Primary cutaneous CD30+ lymphoproliferative disorder – a 10-year follow-up. A case report and differential diagnosis

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Primary cutaneous CD30+ lymphoproliferative disorders (LPDs) are the second most common group of primary cutaneous T-cell lymphomas (CTCLs). The spectrum of LPDs includes lymphomatoid papulosis (LyP), primary cutaneous anaplastic large cell lymphoma (C-ALCL) and borderline cases. The term "borderline lesions" refers to cases where histological features are similar to LyP, but clinically behave as C-ALCL, or to cases where histological features are typical for C-ALCL, but clinically behave as LyP.
We present a clinical and morphological picture of LPD in a 57-year old patient treated in the Department of Oncology and of a relapse after ten years of follow-up and discuss clinical and morphological differential diagnosis and the significance of such diagnosis.

Introduction

Primary cutaneous CD30+ lympho-proliferative disorders (LPDs) are the second most common group of primary cutaneous T-cell lymphomas (CTCLs), accounting for approxi-mately 25-30% of CTCLs. The spectrum of LPDs includes lymphomatoid papulosis (LyP), primary cutaneous anaplastic large cell lymphoma (C-ALCL) and borderline cases [1-9].

LyP is a chronic skin disease, characterized by recurrent and self-healing papulonodular skin lesions, which contain atypical lymphocytes intermingled with a mixed inflammatory infiltrate [1, 4-10].

C-ALCL is a lymphoma composed of large cells with an anaplastic, pleomorphic or immunoblastic cytomorphology. Most (more than 75%) neoplastic cells express the CD30 antigen. There is also no clinical evidence or history of LyP, mycosis fungoides (MF) or another type of CTCL [1, 4-9, 11].

The term "borderline lesions" refers to cases where histological features are similar to LyP, but clinically behave as C-ALCL, or to cases where histological features are typical for C-ALCL, but clinically behave as LyP. Clinical examinations during further follow-up will generally allow for making a diagnosis of LyP or C-ALCL [4, 6, 8, 9].

It is now generally accepted that C-ALCL and LyP represent two ends of a spectrum of LPDs and morphological criteria alone are often insufficient to differentiate between these two entities. The clinical appearance and course are used as decisive criteria for the definitive diagnosis and choice of treatment [4, 6, 8].

Material and methods

Clinical data were retrieved from the archive files of the Department of Oncology.

The original skin biopsies that had been fixed in formaldehyde solution, embedded in paraffin and stained with haematoxylin and eosin were

reviewed. Subsequent slides were immunostained with antibodies CD20, CD79α, CD45RO, CD5, CD3, CD2, CD4, CD8, CD30, granzyme B, ALK-1, EMA, CD15, CD68, CD56, S100, bcl-2.

DNA extraction: Formalin-fixed and paraffin-embedded (FF/PE) samples were deparaffinized and DNA was extracted using the QIAamp DNA Mini Kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer's instructions. T-cell clonality was determined by a PCR-based assay for TCRG gene rearrangement analysis according to previously described protocols [12, 13]. Primers JG12, VG11, VG101 were used [12]. Amplifications were performed with an annealing temperature of 55°C; the number of cycles was 35 [13]. PCR products were analyzed by electrophoresis on 10% polyacrylamide gel. Two samples were analyzed in triplicate.

Clinical findings

A 46-year old male first reported to the Department of Oncology due to lesions confined to the skin involving his buttocks and right hip, persisting for one month. Physical examination demonstrated several infiltrative skin lesions on the right buttock, the largest one measuring approximately 5 cm, with an elevated border and central ulceration measuring 1.5 cm. On the left back and buttock, small papules were seen. On the right hip, pale pink, flat lesions measuring 1 × 1.5 cm were observed.

After two courses of chemotherapy COP (cyclophosphamide + vincristine + prednisone), complete regression of the lesions situated on the left buttock was achieved, but the lesions involving the right hip progressed. In addition, new lesions developed on the right thigh. As a consequence of disease progression, the treatment was switched to the ABVD chemotherapy protocol (doxorubicin + bleomycin + vinblastine + dacarbazine) and radiotherapy of the right buttock (4200 cGy/14fr/200 KV). In view of the fact that new lesions appeared on the chest and back in the course of the above treatment the patient received three courses of CTX + VP + MTX + Adr (cyclophosphamide + vindesine/ platinum + methotrexate + Adriamycin) and right back field radiotherapy (2400 cGy/6 fr/200 KV). At the end of this treatment, all the skin lesions regressed.

One year later, two new skin lesions appeared on the abdomen, measuring approximately 2 cm each, which regressed after administration of topical steroids only.

After nine years without any new lesions, new rapidly growing skin lesions appeared. Physical examination revealed two tumours: a firm, dark red tumour, partially ulcerated, with indistinct border, situated on the abdomen and measuring 5 × 6 cm. The other tumour, with a similar appearance, was located on the left buttock and measured 2 × 3 cm. Radiotherapy of the lesion involving the abdomen (4000 cGy/20 fr/250 KV) resulted in almost complete regression. A new lesion appeared near the right clavicle, measuring 1 cm. The patient received three courses of chemotherapy (chlorambucil + prednisone). The lesion near the clavicle regressed, but the infiltrate on the left buttock remained stable. Radiotherapy of this lesion (4000 cGy/20 fr/250 KV) resulted in complete regression, but new lesions nearby measuring 2.5 × 2.0 cm appeared (Fig. 1). The patient was referred for radiotherapy.

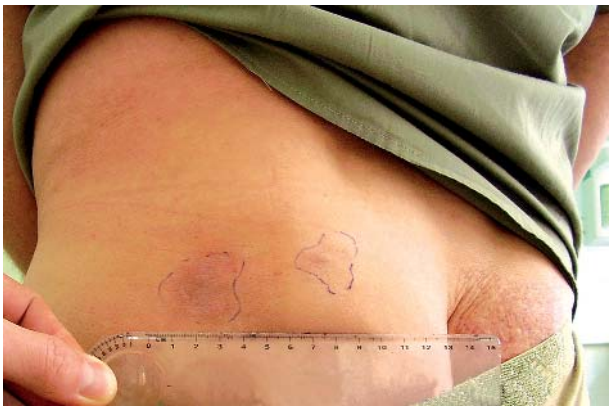

Fig. 1. The larger erythematous area on the left buttock represents regressed tumour after radiotherapy. On the left – two newly developed intradermally located nodules

Histopathological findings

The first biopsy taken from the skin lesion on the buttock revealed a dense irregular lymphoid infiltrate involving the dermis and subcutaneous fat. The epidermis was spared. The infiltrate consisted of large atypical lymphocytes admixed with small lymphocytes. Some of the atypical cells showed morphology of anaplastic cells with round, oval or irregularly shaped nuclei and abundant cytoplasm. Prominent nucleoli were evident in some cells. Mitotic activity in these cells was low.

In biopsy taken subsequently from the same lesion, a denser atypical lymphoid infiltrate was seen in the dermis and subcutaneous tissue. The epidermis was partially ulcerated (Fig. 2). Cohesive sheets of atypical cells, showing anaplastic morphology, admixed with numerous small lymphocytes, were centred on skin adnexa. Mitotic rate was higher (approximately 17 mitoses per 10 high-power fields). The following biopsy

taken from the skin lesion on the right thigh in the course of therapy revealed lymphoid infiltrates located mainly in the reticular dermis and subcutaneous tissue. Irregular infiltrates centred on skin adnexa were similar to those observed in previous biopsies.

The last biopsy taken from the skin lesion on the abdomen showed a diffuse lymphoid infiltrate in the dermis, sparing the epidermis. Irregular infiltrates were composed mainly of large atypical lymphocytes, showing anaplastic morphology and admixed with only a few small lymphocytes. Mitotic rate in large cells was high (approximately 41 mitoses per 10 high-power fields) (Fig. 3). The number of atypical cells was significantly higher as compared to the previous specimens, but the morphology was the same. In none of those biopsies was a granulocytic infiltrate found.

The majority of the large cells expressed antigens CD45RO and CD5, but only some of these cells expressed antigens CD3, CD2, CD8 and granzyme B. Neoplastic cells did not express CD4, ALK-1, CD15 and CD56. CD30 was positive in only 40-50% of the large cells in the biopsy taken from the abdomen (Fig. 4), and in 30-40% of the cell originating from the biopsy taken from the buttock. Antigens CD20, CD79α and bcl-2 revealed only a small amount of admixed B lymphocytes. The reaction with CD68 showed numerous histiocytes admixed with atypical cells. There were also a few S100-positive cells. Small lymphocytes admixed with atypical cells expressed CD45RO, CD3, CD5, CD8 and CD2.

Two specimens were selected for performing the T-cell clonality analysis: the second biopsy taken from the skin lesion on the buttock and

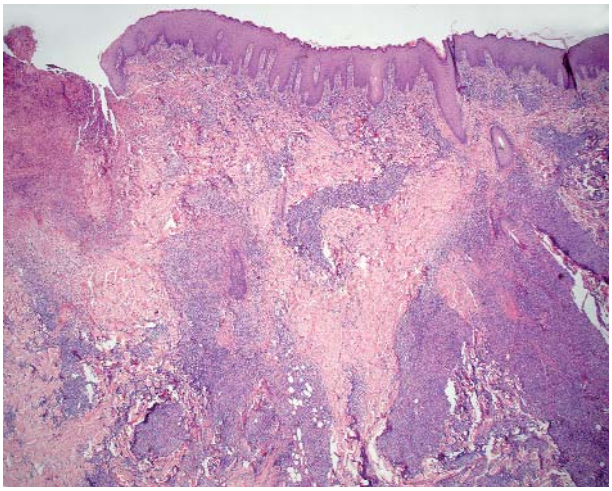

Fig. 2. Partially ulcerated skin with dense lymphoid infiltrate. HE, original magnification 50 ×

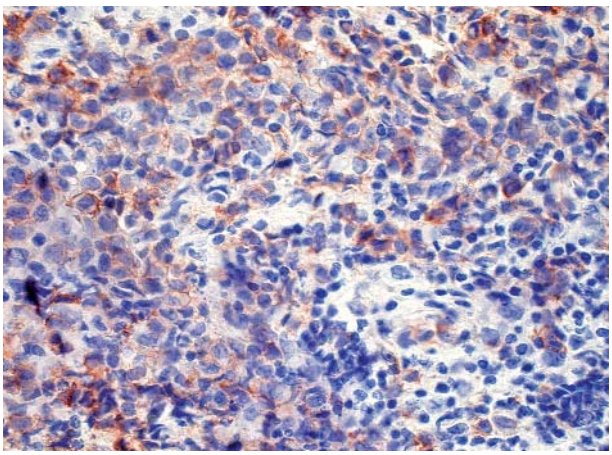

Fig. 4. Large atypical cells show expression of CD30 antigen. Original magnification 400 ×

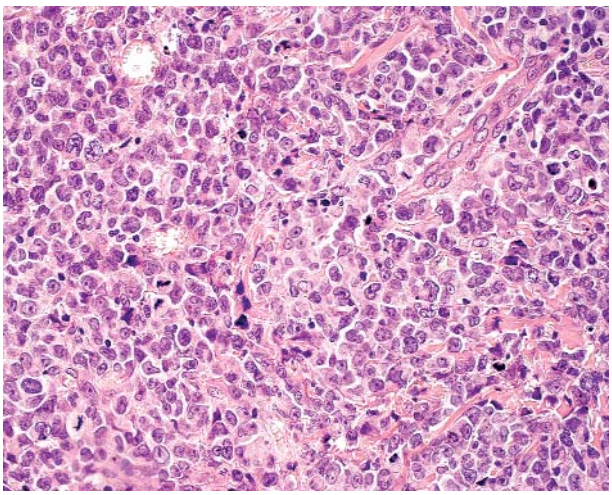

Fig. 3. Numerous large atypical lymphocytes with anaplastic morphology. Numerous mitotic figures and dissection of collagen are seen. HE, original magnification 400 ×

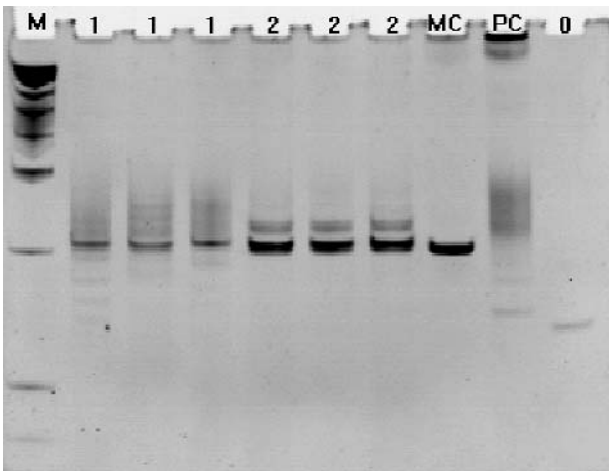

Fig. 5. T-cell clonality analysis: 1 – material from the second biopsy taken from the skin lesion on the buttock, 2 – material from the last biopsy taken from the skin lesion on the abdomen; M – size standard, MC – monoclonal control, PC – polyclonal control, 0 – control without DNA

the last biopsy taken from the skin lesion on the abdomen. In the first material, the analysis showed one discrete band on a smear pattern that corresponded to a clonal T-cell population and a coexisting polyclonal background.

The second material revealed an oligoclonal population of T-cells with a strong dominant clone on a very weak polyclonal background. Both tissues (the present and retrospective tissue sample) showed a dominant equal-sized band that may indicate a common origin of the T-cell population (Fig. 5).

Finally a diagnosis of LPD, borderline between Lyp and C-ALCL, was made.

Discussion

Lesions in LyP occur often as crops of papules and/or nodules with a propensity for clustering. They regress spontaneously within 3 to 12 weeks, and may persist behind superficial scars or hyperpigmentation. New lesions can appear in the same or different locations. Sometimes larger lesions develop (usually not exceeding 2 cm in diameter), and it can take months before they disappear [2, 4-9].

C-ALCL typically presents as a solitary, firm, large, often ulcerated tumour, which grows rapidly. Approximately 20% of patients have multifocal disease (two or more lesions at different anatomic sites). Occasionally, satellites in the vicinity of a larger tumour are found or grouped nodules or papules. Patients with C-ALCL may also present with widespread papular eruptions, similar to LyP [10]. Skin lesions can show features of partial or complete remission, similar to LyP. Cutaneous relapses are common. Extracutaneous spread occurs in approximately 10% of patients; most commonly, regional lymph nodes are involved [2, 4-10, 14]. According to some authors, skin relapses in C-ALCL most often (in 75%) occur within 12 to 24 months [15]. Only in the material of the Dutch Cutaneous Lymphoma Group did disease-free survival range from 1 to 192 months [2]. LyP tends to last for years (from a few months to more than 40 years) [4, 6].

From the clinical point of view, differential diagnosis between C-ALCL and LyP can be

Table I. Morphological features useful in differential diagnosis between LyP and C-ALCL

Lyp C	C-ALCL
• Absence or only limited involvement of subcutaneous fat [9]	• The infiltrate involves deeper dermis and subcutaneous fat
• Morphology of neoplastic cells closer to that of immunoblasts [5]	• More numerous neoplastic cells (but strict criteria are not given)
• Inflammatory infiltrate intermingled with large cells [5]	• Neoplastic cells more often show anaplastic morphology
• Neutrophils found in most sections [10]	• Inflammatory infiltrate, mainly small lymphocytes, is found at the periphery of the lesion [5]

Table II. Differential diagnosis of LPDs [2, 4, 6, 7, 9, 10]

Lymphomas	Reactive changes
• CD30+ cutaneous lymphoma secondary to mycosis fungoides (MF)	• Parasitic (e.g. scabies), viral (e.g. Herpes simplex, varicella zoster, parapoxviruses, poxviruses) and bacterial (tuberculosis) infections
• Systemic ALCL with secondary skin involvement	• Arthropod bite reactions
• Extranodal NK/T – cell lymphoma, nasal type	• PLEVA
• Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma	• Atopic dermatitis
• Pagetoid reticulosis	• Drug-induced reactions
• CD30+ cutaneous B-cell lymphomas	
• Hodgkin's lymphoma	

difficult, even if not impossible, particularly when the patient presents with large tumours (several cm), which can persist for months until spontaneous regression occurs. It is still a matter of debate whether such lesions should be considered as part of the spectrum of clinical manifestation of LyP or whether those tumours represent concurrent C-ALCL [7].

The histological features in LyP are extremely variable and depend on the stage of the lesion and disease. Three histological subtypes have been described, which represent a spectrum with overlapping features. In type C lesions, mostly resembling C-ALCL large CD30+ cells form a monotonous population or large clusters with relatively few admixed inflammatory cells. In C-ALCL, there is a diffuse infiltrate with cohesive sheets of large CD30+ cells. Usually denser than that seen in LyP, the infiltrate reaches the subcutaneous tissue. Most commonly, tumour cells have features of anaplastic cells, showing round, oval or irregularly shaped nuclei, prominent eosinophilic nucleoli, and abundant cytoplasm. Reactive small lymphocytes are often present at the periphery of the lesion [2, 4-8]. The histological differences between LyP type C and C-ALCL are summarized in Table II.

Neoplastic cells in both LyP and C-ALCL generally show the same phenotype of activated CD4+ T lymphocytes with a variable loss of CD2, CD5 and/or CD3. Rare cases (less than 5%) have a CD8+ T-cell phenotype and very rarely cells are double negative (CD4-/CD8-). C-ALCL is defined as showing expression of CD30 in more than 75% of neoplastic cells. Neoplastic cells in LPDs do not express epithelial membrane antigen (EMA) and anaplastic lymphoma kinase (ALK), in contrast to the often positive staining in systemic anaplastic large cell lymphoma. Unlike Hodgkin and Reed-Sternberg cells in Hodgkin's lymphoma, neoplastic cells in LPD usually do not express CD15 [2-7, 9, 11, 14, 17]. Numerous histiocytes seen intermingled with neoplastic cells have led in the past to erroneous classification of C-ALCL as regressive atypical histiocytosis [14].

The histological picture of the presented case lies between C-ALCL and LyP type C. Sheets of large atypical cells, the involvement of the subcutaneous tissue in all the specimens, morphology of these cells consistent with anaplastic cells and a high mitotic index are closer to the diagnosis of C-ALCL. Nevertheless, the percentage of large cells expressing CD30 does not reach 75%. No one has ever questioned these criteria. Some authors have stressed the importance of these quantitative criteria in avoiding terminological confusion only, because the similarity of cutaneous infiltrates in both LyP and C-ALCL suggest that it would be better to regard them as part of a continuous spectrum of LPDs.

We have also observed in the reviewed specimens small lymphocytes not only at the periphery of the lesion, but also intermingled with the infiltrate, which is a feature of LyP. Moreover, clustering of the infiltrate around skin adnexa, which was seen in the first three specimens, is suggestive of LyP [1].

In the largest series of borderline cases (14 cases from 84 LPDs), described by Paulli *et al.* [1], the clinical presentation and prognosis were similar to LyP. Probably for this reason some authors include borderline cases in the category of LyP (three cases from 43 LPDs [3]), or define LyP type C as borderline cases [10]. Some authors did not even find borderline cases in their material (56 cases of LPDs [9] or 208 cases of LPDs [2]). For the diagnosis of C-ALCL there should be no clinical evidence or history of CTCL. It seems that it should not apply to previous LPDs, because the prognosis and clinical behaviour of relapses in LyP, C-ALCL and C-ALCL secondary to LyP are not different from those characteristic of primary lesions [3, 9].

The majority of C-ALCL lesions and approximately 60-70% of LyP lesions show clonal rearrangement of T-cell receptor genes. The same rearrangements have been shown in both LyP and lymphomas secondary to LyP. The translocation (2; 5) (p23; q35) and its variants was not demonstrated in LyP, and was not or only rarely found in C-ALCL [4, 6].

The differential diagnosis of LPDs includes other types of lymphomas and also benign conditions, which are listed in Table 3.

LyP has a favourable prognosis – the disease-free specific 5-year survival reaches 100%. Nevertheless, 5-20% of patients develop other cutaneous or nodal lymphomas – mycosis fungoides, Hodgkin's lymphoma, ALCL or C-ALCL [4, 6, 9]. C-ALCL has a similar favourable prognosis with a disease-free specific 5-year survival reaching 90% [4, 6].

The choice of treatment is based on the size, extent and clinical behaviour of the lesions.

There is no available curative therapy of LyP and no known therapy can alter the natural history of LyP or lower the risk of developing secondary lymphomas, with a possible exception of preventing the progression to CD30+ lymphoma. Results of local-directed therapies in C-ALCL (excision, radiotherapy+/-excision) were similar to systemic chemotherapy (CHOP)

with similar remission and relapse rates [9]. All patients treated with chemotherapy (CHOP) with multifocal lesions suffered from one or more skin relapses. Relapses after systemic chemotherapy occur also in LyP [2].

Most authors emphasize that differential diagnosis between type C LyP and C-ALCL may be difficult, if not impossible, but biological differences between LyP and C-ALCL are not as distinct as has been thought; relapses after systemic chemotherapy occur in both lesions. It seems likely that there are no strict boundaries between the spectrum of LPDs, particularly between C-ALCL and type C LyP [10].

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