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Case Report Open Access

A Rare Presentation of Cutaneous Pseudolymphoma as a Preleukaemic State

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Abstract

A patient presented with progressive and unresponsive erythematous rash affecting his trunk and limbs over a period of 5 years. His systemic examination and extensive relevant investigations were normal throughout this period. Skin biopsies at different times showed features of annular erythema, cutaneous pseudolymphoma and sub-acute dermatitis. Five years after the initial presentation, he developed erythroderma, leonine facies, lymphadenopathy and peripheral lymphocytosis. CT chest and abdomen revealed generalised lymphadenopathy. Skin biopsy and immunophenotyping was suggestive of Sezary syndrome. However, peripheral blood smear examination was highly suggestive of T-cell prolymphocytic leukaemia (TPLL). Subsequent molecular genetic analysis was consistent with TPLL. To the best of our knowledge, there are no reports of cutaneous pseudolymphoma transforming to TPLL in the literature. The long indolent course of apparently benign skin disease before transforming into TPLL appears to be unique in our case. An analogy can be made with cutaneous T-Cell lymphoma both in terms of the difficulty in proving the diagnosis-needing multiple skin biopsies, and in the possible link between cutaneous and systemic disease. TPLL should be considered as a rare cause of erythroderma, which may clinically and histologically mimic Sezary syndrome.

Keywords: Erythroderma; Cutaneous; Lymphocytosis

Introduction

Erythroderma is defined as erythema and scaling affecting more than 90% of the body surface. The commonest cause of erythroderma was due to pre-existing inflammatory skin disease with an incidence between 27-68% in various case series [1]. Malignancies were the least common cause of erythroderma in these series, with cutaneous T-cell lymphoma (CTCL) as the most frequent malignant cause of erythroderma with a median incidence of 3% (range, 0-18%) [1]. Such patients with a malignant cause of erythroderma may have non-specific histological features for many years before the actual diagnosis can be established. Cutaneous pseudo-lymphomas are considered as a heterogenous group of benign T-cell or B-cell lympho proliferative process and have many potential causes [2]. There are reports that suggest pseudo lymphomas can progress into overt lymphoma in some patients [3,4]. However it is unclear if these patients were misdiagnosed at the initial stage or developed lymphoma due to persistent antigenic stimulation [5].

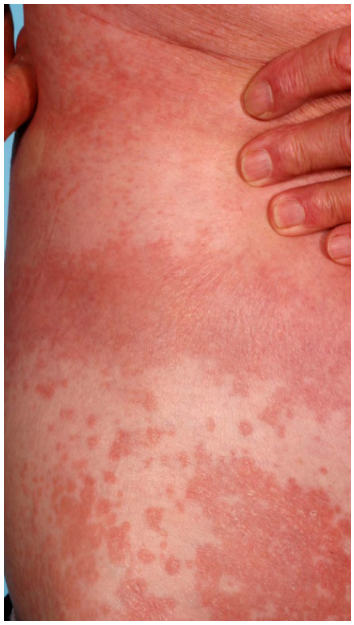

Figure 1: Initial presentation of erythematous patches on the trunk.

Case Report

A 75-year-old male presented with a one year history of a persistent erythematous eruption affecting his trunk and limbs (Figure 1). Systemic examination was normal. An initial diagnosis of a drug eruption to quinine was made; stopping this drug and using super potent topical steroid produced moderate improvement. Over the next 4 years, he developed scaly erythematous papules and plaques affecting his trunk and limbs (Figures 2a and 2b). His disease was gradually progressive becoming more extensive in distribution and persistent despite treatment. Systemic examination, full blood count, peripheral blood film examination, renal and liver functions were normal throughout this period.

Two skin biopsies performed at various stages of presentation during this time showed features of annular erythema and sub-acute

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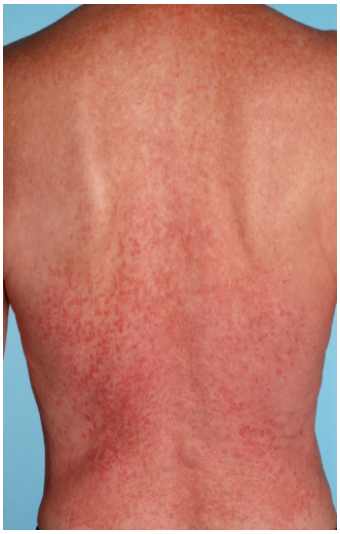

Figure 2a: Progressive skin disease -erythematous papules on the trunk.

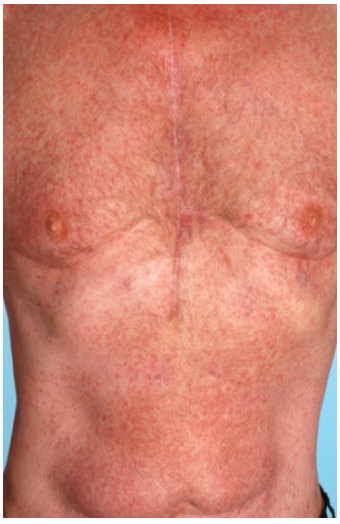

Figure 2b: Progressive skin disease -erythematous papules on the trunk.

dermatitis. A third biopsy showed patchy upper dermal infiltrate composed of lymphoid cells. Most of the lymphocytes were small although showed some degree of nuclear irregularity. In addition, there were a significant number of cells with a blast morphology showing considerable nuclear atypia. Only a small number of lymphocytes extended into the overlying epidermis with some spongiotic reaction noted. Abroad range of immunohistochemical stains showed that the bulk of cells are of T-lineage but a modest population of cells marking as B-cell lineage. The blast cell population were a mixture of T and B cell lineage. Molecular genetic analysis failed to show clonal re-arrangement of T-cell receptor gene. The immunoglobulin gene re-arrangement tests failed. Hence the conclusion at that stage was a reactive pseudo lymphomatous process. He partially improved with narrow band UVB and oral PUVA phototherapy.

Five years after the initial presentation, he developed leonine-like facial swelling and erythroderma (Figures 3a and 3b). Systemic examination showed palpable axillary and inguinal lymphadenopathy. Full blood count demonstrated a marked peripheral lymphocytosis. CT scan showed hepato splenomegaly and generalised lymphadenopathy.

Skin biopsy showed atypical lymphocytes with many cerebriform nuclei in a band like infiltrate in the upper and mid dermis (Figures 4a and 4b), epidermotropism (Figure 4c) and with an immunophenotype pattern of strong staining to CD3 and CD4 but down regulation of other T-cell markers. The clinical picture, laboratory imaging and dermatopathological findings raised a possible diagnosis of Sezary syndrome (SS).

However, peripheral blood smear examination showed large atypical lymphocytes with plentiful cytoplasm and expressing CD2, CD3, CD4, CD5 and CD7 markers, typical of T-cell prolymphocytic leukaemia (TPLL). Subsequent cytogenetic analysis demonstrated a complex karyotype including inversion of the long arm of chromosome 14, consistent with TPLL. Management with dexamethasone produced only moderate and short term response. Subsequent management with

Figure 3a: Leonine facial appearance and erythroderma.

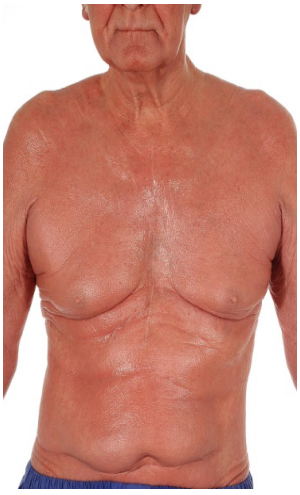

Figure 3b: Leonine facial appearance and erythroderma.

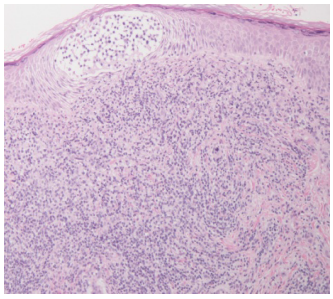

Figure 4a: H&E X40 Band like lymphoid infiltrate in the upper and mid dermis.

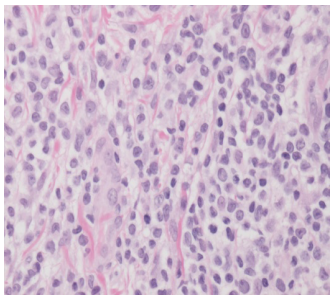

Figure 4b: H&E X40 Band like lymphoid infiltrate in the upper and mid dermis.

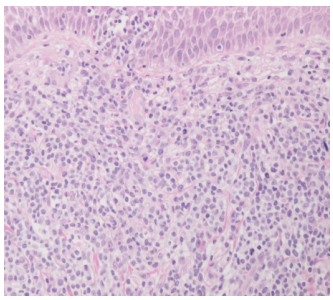

Figure 4c: H&E X100 Epidermotropism.

CAMPATH (alemtuzumab-CD52 monoclonal antibody) produced excellent response initially but the treatment course was not completed due to severe pancytopenia. The disease relapsed and was progressive from that stage leading to death.

Discussion

TPLL is a rare aggressive mature T-cell leukaemia. It accounted for 37.5% of cases in a series of 175 adult patients with mature T-cell malignancies [6]. The characteristic clinical features of TPLL include splenomegaly, lymphadenopathy, skin disease and a high leukocyte count. The cutaneous features occurred in 25-28% of cases of TPLL in various case series [7,8]. Skin disease has been reported at the time of initial diagnosis or later, heralding aggressive clinical course in such cases. The various cutaneous manifestations include facial swelling with erythema, alopecia, symmetrical petechial rash in the periorbital area, nodules and erythroderma [7,9]. Cutaneous histological features include grenz zone, dermal peri-vascular and peri-appendegeal infiltrate composed of medium-sized lymphoid cells with prominent nucleoli, similar to peripheral blood smear examination. Peripheral blood smear examination shows characteristic tumour cells with a prominent nucleolus and deep basophilic cytoplasm but the nuclear contours and prevalence of distinctive central nucleoli are quite variable [10]. The immunophenotype profile is usually positive for CD3, CD2, CD4, CD5, CD7, CD45, and CD45RO. Other markers of immaturity such as CD34, CD1a and terminal deoxynucleotiyl transferase are absent. Expression of T-cell leukaemia (TCL)-1 oncoprotein can be reasonably specific for TPLL [10]. The most distinctive cytogenetic abnormality in TPLL is inversion of the long arm of chromosome 14 [10].

To the best of our knowledge, there are no previous reports of cutaneous pseudolymphoma transforming to TPLL. The long indolent course of apparently benign skin disease before the final diagnosis of TPLL appears to be unique in our case. However, the disease was rapidly progressive from that stage of transformation. In our case, the cutaneous histology was not diagnostic and was suggestive of SS. Peripheral blood smear examination and immune phenotyping was the key in making the diagnosis in our case.

It is impossible to completely prove a link between his pre-existing long term skin condition which we have classified as pseudo-lymphoma and his subsequent development of TPLL. This could only be proved if we had a clonal marker in the initial skin biopsy that was demonstrated to evolve when he developed TPLL. Despite looking for this we could not detect an initial clonal marker in the initial biopsy and if we had, we would not have classified it as pseudo-lymphoma. The characteristics of his skin rash and T-cell phenotype suggest it is likely that the two conditions are linked.

TPLL is an aggressive disease with a median survival of 7 months with conventional treatment [11]. The advent of monoclonal antibodies has improved treatment options in this condition. Alemtuzumab is a humanised IgG1 antibody that targets the CD52 antigen highly expressed on normal, malignant T- and B-lymphocytes and on monocytes but not on haematopoietic stem cells [12]. The mechanism of action is not fully understood but it can cause antibody-dependent cellular cytotoxicity, complement activation and direct apoptosis [12]. A study of 39 patients treated with intravenous alemtuzumab 30 mg 3 times weekly until a maximum response showed complete remission (CR) in 60% of patients, partial remission (PR) in 16% of patients and a median disease free interval of 7 months after the treatment [11]. Further follow-up of this series of patients showed that the median survival was 2 years for patients achieving a CR and 9 months for those in PR [11].

Patients with asymptomatic lymphocytosis who are relatively stable or slowly progressive can be monitored. The first line treatment for rapidly progressive disease is intravenous alemtuzumab which is also effective for the skin disease. Pentostatin (purine analogues) can be considered along with alemtuzumab for patients showing slow response to alemtuzumab on its own. In spite of satisfactory response with alemtuzumab, patients tend to relapse with T-PLL. Autologous and allogenic hematopoietic stem cell transplantation has been found to be useful in such patients [11].

The differential diagnoses of erythroderma due to TPLL include SS, erythrodermic mycosis fungoides (MF) and adult T-cell leukemia-lymphoma (ATLL).SS is characterised by erythroderma, peripheral lymphadenopathy and atypical circulating lymphocytes called as Sezary cells or Lutzner cells [13]. Sezary cells exhibit distinctive cerebriorm nuclear outlines best detected on high magnification [10]. SS can present primarily as erythroderma without pre-existing skin disease or can develop secondarily in patients with mycosis fungoides. The diagnostic criteria for this syndrome are that the circulating

monoclonal lymphocyte population should be identified by molecular or cytogenetic methods and there should be an identity between the circulating T-lymphocyte clone and the clone present in the skin, in addition to one of the following: atleast 1,000 Sezary cells per mm3 of peripheral blood, an increased population of CD4+/CD7- in peripheral blood with remarkable predominance of CD4 cells in relation to CD8 cells (CD4/CD8 ratio>10), Sezary cells with a diameter >14 μm representing >20% of the circulating lymphocytes and, aberrant expression of pan T-cell antigens [13]. Patients with MF can sometimes progress to erythroderma without blood findings of SS called as erythrodermic MF [13].

ATLL can present as solitary or widespread papules, nodules, tumours or erythroderma. The clinical features in an acute form of ATLL include marked leucocytosis, lymphadenopathy, hepatoslpenomegaly, skin involvement and hypercalcemia [14]. Skin histology usually shows epidermotropic infiltrate of medium to large cells which have pleomorphic nuclear morphology [14]. The tumour cells in the peripheral blood have characteristic polylobulated nuclei called flower cells [10]. The immunophenotypic profile includes expression of CD2, CD3, CD4 and CD5. Weak expression or absence of CD7, absent CD8 and positive CD25 are features of ATLL [10]. Serologic confirmation of HTLV-1 infection will be present and monoclonal integration of HTLV-1 proviral genome can be demonstrated. No specific cytogenetic abnormalities are noted but most cases exhibit an abnormal karyotype [10].

Our case can be considered analogousto cutaneous T-cell lymphoma both in terms of the difficulty in proving the diagnosis - needing multiple skin biopsies, and possible link between cutaneous and systemic disease that occurred after a latent period. TPLL should be considered as a rare cause of erythroderma, which may clinically and histologically mimic Sezary syndrome.

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