



CLINICAL RELEVANCE OF NKT CELLS AND SOLUBLE MIC-A IN HODGKIN LYMPHOMA

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BACKGROUND

Hodgkin lymphoma (HL) is a neoplastic lymphoid disease characterized by the presence of a scarce number of Reed-Stenberg (HRS) malignant cells (1). Most of these patients achieve response after treatment, but 5-10% of them become refractory (2). It is very important in this fraction of patients to understand the mechanisms used by malignant cells to avoid the anti-tumoral immune response and consequently, the development of resistance to any treatment modality (3). Innate and adaptive immune responses are crucial in the pathophysiology of the disease (6), unfortunately, in HL patients, these cells within the tumor are mainly exhausted and dysfunctional (10). One of the most important cells in the tumor environment are the NK cells [13]. It has been demonstrated that some signaling pathways are downregulated in NK cells of HL patients that may explain the impaired function of these cells and a possible mechanism of deficient immune surveillance in this disease [14]. MHC class I chain-related proteins A and B (MIC-A and MIC-B) are present on the surface of some cancer cells and naturally bind to its receptor NKG2D expressed on NK cells, $\gamma\delta$ T cells, and CD8+ lymphocytes, inducing a cytotoxic and anti-tumoral response; however, MIC-A and MIC-B can be shed by tumor cells in their soluble form (sMIC-A and sMIC-B), a phenomenon that may impair the anti-tumoral effect of lymphocyte subsets, contributing to tumor escape by HRS cells [15]. By the other hand, studies attempting to analyze the number and function of lymphocyte subsets in peripheral blood of HL patients are limited.

OBJETIVE: The aim of this study was to evaluate the number of peripheral blood lymphocyte subsets, and sMIC-A, and sMIC-B in patients with newly diagnosed HL in comparison to healthy controls.

MATERIALS & METHODS

Between August 2008 and August 2010, 36 patients with newly diagnosed HL and 72 healthy donors were included in the study. All patients were treated with conventional chemotherapy (ABVD regimen) and were followed-up until death, lost to follow-up, or last medical visit (August 18, 2020), using their electronic files.

Peripheral blood samples with EDTA anticoagulant were obtained from patients prior chemotherapy for the analysis of Lymphocyte subsets [CD4+, CD8+ T cells, NK, NKT, invariant NKT (iNKT) cells, type 1 and 2 dendritic cells, $\gamma\delta$ T cells, regulatory T cells, and B cells] by flow cytometry using monoclonal antibodies. Soluble MIC-A and MIC-B were analyzed in the plasma separated from the same anticoagulated blood sample by ELISA technique using the RayBio Human MIC-A and MIC-B ELISA Kit. Samples from healthy donors (HD) who underwent the same determinations were included as controls. Statistical analysis was performed using the SPSS software (Chicago, IL 19 v).

RESULTS

After chemotherapy, 30 (83%) patients achieved complete remission, four (11%) partial remission, and two (6%) patients had failure to treatment. CD4 T lymphocytes, B cells, monocytes, NK, and NKT cells were decreased in patients with HL in comparison to healthy controls. By contrast, $\gamma\delta$ T cells were increased in patients with HL. sMIC-B and sMIC-A serum levels were significantly increased in patients with HL vs controls.

The median progression-free survival (PFS) was 86 months. PFS was better in patients who had sMIC-A <100ng/mL (1A) and NK cell numbers above 150 μ L (1B). PFS was lower in patients with B cell counts <40 μ L (1C, P<0.05) and monocyte counts <75 μ L (P<0.03, 1D). PFS was worse in patients having NKT cells >40 μ L (2E, P<0.05).

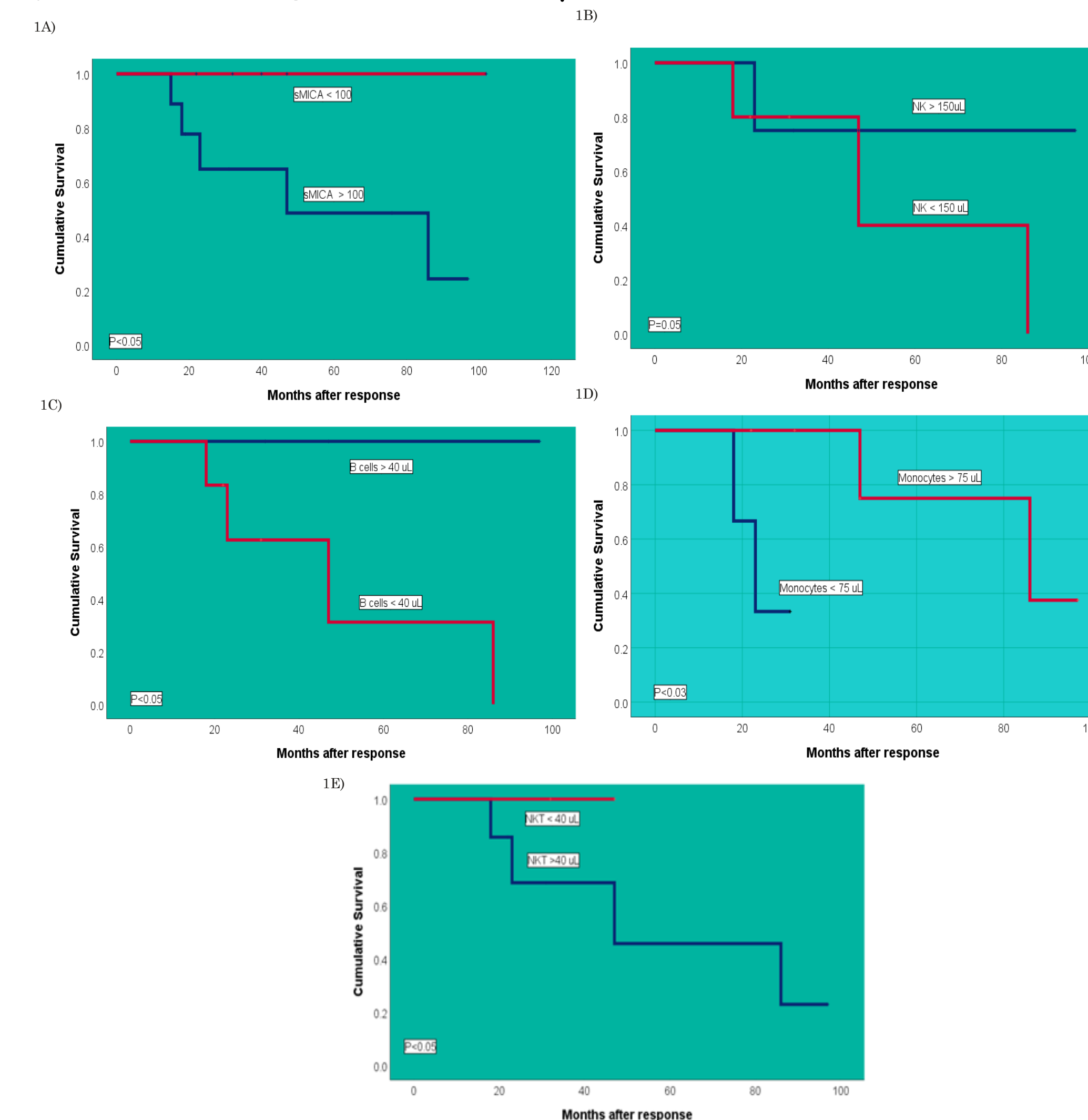


Figure 1. PFS in patients who had soluble MIC-A >or< 100 ng/mL (1A), peripheral blood NK cells >or< 150 μ L (1B), peripheral blood B cells >or< 40 μ L (2C), peripheral blood monocytes >or< 75 μ L (2D), or peripheral blood NKT cells >or< 40 μ L (2E).

Overall survival (OS) was better in patients with sMIC-A values <100 ng/mL and NKT cells < 40 μ L.

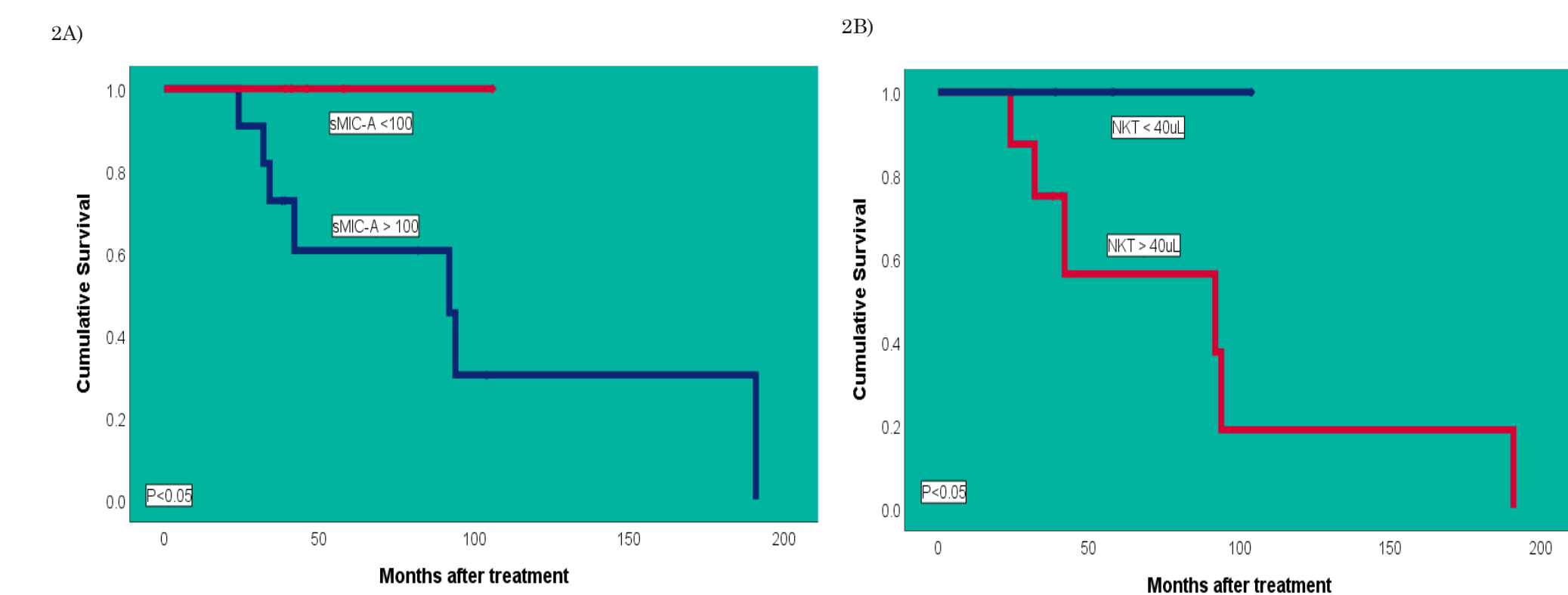


Figure 2. OS in patients who had soluble MIC-A >or< 100ng/mL (2A), and peripheral blood NKT cells >or< 40 μ L (2B).

CONCLUSIONS

In conclusion, peripheral blood CD4 T lymphocytes, B cells, monocytes, NK, and NKT cells were decreased in patients with HL in comparison to healthy controls. By contrast, s-MIC-A and peripheral blood $\gamma\delta$ T cells were found increased in HL patients. s-MIC-A, peripheral blood NK cell, B cell, monocyte, and NKT cell numbers had prognostic significance for PFS and s-MIC-A and peripheral blood NKT cell numbers had clinical relevance for OS. These findings may contribute, at least in part, with the explanation of many different mechanisms of tumor scape of immune surveillance in this disease.

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