Virchows Arch (2001) 438:298–301
DOI 10.1007/s004280000320

CASE REPORT

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Subcutaneous lymphoid hyperplasia arising at site of ethnic scarifications and mimicking subcutaneous panniculitis-like T-cell lymphoma

Received: 6 April 2000 / Accepted: 29 August 2000 / Published online: 21 November 2000

Abstract The case of a 40-year-old black man, who developed a very unusual tumour-like lymphoid hyperplasia involving primarily the subcutaneous tissue, is reported. The lesion, which arose at a site of tribal scarifications, displayed a deceptive morphology that closely resembled subcutaneous panniculitis-like T-cell lymphoma (SPTCL). An accurate diagnosis could only be made following detailed immunohistochemical and molecular studies. Although SPTCL has been thought to represent a very specific clinicopathologic entity, the present case illustrates that its histological appearance can, however, be closely mimicked by reactive and benign conditions.

Keywords Subcutaneous panniculitic T-cell lymphoma · Pseudolymphoma · Subcutis · Scarification

Introduction

Various inflammatory diseases of the skin may resemble cutaneous lymphomas clinically and/or histologically [10]. Depending on the predominant cell type that makes up the infiltrate, these pseudoneoplastic conditions have been divided into T- and B-cell pseudolymphomas, respectively [2, 10]. They mostly involve the dermis and, at times, may extend to the subcutaneous fat. However, lymphoid hyperplasia, arising exclusively in the subcutaneous tissue, remains distinctly rare [4, 6]. Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a distinct neoplasm that usually follows an aggressive clinical course. This rare tumour preferentially involves the subcutaneous tissue of the extremities and/or of the trunk, and a significant number of cases are complicated by a haemophagocytic syndrome [3, 7, 11, 14, 16]. Histologically, this neoplastic disorder is made up primarily of small- or medium-sized lymphocytes that involve the subcutaneous fat in a way very similar to that of a lobular panniculitis [7, 11, 14, 16]. When investigated using immunohistochemistry, most SPTCL cases show a CD3+, CD4–, CD8+, CD56– T-cell phenotype and consistently express markers of cytotoxic T lymphocytes, such as cytolytic granule-associated protein TIA-1, perforin, or granzyme B. In this context, rimming of fat spaces by CD8-positive lymphocytes is usually considered as a characteristic feature of SPTCL [2]. With regard to the T-cell receptor (TCR) phenotype, the αβ TCR subtype is more frequently found than the γδ TCR one [11]. On molecular grounds, TCR gene rearrangement analysis usually demonstrates clonal rearrangements of the genes coding for the β, the γ, or the δ subunits of the TCR [7, 11, 14].

Herein, we report a very unusual form of lymphoid hyperplasia, primarily involving the subcutis and, by morphology, closely mimicking SPTCL. In addition, this lesion arose at a site of tribal scarifications, therefore suggesting a possible relationship between the two conditions.

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Case report

A 40-year-old black man, originating from Benin, was referred to the hospital because of a tumour mass of the right cheek. The tumour mass, which spontaneously appeared 6 weeks before, was characteristically localised under ethnic scars. These tribal scarifications were made in the youth, and the patient had no significant medical history apart from a positive serology for hepatitis A virus and a primary tuberculosis infection, 10 years before. Neither recent drug intake nor arthropod bite were recorded. Laboratory findings didn't disclose any significant alterations with the exception of a slight increase in lipase serum levels (43 mU/ml). Antinuclear antibody (ANA), rheumatoid factor, and antineutrophil cy-

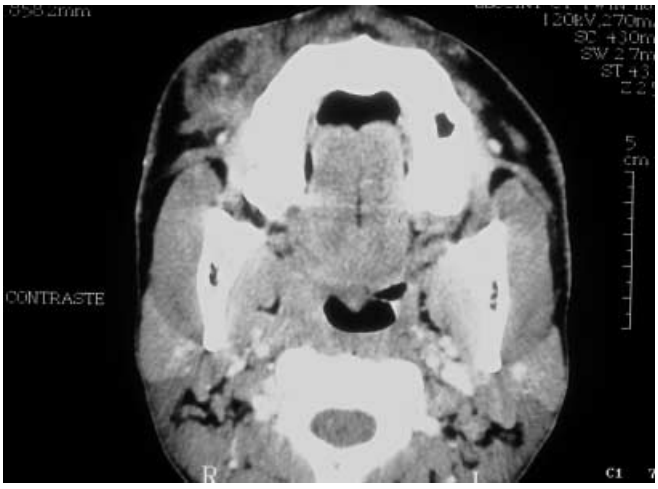

Fig. 1 This computed tomography scan shows a rather well-circumscribed tumour involving the soft tissues of the right cheek (*upper left*)

toplasmic autoantibody (ANCA) serum investigations were negative. While prior immunizations against cat scratch disease, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) were detected, no serum antibodies to *Borrelia burgdorferi*, *Chlamydia psittaci*, *Toxoplasma gondii*, human immunodeficiency virus (HIV), hepatitis B and C viruses, or to the microorganisms that are responsible for syphilis, brucellosis and leishmaniasis could be found. Both echographic and computed tomography (CT) scan procedures demonstrated a 3.6×2×1.4-cm tumour process involving the outer part of the cheek's wall (Fig. 1). Complementary clinical investigations and systemic image studies failed to reveal systemic involvement. Therefore, a surgical but incomplete excision was performed for diagnostic purposes. Since the lesion was considered as probably benign, no further therapy was given. The facial nodule locally recurred and increased in size 10 months after the initial diagnosis. There was still no evidence of disseminated disease, and a new biopsy was performed.

Materials and methods

Formalin-fixed tissue samples from the initial lesion and its recurrence were routinely processed and embedded in paraffin, according to standard histological techniques. Sections were stained with haematoxylin and eosin. Immunohistochemical studies were performed on paraffin sections using a Ventana Nexes Staining System (Ventana Medical Systems, Tucson, Ariz.). Antibodies directed against the following antigens were used: CD43, BioGenex, San Ramon, Calif.; κ and λ immunoglobulin (Ig) light chains, CD3, CD8, CD20, CD21, CD35, CD45RO and CD79a, Dako A/S, Glostrup, Denmark; CD5 and CD57 Novocastra Laboratories Ltd, Newcastle-upon-Tyne, UK; granzyme B: Monosan, AM Uden, NL; CD30: NeoMarkers, Union City, Calif.; TIA-1, Immunotech SA, Marseille, France.

In order to investigate the possible role of EBV infection in the pathogenesis of this disorder, an in situ hybridisation (ISH) for EBV-encoded RNA (EBER) was performed, using a supersensitive ISH detection system (BioGenex, San Ramon, Calif.). The search for clonal Ig heavy chain (IgH) gene rearrangement was performed using the polymerase chain reaction (PCR) analysis [12]. For this purpose, formalin-fixed paraffin-embedded tissue from the lesions was used. Briefly, five 10-µm thick sections were dewaxed and subsequently digested with proteinase K (200 µg/ml) in buffer [50 mM Tris (pH 8.5), 1 mM ethylene diamine tetraacetic acid (EDTA), 0.45% Tween20] for 48 h at 37°C. For the IgH PCR analysis, consensus primers complementary to the IgH framework 3 region (5'-CTGTCGACACGGCCGTGTATTACTG-3') and to the junction genes (5'-AACTGCAGAGGAGACG-GTGACC-3') were used. The PCR reaction mixture consisted of: primers (0.2 µM), dNTP (200 µM), $MgCl_2$ (2.5 mM), KCl (50 mM), Tris (10 mM), gelatin (0.01%), Tween20 (0.045%) and *Taq* polymerase (1 U) (Promega Benelux BV, Leiden, NL). The thermocycler conditions were: denaturation at 94°C, annealing at 59°C and extension at 72°C, each for 40 s with a total of 50 cycles. The PCR products were size-fractionated by 8% polyacrylamide-gel electrophoresis and ethidium bromide staining.

PCR analysis of the genes coding for the γ-chain of the T-cell receptor (TCR) was also performed. Multiplex PCR analysis with primers directed to the genes coding for the variable (V) and the joining (J) regions of the TCR γ-chain was done to distinguish the allelic configuration of a rearrangement. A GC-clamp (5'-CGC-CCGCCGCGCCCC GCGCCCGGCCCGCCGCCCCCGCCCG3') was attached to all V primers. This, combined with a denaturing gradient gel electrophoresis (DGGE), ensures that the VJ-amplified products are separated on melting differences in the VJ joining N region. Primers directed to four V-genes [Vγ2: 5'-(GC)-TA-CATCCACTGGTACCTACACCAG-3'; Vγ9: 5'-(GC)-GAAAGG-AATCTGGCATTCCGTCAG-3'; Vγ10: 5'-(GC)-AAGCAACAA-AGTGGAG GCAAGAAAG-3'; Vγ11: 5'-(GC)-AGTAAAAATG-CTCACACTTCCACTTC-3'] and three J-genes [Jγp: 5'-AAGCT-TTGTTCCGGGACCAAATAC-3'; Jγp1,2: 5'-GAAGTTACTAT-GAGC(C/T)TAGTCCCTT-3' and Jγ2: 5'-TACCTGTGAC AAC-AAGTGTTGTTC-3'] were used [5]. The PCR reaction mixtures (four for each sample) consisted of one of the V gene primers (1 µM), the three J gene primers (1 µM), dNTP (200 µM), $MgCl_2$ (2.5 mM), KCl (50 mM), Tris (10 mM), and Amplitaq Gold (2.5 U) in a total reaction volume of 50 µl. After denaturation at 94°C for 10 min, the samples were subjected to 45 cycles of amplification: denaturation at 94°C for 75 s, annealing at 66°C for 75 s and extension at 72°C for 1 s (1 s added for each cycle). A final extension of 2 min at 72°C was also added. After PCR, the samples were vacuum dried and dissolved in 5 ml loading buffer. The samples were run on a 10–60% denaturing gradient in tris acetic acid EDTA (TAE) buffer at 60°C and 160 V for 5 h. Gels were stained with ethidium bromide and photographed under ultraviolet illumination.

Pathological findings

Pathological study of the initial lesion and that of the recurrence revealed similar findings. Both tumours were composed of lymphoid cells of heterogeneous morphology involving the subcutaneous tissue (Fig. 2 and Fig. 3). The pattern of adipose tissue infiltration typically resembled that of a lobular panniculitis with some myxoid degeneration of the adipocytes. There was also some vascular hyperplasia. At higher magnification, the cellular infiltrate was composed of a few large or medium-sized cells, scattered among numerous small lymphocytes, some plasma cells, and histiocytes. The latter occasionally exhibited features of erythrophagocytosis (Fig. 4) but didn't cluster together to form granulomas. In addition, some areas featuring karyorrhectic bodies were also noticed (Fig. 5).

The overall immunophenotypic results visualised relatively distinct B-cell areas accompanied by a T-cell population. The B-cell component, recognised by the expression of CD20 and CD79a, comprised a majority of small lymphocytes and a minority of larger cells. CD21 and CD35 immunostainings occasionally showed the presence of follicular dendritic cells in some of

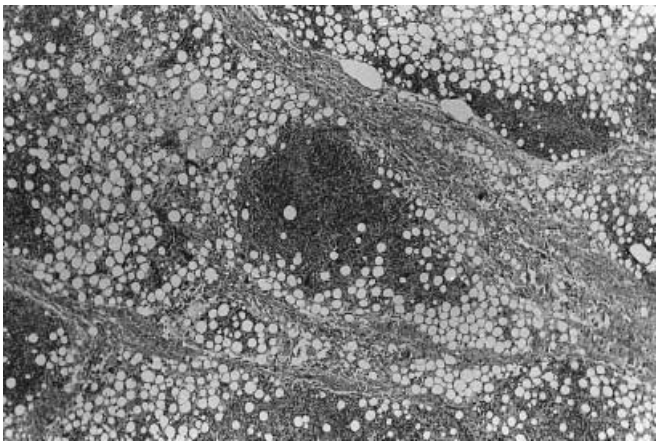

Fig. 2 Low power view of the tumour: a dense and diffuse lymphocytic infiltrate involves the lobules of the subcutaneous fat. Haematoxylin and eosin stain, ×40

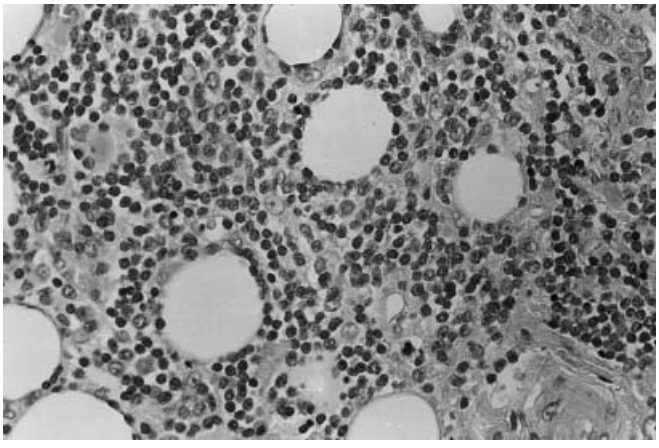

Fig. 3 This high power view shows the cytologic composition of the lymphoid infiltrate. There is also rimming of the fat spaces by lymphocytes, a feature usually considered as characteristic of subcutaneous panniculitis-like T-cell lymphoma. Haematoxylin and eosin stain, ×400

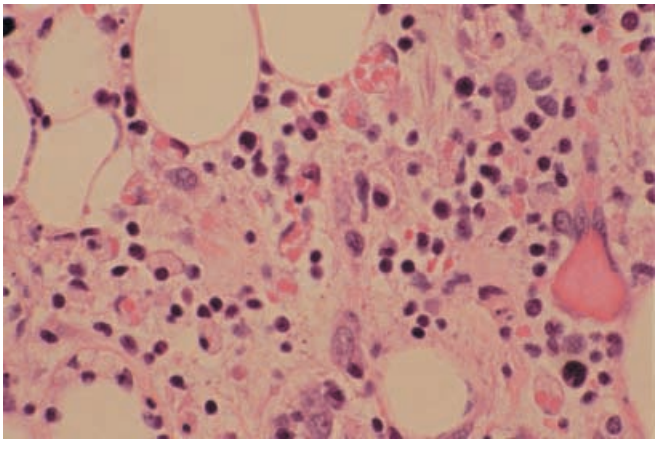

Fig. 4 This high power view reveals several histiocytes featuring erythrophagocytosis. Haematoxylin and eosin stain, ×500

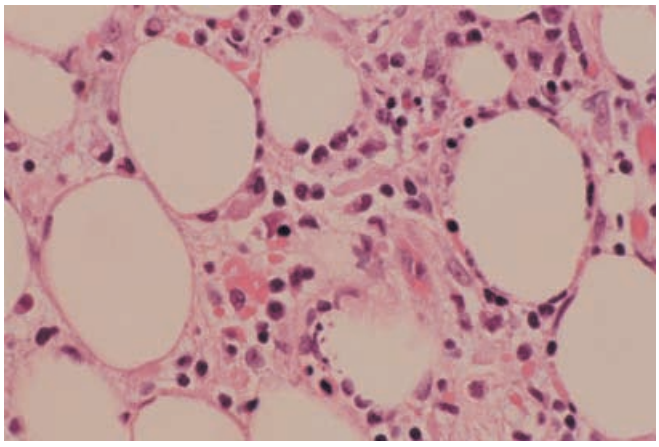

Fig. 5 This high power view shows some karyorrhectic bodies and one histiocyte featuring erythrophagocytosis. Haematoxylin and eosin stain, ×500

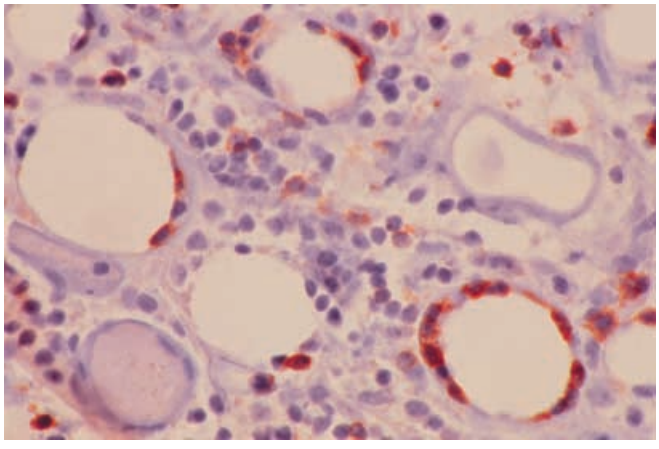

Fig. 6 CD8 immunostaining: there is rimming of some fat spaces by CD8-positive lymphocytes. Immunoperoxidase, ×400

these B-cell aggregates. However, no organised network like those seen in B-cell follicles could be found. Plasma cells didn't demonstrate Ig light chain restriction. The remaining lymphoid cells were T-cells expressing CD3, CD5, CD45RO and CD43 antigens. Only a limited number of cells were CD8, CD57, TIA-1 and granzyme-B positive. Interestingly, fat spaces were surrounded by some CD8-positive T lymphocytes (Fig. 6). Finally, some larger cells were also CD30 positive.

PCR analysis of DNA extracted from paraffin-embedded tumour samples didn't demonstrate any clonal rearrangement of the genes coding for the IgH or for the γ-chain of the TCR (data not shown). Using ISH for EBER, no EBV transcript could be detected (data not shown). Based on these data, a diagnosis of lymphoid hyperplasia involving primarily the subcutis was proposed.

Discussion

This study describes an unusual variant of lymphoid hyperplasia involving the subcutaneous tissue and showing lobular panniculitis-like changes. Of the various diseases featuring such histological alterations, one of the conditions that most closely resembles the present lesion is SPTCL [3, 7, 11, 14, 16]. Indeed, many of the histological features that are observed in this case may also be found in SPTCL. These include a prominent lymphoid infiltrate that involves the subcutaneous fat in a way very similar to that of a lobular panniculitis, some large cells set in a background composed of small lymphocytes, plasma cells and histiocytes, some rimming of the adipocytes by CD8-positive T lymphocytes, occasional phagocytosis of red blood cells by macrophages, karyorrhexis and stromal alterations, such as myxoid changes involving the lobular adipocytes. However, some findings do not support a diagnosis of SPTCL.

First, the absence of clinical deterioration and the local but chronic growth without systemic dissemination are clinically more suggestive of a benign process than a malignant one. Although SPTCL may occasionally behave in a more indolent way [11], it is mostly a highly malignant neoplasm that pursues an aggressive course, usually associated with severe clinical symptoms [3, 7, 11, 14, 16].

In addition, phenotypically, the presence of B-cell aggregates and polytypic plasma cells intermingled with T-cells rather suggests a reactive lymphoid infiltrate. In this regard, it is worth noting that B cells may be occasionally found in SPTCL, but they are usually infrequent and scattered within the neoplastic infiltrate [7].

Finally, on molecular grounds, the absence of clonal rearrangement of the genes coding for the IgH or for the γ-chain of the TCR in both initial and recurring lesions also favours a reactive condition. In this case, the triggering or predisposing factors that are responsible for such a subcutaneous pseudolymphoma remain yet to be elucidated since most of the classical causes of cutaneous lymphoid hyperplasia, including those related to connective tissue diseases or to viral infections [8, 10, 15], were not demonstrable.

In this context, the close vicinity with the scarifications may indicate a possible connection between the two conditions. It is worth noting that these scarifications are usually obtained by incising the skin and by applying, thereafter, a dressing made of various traditional plants. The composition of this dressing may vary from place to place, but it may contain either cashew nut extracts or squashed leafs originating from various *Euphorbiacae* species. The penetrating sap induces a strong local inflammatory response, which persists during a few days (A. Diedhiou, personal communication). Since both cashew nut and plants belonging to the *Euphorbiacae* species contain substances with strong immune properties [9, 13], we can conceive that all of the aforementioned histological changes found in this patient are the consequence of a delayed persistent immunisation reaction to one or several of these immunostimulating compounds, introduced at the time of the scarification process. This speculative assumption is in other respects supported by the description of hypertrophic lesions that arise several years later on areas with scarifications [1].

Whatever the precise pathogenesis may be, this observation illustrates that, although SPTCL represents a very specific clinicopathologic entity, it may, however, have been histologically mimicked by a reactive condition, such as lymphoid hyperplasia involving the subcutis.

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