of all extranodal non-Hodgkin lymphomas.⁷ Not all breast lymphomas are ALCL; in fact, approximately 90% of primary breast lymphomas are of B-cell origin. Follicular lymphoma, lymphoplasmacytic lymphoma, mycosis fungoides, and Sézary syndrome have also been diagnosed in association with breast implants.^{8–10}

Breast implant-associated ALCL

Silicone gel prostheses have been used for esthetic operations since 1962 and, according to some estimates, over 10 million augmentations with implants have been performed to date.¹¹ The first case of BI-ALCL was reported in 1997.¹² Since then, there have been several other case reports and series,^{7,13–45} with the largest series of 173 patients gathered from around the world and published by Brody et al.²⁰ The actual lifetime risk of developing BI-ALCL is yet to be confirmed but, based on the number of published cases in the US and other countries, the estimated risk is 18.2–67.6 times higher among women with breast implants compared with women without implants that develop breast ALCL. Furthermore, 1 in 500,000–3,000,000 women with implants per year are estimated develop BI-ALCL.^{7,32,46,47} This may be an underestimation of the risk, however, as more cases with late seromas are being investigated due to the increasing awareness of BI-ALCL.

Several risk factors are suggested, but a clear understanding of the underlying causes remains unclear. The presence of a subclinical biofilm on the implant surface, capsular contracture, repeated capsular trauma, genetic predisposition, or an autoimmune etiology have been theorized.² A direct/indirect immunologic response, direct toxic damage from the silicone components, or both have also been hypothesized.⁴⁶

BI-ALCL appears to have two distinctively different pathologic entities. The more common is *in-situ* disease, which is confined within the seroma, i.e., periprosthetic effusion around the breast implant, or on the inner layer of the capsule surrounding the implant. *In situ* disease does not manifest as a palpable breast mass or tumor, and is often misinterpreted as a benign seroma due to subclinical infection. A smaller portion of patients present with an infiltrative disease course, with a tumor growing through the capsule or outside of it, forming a palpable breast mass with or without periprosthetic effusion. BI-ALCL

with lymph node involvement and no breast mass has also been described.⁴² Infiltrative disease, with or without lymph node involvement, is associated with a significantly worse prognosis, with disease-related mortality as high as 40% in 2 years.⁴⁸

Ann Arbor staging is currently most widely applied.⁴⁸ The most common stage at diagnosis is IE (61%).⁴⁹ In the systematic review reported by Gidengil et al. in 2015, however, 11% of cases were stage IIE with axillary lymphadenopathy.⁴⁹ Only rarely was BI-ALCL disseminated (stage IV in 3%).⁴⁹

Recently, a TNM classification was proposed (Table 1).⁵⁰ This staging differs from the commonly used Ann Arbor staging and appears to predict overall survival more accurately than the Ann Arbor system. Moreover, BI-ALCL seems to behave more similarly to other breast malignancies than to lymphomas with regard to the treatment, including surgical excision, and the clinical course of the disease.⁵¹

Diagnosis of BI-ALCL

BI-ALCL can present as a late periprosthetic effusion, an effusion in combination with a palpable mass, a breast mass alone, or without a seroma or mass and only detectable lymph node involvement. The most common manifestation, however, is late effusion (48%–70%) and cytology reveals ALCL-positivity in 79% of cases.^{32,52} Effusion volumes can range from 20 to 1000 cc and the fluid is typically viscous. The median time to ALCL after implantation is 9 years (range, 1–32 years).³² In 17%–31% of cases, a mass in the breast is documented, with a mean size of 3.5 cm.^{52,53} The surrounding capsule may be thickened and fibrous or completely normal.² Other local symptoms may include pain (21%), redness (14%), capsular contracture (7%), skin lesions (7%), and fever (7%)^{16,32,51}

Imaging findings

BI-ALCL shows no specific signs in imaging. In most cases, the indication for breast imaging is delayed (>1 year) periprosthetic fluid collection (Fig. 1), followed by a capsular mass, and in 1 of 8 cases, lymphadenopathy.² Mammography is often the first method of choice to study a symptomatic breast. Adrada et al. reported imaging studies of 44 BI-ALCL patients and found that the sensitivity/specificity of mammography for detecting an abnormality is 73%/50%, but mammography does not distinguish if the abnormality is fluid or a mass.¹³ Very often, effusion within the capsule is the only imaging finding in BI-ALCL.^{27,31,34} Ultrasound and magnetic resonance imaging (MRI) are the best imaging modalities for detecting effusion; the sensitivity/specificity of ultrasound for detecting effusion are 84%/75% and of MRI, 82%/33%; the sensitivity/specificity of computed tomography (CT) are 55%/83% and those of positron emission tomography (PET) or PET-CT are 38%/83%.¹³ The sensitivity

Table 1
Proposed TNM staging for breast implant-associated anaplastic large-cell lymphoma.⁵⁰

T: tumor extent		N: lymph node		M: metastasis	
T1	Confined to effusion or a layer on luminal side of capsule	N0	No lymph node involvement	M0	No distant spread
T2	Early capsule infiltration	N1	One regional lymph node positive	M1	Spread to other organs/distant sites
T3	Cell aggregates or sheets infiltrating the capsule	N2	Multiple regional lymph nodes positive		
T4	Lymphoma infiltrates beyond the capsule				
Stage IA	T1N0M0				
Stage IB	T2N0M0				
Stage IC	T3N0M0				
Stage IIA	T4N0M0				
Stage IIB	T1-3N1M0				
Stage III	T4N1-2M0				
Stage IV	TanyNany M1				

of these imaging methods for detecting a mass lesion is 46% (ultrasonography), 50% (MRI), 50% (CT), and 64% (PET/PET-CT).¹³ Lymphadenopathy can be seen in ultrasound, MRI, CT, or PET-CT.^{13,42} In routine practice, mammography reveals abnormalities and ultrasound distinguishes fluid from a mass. Ultrasound has the added benefit of being readily available for image-guided aspiration of the fluid for diagnosis. Histological sample is

recommended when a solid mass is detected.² MRI is recommended when ultrasound is inconclusive.⁵⁴ In the case on lymphoma diagnosis, preoperative body-CT is indicated for staging and PET-CT has the added value as a problem solving method (see Table 1).

Pathology

Cytologic analysis is crucial for diagnosis. All cases of late periprosthetic effusion should be screened for BI-ALCL. In these cases, aspiration is indicated, and pathology examination should first and foremost exclude ALCL by staining for CD30.² A biopsy is not recommended as the first step, but in cases in which implant removal is performed, the gross and histopathologic examination of the capsule for possible ALCL is pertinent for diagnosis and detection of infiltrative growth. Similarly, if lymph node enlargement is detected, an excisional biopsy of the enlarged lymph nodes is recommended for further pathologic examination. Fresh, unfixed abundant cytologic (e.g. whole aspirate) or tissue specimens are recommended for pathology to enable full chromosomal and immunophenotypic analyses. Cytologic diagnosis is based on identification of large pleomorphic lymphoid cells (Fig. 2a) with characteristic immunophenotype by flow cytometry and immunohistochemistry. Histopathology may demonstrate BI-ALCL as individual cells, cell clusters in aggregates, or coherent sheets lining the capsule surface, or an infiltrative phase.⁵⁵ Neoplastic cells are CD30 positive (Fig. 2b) with frequent co-expression of EMA and incomplete cytotoxic T-cell phenotype (CD4 + 80%–84%, CD43 + 80%–88%, CD3 + 30%–46%, CD45 + 36%, and CD2 + 30%). Expression of CD5, CD7 or CD8 is rare.⁴³ ALK staining is consistently absent.² CD15 and PAX-5 may be positive,

Figure 1. Breast MRI, 3T, T1 fat saturated sequence with contrast media. On the left side, the fibrotic capsule is thickened and enhances with gadolinium and there is excess of periprosthetic fluid. The silicone implants are intact on both sides.

Figure 2. a: MGG staining of the periprosthetic effusion aspirate in a BI-ALCL patient shows large lymphoid cells with abundant, granular cytoplasm and pleomorphic, often kidney or horse-shoe shaped nuclei, in a background of a sparse inflammatory infiltrate. b: The neoplastic cells express CD30 by immunohistochemistry and flow cytometry (not shown).

which can cause differential diagnostic problems to classical Hodgkin lymphoma especially in the infiltrative BI-ALCL subtype. T-cell receptors are often rearranged. Nuclear pSTAT3 expression is common, suggesting a constitutive activation of STAT3.⁴⁸

Treatment

In contrast to lymphomas, BI-ALCL is often curable with surgery alone. The mainstay of treatment is complete removal of the prosthesis and the capsule with negative margins (Fig. 3). In infiltrative cases (T3–4), the extracapsular mass should also be excised with negative margins. If there is lymph node involvement at the time of surgery, the affected lymph nodes should be removed according to current understanding.⁵¹ Due to the limited number of patients treated with lymph node clearance for locoregional disease, however, the role of lymph node clearance remains unclear. Lymph node involvement seems to be widespread to the nearby lymph node basins, and sentinel node biopsy is currently not recommended as part of treatment. When

Figure 3. A previously unreported case of ALCL treated in the Department of Plastic Surgery, and Breast Surgery Unit, Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland. The implant and its capsule together with the old subglandular capsule were removed en bloc in the operation, which yielded negative margins, as the tumor was confined to the periprosthetic effusion around the implant (T1N0M0, Ann Arbor IE). The patient received no additional treatment according to the current protocol⁵¹ and at 6-month postoperative follow-up with breast MRI, regional lymph node ultrasound and clinical examination there was no sign of recurrence of the disease.

complete removal of the disease and implant is performed, 6%–11% of patients experience a recurrence.^{51,52} The presence of a breast mass or lymphoma that spreads beyond the capsule may indicate a more aggressive clinical course.^{2,48} The rate of events is 2.6-fold higher for stage II disease and 2.7-fold higher for stage III disease compared to stage I disease. Among patients with proper surgical excision, the rate of events is 0% for T1–T2 patients and 14.3% for T4 patients.⁵¹ The median overall survival is 12–13 years.^{32,51} Overall survival and progression-free survival are similar, whether or not patients receive chemotherapy after surgery.³² Surgeons together with the patient should also consider removing the contralateral implant, as BI-ALCL is bilateral in 4.6% of patients.⁵⁰ Implantation of a new breast prosthesis is not recommended after BI-ALCL has been diagnosed.

When chemotherapy alone is used, relapse occurs in 54.5%. Thus, systemic chemotherapy alone is not sufficient for this disease, contrary to other lymphomas. In advanced cases, chemotherapy should be considered. The most common protocol is the CHOP regimen, and the addition of etoposide (CHOEP) improves the outcome.¹

National Comprehensive Cancer Network guidelines recommend CHOP with a 14- or 21-day interval or CHOEP for the treatment of systemic disease.⁵⁴ CHOEP is more toxic and cannot be used in most cases in the elderly. The guidelines also suggest dose-adjusted-EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin), but this has only been studied in the treatment of AIDS-associated anaplastic large-cell lymphoma.⁵⁶

STAT3-positivity suggests a potential role for etoposide in the treatment of advanced cases of BI-ALCL.^{1,48} STAT3 can also be regulated by histone deacetylase inhibitors, particularly panobinostat, romidepsin, vorinostat, and belinostat. These drugs induce histone acetylation, resulting in growth arrest, cellular differentiation, and apoptosis. Panobinostat, romidepsin, and vorinostat are currently being used in phase I and II studies to treat all anaplastic large cell lymphomas among other lymphomas, but most of the results have not yet been reported. These drugs have been studied alone or in combination with everolimus, bortezomib, lenalomid, and chemotherapy combination of ifosfamide, carboplatin, and etoposide (ICE), and alisertib.⁵⁷ Some of the phase I/II studies have been published; one of them, however – a report of the combination of vorinostat, lenalidomide, and dexamethasone – included only one case with anaplastic large cell lymphoma.⁵⁸

Radiotherapy is recommended for the treatment of local residual disease that cannot be surgically resected.⁵⁴ The common lymphoma radiotherapy dose of 30.6 Gy in 17 fractions is reported to have good results.²⁴

Historically, there are very few treatment choices for relapsed ALK-negative lymphoma. Pralatrexate, an antifolate agent, and romidepsin, a histone deacetylase inhibitor, have been used. In phase II studies, both agents demonstrate response rates of less than 30% and complete response rates of less than 15%.^{59,60} Currently, the most commonly used treatment and the only globally approved salvage treatment is the anti-CD30 antibody conjugate brentuximab vedotin. This drug delivers the potent antimicrotubule agent monomethylauristatin E to CD30-positive malignant cells. Among ALK-negative patients, the response rate is 88% and the complete response rate is 52%. The median duration of the response is 12.6 months and incomplete responders, 13.2 months.⁶¹

Some BI-ALCL patients have undergone autologous stem cell transplantation,⁴⁸ but the long-term results have not yet been reported. In one reported series, eight systemic ALCL patients underwent allogeneic transplantation after brentuximab vedotin, and half are in remission.⁶²

Prognosis and follow-up

The prognosis of the disease mostly depends on the aggressiveness of the disease at the time of diagnosis. After complete surgery, relapse occurs in 6%–11% of patients during the first year.^{51,52} All relapses after any kind of therapy occur within the first 3 years.⁵⁰ In one series, local relapse occurred in 36% of cases and distant relapse occurred in the remaining 64%.⁴⁸ Median progression-free survival in BI-ALCL with a mass is 1.8 years, while it is not reached in patients without a mass.³²

At the present time, only the National Comprehensive Cancer Network has published a recommendation for follow-up.⁶³ If complete excision with no residual disease is achieved, clinical follow-up should be done every 3–6

months for 2 years, and thereafter as clinically indicated. CT or PET-CT can be performed every 6 months for 2 years, and then as clinically indicated.^{54,63} No clear consensus exists on when to perform reconstructive breast surgery after BI-ALCL if needed.

Discussion

The number of reported BI-ALCL cases seems to be growing steadily. This article adds another case – the first patient diagnosed with BI-ALCL in Finland. The diagnosis of BI-ALCL is not straightforward, even in cases when it is suspected, as demonstrated by the case presented here. Not all laboratories are equipped to perform lymphoma diagnostics, and thus suspected cases with late seroma formation should be referred to a center with sufficient diagnostic capabilities. BI-ALCL should be suspected whenever a patient with breast implants presents with persistent seroma formation around the prosthesis, or with other signs, such as redness, swelling, pain, pruritus, or mass associated with the breast prosthesis.

BI-ALCL is currently underdiagnosed. Not all cases have been properly diagnosed, and not all diagnosed cases are reported in the literature. The United States Food and Drug Administration recommend reporting all BI-ALCL cases to the PROFILE-registry: www.thepsf.org/PROFILE. Given the nature of *in situ* BI-ALCL, it is possible that cases with persistent periprosthetic effusion formation have been misdiagnosed as subclinical infections and treated by removing the prosthesis without testing the fluid for CD30 positivity. It is not well understood if *in situ* ALCL will progress without the irritation of the implant, or if it will remain dormant after implant removal. The growing awareness of BI-ALCL is likely to lead to better diagnostics, and we may see an increase in the number of BI-ALCL cases in the following years. For a clear picture of the magnitude of this clinical problem, epidemiologic studies are also needed.

Currently, the risk of developing a BI-ALCL calculated from known cases and the estimated number of breast implants used is 18.2–67.6-fold higher than that in patients without implants who develop breast ALCL. In the general population, this is a small number compared with other forms of breast malignancies. Although the overall risk of BI-ALCL is small, informed consent in breast augmentation and reconstruction with implants should include the risk of BI-ALCL and the patient should be educated about the signs of late periprosthetic effusion or other symptoms typical of BI-ALCL.⁶⁴

The cause of BI-ALCL is still largely unknown. From the implant point of view, a direct reaction to leaked silicone particles may have a role; second, the implant surface and the reaction of surrounding tissue to it seem to be important. Originally, the surface of breast implants was smooth until 1986, when McGhan and Mentor introduced textured silicone implants, with the exception of

polyurethane-covered implants, that had been used since 1970.⁶⁵ The introduction of textured silicone implants aimed to reduce the number of capsular contractures encountered with smooth implants, and to avoid malrotation.⁶⁵ Doren et al. report that BI-ALCL has been diagnosed uniformly among patients with textured implants.⁴⁷ So far, this is perhaps the most convincing evidence supporting the hypothesis of BI-ALCL developing as a consequence of repeated trauma caused by the interaction between the rough implant surface and the inner layer of the capsule. Unfortunately, the implant type is not provided in all published cases, but not a single case with a known smooth implant with BI-ALCL has been published to date.⁴⁷

The tissue reaction to a smooth silicone surface differs considerably from that to a textured surface. The textured surface induces a prolonged giant cell reaction compared to the smooth implant surface.⁶⁵ Adherence of the implant to the capsule and repeated detachment due to minor trauma may cause irritation, T-cell proliferation, and formation of a late seroma.⁴⁶ Late periprosthetic effusion occurs in 35.4% of implants associated with BI-ALCL compared to 0.1% in overall augmentation.⁶⁶

Another suggested cause of BI-ALCL is chronic bacterial biofilm infection associated with an increased risk for capsular contracture. In both human and animal models, this results in increased T-cell proliferation, which Hu et al. hypothesized increases the risk of ALCL.⁶⁷ The number of animals developing more severe capsular contracture was small, however, and the specific role of bacteria remains unclear compared to the direct irritation from silicone particles dislodged from the implant surface, as seen, for example, in silicone wrist implants.⁶⁸ In another paper by Hu et al., a significant amount of bacteria was detected in both capsular contracture samples and ALCL samples, with a distinctively differing microbiome, showing *Staphylococcus aureus* in the non-tumor samples compared to *Ralstonia* spp in 26 ALCL samples, a bacteria that was previously associated with implant infection.⁶⁹ It therefore seems that bacterial contamination may contribute to ALCL formation, but more so to the formation of more commonly found capsular contracture without tumor growth. The role that chronic biofilm infection plays in BI-ALCL remains unclear, and there are probably several overlapping contributing factors involved in the process. Despite the lack of official guidelines, it is relatively certain that complete surgical excision of the capsule and the implant with negative margins is the most important part of the treatment.⁵¹ In cases with extracapsular involvement, with or without lymph node metastasis, the prognosis is sharply worse. Even in those cases, surgical excision of the affected tissue is recommended. This is noteworthy, as other lymphomas are not treated surgically. In advanced cases, treatment protocols are the same as for other ALCLs, as outlined earlier in this paper.^{1,54}

The growing body of evidence for BI-ALCL has raised ethical concerns regarding esthetic augmentations and breast

reconstruction with implants. So far, the risk of developing a malignant tumor related to breast implants seems low, but the risk is still real and for those affected, the outcome is disastrous. The risk of BI-ALCL is likely still underestimated. It is reasonable to question whether breast augmentation with implants that may predispose the patient to malignant neoplasm can be considered ethical, and if so, should surgeons move toward choosing a smooth implant in the face of recent evidence pointing toward textured implants as a potential main causative factor? At the very least, informed consent should include the risk of developing BI-ALCL, and the patients must be educated about the signs and symptoms of the disease. The risk of BI-ALCL after augmentation mammoplasty is compared with the risk associated with orthopedic implants. This comparison is not feasible though, as augmentation is performed for purely esthetic reasons, thus avoiding this type of surgery does not lead to loss of function of any kind. Patients who are affected may later seek medicolegal compensation. For breast reconstruction, there are several options available for autologous reconstruction that may yield better functional and esthetic results compared to implant reconstruction. In recent years, primary breast reconstruction has moved toward implant reconstruction in many countries. The patients must be informed of the possible risks of developing BI-ALCL in association with implant reconstruction, and be offered a chance for autologous reconstruction as an option. After the diagnosis and treatment of BI-ALCL, it has been recommended, that only autologous reconstruction would be offered until further evidence is gathered.⁷⁰

Complete understanding of BI-ALCL requires further research. The cause of the disease is ultimately unclear, despite recent evidence. Many cases probably are unreported, and further epidemiologic studies are needed. The type of implant may be an important causative factor, but this needs to be further verified. Finally, professionals must be educated about the risks and management of future cases for timely diagnosis and treatment.

Conflict of interest

The authors have no financial interest to declare in relation to the content of this article.

Acknowledgement

This work was financially supported by the Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital, Grant 9S025.

References

1. Ferreri AJM, Govi S, Pileri SA, Savage KJ. Anaplastic large cell lymphoma, ALK-negative. *Crit Rev Oncol Hematol* 2013 Feb; **85**(2):206–15.
2. Clemens MW, Miranda RN. Coming of age. *Clin Plast Surg* 2015 Oct;**42**(4):605–13.

3. Ekström Smedby K, Vajdic CM, Falster M, et al. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. *Blood* 2008 Apr 15; **111**(8):4029–38.
4. Brogi E, Harris NL. Lymphomas of the breast: pathology and clinical behavior. *Semin Oncol* 1999 Jun; **26**(3):357–64.
5. Domchek SM, Hecht JL, Fleming MD, Pinkus GS, Canellos GP. Lymphomas of the breast: primary and secondary involvement. *Cancer* 2002 Jan 1; **94**(1):6–13.
6. Talwalkar SS, Miranda RN, Valbuena JR, Routbort MJ, Martin AW, Medeiros LJ. Lymphomas involving the breast: a study of 106 cases comparing localized and disseminated neoplasms. *Am J Surg Pathol* 2008 Sep; **32**(9):1299–309.
7. de Jong D. Anaplastic large-cell lymphoma in women with breast implants. *JAMA* 2008 Nov 5; **300**(17):2030.
8. Kim B, Roth C, Young VL, et al. Anaplastic large cell lymphoma and breast implants: results from a structured Expert consultation process. *Plast Reconstr Surg* 2011 Sep; **128**(3):629–39.
9. Engberg AK, Bunick CG, Subtil A, Ko CJ, Girardi M. Development of a plaque infiltrated with large CD30+ T cells over a silicone-containing device in a patient with history of Sezary syndrome. *J Clin Oncol* 2013 Feb 20; **31**(6):e87–9.
10. Sendagorta E, Ledo A. Sézary syndrome in association with silicone breast implant. *J Am Acad Dermatol* 1995 Dec; **33**(6):1060–1.
11. Bizjak M, Selmi C, Praprotnik S, et al. Silicone implants and lymphoma: the role of inflammation. *J Autoimmun* 2015 Dec; **65**:64–73.
12. Keech JA, Creech BJ. Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant. *Plast Reconstr Surg* 1997 Aug; **100**(2):554–5.
13. Adrada BE, Miranda RN, Rauch GM, et al. Breast implant-associated anaplastic large cell lymphoma: sensitivity, specificity, and findings of imaging studies in 44 patients. *Breast Cancer Res Treat* 2014 Aug; **147**(1):1–14.
14. Aladily TN, Medeiros LJ, Amin MB, et al. Anaplastic large cell lymphoma associated with breast implants: a report of 13 cases. *Am J Surg Pathol* 2012 Jul; **36**(7):1000–8.
15. Aladily TN, Nathwani BN, Miranda RN, et al. Extranodal NK/T-cell lymphoma, nasal type, arising in association with saline breast implant: expanding the spectrum of breast implant-associated lymphomas. *Am J Surg Pathol* 2012 Oct; **1**.
16. Alcalá R, Llombart B, Lavernia J, Traves V, Guillén C, Sanmartín O. Skin involvement as the first manifestation of breast implant-associated anaplastic large cell lymphoma: skin involvement as the first manifestation of breast implant-associated ALCL. *J Cutan Pathol* 2016 Jul; **43**(7):602–8.
17. Alobeid B, Sevilla DW, El-Tamer MB, Murty VV, Savage DG, Bhagat G. Aggressive presentation of breast implant-associated ALK-1 negative anaplastic large cell lymphoma with bilateral axillary lymph node involvement. *Leuk Lymphoma* 2009 May; **50**(5):831–3.
18. Bautista-Quach MA, Nademanee A, Weisenburger DD, Chen W, Kim YS. Implant-associated primary anaplastic large-cell lymphoma with simultaneous involvement of bilateral breast capsules. *Clin Breast Cancer* 2013 Dec; **13**(6):492–5.
19. Bodin F, Sinna R. Anaplastic large cell lymphoma occurring in women with breast implants: analysis of 173 cases. *Plast Reconstr Surg* 2015 Oct; **136**(4):555e–6e.
20. Brody GS, Deapen D, Taylor CR, et al. Anaplastic large cell lymphoma occurring in women with breast implants: analysis of 173 cases. *Plast Reconstr Surg* 2015 Mar; **135**(3):695–705.
21. Carty MJ, Pribaz JJ, Antin JH, et al. A patient death attributable to implant-related primary anaplastic large cell lymphoma of the breast. *Plast Reconstr Surg* 2011 Sep; **128**(3):112e–8e.
22. De Silva IM, Teague JA, Blake WE. Breast implant associated anaplastic large cell lymphoma: a case report and reconstructive option. *J Plast Reconstr Aesthet Surg* 2013 Dec; **66**(12):1773–6.
23. Duvic M, Moore D, Menter A, Vonderheid EC. Cutaneous T-cell lymphoma in association with silicone breast implants. *J Am Acad Dermatol* 1995 Jun; **32**(6):939–42.
24. Estes CF, Zhang D, Reyes R, Korentager R, McGinness M, Lominska C. Locally advanced breast implant-associated anaplastic large-cell lymphoma: a case report of successful treatment with radiation and chemotherapy. *Front Oncol [Internet]* 2015 Feb 18; **5**. [cited 2017 Feb 12]. Available from: <http://journal.frontiersin.org/Article/10.3389/fonc.2015.00026/abstract>.
25. Hanson SE, Gutowski KA. Primary T-cell lymphoma associated with breast implant capsule. *Plast Reconstr Surg* 2010 Jul; **126**(1):39e–41e.
26. Hoda S, Rao R, Hoda RS. Breast implant-associated anaplastic large cell lymphoma. *Int J Surg Pathol* 2015 May 1; **23**(3):209–10.
27. Hwang M-J, Brown H, Murrin R, Momtahan N, Sterne GD. Breast implant-associated anaplastic large cell lymphoma: a case report and literature review. *Aesthet Plast Surg* 2015 Jun; **39**(3):391–5.
28. Lazzeri D, Agostini T, Bocci G, et al. ALK-1—negative anaplastic large cell lymphoma associated with breast implants: a new clinical entity. *Clin Breast Cancer* 2011 Oct; **11**(5):283–96.
29. Lazzeri D, Agostini T, Giannotti G, et al. Null-type anaplastic lymphoma kinase—negative anaplastic large cell lymphoma arising in a silicone breast implant capsule. *Plast Reconstr Surg* 2011 Jun; **127**(6):159e–62e.
30. Lee Y-S, Filie A, Arthur D, Fojo AT, Jaffe ES. Breast implant-associated anaplastic large cell lymphoma in a patient with Li-Fraumeni syndrome. *Histopathology* 2015 Dec; **67**(6):925–7.
31. Letter H, Rop B, Edison MN, Turner P. Breast implant-associated anaplastic large cell lymphoma: a case report and literature review. *Cureus* 2016 Mar 26; **8**(3):e546.
32. Miranda RN, Aladily TN, Prince HM, et al. Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients. *J Clin Oncol* 2014 Jan 10; **32**(2):114–20.
33. Newman MK, Zimmel NJ, Bandak AZ, Kaplan BJ. Primary breast lymphoma in a patient with silicone breast implants: a case report and review of the literature. *J Plast Reconstr Aesthet Surg* 2008 Jul; **61**(7):822–5.
34. Olack B, Gupta R, Brooks GS. Anaplastic large cell lymphoma arising in a saline breast implant capsule after tissue expander breast reconstruction. *Ann Plast Surg* 2007 Jul; **59**(1):56–7.
35. Parthasarathy M, Orrell J, Mortimer C, Ball L. Chemotherapy-resistant breast implant-associated anaplastic large cell lymphoma. *Case Rep* 2013 Nov 27; **2013**(nov27 1). bcr2013201950.
36. Popplewell L, Thomas SH, Huang Q, Chang KL, Forman SJ. Primary anaplastic large-cell lymphoma associated with breast implants. *Leuk Lymphoma* 2011 Aug; **52**(8):1481–7.
37. Roden AC, Macon WR, Keeney GL, Myers JL, Feldman AL, Dogan A. Seroma-associated primary anaplastic large-cell lymphoma adjacent to breast implants: an indolent T-cell lymphoproliferative disorder. *Mod Pathol* 2008 Apr; **21**(4):455–63.
38. Singh E, Frost E, Morris EJ, Raza S. Anaplastic lymphoma masquerading as breast abscess in a patient with silicone implants. *Breast J* 2013 Oct; **19**(5):543–5.
39. Smith TJ, Ramsaroop R. Breast implant related anaplastic large cell lymphoma presenting as late onset peri-implant effusion. *Breast* 2012 Feb; **21**(1):102–4.
40. Sørensen K, Murphy J, Lennard A, Wadehra V, Menon GK, Collis N. Anaplastic large cell lymphoma in a reconstructed breast using a silicone implant: a UK case report. *J Plast Reconstr Aesthet Surg* 2014 Apr; **67**(4):561–3.
41. Talagas M, Uguen A, Charles-Petillon F, et al. Breast implant-associated anaplastic large-cell lymphoma can Be a diagnostic challenge for pathologists. *Acta Cytol* 2014; **58**(1):103–7.
42. Tardío JC, Granados R. Axillary lymphadenopathy: an outstanding presentation for breast implant-associated ALK-negative anaplastic large cell lymphoma. *Int J Surg Pathol* 2015; **23**(5):424–8.

43. Taylor CR, Siddiqi IN, Brody GS. Anaplastic large cell lymphoma occurring in association with breast implants: review of pathologic and immunohistochemical features in 103 cases. *Appl Immunohistochem Mol Morphol* 2013 Jan;**21**(1):13–20.
44. Taylor KO, Webster HR, Prince HM. Anaplastic large cell lymphoma and breast implants: five Australian cases. *Plast Reconstr Surg* 2012 Apr;**129**(4):610e–7e.
45. Wong AK, Lopategui J, Clancy S, Kulber D, Bose S. Anaplastic large cell lymphoma associated with a breast implant capsule: a case report and review of the literature. *Am J Surg Pathol* 2008 Aug;**32**(8):1265–8.
46. Ye X, Shokrollahi K, Rozen WM, et al. Anaplastic large cell lymphoma (ALCL) and breast implants: breaking down the evidence. *Mutat Res Mutat Res* 2014 Oct;**762**:123–32.
47. Doren EL, Miranda RN, Selber JC, et al. United States epidemiology of breast implant-associated anaplastic large cell lymphoma. *Plast Reconstr Surg* 2017 May;**139**(5):1042–50.
48. Laurent C, Delas A, Gaulard P, et al. Breast implant-associated anaplastic large cell lymphoma: two distinct clinicopathological variants with different outcomes. *Ann Oncol* 2016 Feb;**27**(2):306–14.
49. Gidengil CA, Predmore Z, Mattke S, van Busum K, Kim B. Breast implant-associated anaplastic large cell lymphoma: a systematic review. *Plast Reconstr Surg* 2015 Mar;**135**(3):713–20.
50. Sobin LH, Gospodarowicz MK, Wittekind C. International union against cancer. In: . 7th ed. *TNM classification of malignant tumours* Chichester, West Sussex, UK ; Hoboken, NJ: Wiley-Blackwell; 2010. 309pp.
51. Clemens MW, Medeiros LJ, Butler CE, et al. Complete surgical excision is essential for the management of patients with breast implant-associated anaplastic large-cell lymphoma. *J Clin Oncol* 2016 Jan 10;**34**(2):160–8.
52. Kim B, Roth C, Chung KC, et al. Anaplastic large cell lymphoma and breast implants: a systematic review. *Plast Reconstr Surg* 2011 Jun;**127**(6):2141–50.
53. Clemens MW, Collins MS, Butler CE, et al. Characteristics and treatment of patients with breast implant-associated anaplastic large cell lymphoma presenting with aggressive features. *Plast Reconstr Surg* 2015;**136**(4S):119–20.
54. NCCN — Evidence-Based Cancer Guidelines, Oncology Drug Compendium, Oncology Continuing Medical Education [Internet]. [cited 2017 Feb 18]. Available from: <https://www.nccn.org/>.
55. George EV, Pharm J, Houston C, et al. Breast implant-associated ALK-negative anaplastic large cell lymphoma: a case report and discussion of possible pathogenesis. *Int J Clin Exp Pathol* 2013;**6**(8):1631–42.
56. Nagajothi N, Dham SK, Gelfand Y, Sanmugarajah J. Treatment of AIDS-associated anaplastic large-cell lymphoma with dose-adjusted EPOCH chemotherapy. *J Natl Med Assoc* 2007 Jul;**99**(7):799–801.
57. Home — ClinicalTrials.gov [Internet]. [cited 2017 Feb 18]. Available from: <https://clinicaltrials.gov/>.
58. Hopfinger G, Nösslinger T, Lang A, et al. Lenalidomide in combination with vorinostat and dexamethasone for the treatment of relapsed/refractory peripheral T cell lymphoma (PTCL): report of a phase I/II trial. *Ann Hematol* 2014 Mar;**93**(3):459–62.
59. Coiffier B, Federico M, Caballero D, et al. Therapeutic options in relapsed or refractory peripheral T-cell lymphoma. *Cancer Treat Rev* 2014 Oct;**40**(9):1080–8.
60. O'Connor OA, Horwitz S, Masszi T, et al. Belinostat in patients with relapsed or refractory peripheral T-cell lymphoma: results of the pivotal phase II BELIEF (CLN-19) study. *J Clin Oncol Off J Am Soc Clin Oncol* 2015 Aug 10;**33**(23):2492–9.
61. Pro B, Horwitz SM, Prince HM, et al. Romidepsin induces durable responses in patients with relapsed or refractory angioimmunoblastic T-cell lymphoma. *Hematol Oncol* 2016 Jul 12. <http://dx.doi.org/10.1002/hon.2320>.
62. Fanale MA, Horwitz SM, Forero-Torres A, et al. Brentuximab vedotin in the front-line treatment of patients with CD30+ peripheral T-cell lymphomas: results of a phase I study. *J Clin Oncol Off J Am Soc Clin Oncol* 2014 Oct 1;**32**(28):3137–43.
63. Clemens MW, Horwitz SM. NCCN consensus guidelines for the diagnosis and management of breast implant-associated anaplastic large cell lymphoma. *Aesthet Surg J* 2017 Mar 1;**37**(3):285–9.
64. Clemens MW, Miranda RN, Butler CE. Breast implant informed consent should include the risk of anaplastic large cell lymphoma. *Plast Reconstr Surg* 2016 Apr;**137**(4):1117–22.
65. Maxwell GP, Gabriel A. The evolution of breast implants. *Clin Plast Surg* 2009 Jan;**36**(1):1–13.
66. Mazzocchi M, Dessy LA, Carlesimo B, Marchetti F, Scuderi N. Late seroma formation after breast surgery with textured silicone implants: a problem worth bearing in mind. *Plast Reconstr Surg* 2010 Apr;**125**(4):176e–7e.
67. Hu H, Jacombs A, Vickery K, Merten SL, Pennington DG, Deva AK. Chronic biofilm infection in breast implants is associated with an increased T-cell lymphocytic infiltrate: implications for breast implant-associated lymphoma. *Plast Reconstr Surg* 2015 Feb;**135**(2):319–29.
68. Minami A, Iwasaki N, Kutsumi K, Suenaga N, Yasuda K. A long-term follow-up of silicone-rubber interposition arthroplasty for osteoarthritis of the thumb carpometacarpal joint. *Hand Surg Int J Devoted Hand Up Limb Surg Relat Res J Asia-Pac Fed Soc Surg Hand* 2005 Jul;**10**(1):77–82.
69. Hu H, Johani K, Almatroudi A, et al. Bacterial biofilm infection detected in breast implant-associated anaplastic large-cell lymphoma. *Plast Reconstr Surg* 2016 Jun;**137**(6):1659–69.
70. Santanelli di Pompeo F, Laporta R, Sorotos M, et al. Breast implant-associated anaplastic large cell lymphoma: proposal for a monitoring protocol. *Plast Reconstr Surg* 2015 Aug;**136**(2):144e–51e.