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CASE REPORT

Erythema multiforme-like lesions in primary cutaneous aggressive cytotoxic epidermotropic CD8+ T-cell lymphoma:A diagnostic and therapeutic challenge

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ABSTRACT

Primary cutaneous aggressive cytotoxic epidermotropic CD8+ T-cell lymphoma is an extremely rare, rapidly progressing, cutaneous lymphoma, with frequent systemic involvement and poor prognosis, that still represents a diagnostic and therapeutic challenge, especially in the early stage. Herein, we report a case of an elderly woman with a fulminant course, who at onset presented with clinical and pathological features mimicking erythema multiforme (EM) and treated with cyclosporine that led to rapid deterioration with fatal outcome 6 months after disease onset. Histopathology showed a lichenoid, epidermotropic and nodular, angiocentric, dermal and subcutaneous infiltrate of βF1, CD8+, CD45RA+ small to medium-sized atypical lymphoid cells, which strongly expressed cytotoxic markers. Monoclonal T-cell-γ receptor was clonally rearranged and array-CGH showed numerous chromosomal imbalances. This case evidences the clinical, pathological and therapeutic challenges involved in this tumor. The first biopsy showed an interface dermatitis-like pattern, revealing the deceptive features that early cutaneous infiltrates of this aggressive lymphoma may have. A high suspicion for aggressive CTCL and a low threshold for repeat biopsies should be maintained when faced with rapidly progressing and/or ulcerative EM-like lesions, especially if immunomodulatory therapy is being considered.

KEYWORDS

erythema, interface dermatitis, multiforme-like, primary cutaneous aggressive cytotoxic CD8+ T-cell lymphoma

Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (pCAECD8+ CTCL), is an extremely rare, rapidly progressing cutaneous lymphoma, with frequent systemic involvement, first recognized as a distinct clinicopathologic entity by Berti et al.[1] As the name suggests, this entity has an aggressive behavior and exhibits marked epidermotropism on histopathologic analysis. Conventional treatment modalities for classic CTCL are often ineffective and the prognosis is poor with a median survival of 12 months.[2,3] Despite proposals of diagnostic criteria,[4] this tumor is still a diagnostic and therapeutic challenge, especially in its early stage where the clinical and pathologic findings may be subtle and/or mimic an inflammatory dermatosis such as Mucha-Haberman disease,[5] psoriasiform dermatitis,[6,7] pyoderma gangrenosum8 or an indolent form of CTCL, like mycosis fungoides (MF) and lymphomatoid papulosis.[1]
Herein, we describe the clinicopathologic and cytogenetic features of a case of pCAECD8+ CTCL with a fulminant course in an elderly woman who presented at onset with targetoid erythematous patches, clinically and pathologically misdiagnosed elsewhere as erythema multiforme (EM).

CASE REPORT

A 78-year-old woman, in poor general health, with fever, was referred to us with a 4-month history of disseminated, annular, target-like, erythemato-violaceous plaques with central crusts and erythematous-violaceous halos. The dermatosis had begun on the extremities, back and face. When she had been visited

elsewhere for the first time, a diagnosis of atypical EM was made and a 1-month course of oral prednisone 50 mg/day was administered and the diagnosis was sustained by a skin biopsy. As no response was observed within a few weeks and new lesions continued to appear, CsA 5 mg/kg/day was administered for 1 month. Despite this, her dermatosis worsened and ulcerative lesions developed with dissemination; therefore, the treatment was suspended.

Two clinical photographs and a histologic biopsy specimen that had been taken elsewhere at disease onset were available. On review, the initial clinical lesions were erythematous violaceous patches and plaques vaguely reminiscent of EM (Figure 1A,C) and the pathologic changes resembled those of an interface dermatitis with diffuse basilar vacuolization of the epidermis accompanied by a scant infiltrate of small-sized lymphocytes tagging along the dermalepidermal junction with suprabasilar lymphocytosis around apoptotic keratinocytes (Figure 1B,D). On admission to our hospital, almost all the patient's skin was covered by ulcerated plaques admixed with a few target-like patches and plaques with a grey necrotic center and an erythematous violacous halo (Figure 2). There was no involvement of palms or soles or the visible mucosae nor lymphadenopathy.

A new biopsy was taken from a nonulcerated plaque on the upper arm. Histopathology showed a lichenoid and nodular dermal infiltrate of pleomorphic, small to medium-sized lymphoid cells with scant cytoplasm and irregular nuclear contour admixed with hemorrhage foci (Figure 3A). The neoplastic cells exhibited marked tropism for the basal cell layer, acrosyringia and acrothrichia, with ballooned and necrotic keratinocytes (Figure 3B). There was prominent angiocentric infiltration and angiodestruction (Figure 3C). The subcutaneous fat was also infiltrated with rimming of atypical lymphocytes around the adipocytes (Figure 3D). Immunohistochemically, the majority of atypical lymphocytes were βF1, CD3, CD8, CD45RA, CD7, granzyme B, perforine and TIA-1 positive, whilst about 20% of atypical lymphoid cells were double CD4/CD8 negative. CD2 and CD5 were markedly reduced, whilst CD4, CD20, CD30, CD56, TdT and γδ were negative (Figure 4). CD15 was expressed in about 30% of cells. Ki67 proliferation index was elevated (80%). In situ hybridization for EBER was negative. Molecular analysis showed monoclonal T-cell-γ receptor rearrangement. Array-based comparative genomic hybridization (CGH) analysis of DNA samples extracted from frozen specimens from a cutaneous lesion showed numerous chromosomal imbalances, including amplifications of chromosome 17, long arm of chromosomes 7 and 9 and some regions of chromosomes 14 and 20 and major losses on short arm of chromosomes 8 and 18 and on long arm of chromosome 13 (Figure 5).

Staging investigations showed multiple tumors in the lungs, mesentherium and orbits at CT-scan, whilst bone marrow biopsy and peripheral blood cytometry results were normal. HIV, HTLV 1, HBV, HCV and EBV serologies were negative. A CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) cycle was administered, but the patient died 2 months after having been admitted to our care, 6 months after the onset of her disease.

DISCUSSION

pCAECD8+ CTCL is a rare variant of cutaneous lymphoma and is still considered a provisional entity in the latest 2016 World Health Organization Classification of Cutaneous lymphomas.[9] Whilst no single criterion is pathognomonic alone for this lymphoma, diagnosis and differentiation from other primary or secondary cytotoxic CD8+ T-cell malignancies relies on the careful integration of the clinical, histopathologic, immunophenotypic and molecular findings.[1,2,4,9] A short history of localized or disseminated multiple papules, plaques and tumors, which tend to ulcerate with central necrosis and hemorragic crusting, without any precursor lesions, is characteristic. The course is rapidly progressive with strong tendency to disseminate to the visceral organs, including the lung and central nervous system, whilst the lymph nodes are often spared. Less aggressive clinical presentations have also been reported,[10–14] but whether they are true examples of pCAECD8+ CTCL or rather represent indolent forms of CD8+ CTCL may be questioned.[4]

Histopathologically, completely developed lesions are characterized by dense, dermal and sometimes hypodermal infiltrates of small-medium or medium-large, pleomorphic and/or blastic lymphocytes exhibiting epidermal and/or adnexal tropism associated with keratinocyte ballooning and necrosis. Angiocentricity and angiodestruction are infrequent and late findings, often signaling a patient who has, or will have, a more aggressive clinical course. The neoplastic cells characteristically show a high Ki-67 proliferation index, are consistently EBV negative and usually CD4-/CD8+ and CD45RA+ with a strong cytotoxic marker expression,

whilst CD2 is typically lost.[4,15–18] However, it is not infrequent to find cases with CD4/CD8 double negative or CD45RA partial or total negative phenotypes.[18] Expression of a CD2−/CD7+ or CD15+ phenotype has been associated with rapid progression and poor prognosis.[15,19] Our case had CD2−/CD7+ CD15+ and a partially double CD4/CD8 negative phenotype, reinforcing the previous observations.

Although the diagnosis of overt pCAECD8+ TCL can be made on the basis of the aforementioned criteria, this malignancy may still represent a diagnostic challenge in its early stage, where the clinical and pathologic findings may still be subtle and mimic a variety of inflammatory dermatoses.[5–8] When the patient had been visited at the onset of the disease, the targetoid appearance of the early cutaneous lesions had led the referral dermatologist to a clinical suspicion of EM that, in turn, had been substantied by the interface dermatisis-like changes observed on the biopsy performed. A thorough PubMed search failed to identify cases of pCAE-CD8+ CTCL presenting with EM-like lesions. However, Kuo et al[20] reported a case of rapidly progressing, primary cutaneous T-cell lymphoma with CD8 immunophenotype and angiocentric and angioinvasive features initially misinterpreted as atypical EM where the final diagnosis was reached after repeated skin biopsies. Although the immunophenotypic study of this case did not include any cytotoxic markers, it might well represent a further example of pCAECD8+ CTCL presenting with EMlike lesions. Interestingly, a wider PubMed search also revealed that EM-like cutaneous lesions may be a clinical presenting feature of other T-cell malignancies, such as aggressive mature T-cell and NK/T-cell lymphoma, adult T-cell lymphoma/leukemia,[21] refractory celiac disease,[22] extra-nodal NK/T-cell lymphoma[23] and monomorphic epitheliotropic intestinal T-cell lymphoma,[24] reflecting the functional attributes of the neoplastic lymphocytes that can recapitulate, at least in part, the clinical aspects of some cytotoxic, CD8+ T-cell mediated, reactive skin disorders.[25–27]

An accurate and timely diagnosis of pCAE-CD8+ CTCL is crucial, as aggressive treatment strategies, such as multiagent chemotherapy and allogeneic stem-cell transplantation in selected cases might be considered and discussed at an early stage of the disease.[28] The misdiagnosis of our patient's condition at presentation not only delayed the correct diagnosis but also the correct therapy. In fact, the patient deteriorated rapidly after a CsA course, a drug with properties that reduce the T-cell mediated immune reaction activity.[29] Although these effects may be beneficial in autoimmune reactive disorders, a negative influence may well be expected when treating aggressive CTCL, where the immunesurveillance mechanisms by activated cytotoxic T-cells against neoplastic lymphocytes are severely impaired [30,31]

In conclusion, the case reported herein highlights the diagnostic and therapeutic challenges that pCAECD8+ CTCL may have, especially in early stage, that is, (1) clinically, the earliest skin lesions had a targetoid appearance reminiscent of EM; (2) pathologically, the biopsy from an early lesion showed an interface dermatitis-like pattern, revealing the deceptive features of the early cutaneous infiltrates of this aggressive lymphoma. Therefore, a high suspicion for aggressive CTCL and a low threshold for repeat biopsies should be maintained when faced with unresponsive and/or rapidly progressing and/or ulcerative EM-like skin lesions in adults, especially if immunomodulatory therapy is being considered.

Lastly, molecular information may be helpful to make an accurate diagnosis and plan the most appropriate therapy for these patients [32,33] Indeed, not only can cytogenetic changes be seen very early on in the disease process, but also the extent of chromosomal aberrations increases with disease stage and in more aggressive CTCL subtypes, as observed in our study.

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FIGURES

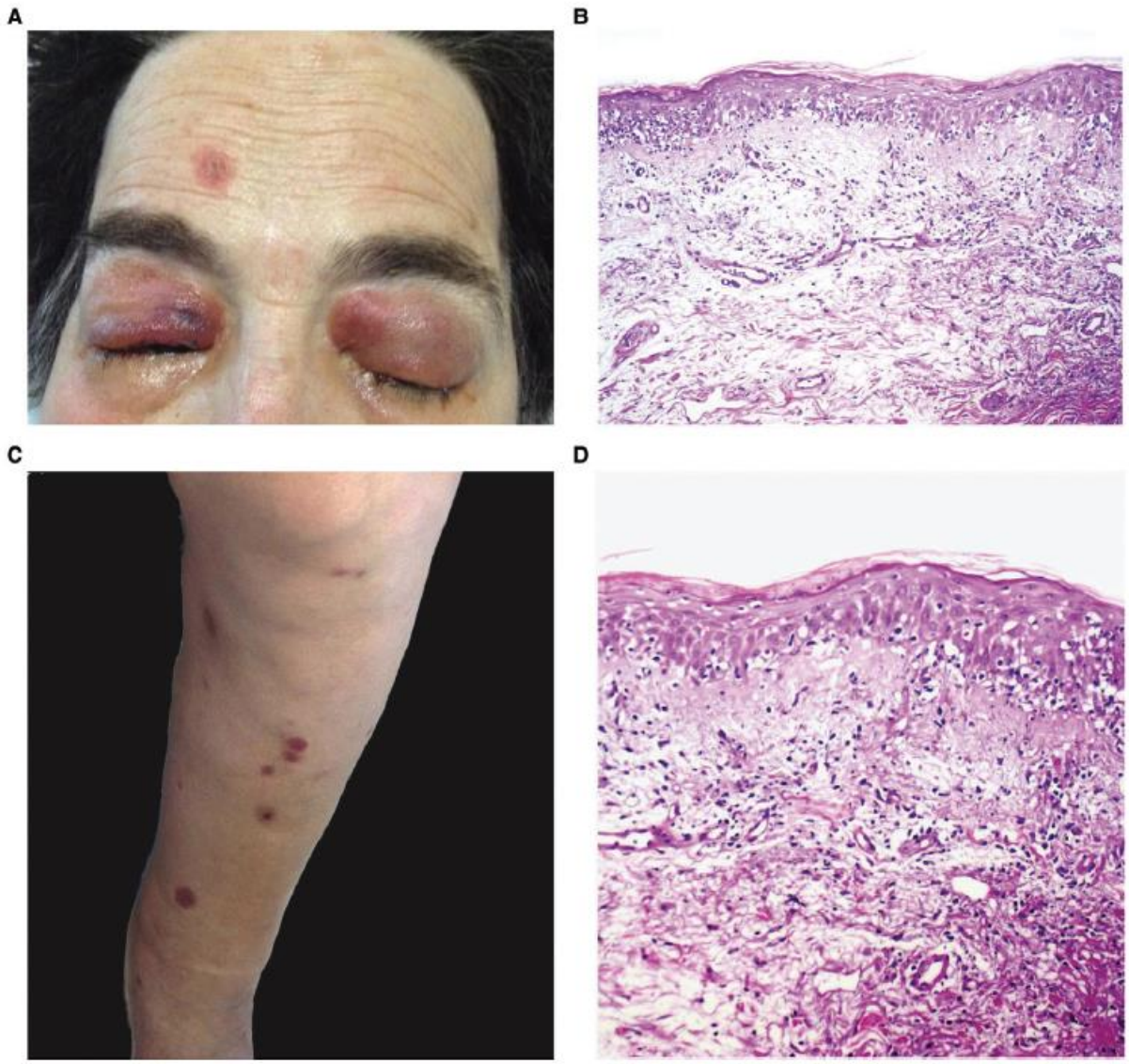

FIGURE 1 A and C, Clinical appearance of cutaneous lesions at onset with erythematous violaceous patches and plaques on the eyelids, forehead and legs. B and D, Biopsy specimen from an early lesion showing an interface vacuolar dermatitis with basilar vacuolization and prominent lymphocyte “exocytosis” with many apoptotic keratinocytes

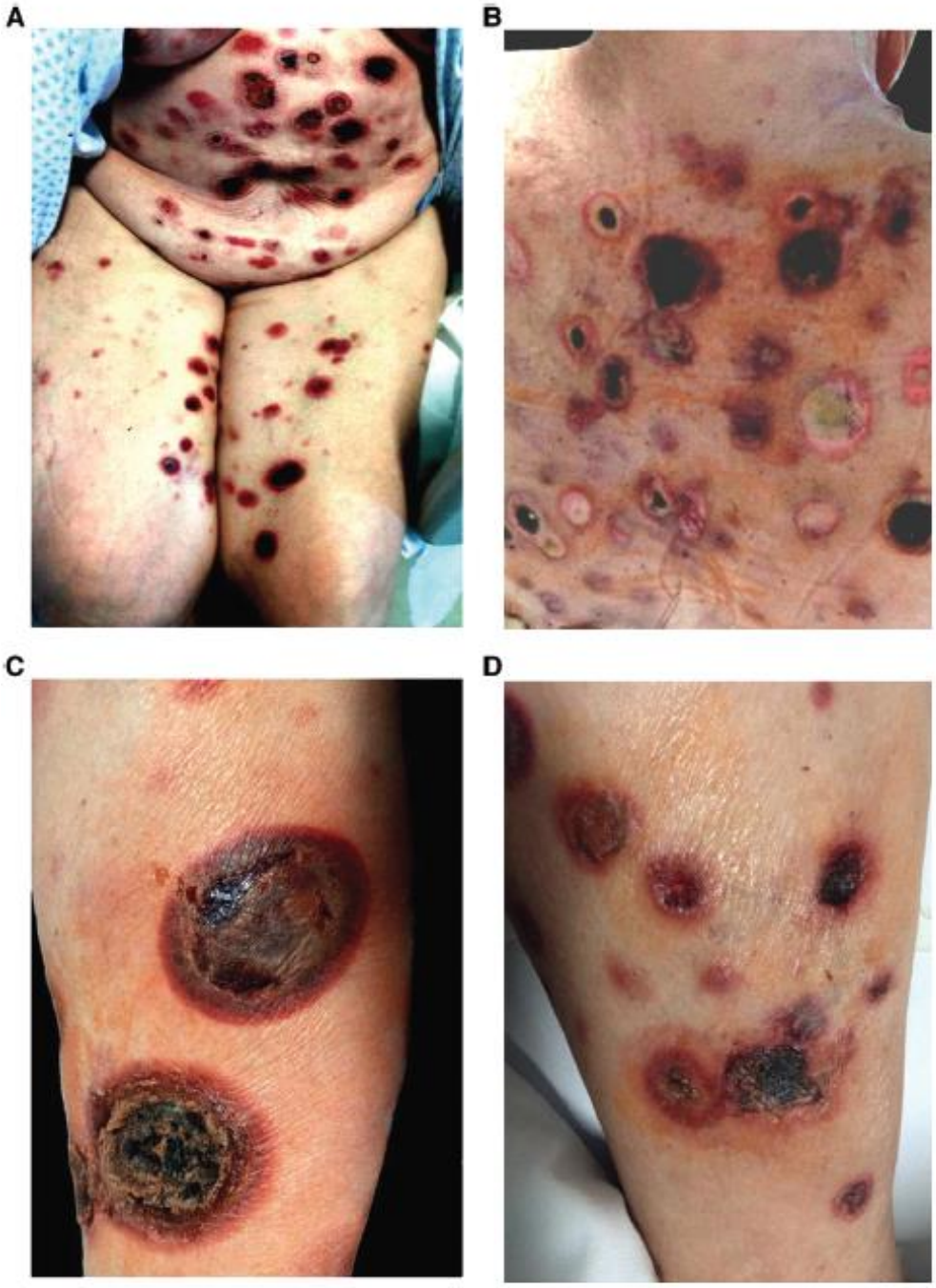

FIGURE 2 A, Widespread erythematous violaceous patches and plaques with many lesions with central necrosis and crusting on the trunk and lower extremities. B, Lesions at different stages of evolution on the back. C, Targetoid plaques with necrotic center and crusts on the upper arm. D, Ulcerated plaques on the leg

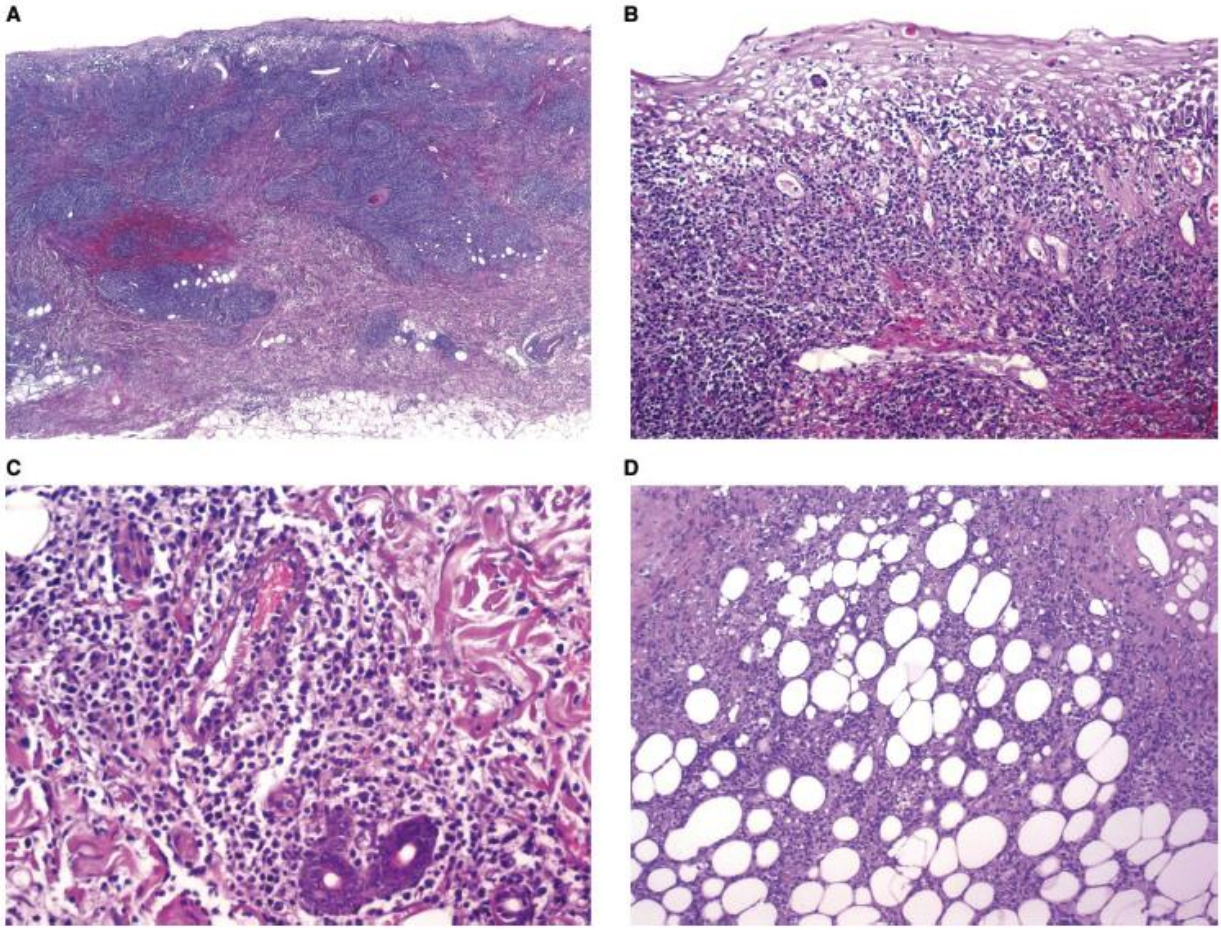

FIGURE 3 A, Dense, nodular and lichenoid lymphoid infiltrate throughout the dermis. Numerous foci of hemorrhage are apparent. B, Small to medium pleomorphic epidermotropic lymphocytes and keratinocyte apoptosis. C, Prominent angiocentricity with early angiodestruction. Notice pleomorphic medium-sized lymphocytes. D, Subcutaneous fat infiltration by neoplastic lymphocytes

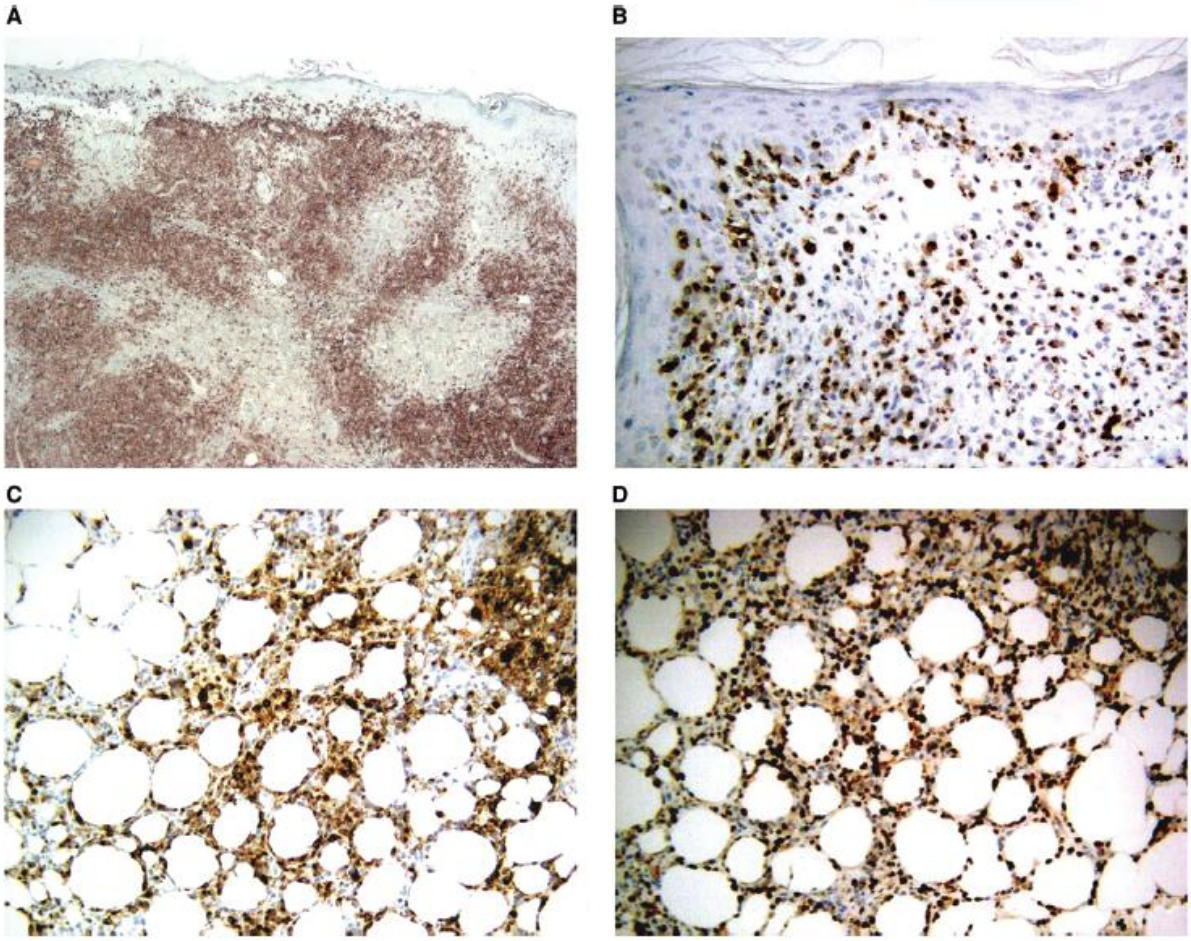

FIGURE 4 A, Staining for CD8 showing dense perivascular and lichenoid infiltrate of lymphoid cells with prominent epidermotropism. B, Strong granzyme B expression of neoplastic lymphocytes. C, Granzyme B positivity by lymphoid infiltrate in the hypodermis. D, Staining for Ki-67 highlighting numerous proliferating atypical lymphocytes in the subcutaneous fat

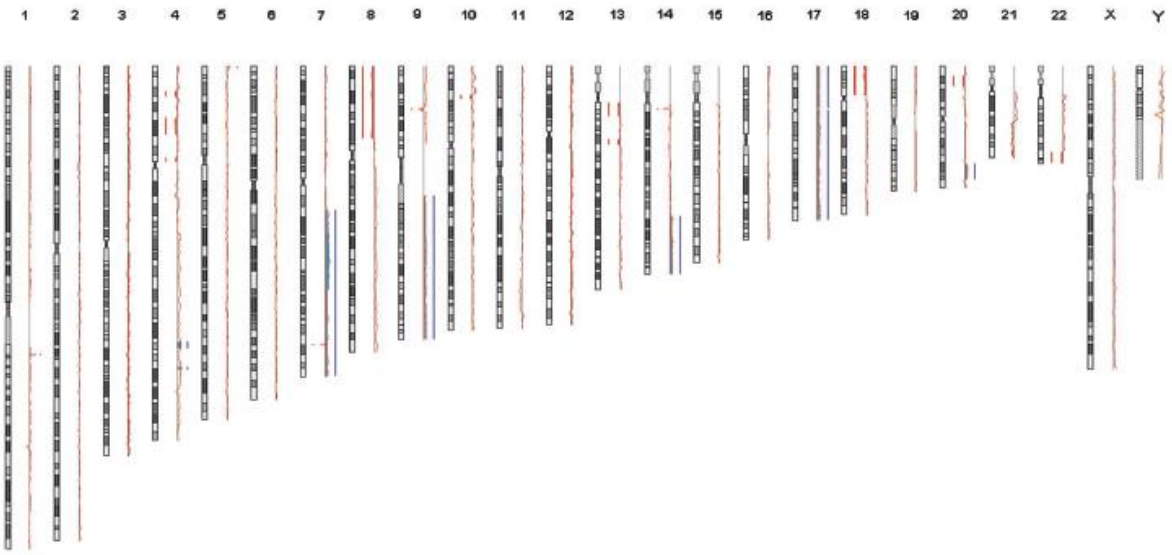

FIGURE 5 Array-based comparative genomic hybridization (array-CGH). The most relevant gains are amplifications of chromosome 17, long arm of chromosomes 7 and 9 and some regions of chromosomes 14 and 20. Major regions of chromosomal losses are on short arm of chromosomes 8 and 18 and on long arm of chromosome 13