

# What Cytokines Can Tell Us About the Pathogenesis of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

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## Abstract

Cytokines, their receptors, and downstream signaling partners, especially JAK1/2 and STAT3, are key biomarkers in lymphoproliferative disorders including systemic anaplastic large cell lymphoma (ALCL). Here we review their role in breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). Early results suggest that, in addition to CD30, IL-9, IL-10, and IL-13 can distinguish malignant from benign seromas. IL-6 is increased in both benign and malignant seromas. IFN $\gamma$  may identify a subset of BIA-ALCL with a different clinical course. Immunohistochemical detection of nuclear transcription factors—which regulate cytokine signaling—and phosphorylated janus kinases/signal transducers and activators of transcription can inform the identification and malignant potential of CD30+ cells. The innate immune response is the first line of defense against microbes suspected to initiate BIA-ALCL. Innate lymphoid cells are grouped according to the cytokines they produce and could potentially be identified as precursors to BIA-ALCL. Cytokines modulate the tumor microenvironment and hence the pathology of BIA-ALCL such as the influx of eosinophils and capsular fibrosis mediated by IL-13. The plasticity of T cells and innate immune cells theoretically can enable therapeutic manipulations toward a less aggressive phenotype. Cytokine receptors targeted in clinical trials of inflammatory and autoimmune disorders could afford opportunities for immunotherapy of BIA-ALCL.

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This review is intended to bring the readers' attention to the importance of cytokines in the pathogenesis of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). We will discuss the influence of cytokines on the microenvironment of tumor cells and how they thereby play a major role in determining the histopathology of BIA-ALCL. We discovered that the neoplastic cells produce a restricted group of cytokines that should help to clarify the cellular origin of BIA-ALCL. The detection of select cytokines in malignant but not benign seromas is being investigated as a strategy for early diagnosis, clinical follow-up, and novel therapies. The following outline describes the specific topics that will be addressed.

1. Definition of cytokines
2. Cytokine receptors bind cytokines and activate downstream kinases
3. Cytokine expression is regulated by transcription factors
4. Cytokines are produced by immune cells

5. T lymphocytes and innate lymphoid cells can alter their cytokine profile in a phenomenon called context-dependent plasticity
6. Cytokines shape the tumor microenvironment
7. Cytokines can be growth factors for tumor cells
8. Cytokines for the diagnosis of ALCL
9. Therapies targeting cytokines or their receptors

## Definition of Cytokines

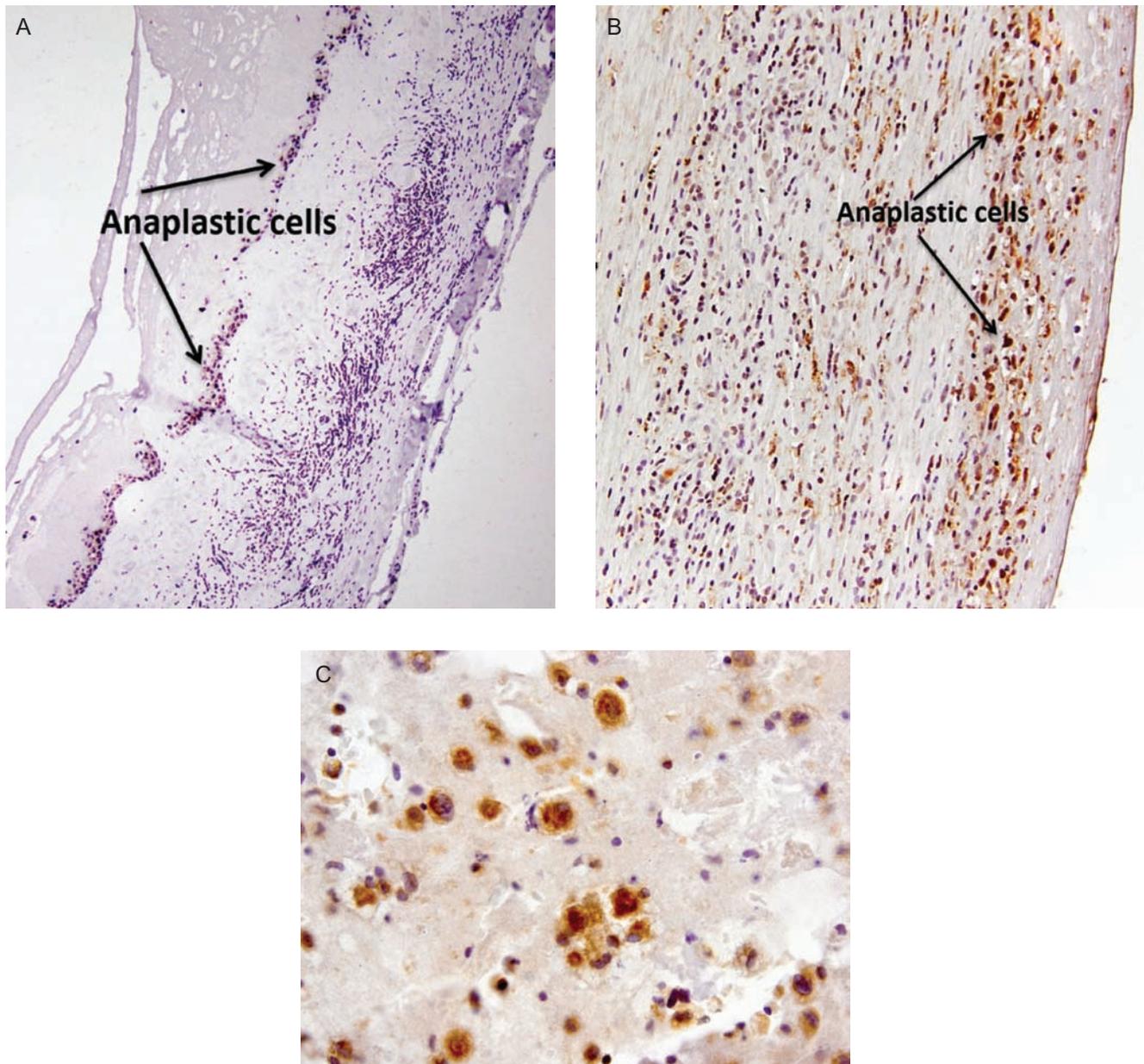
Cytokines are small signaling proteins produced and released primarily by immune cells, but also stromal and epithelial cells, that regulate immune responses to external

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**Figure 1.** Anaplastic cells, but not small lymphocytes, express (A) janus kinase-1, (B) pSTAT3 (200x), and (C) suppressor of cytokine signaling 3 (600x).

stimuli and attract cells to sites of inflammation. We will show that the neoplastic cells of BIA-ALCL have properties of immune cells that release cytokines shaping the microenvironment of BIA-ALCL.

### **Cytokine Receptors Bind Cytokines and Activate Downstream Kinases**

Cytokine signaling plays a key role in the pathogenesis of BIA-ALCL, as first described by Lechner et al<sup>1</sup> and amplified by Chen et al.<sup>2</sup> Many cytokines involved in the pathogenesis of autoimmune and inflammatory diseases utilize

janus kinases (JAKs) and signal transducers and activators of transcription (STATs) to transduce intracellular signals.<sup>3</sup> Cytokine signaling requires high-affinity membrane receptors. Upon interaction with cognate cytokines, receptors undergo conformational changes that activate associated JAKs and downstream signaling pathways including STATs. Phosphorylated STATs dimerize and translocate to the cell nucleus, where they initiate gene transcription. Recent studies have revealed recurrent mutations of JAKs and STATs in BIA-ALCL.<sup>2,4,5</sup> These mutations result in the over-expression of phosphorylated JAKs and STATs in the nuclei of neoplastic cells, as illustrated in Figure 1. Cytokine

**Table 1.** Lymphoid Cell Transcription Factors, Cytokines, and Functions

Cell type	Th1/ILC1	Th2/ILC2	Th17/ILC3	Treg	Th9	Th22	Tfh
Transcription factor	Tbet	GATA3	RORC ( $\gamma$ t)	FoxP3	PU.1	AhR	Bcl-6
Main cytokines produced	IFN $\gamma$ , TNF $\alpha$	IL5, IL4, IL13	IL17A, IL17F, IL21, IL22, IL26	IL10 TGF $\beta$	IL9	IL22	IL2 IL10 IFN $\gamma$
Main functions	Innate pathway Intracellular immunity	Humoral immunity Response to extracellular pathogens Allergy	Response to fungi, extracellular bacteria	Immune suppression Tolerance	Defense against helminth infections, chronic allergic inflammation	Synergize with Th17 cells to promote innate immunity in skin, GI and respiratory tracts	Regulate antigen-specific B cell immunity
Tissue manifestation	Neutrophils Dendritic cells	Eosinophils Plasma cells Fibrosis	Neutrophils Macrophages		Eosinophils	Tissue repair	B cell follicles

AhR, aryl-hydrocarbon receptor; GI, gastrointestinal; ILCs, innate lymphoid cells; Th, T helper cells.

signaling is modulated by specific inhibitor proteins known as suppressors of cytokine signaling, which have also been demonstrated to be active in BIA-ALCL (Figure 1).

### Cytokine Expression Is Regulated by Transcription Factors

A list of transcription factors and the cytokines they regulate is shown in Table 1. More than one transcription factor may be operative within a cell, so cytokine expression depends on the dominance of one transcription factor. Transcription factors are mainly intranuclear and are a convenient target to identify cells by immunohistochemistry. Utilizing immunohistochemistry together with morphology, one can assign certain transcription factors and cytokines to neoplastic cells vs nonmalignant cells. Thus, a neoplastic cell expressing both GATA3 and IL-4 or IL-13 can be assigned to the Th2 or ILC2 lineage, whereas one expressing Tbet and IFN $\gamma$  should belong to the Th1/ILC1 lineage. The Th17 cytokine IL-21 (IL-17E) has been detected by us in malignant seroma fluids and is supernatant of TLBR1 cell culture. IL-26 was reported to be produced by neoplastic cells in BIA-ALCL by Suzanne Turner, PhD, Cambridge University, UK (Allergan Advisory Board Meeting, April 31, 2018, New York, NY).

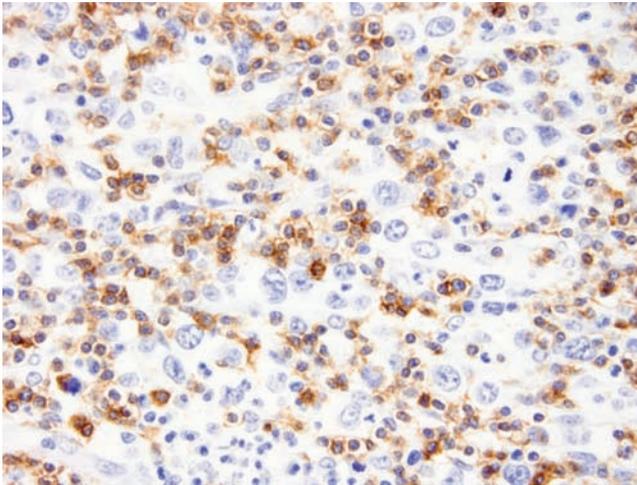
### Cytokines Are Produced by Immune Cells

Cytokines are produced by cells of innate and adaptive immunity. The innate immune system is responsible for the first response to microbial challenges. Hu et al<sup>6,7</sup> have demonstrated that Gram-negative bacteria are likely to initiate an immune response as an early step in the pathogenesis of BIA-ALCL. The innate immune system includes lymphoid cells, macrophages, dendritic cells, mast cells, basophils, neutrophils, and eosinophils. ILC

lymphoid subsets are considered to belong to the same family that includes natural killer (NK) cells because they all rely on the common  $\gamma$ -chain of the IL-2 receptor for their development and function and depend on the transcriptional repressor Id2 for their development.<sup>8,9</sup> Both IL-4 and IL-13 are produced by type 2 innate lymphoid and CD4<sup>+</sup> Th2 cells.<sup>10</sup> However, basophils, mast cells, CD8<sup>+</sup> Th cells, eosinophils, and NK cells can also secrete these cytokines.<sup>9-11</sup> Adaptive immunity is the province of memory lymphocytes. In BIA-ALCL, the neoplastic cells clearly are lymphoid cells. It has been assumed that the neoplastic cells are derived from T lymphocytes. However, the neoplastic cells lack surface antigen receptors, which is a characteristic of innate lymphoid cells and NK cells. Our laboratory has shown that the neoplastic cells of BIA-ALCL have low levels of RNA transcripts for TCR $\alpha$  and TCR $\beta$ . By flow cytometry, we detected TCR $\beta$  within the cytoplasm of TLBR cell lines, albeit at low levels, but not on the cell surface. In clinical samples, we detected no expression of TCR $\beta$  on or within neoplastic cells utilizing immunohistochemistry (Figure 2). Schleussner et al<sup>12</sup> recently reported that neoplastic cells in ALK<sup>+</sup> systemic ALCL may be derived from ILC3 cells. Thus, it remains subject to further investigation whether BIA-ALCL cells are derived from innate lymphoid cells, NK cells, or immature T lymphocytes.

Cytokines are also produced by stromal cells including endothelial cells, fibroblasts, and adipocytes, which I herein distinguish from nonlymphoid innate immune cells (eg, mast cells, basophils, eosinophils, macrophages, and other dendritic cells).

To determine whether specific cytokines produced by inflammatory and stromal cells instead of neoplastic cells can be approached by immunohistochemistry of involved tissues, by investigation of neoplastic cell culture supernatants and flow cytometry of seroma fluids. In this manner,



**Figure 2.** Small nonmalignant T cells, but not large anaplastic cells, in breast implant-associated anaplastic large cell lymphoma express the T cell receptor beta framework antigen (600x).

we have shown that neoplastic cells specifically can produce IL-13, IL-4, IFN $\gamma$ , and IL-17F.<sup>13,14</sup> At the same time, we found that IL-6, which is produced by neoplastic cells, is likely also produced by nonneoplastic cells demonstrated by high IL-6 levels in benign late seromas. We plan further studies to localize specific cytokines to neoplastic cells in seromas by flow cytometry and confocal immunofluorescence microscopy.

### Cytokines of T Lymphocytes Are Subject to Context-Dependent Plasticity

The functional phenotype of T cells is modulated by external cytokine signals in a phenomenon referred to as context-dependent plasticity.<sup>15</sup> Phenotypic changes result from repolarization of T cells under the influence of cytokines. Plasticity is especially noteworthy for Th17 cells, which have reciprocal relationships with Th1 cells and regulatory T cells. IL-6, combined with TGF- $\beta$ , preferentially induces the differentiation of naïve CD4-positive T cells into Th17 cells, whereas IL-6 inhibits TGF- $\beta$  induced Treg development. As a consequence, Th17/Treg imbalance may cause the onset and progression of autoimmune and chronic inflammatory diseases.<sup>16</sup> Th17 polarization is associated with higher in vivo survival and self-renewal capacity and less senescence than Th1 polarized cells, which have less plasticity and more phenotypic stability.<sup>17</sup> It is interesting to speculate and test the hypothesis that tumors that derive from neoplastic Th17 cells have a more aggressive phenotype than those derived from Th1 cells and repolarization of neoplastic cells toward Th1 could provide therapeutic opportunities.

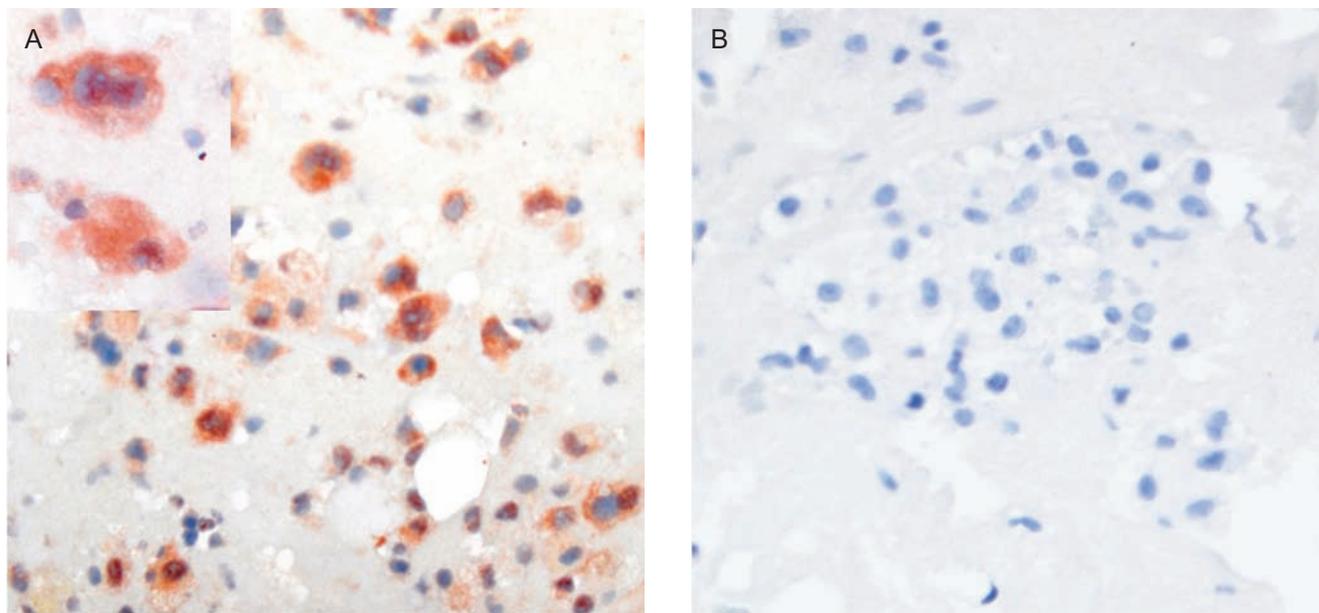
Th1 and Th17 cells can be repolarized to lose expression of their characteristic cytokines IFN- $\gamma$  and IL-17A, respectively, and acquire expression of Th2 cytokine IL-4.<sup>18</sup> This plasticity may contribute to protection against microbes in development of BIA-ALCL.<sup>6</sup> Interferons can direct CD4 + Th2 cells to differentiate into a stable subset of IL-17-producing T<sub>H</sub>2 cells that coexpress GATA3 and ROR- $\gamma$ t in severe chronic allergic inflammation with mixed neutrophilic and eosinophilic infiltrates as found in BIA-ALCL.<sup>19</sup> We have described neoplastic cells producing IL-17F<sup>13</sup> and Th2 cytokine IL-13 associated with allergic inflammation in BIA-ALCL.<sup>14</sup> IL-9 also is associated with allergic inflammation and asthma,<sup>20</sup> and has been associated with the pathogenesis of systemic ALCL.<sup>21</sup> We detected IL-9 in BIA-ALCL (TLBR) cell culture supernates and malignant but not benign late seromas, indicating it is produced by the neoplastic cells.

MicroRNAs influence T lymphocyte development, differentiation, and function.<sup>22</sup> Th17 differentiation is promoted by microRNA-132-212 cluster induced by the aryl-hydrocarbon receptor (AhR).<sup>23</sup> We detected AhR activity in anaplastic cells, and therefore the AhR may play a role in BIA-ALCL (Figure 3).

### BIA-ALCL Cells Potentially Can Be Assigned to Th/ILC Subsets According to the Cytokines They Produce

Both innate lymphoid cells and memory T lymphocytes have been categorized according to the cytokines they produce (Table 1). Our studies and those of others suggest that it is possible to assign neoplastic cells in BIA-ALCL to one or more categories of cytokine-producing cells. This may reveal some heterogeneity in the cellular origin of neoplastic cells (ie, some may be derived from Th1/ILC1, Th2/ILC2, or Th17/ILC3 cells). Accordingly, specific subsets may be associated with a different pathophysiology and prognosis.

An attractive candidate for BIA-ALCL lineage is ILC1/NK cells, which do not express the TCR or CD3 and contain granzyme and perforin.<sup>8</sup> IL-13+ and IFN $\gamma$ + subsets have been identified in adult and neonatal NK cells.<sup>24</sup> Nonmalignant NK cells appear to develop from immature CD56(-)IL-13(+) and to mature CD56(+)IL-13(-) IFN- $\gamma$ (+) NK cells.<sup>25</sup> Differentiation of CD56(-)IL-13(+) NK cells is supported by IL-4 and inhibited by IL-12. CD56(+)IL-13(-) IFN- $\gamma$ (+) NK cells are induced by IL-12 and inhibited by IL-4 and IL-13. We have detected elevated levels of IL-13 or IFN $\gamma$  in supernatants of BIA-ALCL cell cultures and some malignant seromas, consistent with their production by neoplastic cells derived from these NK subsets.



**Figure 3.** (A) Anaplastic cells express cytoplasmic and nuclear Aryl hydrocarbon receptor in this case of breast implant-associated anaplastic large cell lymphoma (400x, upper left inset 1200x). (B) Control omitting primary antibody.

### Cytokines Shape the Tumor Microenvironment

Cytokines (and chemokines) affect the recruitment of other cells and stimulate cell growth. For example, IL-13 secreted by neoplastic cells in BIA-ALCL appear to cause fibrosis and the accumulation of eosinophils found in capsules and lymph nodes affected by BIA-ALCL (Figure 4).<sup>14</sup> In the same manner, IL-13 is secreted by Hodgkin's lymphoma cells, which are often surrounded by eosinophils and bands of fibrous tissue.<sup>26</sup> IL-13 positive small lymphocytes were also detected in some involved capsules and in 3 of 32 capsules without ALCL compared with 14 of 15 involved capsules or lymph nodes ( $P < 0.001$ ). IL-13 was also detected in supernatants of TLBR1, TLBR2, and TLBR4 cell cultures and 4 of 5 malignant seromas but in none of 5 benign seromas tested thus far, suggesting that IL-13 may be part of a panel for the diagnosis of malignant seromas. Whether plasma/serum IL-13 is elevated in patients with malignant seromas remains to be evaluated. IL-9 also is associated with tissue eosinophilia and allergic inflammation<sup>27</sup> and is produced by neoplastic cells in BIA-ALCL cell cultures and malignant seromas (unpublished data).

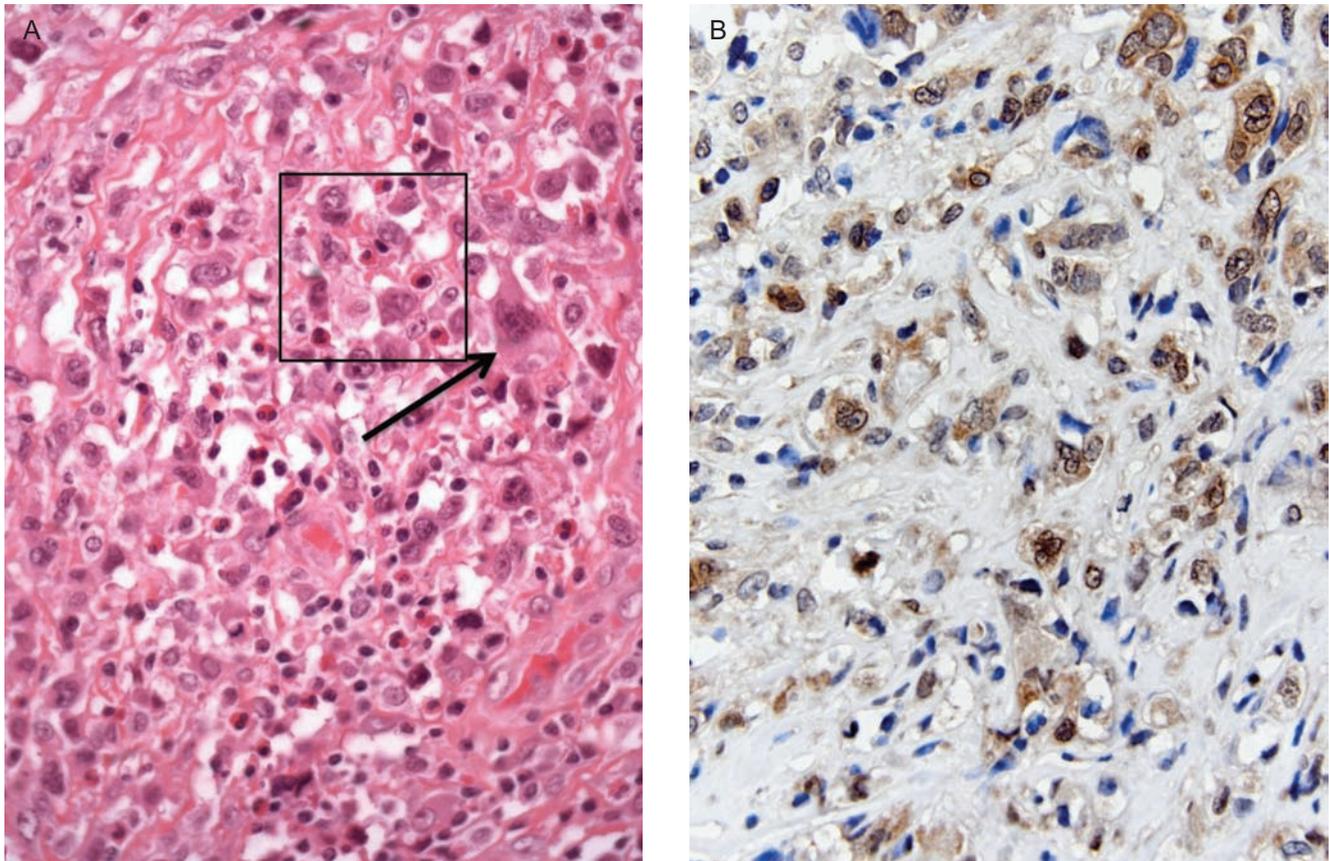
### Cytokines as Growth Factors for Neoplastic Cells

IL-13 is an autocrine growth factor for neoplastic cells in Hodgkin's lymphoma, mycosis fungoides, and NK/T

cell lymphomas.<sup>28-30</sup> Whether IL-13 is also an autocrine growth factor for BIA-ALCL has not yet been determined. IL-9 has been shown to be an autocrine growth factor for ALK+ ALCL but has not yet been evaluated for growth regulation of BIA-ALCL.<sup>31</sup>

### Therapies Targeting Cytokines, Their Receptors, and Downstream Kinases

Targeting IL-4/IL-13 signaling has been effective in Hodgkin's lymphoma and mycosis fungoides.<sup>29,32</sup> Dupilumab, a fully human monoclonal antibody targeting IL-4/IL-13 signaling, has been effective in clinical trials treating severe asthma<sup>33</sup> and atopic dermatitis,<sup>34</sup> and it could be considered for the treatment of BIA-ALCL. IL-6 has been proposed as a driving cytokine in BIA-ALCL, but neutralization did not significantly inhibit *in vitro* growth.<sup>1</sup> Nevertheless, clinical trials targeting IL-6R with a humanized monoclonal antibody, tocilizumab, have shown promise in chronic inflammatory, autoimmune, and lymphoproliferative diseases (eg, rheumatoid arthritis and Castleman's lymphoproliferative disease<sup>35</sup>). IL-6 targeted therapy, while not effective in overt malignancy, might be effective in developing BIA-ALCL. Another approach is directed against the downstream effects of IL-6 signaling, namely JAK/STAT signaling. Ruxolitinib, a JAK1/2 inhibitor, is effective in suppressing the growth of BIA-ALCL lines<sup>2</sup> and patient-derived systemic ALCL xenografts.<sup>36</sup> Targeted suppression of JAK/STAT signaling in a pre-clinical model is under investigation (Giorgio Inghirami,



**Figure 4.** Anaplastic cells (arrow) surrounded by eosinophils (rectangle) and fibrosis (A), IL-13-brown stain (B) (400x).

Weill-Cornell Medical Center, New York, NY, personal communication, August 18, 2018).

### **Cytokines and Their Receptors Can Be Utilized for the Diagnosis of BIA-ALCL**

CD30 is a hallmark antigen for BIA-ALCL. CD30 is a member of the tumor necrosis factor receptor superfamily.<sup>37</sup> A recent study showed the effectiveness of CD30 ELISA for screening of delayed seromas for BIA-ALCL.<sup>38</sup> Our preliminary studies show promising results for cytokine utilization in diagnosis and patient screening for BIA-ALCL. Specifically, we found that IL-9, IL-10, and IL-13 are elevated only in malignant, not benign, late seromas, although the number of cases is still too small to be significant. Interestingly, IL-6, which is thought to be a driver of malignancy, is observed to be elevated in both benign and malignant seromas, possibly supporting the concept of BIA-ALCL as the malignant end of a progressive lymphoproliferative disorder. Because IL-6 is a driver of chronic inflammation, which is agreed to be the context within which BIA-ALCL develops, it will be important to identify biomarker(s) that appear early in the development of overt malignancy. Possible biomarkers include nuclear JUNB,

SATB1, ERK1/2, and pSTAT3.<sup>13</sup> Support for the concept of BIA-ALCL as part of a lymphoproliferative disorder includes late onset from prosthesis implantation, CD30+ cells in some late benign seromas,<sup>39</sup> chronic clinical course, and similarities in morphology and immunophenotype to cutaneous ALCL, which is preceded by spontaneously healing skin lesions of lymphomatoid papulosis.<sup>40</sup> Within CD30+ cutaneous lymphoproliferative disorders, IL-6 serum levels correlate with soluble CD30 serum levels, and elevated serum IL-6 and CD30 are associated with an unfavorable prognosis.<sup>41</sup>

### **CONCLUSIONS**

Cytokines are key mediators of intercellular signaling and can serve as autocrine growth factors for neoplastic cells. Cytokine-receptor complexes activate associated JAKs to initiate various downstream signaling pathways, including STATs, that dimerize and translocate to the nucleus, where they influence transcription to mediate key phenotypic changes in the cell. Cytokines shape the tumor microenvironment through effects on neighboring cells. Cytokines and their receptors can be utilized as distinctive markers to identify lymphoid cells and their derivative neoplastic

counterparts. They may also serve as targets for novel therapies. Measurement of select cytokines (IL9, IL-10, IL13, IFN $\gamma$ ) and their receptors (eg, CD30) in late seromas can provide an approach for patient screening for BIA-ALCL.

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