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

Naoki Oishi, MD, PhD; Roberto N. Miranda, MD; and Andrew L. Feldman, MD

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. 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. In addition to its unique clinical presentation, recent studies have shown that BIA-ALCL has characteristic genetic and molecular signatures. 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. 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. ALCLs are classified based on clinical presentation and the presence or absence of a
rearrangement involving the ALK gene (or demonstration of the resultant ALK fusion protein by immunohistochemistry [IHC]).

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. 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.

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. 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.

**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. 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. 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. 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. ALK rearrangements are usually seen in the context of systemic disease, but also may occur in rare primary cutaneous ALCLs.

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. DUSP22/IRF4 rearrangements are present in up to 30% of systemic ALK-negative ALCLs and in up to 20% of primary cutaneous CD30-positive lymphoproliferative disorders, including primary cutaneous ALCL and lymphomatoid papulosis. Notably, systemic ALK-negative ALCL with DUSP22 rearrangement shows excellent overall survival similar to ALK-positive ALCL after chemotherapy. TP63 rearrangements most commonly occur as inv(3)(q26q28) generating a TBL1XR1-TP63 fusion and account for approximately 8% of ALK-negative ALCLs. TP63-rearranged ALCL shows significantly worse overall survival than ALK-positive and DUSP22-rearranged ALCLs. 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. 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.

**Genetic Events Activating the JAK-STAT3 Pathway**

The JAK-STAT pathway is frequently dysregulated in human T-cell neoplasms including ALCLs. 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-STAT3 pathway. In ALK-positive ALCLs, ALK fusion proteins have been shown to activate the JAK-STAT3 pathway by phosphorylating STAT3. In ALK-negative ALCLs, STAT3 and JAK1 mutations have been identified in up to 40% of systemic ALK-negative ALCLs and may cooccur. Most reported STAT3 mutations, including Y640F, N647I, and D661Y, affect its SH2 domain, which is necessary for receptor association and tyrosine phosphodimer formation. In contrast, JAK1 mutations, such as G1097D/S/N, predominantly affect its JH1 kinase domain. In other ALK-negative ALCLs, chromosomal rearrangements give
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 ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC. As summarized in Table 1, there have been 46 and 37 cases of BIA-ALCL examined for ALK by IHC.

Although larger studies might identify rare genetic alterations, 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.

**Gene Rearrangements and Mutations in BIA-ALCL**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Method</th>
<th>DUSP22</th>
<th>TP63</th>
<th>Matched germline DNA tested</th>
<th>JAK1</th>
<th>JAK3</th>
<th>STAT3</th>
</tr>
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<tbody>
<tr>
<td>Oishi et al7</td>
<td>FISH + IHC</td>
<td>0/36</td>
<td>0/36</td>
<td>Targeted NGS</td>
<td>No</td>
<td>1/15</td>
<td>0/15</td>
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<tr>
<td>Letourneau et al8</td>
<td>FISH</td>
<td>0/1</td>
<td>0/1</td>
<td>Targeted NGS</td>
<td>No</td>
<td>1/1*</td>
<td>0/1</td>
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<tr>
<td>Blombery et al9</td>
<td>WES</td>
<td>Yes</td>
<td>1/2</td>
<td>1/2*</td>
<td>1/2</td>
<td></td>
<td></td>
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<tr>
<td>Laurent et al10</td>
<td>FISH</td>
<td>0/9</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Di Napoli et al11</td>
<td>Targeted NGS</td>
<td>Yes</td>
<td>0/5</td>
<td>0/5</td>
<td>1/5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>0/46</td>
<td>0/37</td>
<td></td>
<td>3/23 (13%)</td>
<td>1/23 (4%)</td>
<td>6/23 (26%)</td>
</tr>
</tbody>
</table>

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-STAT 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
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.40-43 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 STAT3.4 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.44-47 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 TP53.5 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.6 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).5-7,44,60 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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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. 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.

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.

**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.

**Disclosures**

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**REFERENCES**


**Table 2. Cytogenetics of Breast Implant-Associated ALCLs**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample</th>
<th>Method</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>George et al[63]</td>
<td>Tumor cells from seroma fluid</td>
<td>Karyotyping</td>
<td>45, XX [cp19] dup(X)(q11q28),+1, del(1)(p32), 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]</td>
</tr>
<tr>
<td>Alobeid et al[64]</td>
<td>Tumor cells</td>
<td>Karyotyping</td>
<td>Highly complex abnormalities: 116-123,55M4,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)(q15.1q22.1)x3, add(12)(q24.1), +13, −14, −15, i(17)(q10), +19, −20, +1~8mar[cp13]/46,XX,inv(11)(p15.1q22.1)[7]</td>
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<tr>
<td>Lechner et al[60]</td>
<td>TLBR-1</td>
<td>Karyotyping</td>
<td>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</td>
</tr>
<tr>
<td>Lechner et al[64]</td>
<td>TLBR-2</td>
<td>Karyotyping</td>
<td>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</td>
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<tr>
<td>Lechner et al[44]</td>
<td>TLBR-3</td>
<td>Karyotyping</td>
<td>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</td>
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<tr>
<td>Blombery et al[3]</td>
<td>Effusion cytology specimen (case 1)</td>
<td>WES</td>
<td>Copy number gain of 19p, copy number loss of 1p and 10p</td>
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<tr>
<td>Blombery et al[3]</td>
<td>Effusion cytology specimen (case 2)</td>
<td>WES</td>
<td>None</td>
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</table>

ALCL, anaplastic large cell lymphoma; WES, whole exome sequencing.
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34. King RL, Dao LN, McPhail ED, et al. Morphologic features of ALK-negative anaplastic large cell lymphomas


