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CASE REPORT

Aberrant expression of CD56 by circulating Sézary syndrome malignant T lymphocytes

Nicolas Thonnart, Caroline Ram-Wolff, Martine Bagot, Armand Bensussan, Anne Marie-Cardine

Nicolas Thonnart, Martine Bagot, Armand Bensussan, Anne Marie-Cardine, INSERM U976, Saint Louis Hospital, 75010 Paris, France
Nicolas Thonnart, Martine Bagot, Armand Bensussan, Anne Marie-Cardine, University Paris Diderot, Sorbonne Paris Cité, 75013 Paris, France
Caroline Ram-Wolff, Martine Bagot, AP-HP, Department of Dermatology, Saint Louis Hospital, 75010 Paris, France
Author contributions: Marie-Cardine A designed the report and interpreted the data; Thonnart N performed the experiments; Ram-Wolff C and Bagot M were attending doctors for the patients; Ram-Wolff C, Bensussan A and Marie-Cardine A wrote the paper; Thonnart N and Ram-Wolff C equally contributed to this work.
Correspondence to: Dr. Anne Marie-Cardine, INSERM U976, Saint Louis Hospital, 1 avenue Claude Vellefaux, 75010 Paris, France. anne.marie-cardine@inserm.fr
Telephone: +33-1-53722050 Fax: +33-1-53722051
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Abstract

Sézary syndrome (SS) is an aggressive variant of cutaneous T cell lymphoma characterized by the presence of malignant T cells in the skin, peripheral blood and lymph nodes. The tumoral population typically displays a $CD3^+$ $CD4^+$ $CD45RO^+$ memory T cell phenotype. We report a case of SS with an aberrant $CD56^+$ immunophenotype. This patient presented with a generalized erythroderma and palpable small axillary lymph nodes. SS (stage IVA) was diagnosed on histological criteria and by the detection of a major T cell clone in skin and blood, an elevated CD4/CD8 T cell ratio and Sézary cells count > 1000/mm^3. Beside the Sézary cell marker KIR3DL2, immunostainings revealed that two third of the malignant cells expressed CD56 but no other natural killer (NK) cell marker such as CD16, CD160 or NKp46. This atypical expression was not linked to an activation-dependent process and remained stable during the time course of the disease. No loss of the pan T-cell markers CD2, CD3 or CD4 was detected while a complete down-modulation of CD26 was observed. Despite several lines of treatment, no durable amelioration was observed and patient died after 10 mo of follow-up. Because this $CD4^+$ $CD56^+$ SS case is the only one reported so far, the functional significance of CD56 expression remained difficult to assess in terms of aggressiveness and prognosis.

Key words: Cutaneous T cell lymphomas; Sézary syndrome; CD56

Core tip: Sézary syndrome (SS) is an aggressive variant of cutaneous T cell lymphoma characterized by the presence of malignant $CD4^+$ memory T cells in the skin, peripheral blood and lymph nodes. We here report a case of SS with an aberrant $CD56^+$ immunophenotype. The aberrant expression of this natural killer cell marker by the tumoral cells raises the question of its relevance in terms of function and prognosis.

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INTRODUCTION

Cutaneous T cell lymphomas (CTCL) represent a heterogeneous group of diseases characterized by clonal accumulation of lymphocytes with initial restriction to the skin. Mycosis fungoides (MF) is the most common form of CTCL that follows an indolent course in most

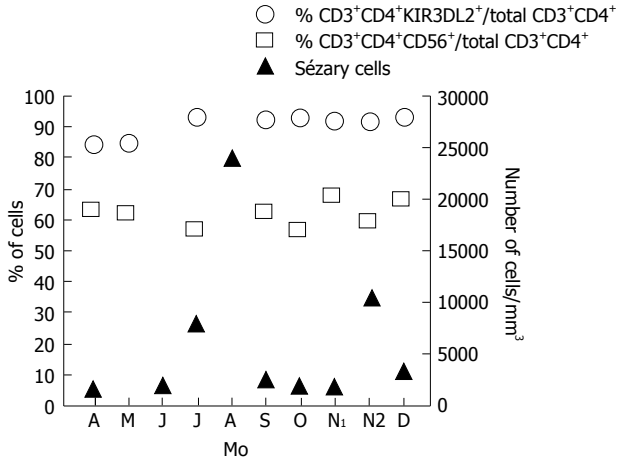

Figure 1 Evolution of the percentage of circulating KIR3DL2$^+$ (○) and CD56+ (□) CD4$^+$ T lymphocytes among the total CD4$^+$ T cell population, and of Sézary cell count (▲) from April to December. N1: November/sample 1; N2: November/sample 2.

cases. Sézary syndrome (SS) is an aggressive leukemic and erythrodermic variant of CTCL, characterized by the presence of a clonal T lymphocyte population with atypical cerebriform nuclei (Sézary cells) in the skin, lymph nodes, and peripheral blood. A consensus statement was proposed by the International Society for Cutaneous Lymphoma and the European Organization for Research and Treatment of Cancer for the establishment of SS diagnosis[1]. The retained criteria are (1) the evidence of a dominant T-cell clone as assessed by polymerase chain reaction or Southern blot; (2) an absolute Sézary cell count of at least 1000/mm^3; (3) a CD4/CD8 T cell ratio of 10 or higher; and (4) expanded CD4$^+$ T cells with abnormal immunophenotype. Regarding this last point, in most cases, Sézary cells show a CD3$^+$ CD4$^+$ CD45RO$^+$ memory T cell phenotype. However, abnormal expression of cellular markers was reported over the last years. Immunophenotypic analyses of SS patient circulating lymphocytes evidenced a frequent down-modulation of CD2, CD3, CD4 or CD45 surface expression[2-4]. In addition, a loss of CD7 or CD26 has also been detected and integrated as part of the diagnosis criteria[5-7]. We further reported that the natural killer (NK) cell receptor KIR3DL2 represents a valuable diagnostic and prognostic marker for SS both in skin and blood[8-10]. Nevertheless, it became more and more obvious that a single marker by itself is not sufficient to identify the entire tumoral burden of all patients, and that the use of multiple markers better ensure a reliable detection of circulating Sézary cells[11].

The surface marker CD56 represents a marker of NK cells. Its expression was initially associated to 3 types of cutaneous lymphoma, namely the extranodal NK/T cell lymphoma of the nasal type, the subcutaneous panniculitis-like T cell lymphoma and the blastic NK cell lymphoma[12]. Until now 8 cases of CD56$^+$ MF have been described[13-17]. We report a patient with SS whose malignant cells are CD4$^+$ T cells that expressed CD56.

CASE REPORT

A 55-year-old man with a history of hypercholesterolemia presented in March 2010 with a two-month history of persistent pruriginous and generalized erythroderma. Small axillary lymph nodes were palpable. Skin biopsy revealed marked epidermotropism of atypical T-cells with Pautrier microabscess. Superficial dermis was also infiltrated with atypical lymphocytes consisting of medium to large cells with hyperchromatic and cerebriform nuclei. A blood cell count revealed 15800/mm^3 leukocytes, 9000/mm^3 neutrophils, 3600/mm^3 lymphocytes and an elevated Sézary cells count of 1896/mm^3 (Figure 1). Flow cytometry analysis revealed an elevated CD4/CD8 ratio of 41 in the peripheral blood. Molecular biology studies confirmed the presence of a clonal T cell identical in blood and skin biopsy. The level of serum LDH was elevated to 562 UI/L. Thoracic, abdominal and pelvic CT-scans were normal. Sézary syndrome (T4NxM0B2) was diagnosed.

In April 2010 the patient started combined treatment with interferon and bimonthly photopheresis for 3 mo with clinical and biological progression (majoration of infiltration of skin with leonine facies, Sézary cell count: 8241/mm^3). In July 2010 bexarotene was started (with continuation of photopheresis) and progression after 2 months of treatment (Sézary cell count: 24211/mm^3) was noted. Gemcitabine was introduced in September 2010 (1000 mg/m^2 at day 1, 8 and 15). Initial amelioration was observed with diminution of Sézary cell count at 2074/mm^3 after 2 cycles. Despite four cycles of gemcitabine, the patient progressed clinically and biologically (Sézary cell count: 11004/mm^3) and died suddenly in December 2010.

From March to December 2010, elevated levels of tumoral cells within the circulating CD3$^+$ CD4$^+$ T lymphocyte population were detected, as assessed by KIR3DL2 staining, with a mean percentage of 90.6% ± 4.5% (Figures 1 and 2). In addition, two-third of the malignant cells were found to express CD56 (mean: 61.5 ± 5.3%; Figures 1 and 2). Notably, the percentage of CD3$^+$ CD4$^+$ KIR3DL2$^+$ CD56$^+$ lymphocytes remained stable over the course of the disease, regardless of the ongoing treatment. Additional flow cytometric analyses of peripheral blood demonstrated that all neoplastic cells have a CD2$^+$ CD3$^+$ CD4$^+$ CD5$^+$ CD7$^+$ CD8$^-$ CD26$^-$ CD27$^+$ CD45RO$^+$ CCR4$^+$ phenotype (Figure 2 and data not shown). Furthermore, none of the specific NK cell markers CD16, NKp46 or CD160 was detected (Figure 2). These cells were also negative for all KIR tested (except for KIR3DL2; data not shown) and did not exhibit an activated NK- or T-cell phenotype as assessed by the lack of expression of NKp44 or CD69 (Figure 2).

DISCUSSION

CD56 is a well-known marker of NK cells that is usually expressed in NK cell tumors such as extranodal NK/T cell lymphoma and aggressive NK cell leukemia. However, atypical cases of CD56$^+$ CTCL have been re-

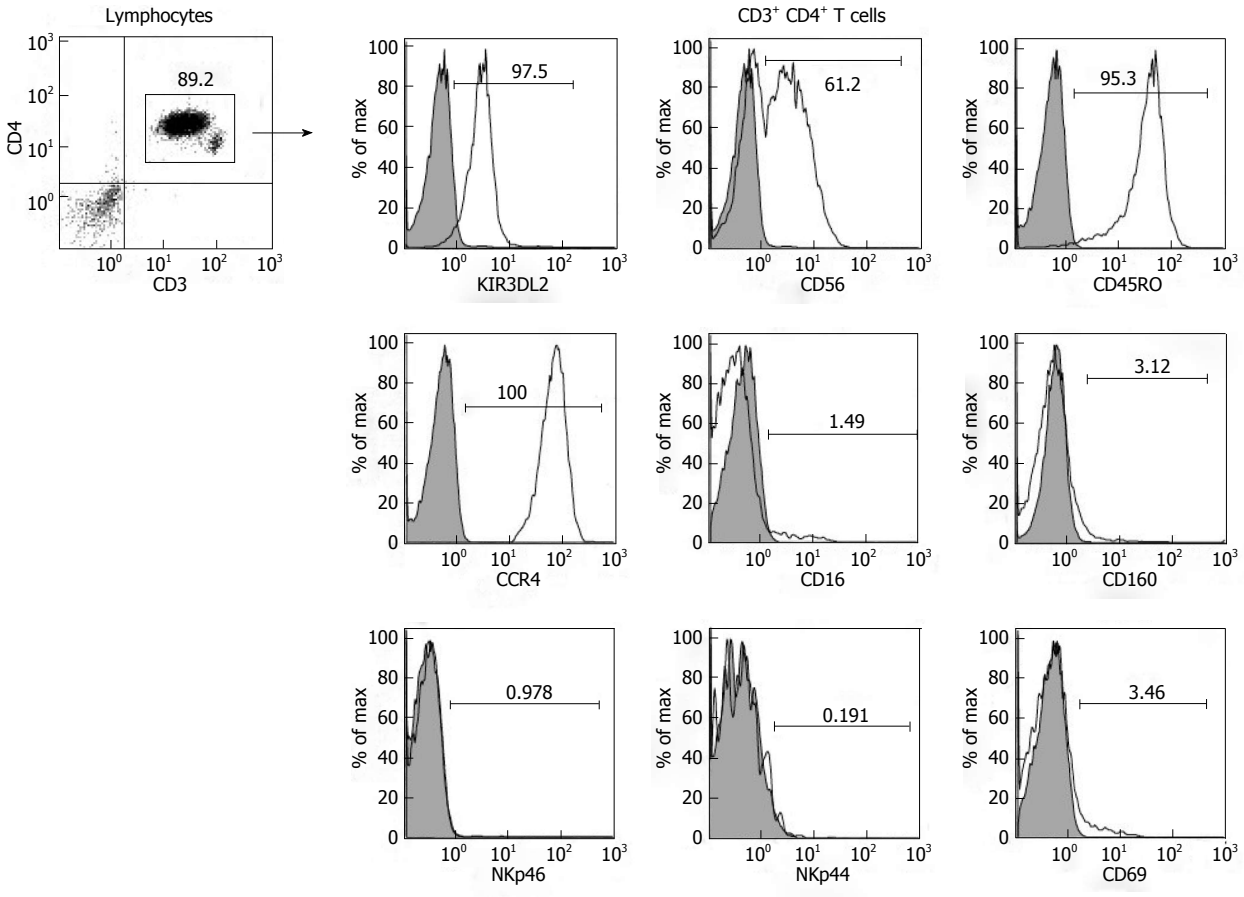

Figure 2 Immunostainings of the CD4$^+$ T lymphocyte population. Cells were positive for KIR3DL2, CD56, CD45RO and CCR4, but negative for the NK cell markers CD16, CD160 and NKp46 and for the activation markers NKp44 and CD69. Analyses were performed on a FC500 flow cytometer (Beckman Coulter).

ported over the last years. Among them six MF patients exhibited malignant cells with a CD4$^-$ CD8$^+$ CD56$^+$ (2 cases) or CD4$^-$ CD8$^-$ CD56$^+$ (4 cases) immunophenotype, consistent with their classification as cytotoxic MF[14,16,17]. All patients were younger than the typical age of disease onset for MF (< 55-60-year-old) and presented with a stage I A or I B disease that followed a slowly progressive course. An atypical CD4$^-$ CD8$^+$ CD56$^+$ phenotype was also described for a 26-year-old Japanese patient who presented with a stage IVA disease, however the appearance of peripheral blood involvement was rather consistent with SS[15]. Finally an additional case of an 85-year-old patient with clinical MF stage I A, whose neoplastic cells were characterized by a CD4$^+$ CD8$^-$ CD56$^+$ phenotype, was reported[13]. To our knowledge, we here report the first case of SS patient with a CD4$^+$ CD8$^-$ CD56$^+$ malignant cell phenotype. Besides CD56, our previous studies already allowed the detection of other NK receptors at the surface of Sézary cells. Thus, we showed that circulating malignant Sézary cells might be distinguished from autologous reactive CD4$^+$ T cells by the detection of the ILT2/CD85j receptor at their cell surface, this receptor exhibiting an exclusive cytoplasmic location in non-malignant T cells. In this tumoral cell context, ILT2 was found to play an inhibitory co-receptor function, its ligation leading to a down-modulation of the CD3-dependent cell activation process[18]. Similarly, apart from KIR3DL2, other KIR receptors such as KIR2DS1/S2 can be detected on Sézary cells. In such case, these activating receptors were found to act as co-stimulatory molecules, their engagement allowing the amplification of the CD3-mediated activation pathway[19]. More recently, we reported the expression of the NK cell receptor NKp46 by Sézary patient malignant cells. While NKp46 represents a fully autonomous activating receptor in NK cells, it acts as an inhibitory co-receptor in Sézary cells, preventing the delivery of activating signals following engagement of the TCR/CD3 complex[20]. Remarkably, in most of the cases, the atypical expression of these NK receptors seems to confer a growth advantage to the tumor cells either by promoting an otherwise low proliferation response to activating stimuli (as seen for KIR2DS1/S2) or by delaying or preventing activation-induced cell-death (*e.g.*, NKp46 or KIR3DL2; A.M-C, personal communication). We observed that one third of the malignant cells were negative for CD56, suggesting that these cells either never expressed the receptor or lose expression during tumoral expansion. Notably, such loss of expression has already been observed for numerous markers such as CD3, CD4, CD7 or CD26. The functional relevance of CD56 expression in the context of MF or SS remains to be established. Previous studies did not favor a direct link between this expression and the aggressiveness of the disease, at least in the reported

cases of MF. The identification of more SS patients with a $CD4^+$ $CD56^+$ malignant cell population will be required to address this issue.

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