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Breast implant-associated anaplastic large cell lymphoma and other rare T-cell lymphomas

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Peripheral T-cell lymphomas (PTCLs) represent account for less than 15% of all non-Hodgkin lymphomas worldwide. In the current WHO classification scheme, more than 25 types of T-cell neoplasms are listed (Table 1)[1]. Considering the non-cutaneous T-cell lymphomas, despite substantial geographic variations in the incidence and the subtype prevalence, a few entities – essentially those presenting as nodal diseases - are relatively common and account for the majority of the cases while extranodal entiites are far less common or distinctively rare. Here, we will review the clinico-pathological features of breast implant-associated anaplastic large cell lymphoma intestinal T-cell neoplasms, with a focus on the recent advances gained in their molecular biology and pathogenesis.

Breast implant-associated anaplastic large cell lymphoma

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a very rare form of T-cell lymphoma that arises in association with breast implants. BIA-ALCL was introduced as a new provisional disease entity in the recently revised WHO classification of lymphoid malignancies, distinct from the other types of ALCLs already recognized (anaplastic lymphoma kinase (ALK)-positive and ALK-negative ALCL, and primary cutaneous ALCL)[1].

Epidemiology

Since the first case was described in 1997, more than 500 cases of BIA-ALCL have been reported in the literature worldwide. An increasing number of dioagnoses were recorded over the recent years reflecting a substantial increase in recognition and awareness of the disease. Notwithstanding these trends, the incidence of BIA-ALCL remains very low. Primary breast lymphomas are represent 1-2% of all non-Hodgkin lymphomas, with most cases diagnosed as diffuse large B-cell lymphomas, follicular or marginal zone B-cell lymphomas.

Among more than 400 breast lymphomas accumulated between 2010 and 2018 in the French lymphoma network, BIA-ALCL represented 10% of the diagnoses[2].

Taking into consideration the very large number of women with breast implants over the world, the individual risk of BIA-ALCL is very small. A recent population-based case-control study based on the pathology registry in the Netherlands established that that BI are associated with a markedly increased risk (400 times) of developing ALCL, but the absolute cumulative risk is estimated to one case for every 50'000 women with BI by the age of 50 years, and one per 7'000 by the age of 75[2]. In another study based on US cases, the lifetime risk of BIA-ALCL in women with textured implants was estimated to 1 in 30'000[3].

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Clinical features

The mean age at diagnosis is in the 50s. Approximately 60% of women who develop BIA-ALCL had implants for cosmetic reasons and 40% had implants for reconstructive purposes after surgery for breast cancer. BIA-ALCL has also been reported in three trangender male to female indivisuals. The median time interval between implant insertion and lymphoma diagnosis is 8-9 years in different studies, but wide variations are observed. There is no significant difference in risk of developing BIA-ALCL according to the content of the implant (saline-filled versus silicone-filled). Conversely, the type of implant outer shell (smooth versus textured) appears to be relevant to risk, since no case of BIA-ALCL has yet been reported in patients who had smooth implants only, while both textured implants and smooth-shell implants with a prior textured implant history have been associated to BIA-ALCL.

Most patients (70-80%) present as a periprosthetic effusion or "late seroma" (defined as an effusion occurring one year or more after initial surgery, a situation requiring further investigation as opposed to fluid collections arising shortly after surgery which are often benign and related to the procedure). A minority of cases (20-20%) present as a tumor mass infiltrating into the adjacent breast parenchyma, with or without an associated effusion. A subset of the

patients (around 20%) may present with regional lymphadenopathy, usually axillary, less frequently supra- or infra-clavicular[4]. However, lymphoma involvement is not proven by biopsy in all instances, so that the actual incidence of locoreginal nodal dissemination is likely lower. Uncommonly, cutanous lesions or B sympoms have been reported at presentation[3].

Morphology

In cases presenting as an effusion, tumor cells may be identified in cytological samples obtained by fine needle aspiration of pericapsular fluid, or on capsulectomy specimens. On smears or cell blocks, the tumor cells are large and pleomorphic, with large nuclei and abundant cytoplasm. Cells with horseshoe-shaped nuclei and a paranuclear cytoplasmic inclusion ("hallmark cells") typically encountered in all forms of ALCL are also found in BIA-ALCL. The neoplastic cells may resemble Hodgkin-like Reed-Sternberg cells. In capsulectomy specimens, the tumor cells are embedded within a proteinaceous and fibrinous meshwork at the surface of the capsule, and may show varying degrees of capsular infiltration. In mass-forming lesions, the tumor cells infiltrate into the adjacent breast tissue and may be accompanied by a pronounced inflammatory component including prominent eosinophilia; necrosis is frequent and sclerosis is sometimes observed. Lymphomatous involvement of axillary lymph nodes is usually characterized by a low tumor burden and can feature a sinusoidal, perifollicular, diffuse or Hodgkin-like pattern, often associated to fibrosis[4].

Immunophenotype

BIA-ALCL has an immunophenotype similar to that of systemic ALK-negative ALCL, and by definition virtually all neoplastic cells strongly positive for CD30 and negative for ALK expression. CD15 is weakly positive in a significant proportion of cases. The expression of T-cell antigens is incomplete: CD43 is almost constantly expressed, CD4 expression is frequent and positivity for CD2 and CD3 is more common than for CD5. CD8 expression is unusual but rare

cases may coexpress CD4 and CD8. An activated cytotoxic immunophenotype denoted by the expression of TIA-1, granzyme B and/or perforin. MUM1 is consistently positive. EBV is consistently negative. BIA-ALCL frequently expresses EMA but is negative for cytokeratins.

Differential diagnoses

The cytology and immunophenotyped of BIA-ALCL overlap with those of other systemic ALK-negative ALCL. Although rarely, systemic ALCL in patients with breast implants may manifest in the breast with a presentation mimicking BI-ALCL. Likewise, primary cutaneous ALCL may involve the skin of the breast in women harboring breast implants. Staging and clinical history are therefore critical to establish the correct diagnosis.

The infiltrative forms of BIA-ALCL may resemble Hodgkin lymphoma morphologically and both entities share a partially overlapping immunophenotype. However, Hodgkin lymphoma is distinctively rare in extarnodal localizations, and Hodgkin/Reed-Sternberg cells are usually negative for T-cell antigens while expressing an attenuated B-cell immunophenotype.

Chronic inflammatory lesions in association to a breast implant may contain occasional CD30+ activated lymphoid cells and must be distinguished from BIA-ALCL.

Molecular and genetic features

The molecular and genetic features of BIA-ALCL are summarized in Table 2.

Antigen receptor genes

The T-cell receptor genes (TRB and/or TRG) are rearranged in most cases. In a study where TRB deep amplicon sequencing was performed, VDJ family usage was not skewed, and analysis of the CDR3 sequences of the dominant clone did not predict affinity for known antigens. Interestingly, analysis of the sequences remaining after substraction of the malignant clone showed a restricted diversity

compared to blood repertoire[5].

Cytogenetics and copy number variations

Three IL2-dependent TLBR (T-cell breast lymphoma) cell lines established from seroma-associated BI-ALCL had clonally abnormal complex karyotypes with a modal number of 47 chromosomes in one cell line (TLBR-1) and a hypertriploid pattern in TLBR-2 and TLBR-3 (reviewed in[6]). Fewer or no alterations numerical alterations have been identified in the few primary BI-ALCL samples examined so far, including the primary tumor from which TLR-1 was derived. In a recent study Blombery *et al.* reported on genome-wide copy number variations in 11 effusion-based BIA-ALCL samples [5]. This genomic assessment was derived from an hybridation-based NGS study of a large panel of hematologically-relevant genes. Detectable gains and/or losses were detected in 8/11 cases. Interestingly, a recurrent focal deletion on chromosome 1p corresponding to a minimal deleted region containing the haploinsiffisient tumor suppressor gene *RPL5*, which encodes a ribosomal protein forming part of the ribosomal 60S subunit, was observed in 5 cases. Other recurrent aberrations included *PRDM1* loss in 3/11 cases and focal high-level amplifications in *TNFRSF11A* which encodes RANK (Receptor Activator of Nuclear Factor kB) in 2 cases. Interestingly, membrane overexpression of RANK was demonstrated by immunohistochemistry in one of these cases. Other cases (one each) harbored gains involving *MYC, P2RX7* and *TMEM119*, or *KIT* and *PDGFRA*.

Sequence variants

So far, a relatively small number of BIA-ALCL have been successfully analyzed by whole exome or, more commonly, targeted next generation sequencing[5-7]. The most recurrent finding consists of *STAT3* activating mutations found overall in 13/34 cases, with a prevalence ranging from 20% to 64%. Recurrent mutations in other genes of the JAK-STAT pathway are also detected, including activating mutations in *JAK1*(4/29 cases) and inactivating mutations *SOCS1*, which encodes a negative regulator of the JAK-STAT pathway (2/16 cases). Mutations

in *STAT5A* or *STAT5B* have not been observed in any of 27 cases tested. Another interesting finding is the presence of somatic *TP53* mutations in 2/17cases, including in one patient who also had a germline *TP53* mutation. A total of four women with known *TP53* germline mutations have been reported to develop BIA-ALCL after reconstructive surgery for breast cancer, raising the question of a potentially increased risk of BIA-ALCLrelated to germline *TP53* alterations. Other somatic mutations in *BCOR*, *SETD2, PTPN, PRKCB* or *DNMT3* were reported in one case each. Most genetic analyses have been carried out on cases which presented as effusions. In the study by Oishi *et al.* which comprised a large proportion cases with tumor cells infiltrating beyond the capsule (T4 stage), there was no enrichment for mutations in the tumoral cases, but the overall frequency of mutations found in that study was low. In one case of BI-ALCL which presented as a solid tumor mass and recurred as an in situ lesion, dual gain-of-function mutations in *JAK1* and *STAT3* were identified in both specimens, a combination previously reported in systemic ALK-negative ALCLs[6].

Gene rearrangements

Rearrangements of the *IRF4*/*DUSP22* locus at 6p25 and of *TP63* which are frequently observed in systemic or primary cutaneous ALCL, have not been found in any of the cases tested so far (0/46 and 0/37, respectively)[2,6,7]. In addition, no structural variants involving the TR genes have been identified[5].

Transcriptomic signature

One study recently examined the gene expression signature of BIA-ALCL, in comparison to that of subsets of normal T cells, and of other ALCLs and T-cell lymphoma entities [8]. It was found that BIA-ALCL cells have a transcriptional profile similar to activated CD4+ memory T cells, with an enrichment in transcripts encoding for IL17, RORC1 and in T regulatory genes, in association with a CD4+ CD25+ FoxP3+ immunophenoptype. Other characteristics of the BIA-ALCL signature include downregulation of the TCR signaling pathway, activation of STAT3, and upregulation of genes involved in cell motility, myeloid

differentiation and viral gene transcription.

Pathogenesis

The pathogenesis of BI-ALCL remains elusive, but several findings suggest that chronic inflammation elicited by silicone-derived products or bacteria adherent to the surface of the prosthesis paly a role in triggering lymphocyte activation, proliferation and expansion and ultimately malignant transformation[2,9]. In particular high bacterial loads of *Ralstonia pickettii* which may produce factors stimulating cytokine secretion have been evidenced at the surface of textured implants with BIA-ALCL. I line with the results of transcriptomic studies, culture experiments with BIA-ALCL native cells or cell lines have demonstrated a Th1/Th17 secretory profile, and cell lines show dependence on cytokines such as IL-, Il-6, and IL-10. Supervening mutations activating the JAK/STAT pathways and/or other genetic alterations likely represent an additional step in the trasformation process to a malignant monoclonal proliferation. Of note is that virtually all BIA-ALCL show evidence of STAT3 activation reflected by nuclear phospho-STAT3 expression, and BIA-ALCL derived cell lines are dependent oin STAT3 activation for their survival.

Staging and outcome

Most patients have excellent outcome, several studies have highlighted an association between the clinical pattern and disease aggressiveness, i.e. most cases presenting as a seroma appear to be cured with surgery alone and infrequently experience recurrences, while the presence of a solid tumor mass is an adverse prognostic factor[2] . Importantly in patients with lymphoma confined to the fibrous periprosthetic capsule, complete surgical excision (total capsulectomy and breast implant removal) is an important determinant of a better overall survival and is the treatment of choice over partial excision, chemotherapy or radiation therapy only[3]. Lymph node involvement at initial presentation was found to correlate with an inferior overall survival [4]. A detailed longitudinal analysis of patients who died of BI-ALCL showed locoregional dissemination of the disease

to the breast, locoregional lymph nodes, chest and mediastinum, but no systemic dissemination typical of other lymphomas. Therefore and because of the importance of complete surgical resection in patients with localized disease, it was suggested to use a TNM staging system similar in its principles to those applied to solid tumors, for evaluating BIA-ALCL[3]. (Table 3)

Intestinal T-cell lymphomas

About 15% of intestinal lymphomas are T-cell lymphomas. The two most common forms of primary intestinal lymphomas, derived from intraepithelial lymphocytes, formerly designated as enteropathy-associated T-cell lymphomas type I and type II, were renamed enteropathy-associated T-cell lymphoma and monomorphic epitheliotropic intestinal T cell lymphoma (MEITL), and represent 5-8% of peripheral T-cell lymphomas[1]. Besides, the intestines can also be involved by virtually any type of T-cell lymphoma, especially EBV-associated ENKTL. Furthermore, peculiar and rare forms of indolent clonal gastrointestinal T-cell lymphoproliferative disorders have been recognized recently.

Enteropathy-associated T-cell lymphoma and monomorphic epitheliotropic intestinal T-cell lymphoma

Table 4 compares the main epidemiological, clinical, histolopathological, and genetic features of EATL and MEITL[1] [10].

These lymphomas tend to occur in adults older than 50 years, with a slight male preponderance. Many cases present with acute abdominal symptoms due to perforation, obstruction, or bleeding. EATL patients, in addition, usually show signs of chronic malabsorption. EATL occurs in individuals with gluten-sensitive enteropathy and is more prevalent in Western populations. However, only 20-73% of individuals are known to have celiac disease prior to the diagnosis of EATL. In some patients, the development of EATL is preceded by refractory celiac disease. The vast majority of patients have the celiac disease–associated HLADQA1*0501, DQB*0201 (HLA-DQ2) genotype and homozygosity for HLA-DQ2 alleles (present in approximately 50% of cases) along with old age are

considered risk factors for developing EATL. MEITL is less common in Western populations and represents the most prevalent type of intestinal T-cell lymphoma in the Asian-Pacific region. Most studies suggest a lack of association with celiac disease. Both EATL and MEITL have a poor prognosis, with <20% five-year survival.

Comparative genomic hybridization-based studies have shown that EATL and MEITL share common recurrent chromosomal imbalances and also have distinctive genetic alterations. Both are characterized by chromosome 9q gains and almost mutually exclusive losses at 16q12.1. Gain of chromosome 7 and losses involving 8p22-23.2, 16q21.1, 11q14.1- q14.2 and 9p21.2-p21.3 are also frequent in both diseases. Conversely, MEITL has more frequent gains of the *MYC* oncogene locus and less frequent gains of chromosomes 1q and 5q as compared with EATL. Additionally, loss of 3p21.31 is a recurrent aberration in MEITL but not in EATL.

MEITL is characterized by highly recurrent alterations of the tumor suppressor gene *SETD2* encoding a non-redundant H3K36-specific trimethyltransferase, in the vast majority of cases. *SETD2* alterations are often biallelic, mainly due to loss-of-function mutations and/or loss of the corresponding locus (3p21.31) and consistently correlate with defective H3K36 trimethylation[11]. Interestingly, *SETD2* is also the most frequently mutated gene in hepatosplenic T-cell lymphoma, another rare form of highly aggressive T-cell lymphoma often observed from gamma-delta T cells and characterized by a sinusoidal infiltrate in the spleen, bone marrow and liver[12]. In another study, *SETD2* alterations were also identified in a smaller proportion of EATLs[13]. Both EATL and MEITL demonstrate recurrent mutation-induced activation of the JAK/STAT pathway mainly due to *STAT3/5B*, *JAK1/3* and *SH2B3* mutations, and RAS pathway genetic aberrations (mutations in *TP53*, *BRAF* and *KRAS*). MEITL also carries frequent mutations in *GNAI2*.

Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract

This term designates clonal T-cell proliferations involving the gastrointestinal mucosa, with a relatively indolent clinical course[1] [14]. Common presenting signs are chronic diarrhea, weight loss, abdominal pain, and/or rectal bleeding. Endoscopic findings include mucosal erythema, nodularity, erosions or small ulcers, and sometimes small polyps without mass lesions. Patients are adults, usually have multiple lesions along the gastro-intestinal tract, most commonly in the small intestines and colon. Some cases have evidence of extra-intestinal disease, with lymph node, liver or bone marrow infiltration. The etiology of these disorders is unknown, although some CD4+ LPDs occurred in individuals with an autoimmune or infectious disease.

Mucosal biopsies reveal a variably dense, monotonous infiltrate of small lymphocytes that show little or no atypia, expanding the lamina propria and displacing the epithelial structures. The infiltrate is composed of CD3+ T cells, either CD4+ (more commonly) or CD8+, and in rare instances CD4-/CD8- or CD4+/CD8+. CD8-positive cases display a cytotoxic profile, and some cases show downregulation or loss of CD5 and/or CD7 expression. The Ki-67 proliferation index is low (<10%). The genetic basis of these LPDs is poorly understood. Non-recurrent chromosome copy number changes have been identified by array-based approaches. *STAT3* mutations (or evidence of STAT3 activation) were not observed in a series largely comprising CD8+ LPDs. Recently, however, recurrent *STAT3-JAK2* fusions have been identified by next-generation sequencing and FISH analysis in 4 of 5 CD4+ LPDs[15].

The differential diagnosis includes on one hand benign conditions, such as celiac disease and inflammatory bowel disease, and on the other hand T-cell lymphomas. Appropriate diagnosis of these indolent T-cell lymphoproliferations is essential to avoid overtreatment with chemotherapy that results in unnecessary toxicity without significant benefit. Most patients are alive with persistent disease after several years of follow-up. However, complete remission occurs rarely and death due to disease progression or transformation has been documented in a few patients.

Table 1. Mature T-cell neoplasms (adapted from Swerdlow SH et al. WHO 2017)[1]

Disseminated/leukemic
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells*
Aggressive NK-cell leukaemia
Systemic EBV-positive T-cell lymphoma of childhood*
Chronic active EBV infection of T- and NK-cell type, systemic form
Adult T-cell leukemia/lymphoma

Nodal
Angioimmunoblastic T-cell lymphoma
Follicular T-cell lymphoma
Nodal peripheral T-cell lymphoma with T follicular helper phenotype
Anaplastic large cell lymphoma, ALK-positive
Anaplastic large cell lymphoma, ALK-negative
Peripheral T-cell lymphoma, not otherwise specified

Extranodal
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma
Indolent T-cell lymphoproliferative disorder of the gastro-intestinal tract*
Hepatosplenic T-cell lymphoma
Breast implant-associated anaplastic large cell lymphoma*

Cutaneous
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sezary syndrome
Primary cutaneous CD30 + lymphoproliferative disorders
   Lymhomatoid papulosis
   Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Rare primary cutaneous CD4+ or CD8+ entities*
Hydroa vacciniforme-like lymphoproliferative disorder
Severe mosquito bite allergy

*Denotes provisional entities

Table 2. Summary of genetic features of BIA-ALCL cases

Copy number variations

     Del(1p) (*RPL5*)   5/11   45%

     PRDM1 loss   3/11   27%

     TNFRSF11 amplification   2/11   18%

Non-recurrent: *MYC* amplification, *PDGFRA* and *KIT* amplification, *TMEM19* amplification

Gene rearrangements

     ALK   0%

     DUSP22   0/46   0%

     TP63   0/37   0%

     TRA, TRB, TRG, TRD   0/11   0%

Mutations

     STAT3   13/34 38%

     STAT5A/5B   0/27   0%

     JAK1   4/29   14%

     JAK3   0/27   0%

     SOCS1   2/16   13%

     TP53   2/17   12%

     Non-recurrent: *BCOR, DNMT3, PTNP1, PRKCB*

Table 3. Proposed TNM staging system for BIA-ALCL (adapted from Mehta-Shah N et al)[3]

T: tumor extent	Stage
T1 Confined to effusion or a layer on luminal side of the capsule	IA T1 N0 M0
T2 Early capsule infiltration	IB T2 N0 M0
T3 Cell aggregates or sheets infiltrating the capsule	IC T3 N0 M0
T4 Infiltration beyond rhe capsule	IIA T4 N0 M0
N: lymph node involvement	IIB T1-3 N1 M0
N0 No lymph node invovlement	III T4 N1-2 M0
N1 One lymph node involved	IV M1
N2 Multiple regional lymph nodes involved	
M: metastasis	
M0 No metastases	
M1 Spread to distant organs/sites	

Table 4. Comparison of pathological and genetic features of EATL and MEITL

	Enteropathy-associated T-cell lymphoma	Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)
Epidemiology	Northern Europe, association with celiac disease (CD) HLA-DQ2/-DQ8 : >90%	Celiac disease uncommon HLA-DQ2/-DQ8 : normal frequency
Morphology	Pleomorphic, medium to large size, some cases anaplastic Inflammation, necrosis common	Monomorphic, small to medium size, epitheliotropic No inflammation, no necrosis
Distant mucosa	Enteropathy	Increased intraepithelial lymphocytes, no atrophy
Immuno-phenotype	CD3+, CD5-, CD8-/+, CD56- Frequently CD30+ Activated cytotoxic MATK+ < 40% of tumor cells	CD3+, CD5-, CD8+/-, CD56+/- CD30- Activated cytotoxic MATK+ > 80% tumor cells Coexpression of B-cell antigens (20%)
TCR expression	Usually TCR silent or αβTCR>> γδTCR	TCR usually expressed γδTCR (Vδ1) > αβTCR
Genomic imbalances	+1q32.2-q41, +5q34-q35.2 +9q, -16q21.1	+8q24 (*MYC*) +9q -16q21.1
Epigenetics	*SETD2* mutations rare	*SETD2* inactivation (>90%)
JAK/STAT pathway	*JAK1* mutations (20-50%) *JAK3* mutations (10%) *STAT3* mutations (20%) *STAT5B* mutations (rare)	*JAK1* mutations (10-20%) *JAK3* mutations (35-50%) *STAT3* mutations (10%) *STAT5B* mutations (50-65%)
MAPK pathway	*KRAS NRAS BRAF* mutations (20%)	*BRAF KRAS NRAS* mutations (50%)
GRP signaling		*GNAI2* mutations (24%)

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