Sézary syndrome with large cell transformation and T-follicular helper phenotype

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INTRODUCTION

T-follicular helper (TFH) phenotype can be observed in different lymphoproliferative disorders, including angioimmunoblastic T-cell lymphoma, mycosis fungoides[1] primary cutaneous cluster of differentiation (CD)4+ small-/medium-sized pleomorphic lymphoproliferative disorder,[2] and Sézary syndrome (SS), apparently without any evidence of prognostic significance.[3] The TFH markers expression has been previously reported in SS,[4] but to our knowledge, SS with large cell transformation and complete TFH phenotype has never been described.

CASE REPORT

An 88-year-old woman presented with a 5-year history of itchy erythematous plaques involving the trunk and the lower limbs. The lesions were resistant to topical and systemic corticosteroids. Clinical examination showed erythroderma (ie erythema covering around 90% of the body surface area) with ill-defined erythematous and edematous plaques, particularly on the back, abdomen, and thighs with superimposed excoriated plaques (Fig 1). Blood chemistry, serum liver enzymes, electrolytes, glucose, measures of renal function, lactate dehydrogenase, and beta-2 microglobulin were within the normal range. Staging ultrasound and total body computed tomography scan revealed generalized superficial lymphadenopathy and no visceral involvement.

Abbreviations used:

BCL:	B-cell lymphoma
CD:	cluster of differentiation
CXCL:	chemokine (C-X-C motif) ligand
PD-1:	programmed cell death protein 1
SS:	Sézary syndrome
TFH:	T-follicular helper

After 1 month of treatment washout, histology of a skin biopsy from a thigh plaque showed psoriasiform hyperplasia, moderate compact hyperorthokeratosis, mild spongiosis, and occasional dyskeratosis. In the superficial dermis, there was a dense perivascular infiltrate, sometimes with lichenoid and vaguely nodular arrangement, mostly composed of lymphocytes with eosinophils and some plasma cells. The lymphocytic infiltrate showed a heterogeneous population of small lymphocytes intermixed with numerous atypical medium and large neoplastic cells, accounting for more than 25% of the infiltrate. Mitoses were easily detectable with a proliferative index of about 30%. Moreover, the lymphocytic infiltrate demonstrated a focal epidermotropism along the basal layer in single cells or Pautrier microabscesses (Fig 2). On immunohistochemical study, the lymphocyte infiltrate was CD4/T-cell receptor beta F1 positive with partial loss of CD7, preserved expression of CD3, CD2, and CD5, and with a focal positivity for CD30.

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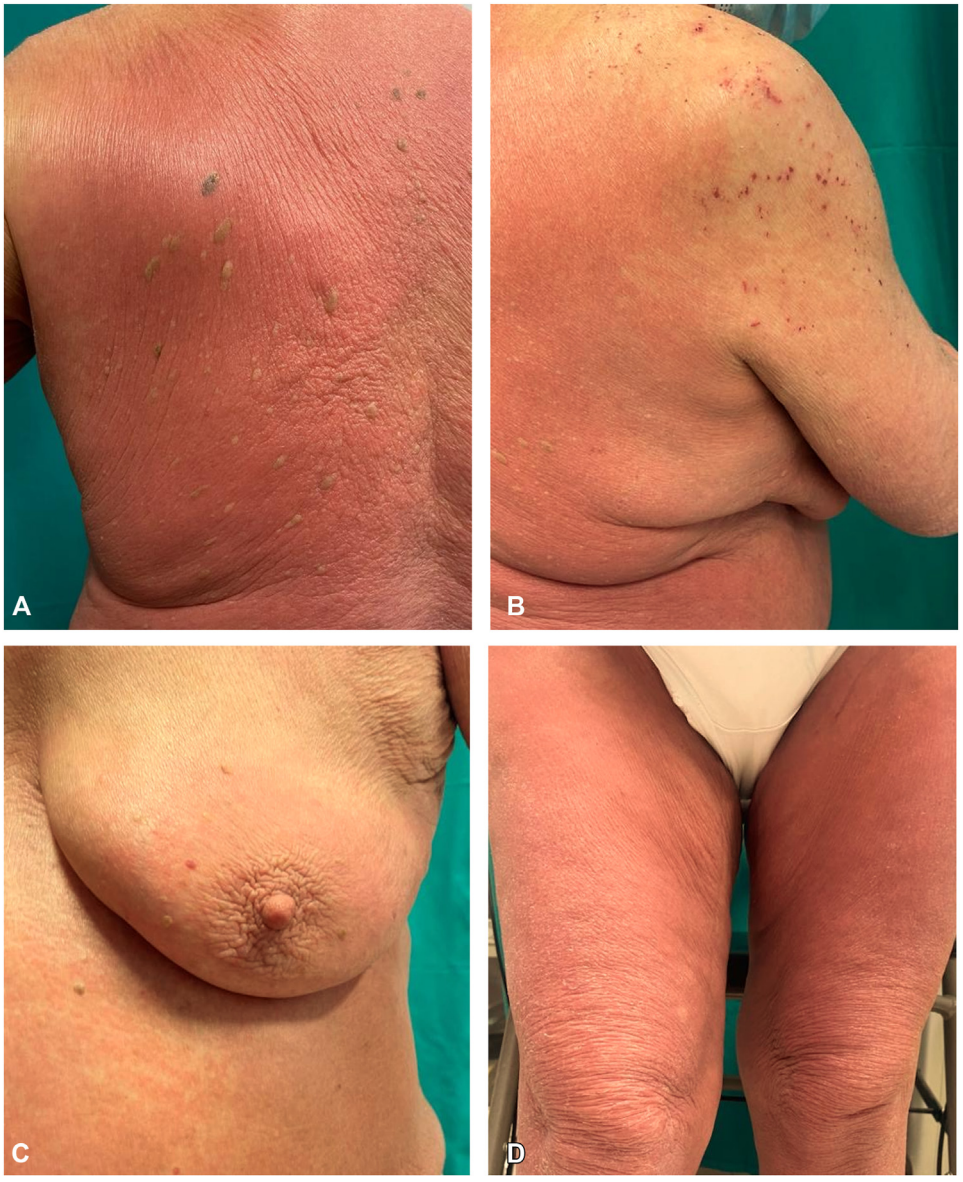

Fig 1. Erythroderma (**A**) with excoriations on the shoulders (**B**) and ill-defined erythematous plaques of the trunk (**C**) and the thighs (**D**).

In addition, the neoplastic cells co-expressed the follicular T helper markers programmed cell death protein 1 (PD-1), chemokine (C-X-C motif) ligand (CXCL)-13 and along with focal positivity for B-cell lymphoma (BCL)6 and CD10 (Fig 3). Epstein-Barr virus-encoded small RNA was negative. T-cell receptor gene rearrangement analysis documented the presence of monoclonal population of lymphocytes in the β and γ chain amplification reaction. Flow cytometry revealed a CD4/CD8 ratio >10 with clonal circulating CD3+ CD4+ CD7 ± CD5+ CD26- Sézary cells accounting for 40% of circulating lymphocytes. A clinic-pathological diagnosis of SS with large cell transformation associated to a TFH phenotype was made. The patient was treated with methotrexate 20 mg weekly with no disease progression at 18-month follow-up.

DISCUSSION

SS is a rare leukemic form of cutaneous T cell lymphoma,[5] characterized frequently by erythroderma with lymphadenopathy and neoplastic typical Sézary cells in the skin, lymph nodes, and peripheral blood. Diagnosis of SS requires at least one of the following criteria: absolute Sézary cells count > 1000/mm3, expansion of CD4+ T-cells with a ratio CD4/CD8 >10, loss of at least one mature T cell antigens as CD2, CD3, CD5, CD7, and CD26, with or

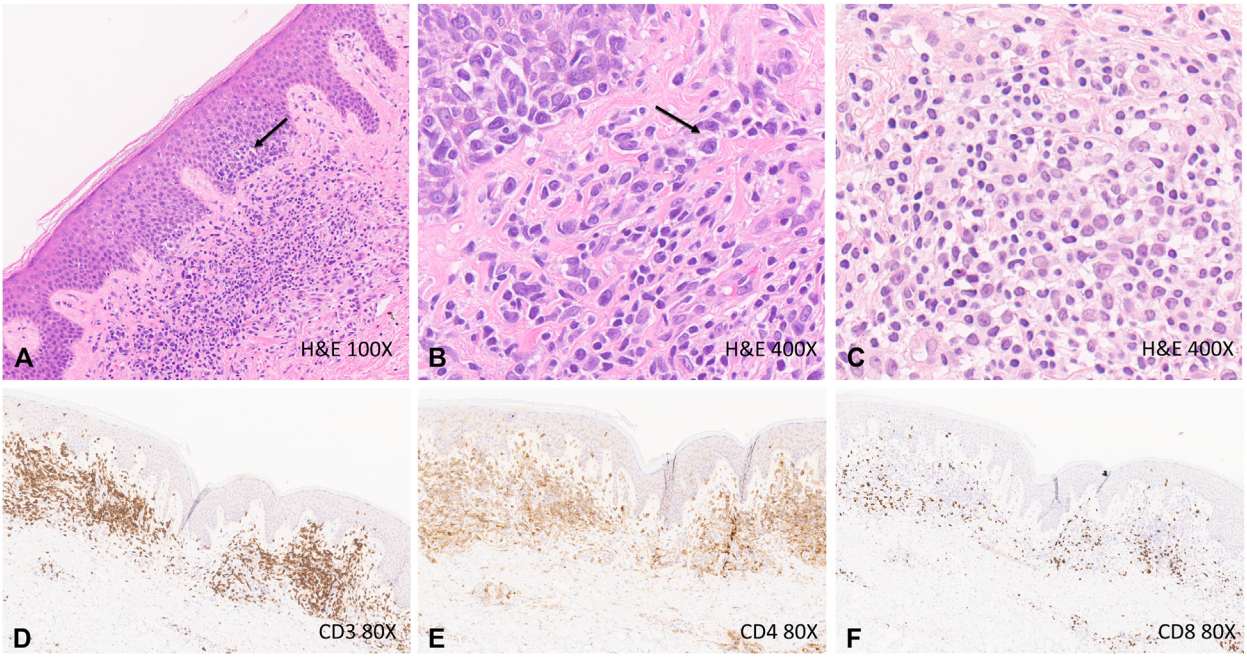

Fig 2. Skin biopsy revealing a dense band-like infiltrate of lymphocytes with focal epidermotropism forming Pautrier microabscesses (*arrow*) (**A,** hematoxylin and eosin 100×). The dermal infiltrate composed of large atypical, pleomorphic lymphocytes (*arrows*) admixed with a population of small lymphocytes (**B,** 400×). Detail of the large cell infiltrate forming small loose aggregates (**C,** 400×). Immunohistochemistry showing diffuse positivity for CD3 (**D,** 200×) and CD4 (**E,** 200×) with focal positivity for CD8 (**F,** 200×).

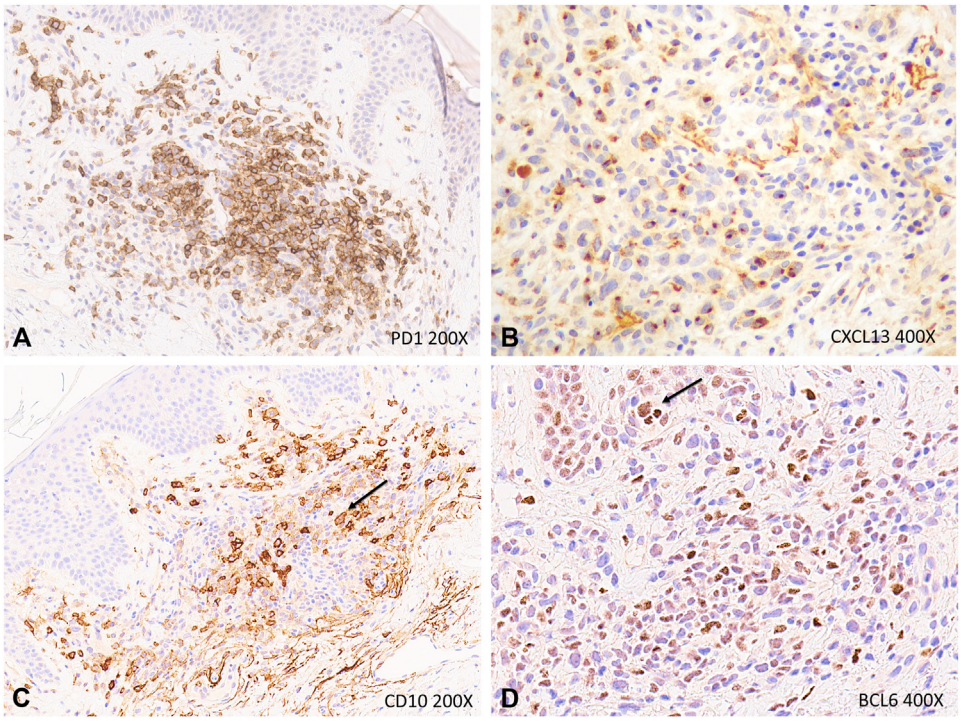

Fig 3. Immunohistochemistry for follicular T helper markers displaying diffuse positivity for PD-1 (**A,** 200×) and CXCL13 in granular pattern (**B,** 400×), focal reactivity for CD10 (*arrow*) (**C,** 200×) and for BLC6 in a subset of cells; note the epidermotropic neoplastic cells were also positive (*arrow*) (**D,** 400×). *BCL6*, B-cell lymphoma 6; *CXCL13*, chemokine (C-X-C motif) ligand-13; *PD-1*, programmed cell death protein 1.

without CD30 positivity, in association with increased lymphocyte count with evidence of a clone of circulating CD4+ T-cells determined by flow cytometry.[5] SS is characterized by poor survival and a variable disease course, with 5-year survival approximated at 11%.[5] In SS and mycosis fungoides, large cell transformation can occur, defined by the histopathological change of neoplastic small lymphocytes into large cells ($\geq 4\times$ the size of a small lymphocyte) comprising more than 25% of the lymphoid infiltrate, or aggregates of large cells in the dermal infiltrate.[5] Transformation has generally poor prognosis and aggressive clinical course, with ranges survival from 19 to 36 months,[6] therefore it should be identified to optimize therapeutic strategies. TFH cells are a subgroup of T-helper lymphocytes, characterized by the expression of at least 3 among the following markers: PD-1, CXCL-13, inducible co-stimulator, BCL6, and CD10.[1] The peculiarity of this case is the co-expression of more than 3 TFH lineage markers in neoplastic cells delineating a complete TFH phenotype in a SS with large cell transformation.[7] The present clinical presentation of erythroderma is nonspecific, including different non-neoplastic conditions as psoriasis, atopic dermatitis, pityriasis rubra pilaris, and drug reactions. Conversely, the histopathological differential diagnosis includes T follicular helper lymphoma (cutaneous and systemic) and angioimmunoblastic T-cell lymphoma with cutaneous involvement. The clinical manifestation of the disease, the lack of papules and nodules, the distribution of the inflammatory infiltrate, and the presence of epidermotropism led to exclude the diagnosis of T follicular helper lymphoma.[8] In addition, the absence of Epstein Barr virus-positive cells, the lack of systemic symptoms, and lymph node involvement ruled out the diagnosis of angioimmunoblastic T-cell lymphoma.[9] Incomplete TFH phenotype has been found also in indolent lymphoproliferative disorders, such as lymphomatoid papulosis, but its biologic and prognostic significance remains to be established.[10] Since TFH markers are not routinely investigated, this phenotype is probably underestimated.

In conclusion, herein, we report an unusual case of SS displaying both a large cell transformation and a complete TFH phenotype, characterized by malignant CD4 T-cells expressing PD-1, CXCL-13, CD10, and BCL6. To our knowledge, a TFH phenotype has never been described in SS with large-cell transformation. Whether this may be explained by the fact that TFH markers have rarely been evaluated in this rare condition or by a true peculiarity of the current case remains to be clarified by further studies. More evidence is necessary to correlate these findings with the clinical course and the prognosis of the disease.

Conflicts of interest

None disclosed.

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