

Review

Paraneoplastic Dermatoses in a Patient with Anaplastic Large-Cell Lymphoma: Case Report and Literature Review

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Key Words

Anaplastic large-cell lymphoma · Literature review · Paraneoplastic dermatosis

Abstract

Background/Aims: Paraneoplastic dermatoses are skin disorders that are associated with malignancy. Anaplastic large T-cell lymphoma (ALTCL) has rarely been associated with paraneoplastic skin manifestations such as gangrenous foot ulcers and erythroderma. **Methods:** We describe a case of ALTCL presenting as a large annular skin rash. The clinical picture, course, and treatment will be discussed along with current hypotheses on the mechanism of paraneoplastic syndromes. **Results:** Skin manifestations in ALTCL most commonly arise in two distinct ways; either as primary cutaneous lymphoma manifestation or as systemic disease with secondary metastasis. Less commonly, systemic disease causes skin manifestations secondary to a paraneoplastic process without infiltration of malignant cells. This is thought to be mediated by an immunologic reaction to tumor antigen or the result of cytokines and other inflammatory markers produced by the tumor itself. **Conclusion:** Paraneoplastic dermatoses could be the initial presentations of systemic lymphoma. Knowledge about their association with anaplastic large-cell lymphoma may help with timely diagnosis. In a patient with unexplained dermatosis associated with B symptoms who is unresponsive to topic treatment, an investigation for systemic lymphoma workup is warranted.

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Introduction

Paraneoplastic dermatoses represent particular cutaneous manifestations of an underlying malignancy without infiltration of malignant cells [1]. The phenomenon of a paraneoplastic dermatosis was first described by Hebra [2] in 1868 when he suggested that pigmen-

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tation of the skin could indicate underlying malignancy [3]. Since that time, many paraneoplastic syndromes have been described. Paraneoplastic conditions most commonly cause endocrine abnormalities; however, a large percentage present with skin findings [4]. Anaplastic large T-cell lymphoma (ALTCL) has only rarely been associated with dermatoses including diffuse erythroderma [5], skin ulceration [6], and pemphigus [7]. Skin manifestations of ALTCL are mostly the result of secondary metastasis. This distinction has prognostic value as patients with metastatic disease have a worse prognosis than patients with paraneoplastic manifestations [8]. The purpose of this article is to review the current literature on paraneoplastic dermatoses associated with ALTCL and to present an interesting case with these findings.

Case

A 64-year-old male presented to the hospital with a rash on his chest, abdomen, and back. In addition, he complained of extreme fatigue, night sweats, and weight loss. He had a past medical history of myasthenia gravis that was diagnosed 10 years prior and squamous cell carcinoma of the tongue that was treated with local resection. His family history consisted of hypertension and coronary artery disease. He was a former smoker and worked at a local automobile manufacturer with no known exposures to toxic chemicals.

Upon arrival to the emergency department, he was found to have a 5-cm, mobile, nontender mass in the right axilla. There was an erythematous macular rash in an annular shape with central clearing located under his left breast. There was confluence of this rash that extended to the mid-anterior abdomen and to his back. He also had erythematous scaly generalized rash on his upper extremities (fig. 1).

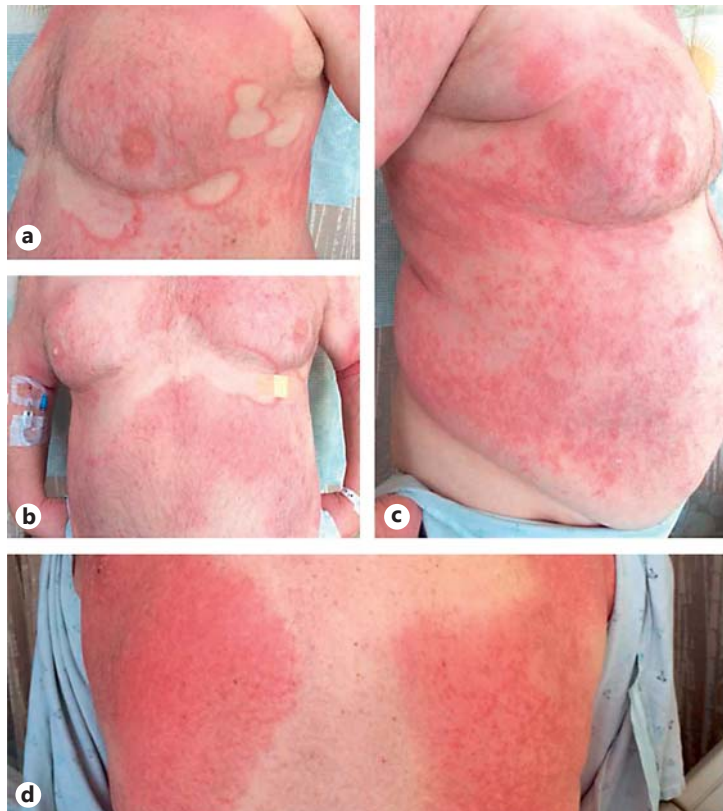


Fig. 1. Clinical appearance: diffuse confluent erythematous scaly plaques over the chest (a), abdomen (b, c), and back (d) with circular areas of sparing. The plaques later fused together, developing into erythroderma.

His complete blood count showed a mildly elevated white blood cell count at 11,100 WBCs/ μ l, a platelet count of 373,000/ μ l, hemoglobin of 11.5 g/dl with a hematocrit of 37.3%, and a differential with an absolute neutrophil count of 9.1 cells/ μ l. Flow cytometry of the peripheral blood was performed and showed no evidence of immunophenotypically abnormal lymphocytes. A computed tomography of the chest showed a 5-cm mass in the right axilla. An excisional biopsy of this mass was performed, and the histologic examination showed a lymph node extensively involved by anaplastic large lymphoma in a sinus pattern, focally in large clusters or sheets (fig. 2a). Cytologically, lymphoma cells were large and anaplastic (fig. 2b). Immunohistochemistry showed that the lymphoma cells stained positively for CD4, CD5 (fig. 2c), CD7, CD30 (fig. 2d), and CD43 but negatively for CD3, CD8, CD15, and anaplastic lymphoma kinase. A skin punch biopsy revealed slight hyperkeratosis, slight spongiosis, slight acanthosis, and a superficial perivascular to somewhat interstitial sparse lymphocytic infiltrate. Occasional intraepidermal lymphocytes were seen, and no large atypical lymphocytes were present (fig. 3). By immunohistochemistry, the infiltrate was composed of admixed CD4-positive and CD8-positive T cells with normal expression of CD2, CD3, CD5, and CD7 and without expression of CD30. PCR was negative for clonal T-cell receptor-gamma gene rearrangement. Bone marrow was negative for lymphoma. Chemotherapy with CHOP therapy was initiated, and the patient reported improvement in his symptoms of fatigue and fevers, as well as resolution of his rash.

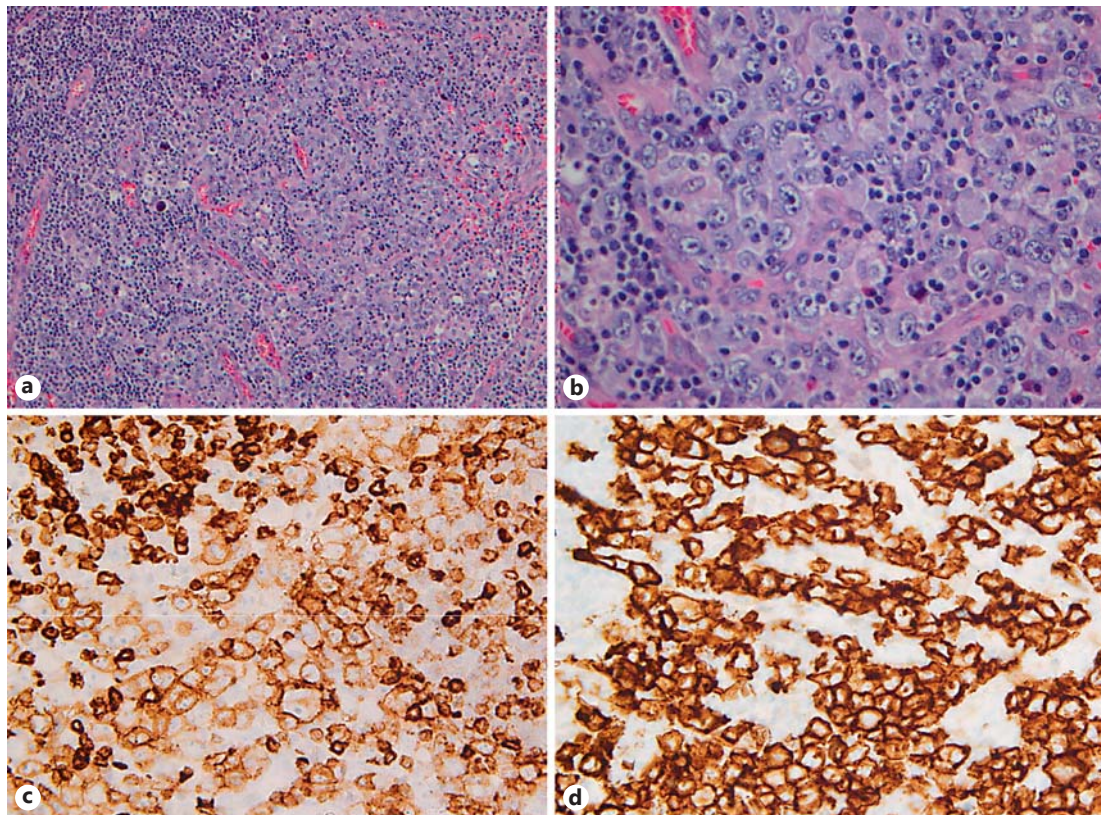


Fig. 2. Excisional biopsy of the right axillary lymph node. **a** Effaced lymph node architecture by predominant population of large, slightly cohesive cells with irregular nuclei (hematoxylin and eosin stain, magnification $\times 100$). **b** Neoplastic cells with abundant amphophilic cytoplasm and occasional hallmark cells with cleaved/kidney-shaped nuclei (hematoxylin and eosin stain, magnification $\times 600$). **c** Positive membranous CD5 staining of neoplastic cells (immunohistochemistry, magnification $\times 600$). **d** Positive membranous CD30 staining of neoplastic cells (immunohistochemistry, magnification $\times 600$).

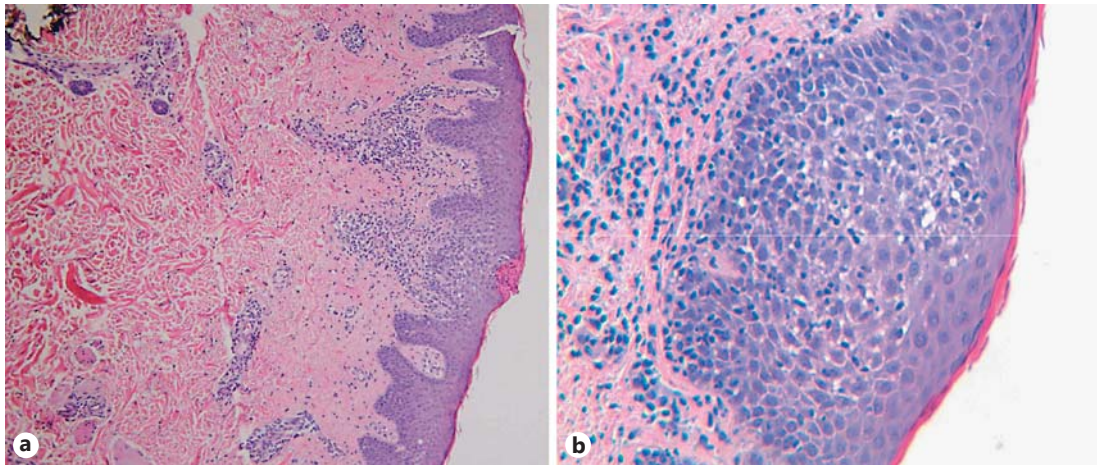


Fig. 3. Abdominal skin punch biopsy. **a** Epidermis with slight hyperkeratosis, slight spongiosis, slight acanthosis, and occasional intraepidermal small lymphocytes (hematoxylin and eosin stain, magnification $\times 100$). **b** Intraepidermal lymphocytes with no significant atypia or marked lining-up of lymphocytes along the dermal-epidermal interface (hematoxylin and eosin stain, magnification $\times 400$).

Discussion

Paraneoplastic syndromes are diagnosed using criteria from Curth's postulates [8]. They include concurrent onset of dermatosis and malignancy; parallel course, where treating the one leads to resolution of the other; uniformity, where there is a statistically significant association between skin findings and malignancy, and genetic association between malignancy and skin findings. The reported case showed pathological features of ALTCL in the right axillary lymph node. The skin punch biopsy from the patient's abdomen revealed only non-specific reactive changes with scanty small lymphocytes without aberrant antigen expression and absence of clonal T-cell gene rearrangement, providing evidence that the skin rash was a nonneoplastic process.

Extensive literature search identified 4 cases of ALTCL-associated paraneoplastic dermatoses [5–7]. The average age of patients was 42.8 ± 23 years (range 23–71). The degree of skin involvement varied between cases, either affecting the entire body or more focal areas such as the face, hands, or feet. Two cases were mild, presenting with diffuse erythema and a dry skin rash [5, 6]. One case presented with multiple punched-out, ulcerative lesions in his lower extremities that responded well to systemic chemotherapy [6]. The last case was severe and presented with a disseminated erythrodermic rash with ulcerative lesions in the mouth and desquamation of the hands and feet. This patient progressed to multi-organ failure and died despite systemic chemotherapy [7]. No paraneoplastic dermatoses have been reported in patients with primary cutaneous anaplastic large-cell lymphoma.

Distinguishing between cutaneous lymphoma and reactive dermatoses due to paraneoplastic syndrome can be difficult. Correlation with clinical history and pathological evaluation of the skin biopsy are essential for definitive diagnosis. Other types of T-cell lymphomas more commonly affecting the skin include Sézary syndrome and mycoses fungoides. Mycoses fungoides most commonly present with pruritic patches or plaques; however, generalized erythroderma is also common and is usually indicative of more advanced disease [9]. Sézary syndrome is closely related to mycoses fungoides and is diagnosed in the presence of $>80\%$ body surface with erythroderma, generalized lymphadenopathy, and blood involvement

defined by a high percentage of circulating atypical lymphocytes with cribriform nuclei called Sézary cells. These skin findings represent infiltration of malignant cells and not a paraneoplastic process. A literature search has shown 1 case of suspected Leser-Trelat sign associated with Sézary syndrome, which is the rapid onset of multiple seborrheic keratosis in multiple areas of the body. However, it was inconclusive as to the true nature of their relationship [10].

The mechanism behind paraneoplastic dermatoses is still largely unknown. It is thought that the skin changes are due to either an immunologic reaction to the tumor antigen directly or indirectly as a result of inflammatory cytokines produced by the tumor. Further understanding of this process could lead to future therapies targeting skin manifestations. The only known treatment for these disorders currently involves treatment of the underlying malignancy, and skin manifestations can be more problematic and debilitating than the underlying malignancy itself.

Paraneoplastic dermatoses can be the initial presentations of systemic lymphoma. Knowledge about their association with ALTCL may help with timely diagnosis. In a patient with unexplained dermatosis associated with B symptoms, an investigation for systemic lymphoma is warranted.

Statement of Ethics

The patient gave written informed consent for the publication of this work.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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