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Letters

MBN 2016 Aesthetic Breast Meeting BIA-ALCL Consensus Conference Report

Sir:

GENETIC MARKERS FOR EARLY DETECTION OF BREAST IMPLANT–ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA IN PLASTIC SURGERY PROCEDURES

We read with great interest the article written by Nava et al.,[1] recently published as a Special Topic article in *Plastic and Reconstructive Surgery* entitled "MBN 2016 Aesthetic Breast Meeting BIA-ALCL Consensus Conference Report." This study focuses on the current pathogenesis, diagnosis, and therapy of breast implant–associated anaplastic large cell lymphoma (BIA-ALCL).

Because BIA-ALCL is a rare type of lymphoma, the pathogenesis of this disease is still not clear, and few clinical data are available.[2] A panel of experts in breast plastic surgery, to improve the production of reliable scientific data, emphasize the need for a consensus "patient registry" document of all new BIA-ALCL cases diagnosed, reporting safety, medical devices, follow-up, and other factors.[1]

We are confident that the actions proposed in the conference report will help the management of BIA-ALCL. Moreover, it is also important to differentiate a simple T-lymphocytosis with no malignant $CD30^+$ lymphocytes from BIA-ALCL early. The early detection is finalized to prevent the risk of lymph node involvement and systemic spread. Currently, the diagnosis of BIA-ALCL is based on the characterization of serum cellular population by the cytologic smear and CD30 status detected by immunocytofluorimetric assays, but this information is not sufficient to support an early diagnosis of BIA-ALCL. Moreover, although the factors leading to anaplastic cell progression are still unclear, the identification of genetic markers underlying the development of neoplastic T-cell diseases is now possible.[3] Here, we report a panel of somatic mutations, known to be associated with malignant transformation of normal T-lymphocytes in anaplastic large T cells (Table 1).

The majority of cases (74 to 90 percent) show clonal rearrangement of *TCR* genes and other genetic variants.[3] Moreover, gene expression profiling studies suggest that ALCL-anaplastic lymphoma kinase–negative lymphoma is different from anaplastic lymphoma kinase–positive lymphoma. Recently, the translocation involving the *DUSP22* gene, t(6;7)(p25.3;q32.3), was found in ALCL-anaplastic lymphoma kinase–negative BIA-ALCL cases. The 6p25.3 translocation inactivates *DUSP22*, a dual-specificity phosphatase that inhibits ERK1/2 signaling in T cells leading to loss of tumor-suppressor function.[4]

Specific evaluation of known genetic variants (mutations) in patients with a late onset, persistent periimplant seroma will help to early differentiate patients with nonmalignant $CD30^+$ T-lymphocytosis from those carrying potential neoplastic T cells.[4] In case of BIA-ALCL patients, this platform must be able to detect low mutant T cells in the wide range of wild-type cells.[5] Available methods for the detection of known point mutations and small deletions or insertions are summarized in Table 2.

We believe that this diagnostic approach will contribute to early diagnosis of BIA-ALCL in seroma samples and to a better understanding of the transformation of normal T-lymphocytes into ALCL of patients with BIA-ALCL, and it may be helpful in designing the most appropriate approach for patient management and personalized therapy. In this scenario, the present process is a multifaceted task that needs the successful cooperation of the clinicians, surgeon, and laboratory manager to develop diagnostic strategies suitable for early diagnosis and eventually personalized therapy.

DOI: 10.1097/PRS.0000000000005015

Table 1. Common Genetic Variants at the Molecular Level Found in ALCL

Genes	Molecular Effect	Clinical Effect
DUSP22	Rearranged in ~30% of cases; variable partners (*FRA7H* most common); associated with favorable prognosis	Clinicopathologic features, including presentation as localized crops of papules; cytologically, large transformed cells in the dermis with smaller atypical cells infiltrating the epidermis, and biphasic staining intensity for CD30 (weaker in the epidermal component)
TP63	Rearranged in ~8% of cases; variable partners	(*TBL1XR1* most common); associated with poor prognosis
Higher expression *BATF3*, *CCND2*, *CCR7*, *CD80*, *CD86*, *CNTFR*, *IL21*, *IL22*, *MSC*, *POPDC3*, *TMEM158*, *TMOD1*, *TNFRSF8*, *ZNF267*		Gene expression profiling has not yet found routine clinical use for ALCL; it has had a clear impact on elucidating ALCL biology
Low expression *CDKN2D*		As above
TCR rearrangements	Rearranged in all BIA-ALCL patients; the test is suitable to identify clonal T-cell expansion	Identification of the TCR αβ/γδ rearrangement is useful for diagnosis and monitoring either the lymphocytosis or BIA-ALCL

Table 2. Widely Used Methods for Genotyping at the Molecular Level

Gel-based detection
Allele-specific amplification
Restriction fragment length polymorphism
Single strand conformation polymorphism
Peptide nucleic acid-mediated clamping PCR
Fluorescent-based detection
FRET probe allelic discrimination (Hyb Probe TaqMan, Beacons, Scorpions)
Locked nucleic acid probe
Invader assay
Pyrosequencing*
High-resolution melting
High-throughput sequencing
Next-generation sequencing
MALDI-TOF mass spectroscopy
Sanger-based conventional sequencing

PCR, polymerase chain reaction; FRET, fluorescence resonance energy transfer; MALDI, matrix-assisted laser desorption/ionization; TOF, time of flight.
*Required pre–polymerase chain reaction step.

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DISCLOSURE

Dr. Santorelli is a consultant and speaker for Allergan, Inc. (Irvine, Calif.). The other authors declare no potential conflicts of interest with respect to the research, authorship, and publication of this communication.

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Reply: MBN 2016 Aesthetic Breast Meeting BIA-ALCL Consensus Conference Report

Sir:

We would like to thank Dr. Santorelli and colleagues for their interest in our consensus conference article.[1] They assert the the diagnosis of breast implant–associated anaplastic large cell lymphoma (BIA-ALCL) based solely on cell morphology on cytology and CD30 immunohistochemistry is not completely sufficient to reliably diagnose BIA-ALCL. As an alternative, Dr. Santorelli et al. propose screening for genetic markers underlying the development of neoplastic T-cell diseases. They report several somatic mutations associated with malignant transformation with several other forms