Diagnosis of Breast Implant Associated ALCL by Analysis of Cytokines in Peri−implant Seromas

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Abstract

Background & Aim: Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA−ALCL) has been recently recognized by the World Health Organization as a T−cell lymphoma associated with breast implants of women after reconstructive surgery for breast cancer, prophylactic mastectomy because of high genetic risk for breast cancer, or cosmetic reasons. Patient survival is significantly improved by detection of BIA−ALCL when remaining localized to an effusion/seroma and lining of the peri−implant capsule. Benign seromas are more common and must be distinguished from BIA−ALCL for patient management.,

Methods: To address the need for early detection of BIA−ALCL, we evaluated 55 cryopreserved peri−implant effusions diagnosed as malignant (25 BIA−ALCL samples) or benign (30 samples including 10 contralateral samples. Seromas were analyzed by flow cytometry for concentration of cytokines IL−2, 4, 5, 6, 9, 10, 13, 17A, 17F, 22, IFN.. and TNFa with the LEGENDplex Human 12−plex T helper (Th) Cytokine Panel (BioLegend, San Diego, CA).

Results: Mean levels of IL−9, IL−10 and IL−13 were elevated 72−, 716− and 22−fold, respectively, in BIA−ALCL compared to benign effusions, and each cytokine separated the two groups with little overlap ($P < 0.0001$). Receiver Operating Characteristic (ROC) curve analysis indicated that each of the three cytokines differentiated between BIA−ALCL and benign samples (Figure 1C), with sensitivity, specificity and Youden's J index, respectively, comprising 0.96/0.8/0.76 for IL−9; 0.92/1.0/0.92 for IL−10, and 0.76/0.97/0.72 for IL−13 therefore giving IL−10 the best predictive diagnostic value.

Conclusion: This study of seroma cytokines in the largest cohort of patients to date shows the diagnostic utility of this approach for detection of early−stage BIA−ALCL. IL−10 was found to have the highest predictive value. The cytokine profile of seromas in BIA−ALCL is distinct from that detected in sera of pediatric and adult patients with systemic ALK+ ALCL which supports the unique pathophysiology of BIA−ALCL.

Clinical Implications: Diagnosis of limited stage disease in seromas permits curative surgery avoiding cytotoxic therapy.

Table 1. Cytokine concentration in BIA-ALCL and benign seroma samples

Cytokine	ALCL Cytokine concentration, pg/ml (mean ± SD) N = 25	Non-ALCL Cytokine concentration, pg/ml (mean ± SD) N = 30	P value*
IL-6	43046 ± 90242	104550 ± 207368	0.2118
IL-9	35839 ± 58465	495 ± 2047	<0.0001
IL-10	17900 ± 27907	25 ± 22	<0.0001
IL-13	8096 ± 11852	369 ± 1467	<0.0001
IFNγ	773 ± 1850	111 ± 373	0.0109
IL-4	41 ± 59	64 ± 170	0.7026
IL-17A	6 ± 14	5 ± 7	0.7874
IL-17F	5 ± 9	7 ± 14	0.3649
IL-22	15278 ± 72967	35 ± 78	0.3681
TNFα	125 ± 260	122 ± 314	0.0658
IL-5	71 ± 129	137 ± 385	0.3822
IL-2	13 ± 26	8 ± 26	0.0814

*Mann-Whitney test