Supplement

Genetics of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

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Abstract

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), a newly included provisional entity in the 2016 revision of the World Health Organization classification, is a distinct form of CD30-positive T-cell non-Hodgkin lymphoma that arises in association with a breast implant after reconstructive or cosmetic surgery. In addition to its characteristic clinical presentation, recent studies using next-generation sequencing have revealed that BIA-ALCL has a unique pattern of genetic alterations. BIA-ALCL is consistently negative for ALCL-related gene rearrangements involving *ALK*, *DUSP22*, and *TP63*. However, the JAK-STAT3 pathway is constitutively activated in BIA-ALCL, which in some cases is associated with recurrent somatic mutations of *JAK1* and/or *STAT3*. These activating mutations, which may be concurrent, are identified in 13% (3/23) and 26% (6/23) of BIA-ALCLs, respectively. Other genetic alterations include point mutations of *DNMT3A* and *TP53*. Although the number of examined cases has been limited, these findings suggest that BIA-ALCL shows more uniform molecular features than systemic and primary cutaneous ALCLs, which show considerable genetic heterogeneity. Targeted therapies inhibiting JAK-STAT signaling are being developed and may offer novel therapeutic options for patients with BIA-ALCL, especially those with advanced disease.

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Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a distinct form of anaplastic large cell lymphoma (ALCL) that is newly included in the 2017 revision of the World Health Organization (WHO) classification as a provisional entity.[1] BIA-ALCL is clinically distinct from other types of ALCL in that it arises in association with a breast implant after reconstructive or cosmetic surgery.[1,2] In addition to its unique clinical presentation, recent studies have shown that BIA-ALCL has characteristic genetic and molecular signatures.[3-7] In this review, we focus on the genetics of BIA-ALCL and discuss its similarities to and differences from other ALCLs.

CLASSIFICATION OF ALCLs

ALCLs comprise a distinctive group of T-cell non-Hodgkin lymphomas that share pathologic features including CD30 expression and at least a subset of cytologically characteristic cells designated "hallmark" cells.[8,9] Despite these unifying morphologic and immunophenotypic characteristics, ALCLs remain heterogeneous, and the current WHO classification acknowledges considerable differences in clinical manifestations, prognosis, and genetic abnormalities.[8-10] ALCLs are classified based on clinical presentation and the presence or absence of a

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rearrangement involving the *ALK* gene (or demonstration of the resultant ALK fusion protein by immunohistochemistry [IHC]).[1,11] Systemic forms of ALCL are divided into ALK-positive and ALK-negative ALCLs. In general, patients with systemic ALK-positive ALCL are young and show favorable outcomes after chemotherapy when compared with those with systemic ALK-negative ALCL.[12,13] In addition to the systemic forms of ALCL, there are two site-specific forms of ALCL, primary cutaneous ALCL and BIA-ALCL, which initially present in the skin and surrounding a breast implant, respectively. Unlike systemic ALCLs, these site-specific ALCLs are not further divided by *ALK* rearrangement status or ALK expression because they are almost always ALK-negative.[1,8]

BIA-ALCL is defined as an ALCL that arises in association with a breast implant. The tumor cells of BIA-ALCL are usually localized to the seroma cavity surrounding a breast implant and may involve the pericapsular fibrous tissue. BIA-ALCL forms a mass lesion in approximately 30% of cases and involves locoregional lymph nodes in approximately 20% of cases; both features are now recognized as adverse prognostic factors.[14,15] Importantly, the cellular morphology and immunophenotype of BIA-ALCL are indistinguishable from those of systemic or cutaneous ALK-negative ALCL: the tumor cells express CD30 and cytotoxic molecules including TIA-1 and granzyme B, whereas expression of T-cell markers such as CD3 and CD7 are frequently diminished or lost.[2,7]

GENETICS OF ALCL: OVERVIEW

Chromosomal Rearrangements of ALK, DUSP22, and TP63

ALCLs are genetically heterogeneous; however, gene rearrangements involving *ALK* subdivide them into 2 large groups: ALK-positive and ALK-negative ALCLs. *ALK* on chromosome 2p23 encodes a receptor tyrosine kinase on the cell surface that plays a physiological role in neuronal development. ALK-positive ALCLs aberrantly express ALK fusion proteins encoded by gene rearrangements juxtaposing fusion partner genes upstream of *ALK*, whereas normal T cells do not express *ALK*.[16,17] The most common gene fusion is *NPM1-ALK* associated with chromosomal translocation t(2;5)(p23;q35), which accounts for up to 85% of ALK-positive ALCLs.[16,17] Other *ALK* rearrangements include *TPM3-ALK* associated with t(1;2)(q25;p23), *ATIC-ALK* associated with inv(2)(p23;q35), and additional rare variants.[16-18] The resulting ALK fusion proteins are oncogenic and foster the proliferation and survival of the neoplastic cells by activating downstream RAS-RAF-MEK-ERK (MAP kinase), PI3K-AKT, and JAK-STAT3 pathways.[9,16,19] *ALK* rearrangements are usually seen in the context of systemic disease,[9] but also may occur in rare primary cutaneous ALCLs.[20]

In ALK-negative ALCLs, recent molecular studies have identified recurrent chromosomal rearrangements involving the *DUSP22*/*IRF4* locus on chromosome 6p25.3 and *TP63* on 3q28, which are most commonly mutually exclusive but occasionally occur concurrently.[18,21] *DUSP22/IRF4* rearrangements are present in up to 30% of systemic ALK-negative ALCLs[10,18] and in up to 20% of primary cutaneous CD30-positive lymphoproliferative disorders, including primary cutaneous ALCL and lymphomatoid papulosis.[22,23] Notably, systemic ALK-negative ALCL with *DUSP22* rearrangement shows excellent overall survival similar to ALK-positive ALCL after chemotherapy.[10,24] *TP63* rearrangements most commonly occur as inv(3)(q26q28) generating a *TBL1XR1-TP63* fusion and account for approximately 8% of ALK-negative ALCLs.[21] *TP63*-rearranged ALCL shows significantly worse overall survival than ALK-positive and *DUSP22*-rearranged ALCLs.[10] Rearrangements of *DUSP22* and *TP63* can be detected by fluorescence in situ hybridization (FISH). IHC for p63 protein is not specific for *TP63* rearrangements but is highly sensitive and can be used to select cases for FISH testing.[25] ALCLs lacking *ALK*, *DUSP22*, and *TP63* rearrangements have been referred to as “triple-negative” ALCLs, which exhibit overall survival intermediate between that of *DUSP22*- and *TP63*-rearranged ALCLs.[10]

Genetic Events Activating the JAK-STAT3 Pathway

The JAK-STAT pathway is frequently dysregulated in human T-cell neoplasms including ALCLs.[26,27] Under physiological conditions, the binding of various ligands to cell-surface receptors causes receptor dimerization and brings the receptor-associated JAKs into proximity. JAKs then phosphorylate the receptor, facilitating binding of two STAT molecules, and subsequently phosphorylate the STAT molecules directly. The phosphorylated STATs form dimers that translocate into the nucleus, bind to DNA, and function as transcription factors.

ALCLs show aberrant activation of the JAK-STAT pathway. In ALK-positive ALCLs, ALK fusion proteins have been shown to activate the JAK-STAT3 pathway by phosphorylating STAT3.[16,19] In ALK-negative ALCLs, *STAT3* and *JAK1* mutations have been identified in up to 40% of systemic ALK-negative ALCLs and may cooccur.[28] Most reported *STAT3* mutations, including Y640F, N647I, and D661Y, affect its SH2 domain, which is necessary for receptor association and tyrosine phosphodimer formation.[28] In contrast, *JAK1* mutations, such as G1097D/S/N, predominantly affect its JH1 kinase domain.[28] In other ALK-negative ALCLs, chromosomal rearrangements give

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Table 1. Genetic Alterations in Breast Implant-Associated ALCLs

	Gene rearrangements			Mutations				
Reference	Method	*DUSP22*	*TP63*	Method	Matched germline DNA tested	*JAK1*	*JAK3*	*STAT3*
Oishi et al[7]	FISH + IHC	0/36	0/36	Targeted NGS	No	1/15	0/15	3/15
Letourneau et al[6]	FISH	0/1	0/1	Targeted NGS	No	1/1[a]	0/1	1/1[a]
Blombery et al[3]				WES	Yes	1/2	1/2[b]	1/2
Laurent et al[5]	FISH	0/9						
Di Napoli et al[4]				Targeted NGS	Yes	0/5	0/5	1/5
Total		0/46	0/37			3/23 (13%)	1/23 (4%)	6/23 (26%)

ALCL, anaplastic large cell lymphoma; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next generation sequencing; WES, whole exome sequencing. [a]Concurrent *JAK1* and *STAT3* in the same patient. [b]Germline mutation and concurrent *JAK1* somatic mutation.

rise to fusion genes involving non-ALK tyrosine kinases, including *FRK*, *ROS1*, and *TYK2*, which lead to STAT3 activation.[28-30] STAT3 transcriptional targets include *TNFRSF8* and *GZMB*,[8,16] encoding the activation marker CD30 and the cytotoxic molecule granzyme B, respectively, and genetic dysregulation of the JAK-STAT3 pathway at least partly explains the characteristic activated and cytotoxic T-cell immunophenotype of most ALCLs. It should be noted that about half of systemic and primary cutaneous ALK-negative ALCLs lack activated STAT3,[28,31,32] a finding particularly associated with the presence of *DUSP22* rearrangements.[33]

GENETICS OF BIA-ALCL

Chromosomal Rearrangements of ALK, DUSP22, and TP63

The current understanding of the genetics of BIA-ALCL is limited by the relatively small number of cases studied to date. Thus far, in contrast to systemic and primary cutaneous ALCLs, BIA-ALCLs have been consistently negative for *ALK*, *DUSP22*, and *TP63* rearrangements (ie, “triple-negative”). All reported BIA-ALCLs have been negative for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for *DUSP22* and *TP63* rearrangements, respectively, and all were negative.[5-7] Although larger studies might identify rare chromosomal rearrangements in BIA-ALCLs, the data thus far suggest that BIA-ALCL shows less genetic heterogeneity than systemic and cutaneous ALCLs, a finding that may indicate a uniform mechanism of lymphomagenesis.

The triple-negative genetic subtype of BIA-ALCL also provides insight into its cellular morphology, because genetic subtype is associated with cytological features. ALK-negative ALCLs with triple-negative genetic subtype often exhibit very large pleomorphic cells with occasional “wreath-like” nuclei, whereas ALCLs with *DUSP22* rearrangements more typically show monotonous sheets of more medium-sized cells with prominent nuclear pseudoinclusions and relatively few large pleomorphic cells.[34] In line with these observations, BIA-ALCLs typically are composed of large pleomorphic cells, often with wreath-like nuclei. Furthermore, the triple-negative genetic subtype of BIA-ALCL might merit the differential diagnosis of ALCLs involving the breast. It is important to recognize that all WHO subtypes of ALCL can involve the breast, including primary cutaneous ALCL and ALK-positive or ALK-negative systemic ALCL.[35] Thus, given the consistent triple-negative genetics of BIA-ALCL, ALK positivity or the presence of a rearrangement of *DUSP22* or *TP63* should prompt consideration of a possible non-BIA origin.

Genetic Events Activating the JAK-STAT3 Pathway

Activation of the JAK-STAT3 pathway, and specifically presence of phosphorylated STAT3, is nearly always present in BIA-ALCL, in contrast to its variable expression in other ALK-negative ALCLs.[5,7] There have been four studies that examined JAK-STAT pathway gene mutations in a total of 23 cases of BIA-ALCL (Table 1).[3,4,6,7] Among JAK-STAT3 pathway genes, *STAT3* mutation is most frequent and found in 26% (6/23) of BIA-ALCLs. These *STAT3* mutations result in an amino acid substitution S614R or Y640F, both of which affect the SH2 domain and have been reported to lead to constitutive activation of the STAT3 protein. Although *STAT3* mutation is also frequent in systemic ALK-negative ALCLs, it is of interest that *STAT3* S614R seems predominant in BIA-ALCLs and accounts for 67% (4/6) of STAT3-mutant cases, whereas *STAT3* Y640F, the most frequent substitution in systemic ALK-negative ALCLs,[28] is relatively rare in BIA-ALCLs. This difference in *STAT3* mutation hotspots suggests that *STAT3* S614R

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mutation may specifically benefit the growth of BIA-ALCL cells in the inflammatory microenvironment surrounding breast prostheses. No BIA-ALCLs have been reported to carry *STAT5B* mutations, which are frequent in T-cell lymphomas involving a γδ-type T-cell receptor phenotype such as enteropathy-associated and hepatosplenic T-cell lymphomas.[36-39]

In addition to *STAT3* mutations, *JAK1* mutations have been found in 13% (3/23) of BIA-ALCLs.[3,4,6,7] All the reported *JAK1* mutations result in G1097V, an amino acid substitution from glycine to valine at codon 1097 within the kinase domain of *JAK1*. As is the case in systemic ALK-negative ALCL, BIA-ALCLs may harbor *JAK1* mutations concurrently with mutations of *STAT3*.[6] *JAK* G1097V has been shown to be a gain-of-function mutation that triggers aberrant phosphorylation of STAT3.[28] Germ-line *JAK3* V722I mutation, which also affects the kinase domain, has been reported in a single case of BIA-ALCL that had concurrent *JAK1* G1097V.[3] Thus, *JAK1* and *JAK3* mutations are additional mechanisms that lead to enhanced STAT3 activation in BIA-ALCLs.

Suppressor of cytokine signaling 1 (*SOCS1*) functions as a negative feedback regulator of the JAK/STAT pathway by inhibiting JAK kinase activity, and loss-of-function *SOCS1* mutations have been identified in various types of lymphomas.[40-43] Of interest, the frameshift deletion of *SOCS1* (P83fs) has been reported in one BIA-ALCL harboring the *STAT3* mutation S614R,[4] further supporting the importance of the JAK-STAT3 pathway in BIA-ALCL.

BIA-ALCLs show consistent nuclear positivity by IHC for phosphorylated STAT3 Y705,[7,44] the most crucial tyrosine residue for STAT3 activation, regardless of the mutational status of JAK-STAT3 pathway genes.[5,7] This observation implies other mechanisms leading to STAT3 activation in BIA-ALCL also exist, which might include PTPase gene losses or epigenetic inactivation, or fusion genes seen in other ALK-negative ALCLs.[27,28,30]

The consistent activation of the JAK-STAT3 pathway also suggests potential therapeutic options for BIA-ALCLs. Several small molecules inhibiting JAKs (jakinibs) and STAT3 have been developed,[45,46] and some are approved by the United States Food and Drug Administration for use in other diseases. For example, ruxolitinib, a JAK1/JAK2 inhibitor, is now widely used for patients with bone marrow myelofibrosis. Another interesting therapeutic target is CD274 (PD-L1), an immune checkpoint molecule on the surface of cancer cells that downregulates T-cell receptor signaling in host T cells resulting in attenuated anti-tumor immune reactions.[47] Blocking the ligation of PD-L1 to PD-1 has been shown effective in various cancers, and several PD-L1 and PD-1 inhibitors have been developed. Of importance, although PD-1 is negative in BIA-ALCLs,[48] PD-L1 is transcriptionally regulated by STAT3 and MYC,[49] and BIA-ALCLs have been reported to express PD-L1.[50] Therefore, targeted therapies against the JAK-STAT3 pathway and/or the PD1/PD-L1 axis may be promising options for patients with BIA-ALCLs, especially those with advanced disease stage.

Other Genetic Alterations

Genetic alterations in BIA-ALCLs other than those involving JAK-STAT3 pathway genes include point mutations of *DNMT3A* and *TP53*.[4] An inactivating nonsense mutation of *DNMT3A* was reported in one BIA-ALCL. *DNMT3A* is a gene encoding DNA methyltransferase 3-α that is thought to function in de novo methylation of DNA, and inactivating mutations have been found in various hematopoietic and lymphoid neoplasms including peripheral T-cell lymphoma and angioimmunoblastic lymphoma.[51-54] The *TP53* D259Y mutation was reported in a single case of BIA-ALCL that also harbored *STAT3* S614R and a *SOCS1* mutation.[4] Lee et al and Pastorello et al have independently reported patients with Li Fraumeni syndrome developing BIA-ALCL; however, the *TP53* mutation was not characterized.[55,56] *TP53* mutations are relatively rare in peripheral T-cell lymphomas,[57-59] and their clinical and biological significance in BIA-ALCL remains to be elucidated.

There are, however, several caveats to interpreting the sequencing data on BIA-ALCL. First, not all the published studies examined matched germline DNA in addition to tumor DNA. Matched constitutional DNA has been analyzed in only 7 of 23 BIA-ALCLs studied by next-generation sequencing.[3,4] Second, only 2 cases of BIA-ALCL have been examined by whole exome sequencing so far,[3] and other studies employed targeted sequencing for selected cancer- or T-cell lymphoma-associated genes. Given the relatively low frequency of JAK-STAT3 gene mutations in BIA-ALCLs, these limitations of the previous studies may result in under-recognition of other somatic or germline genetic alterations associated with the pathogenesis of BIA-ALCL, and further comprehensive genetic studies are warranted.

Cytogenetics

There have been a limited number of reports on the cytogenetic findings in BIA-ALCL (Table 2).[3,44,60] Lechner et al established cell lines of BIA-ALCL, namely TLBR-1, TLBR-2, and TLBR-3, and examined their chromosomal abnormalities by conventional karyotyping.[44,60] All 3 cell lines have complex karyotypes as shown in Table 2. Whereas TLBR-1 has a modal number of 47 chromosomes,[60] TLBR-2 and TLBR-3 exhibit hypertriploid karyotypes with modal numbers of chromosomes of 76 and 81,[44] respectively. In addition to the lack of ALCL-associated chromosomal translocations, these cell lines harbor no other translocations frequently found in B- or T-cell lymphomas. In another study, Blombery et al conducted whole-genome copy number

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Table 2. Cytogenetics of Breast Implant-Associated ALCLs

Reference	Sample	Method	Results
George et al[63]	Tumor cells from seroma fluid	Karyotyping	45, XX [cp19] dup(X)(q11q28),+1, del(1)(q32), i(1)(q10), add(3)(p11), der(3), t(2;3)(p12;p26), +6, der(6) t(6;8)(q12;q21.3)x2, add(8)(q11.2), add(11)(q23), add(14)(p11.1), −15, −17, −20, 80~91, idem [cp2]
Alobeid et al[64]	Tumor cells	Karyotyping	Highly complex abnormalities: 116-123,55N4,XX,71, add(1)(p36.3), i(1)(q10), hsr(1)(q21q25), +2, +3x2, +6, hsr(7)(q32q35)x2, i(8)(q10), +9, +10, inv(11)(p15.1q22.1)x3, add(12)(q24.1), −13, −14, −15, i(17)(q10), +19, −20, +1~8mar[cp13] /46,XX,inv(11)(p15.1q22.1)[7]
Lechner et al[60]	TLBR-1	Karyotyping	Complex karyotype: partial trisomy 2, addition involving 5p, deletion of 10p, unbalanced translocation between chromosomes 12 and 17, and monosomy 16 and 20; presence of subclonal populations with the addition of unknown genetic material to the short arm of chromosomes 13, 15, and 16
Lechner et al[44]	TLBR-2	Karyotyping	Hypertriploid complex karyotype with a modal number of chromosomes of 76, gains of chromosomes 1, 2, 5, 6, 10, 11, 14, 17, and clonal loss of one copy of chromosome 18, relative
Lechner et al[44]	TLBR-3	Karyotyping	Hypertriploid complex karyotype with a modal number of chromosomes of 81, gains of chromosomes X, 2, 5, 7, 8, 10, 11, 12, 14, 19, 20, 21, and 22, and loss of one copy of chromosomes 9, 16, and 17, relative to a triploid genome
Blombery et al[3]	Effusion cytology specimen (case 1)	WES	Copy number gain of 19p, copy number loss of 1p and 10p
Blombery et al[3]	Effusion cytology specimen (case 2)	WES	None

ALCL, anaplastic large cell lymphoma; WES, whole exome sequencing.

analysis on two BIA-ALCLs, and one of them showed multiple copy number changes including copy number loss of 1p and 10p and copy number gain of 19p.[3] The deleted portions of 1p and 10p contained tumor suppressor genes *RPL5* and *GATA3*, respectively, and the focal gain of 19p included *TYK2*, which encodes a JAK family kinase recently reported to lead to phosphorylation of STAT1 and STAT3, increased MCL1 expression, and enhanced cell survival in ALCL.[61] These copy number abnormalities might elicit or enhance aberrant activation of the JAK-STAT3 pathway; however, the number of cases analyzed has been limited, warranting further cytogenetic studies. Quesada et al have summarized cytogenetic abnormalities in 3 other reported cases showing a complex karyotype.[62]

CONCLUSIONS

Taken together, BIA-ALCL is characterized by a triple-negative genetic subtype and activation of the JAK-STAT3 pathway, which is at least partly attributable to point mutations of *JAK1* and *STAT3*. Thus, in addition to its characteristic clinical manifestations arising in association with a breast prosthesis, BIA-ALCL also demonstrates a more uniform molecular signature than other types of ALCL. Given the recent development of JAK inhibitors and antibodies blocking PD1/PD-L1 axis, the activated JAK-STAT3 phenotype and possible expression of PD-L1 may be promising molecular targets in BIA-ALCL, warranting further genetic, functional, and potentially clinical studies.

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REFERENCES

1. Feldman AL, Harris NL, Stein H, et al. Breast implant-associated anaplastic large cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon: International Agency for Research on Cancer; 2017:421-422.
2. 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;36(7):1000-1008.
3. Blombery P, Thompson ER, Jones K, et al. Whole exome sequencing reveals activating JAK1 and STAT3 mutations in breast implant-associated anaplastic large cell lymphoma anaplastic large cell lymphoma. *Haematologica.* 2016;101(9):e387-e390.
4. Di Napoli A, Jain P, Duranti E, et al. Targeted next generation sequencing of breast implant-associated anaplastic large cell lymphoma reveals mutations in JAK/

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STAT signalling pathway genes, TP53 and DNMT3A. *Br J Haematol.* 2018;180(5):741-744.
5. 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;27(2):306-314.
6. Letourneau A, Maerevoet M, Milowich D, et al. Dual JAK1 and STAT3 mutations in a breast implant-associated anaplastic large cell lymphoma. *Virchows Arch.* 2018;473(4):505-511.
7. Oishi N, Brody GS, Ketterling RP, et al. Genetic subtyping of breast implant-associated anaplastic large cell lymphoma. *Blood.* 2018;132(5):544-547.
8. Xing X, Feldman AL. Anaplastic large cell lymphomas: ALK positive, ALK negative, and primary cutaneous. *Adv Anat Pathol.* 2015;22(1):29-49.
9. Zeng Y, Feldman AL. Genetics of anaplastic large cell lymphoma. *Leuk Lymphoma.* 2016;57(1):21-27.
10. Parrilla Castellar ER, Jaffe ES, Said JW, et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. *Blood.* 2014;124(9):1473-1480.
11. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood.* 2016;127(20):2375-2390.
12. Gascoyne RD, Aoun P, Wu D, et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. *Blood.* 1999;93(11):3913-3921.
13. Savage KJ, Harris NL, Vose JM, et al.; International Peripheral T-Cell Lymphoma Project. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the international peripheral T-cell lymphoma project. *Blood.* 2008;111(12):5496-5504.
14. Ferrufino-Schmidt MC, Medeiros LJ, Liu H, et al. Clinicopathologic features and prognostic impact of lymph node involvement in patients with breast implant-associated anaplastic large cell lymphoma. *Am J Surg Pathol.* 2018;42(3):293-305.
15. 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;34(2):160-168.
16. Chiarle R, Voena C, Ambrogio C, Piva R, Inghirami G. The anaplastic lymphoma kinase in the pathogenesis of cancer. *Nat Rev Cancer.* 2008;8(1):11-23.
17. Tsuyama N, Sakamoto K, Sakata S, Dobashi A, Takeuchi K. Anaplastic large cell lymphoma: pathology, genetics, and clinical aspects. *J Clin Exp Hematop.* 2017;57(3):120-142.
18. Feldman AL, Dogan A, Smith DI, et al. Discovery of recurrent t(6;7)(p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively parallel genomic sequencing. *Blood.* 2011;117(3):915-919.
19. Zamo A, Chiarle R, Piva R, et al. Anaplastic lymphoma kinase (ALK) activates Stat3 and protects hematopoietic cells from cell death. *Oncogene.* 2002;21(7):1038-1047.
20. Beylot-Barry M, Lamant L, Vergier B, et al. Detection of t(2;5)(p23;q35) translocation by reverse transcriptase polymerase chain reaction and in situ hybridization in CD30-positive primary cutaneous lymphoma and lymphomatoid papulosis. *Am J Pathol.* 1996;149(2):483-492.
21. Vasmatzis G, Johnson SH, Knudson RA, et al. Genome-wide analysis reveals recurrent structural abnormalities of TP63 and other p53-related genes in peripheral T-cell lymphomas. *Blood.* 2012;120(11):2280-2289.
22. Pham-Ledard A, Prochazkova-Carlotti M, Laharanne E, et al. IRF4 gene rearrangements define a subgroup of CD30-positive cutaneous T-cell lymphoma: a study of 54 cases. *J Invest Dermatol.* 2010;130(3):816-825.
23. Wada DA, Law ME, Hsi ED, et al. Specificity of IRF4 translocations for primary cutaneous anaplastic large cell lymphoma: a multicenter study of 204 skin biopsies. *Mod Pathol.* 2011;24(4):596-605.
24. Pedersen MB, Hamilton-Dutoit SJ, Bendix K, et al. DUSP22 and TP63 rearrangements predict outcome of ALK-negative anaplastic large cell lymphoma: a Danish cohort study. *Blood.* 2017;130(4):554-557.
25. Wang X, Boddicker RL, Dasari S, et al. Expression of p63 protein in anaplastic large cell lymphoma: implications for genetic subtyping. *Hum Pathol.* 2017;64:19-27.
26. Waldmann TA, Chen J. Disorders of the JAK/STAT pathway in T cell lymphoma pathogenesis: implications for immunotherapy. *Annu Rev Immunol.* 2017;35:533-550.
27. Pizzi M, Margolskee E, Inghirami G. Pathogenesis of peripheral T cell lymphoma. *Annu Rev Pathol.* 2018;13:293-320.
28. Crescenzo R, Abate F, Lasorsa E, et al.; European T-Cell Lymphoma Study Group, T-Cell Project: Prospective Collection of Data in Patients with Peripheral T-Cell Lymphoma and the AIRC 5xMille Consortium "Genetics-Driven Targeted Management of Lymphoid Malignancies". Convergent mutations and kinase fusions lead to oncogenic STAT3 activation in anaplastic large cell lymphoma. *Cancer Cell.* 2015;27(4):516-532.
29. Boddicker RL, Razidlo GL, Dasari S, et al. Integrated mate-pair and RNA sequencing identifies novel, targetable gene fusions in peripheral T-cell lymphoma. *Blood.* 2016;128(9):1234-1245.
30. Hu G, Dasari S, Asmann YW, et al. Targetable fusions of the FRK tyrosine kinase in ALK-negative anaplastic large cell lymphoma. *Leukemia.* 2018;32(2):565-569.
31. Khoury JD, Medeiros LJ, Rassidakis GZ, et al. Differential expression and clinical significance of tyrosine-phosphorylated STAT3 in ALK+ and ALK- anaplastic large cell lymphoma. *Clin Cancer Res.* 2003;9(10 Pt 1):3692-3699.
32. Song JY, Song L, Herrera AF, et al. Cyclin D1 expression in peripheral T-cell lymphomas. *Mod Pathol.* 2016;29(11):1306-1312.
33. Luchtel RA, Dasari S, Oishi N, et al. Molecular profiling reveals immunogenic cues in anaplastic large cell lymphomas with DUSP22 rearrangements. *Blood.* 2018;132(13):1386-1398.
34. King RL, Dao LN, McPhail ED, et al. Morphologic features of ALK-negative anaplastic large cell lymphomas

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with DUSP22 rearrangements. *Am J Surg Pathol.* 2016;40(1):36-43.
35. Miranda RN, Lin L, Talwalkar SS, Manning JT, Medeiros LJ. Anaplastic large cell lymphoma involving the breast: a clinicopathologic study of 6 cases and review of the literature. *Arch Pathol Lab Med.* 2009;133(9):1383-1390.
36. Pham HTT, Maurer B, Prchal-Murphy M, et al. STAT5BN642H is a driver mutation for T cell neoplasia. *J Clin Invest.* 2018;128(1):387-401.
37. Moffitt AB, Ondrejka SL, McKinney M, et al. Enteropathy-associated T cell lymphoma subtypes are characterized by loss of function of SETD2. *J Exp Med.* 2017;214(5):1371-1386.
38. McKinney M, Moffitt AB, Gaulard P, et al. The genetic basis of hepatosplenic T-cell lymphoma. *Cancer Discov.* 2017;7(4):369-379.
39. Küçük C, Jiang B, Hu X, et al. Activating mutations of STAT5B and STAT3 in lymphomas derived from γδ-T or NK cells. *Nat Commun.* 2015;6:6025.
40. Mottok A, Renné C, Seifert M, et al. Inactivating SOCS1 mutations are caused by aberrant somatic hypermutation and restricted to a subset of B-cell lymphoma entities. *Blood.* 2009;114(20):4503-4506.
41. Weniger MA, Melzner I, Menz CK, et al. Mutations of the tumor suppressor gene SOCS-1 in classical Hodgkin lymphoma are frequent and associated with nuclear phospho-STAT5 accumulation. *Oncogene.* 2006;25(18):2679-2684.
42. Juskevicius D, Lorber T, Gsponer J, et al. Distinct genetic evolution patterns of relapsing diffuse large B-cell lymphoma revealed by genome-wide copy number aberration and targeted sequencing analysis. *Leukemia.* 2016;30(12):2385-2395.
43. Ehrentraut S, Schneider B, Nagel S, et al. Th17 cytokine differentiation and loss of plasticity after SOCS1 inactivation in a cutaneous T-cell lymphoma. *Oncotarget.* 2016;7(23):34201-34216.
44. Lechner MG, Megiel C, Church CH, et al. Survival signals and targets for therapy in breast implant-associated ALK-anaplastic large cell lymphoma. *Clin Cancer Res.* 2012;18(17):4549-4559.
45. Beebe JD, Liu JY, Zhang JT. Two decades of research in discovery of anticancer drugs targeting STAT3, how close are we? *Pharmacol Ther.* 2018;191:74-91.
46. Meyer SC, Levine RL. Molecular pathways: molecular basis for sensitivity and resistance to JAK kinase inhibitors. *Clin Cancer Res.* 2014;20(8):2051-2059.
47. Goodman A, Patel SP, Kurzrock R. PD-1-PD-L1 immune-checkpoint blockade in B-cell lymphomas. *Nat Rev Clin Oncol.* 2017;14(4):203-220.
48. Di Napoli A, De Cecco L, Piccaluga PP, et al. Transcriptional analysis distinguishes breast implant-associated anaplastic large cell lymphoma from other peripheral T-cell lymphomas. *Mod Pathol.* 2018. doi: 10.1038/s41379-018-0130-7.
49. Atsaves V, Tsesmetzis N, Chioureas D, et al. PD-L1 is commonly expressed and transcriptionally regulated by STAT3 and MYC in ALK-negative anaplastic large-cell lymphoma. *Leukemia.* 2017;31(7):1633-1637.
50. Bianchi A. PD-1/PD-L1 checkpoint in breast implant-associated anaplastic large cell lymphoma: a case report. *Biomed J Sci & Tech Res.* 2018;3(2):doi: 10.26717/BJSTR.2018.03.000865.
51. Odejide O, Weigert O, Lane AA, et al. A targeted mutational landscape of angioimmunoblastic T-cell lymphoma. *Blood.* 2014;123(9):1293-1296.
52. Couronné L, Bastard C, Bernard OA. TET2 and DNMT3A mutations in human T-cell lymphoma. *N Engl J Med.* 2012;366(1):95-96.
53. Palomero T, Couronné L, Khiabanian H, et al. Recurrent mutations in epigenetic regulators, RHOA and FYN kinase in peripheral T cell lymphomas. *Nat Genet.* 2014;46(2):166-170.
54. Sakata-Yanagimoto M, Enami T, Yoshida K, et al. Somatic RHOA mutation in angioimmunoblastic T cell lymphoma. *Nat Genet.* 2014;46(2):171-175.
55. Lee YS, Filie A, Arthur D, Fojo AT, Jaffe ES. Breast implant-associated anaplastic large cell lymphoma in a patient with Li-Fraumeni syndrome. *Histopathology.* 2015;67(6):925-927.
56. Pastorello RG, D'Almeida Costa F, Osório CABT, et al. Breast implant-associated anaplastic large cell lymphoma in a Li-FRAUMENI patient: a case report. *Diagn Pathol.* 2018;13(1):10.
57. Matsushima AY, Cesarman E, Chadburn A, Knowles DM. Post-thymic T cell lymphomas frequently overexpress p53 protein but infrequently exhibit p53 gene mutations. *Am J Pathol.* 1994;144(3):573-584.
58. Petit B, Leroy K, Kanavaros P, et al. Expression of p53 protein in T- and natural killer-cell lymphomas is associated with some clinicopathologic entities but rarely related to p53 mutations. *Hum Pathol.* 2001;32(2):196-204.
59. Rassidakis GZ, Thomaides A, Wang S, et al. p53 gene mutations are uncommon but p53 is commonly expressed in anaplastic large-cell lymphoma. *Leukemia.* 2005;19(9):1663-1669.
60. Lechner MG, Lade S, Liebertz DJ, et al. Breast implant-associated, ALK-negative, T-cell, anaplastic, large-cell lymphoma: establishment and characterization of a model cell line (TLBR-1) for this newly emerging clinical entity. *Cancer.* 2011;117(7):1478-1489.
61. Prutsch N, Gurnhofer E, Suske T, et al. Dependency on the TYK2/STAT1/MCL1 axis in anaplastic large cell lymphoma. *Leukemia.* 2018. doi: 10.1038/s41375-018-0239-1.
62. Quesada AE, Medeiros LJ, Clemens MW, Ferrufino-Schmidt MC, Pina-Oviedo S, Miranda RN. Breast implant-associated anaplastic large cell lymphoma: a review. *Mod Pathol.* 2018. doi: 10.1038/s41379-018-0134-3.
63. 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):1631-1642.
64. 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;50(5):831-833.

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