The occurrence of primary cutaneous anaplastic large cell lymphoma (PCALCL) in immunocompromised patients is rare. Only 11 cases have been reported to date, all of them in organ transplant recipients and none in patient with idiopathic CD4+ T-cell lymphocytopaenia. We describe here the original clinical pattern of deep, fascia and muscle-penetrating PCALCL of the lower limb in two immunocompromised patients, one in a renal transplant recipient, the other in a patient with idiopathic CD4+ T-cell lymphocytopaenia. Both patients experienced a negative outcome, contrasting with the usually indolent course of PCALCL in immunocompetent patients, since both died of complications related to the lymphoma 30 and 13 months later, respectively. The unusual clinical aggressiveness of these two cases of PCALCL suggests that, in this peculiar subset with a deep structures involvement hallmark, a worse prognosis could be expected, especially in immunocompromised patients. This information should be taken into consideration when making therapeutic choices. **Key words:** primary cutaneous anaplastic large cell lymphoma; fascia; renal transplantation; lymphocytopaenia.

(Accepted April 6, 2009.)

The occurrence of primary cutaneous anaplastic large cell lymphomas (PCALCL) in a setting of organ grafting has been reported in only 11 patients to date (1–8), whereas no case has been described in patients with idiopathic CD4+ T-cell lymphocytopaenia. We report here on two additional and strikingly similar observations in immunocompromised patients featuring a common and unusual pattern of deep-penetrating PCALCL involving fascia and muscle with fatal outcome. This outcome contrasts sharply with the usual indolent course of this particular subset of primary cutaneous lymphomas in immunocompetent hosts (9).

**CASE REPORTS**

**Case 1.** In March 1990 a 43-old-year man received a kidney graft from a cadaveric donor, but experienced chronic rejection despite mycophenolate mofetil (MMF) and cyclosporine prophylaxis. He was first referred in February 2001 for evaluation of a 3-cm diameter, violaceous, ulcerated nodule of the left popliteal fold (Fig. 1) that had been present for three preceding weeks, accompanied by an increasing swelling of the left leg. Regional lymph nodes were not palpable and physical examination was otherwise unremarkable. A biopsy of this nodule displayed an undifferentiated tumour with monotonous sheets of pleomorphic, large cells throughout the dermis; immunostaining was negative for a large panel of antibodies, including CD45. Pelvic-abdominal computerized tomography (CT) scan showed no evidence of visceral dissemination or lymph node involvement. Magnetic resonance imaging (MRI) of the left leg disclosed a hypersignal in T2 mode of the dermal and hypodermal components of the lesion, with no clue for muscle or bone infiltration. The popliteal nodule was then removed surgically. The subcutis was infiltrated by large pleomorphic lymphoid cells (Fig. 2a and b) expressing CD2 and CD30 but not CD3, CD4, CD5, CD7, CD20, anaplastic lymphoma kinase (ALK1) or epithelial membrane antigen (EMA) (Fig. 2c). Epstein Barr virus (EBV)
markers (EBER and LMP1) were also negative. A clonal T-cell receptor gamma gene dominant rearrangement was detected in the tumour. PCALCL of T-cell phenotype was finally diagnosed. MMF prophylaxis was stopped, and no additional therapy was implemented. Seven months later another 4-cm diameter nodule appeared on the posterior aspect of the left thigh with identical histological and immunohistochemical features. A third nodule appeared on the popliteal region in April 2002 and a radiotherapy (total dose: 40 Gy) achieved complete clinical remission. In November 2002 the patient developed a prominent swelling and infiltration of the left calf and the distal part of the left thigh with no subsequent cutaneous lesion. MRI of the left lower limb showed a massive tumour infiltration penetrating deep into the tissues down to fascia level in contact with the knee and the inferior gemellus muscle. Bone marrow biopsy was normal. Six courses of CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone) followed by three courses of carboplatin-based chemotherapy failed to prevent dissemination to the left hip and lateral thoracic region. The patient died of sepsis in August 2003, 30 months after the initial diagnosis.

Case 2. A 63-year-old man with no medical background apart from a non-insulin requiring diabetes mellitus and a possible malabsorption was referred in June 2006 for evaluation of an inflammatory, oedematous infiltration of the inner part of the right lower limb, mainly localized on the mid-third of the thigh (Fig. 3a) and topped by a 5-cm diameter violaceous, indolent skin nodule. This plaque had been slowly increasing in size over the preceding 6 months and reached the inguinal fold at presentation. Three additional indolent, firm and partly ulcerated skin nodules subsequently appeared on the pubic area (Fig. 3b). Regional lymph nodes were not palpable and the physical examination was otherwise unremarkable. Standard blood tests showed a marked lymphocytopenia at 0.4 × 10^9/l (CD3 cells: 0.14 × 10^9/l; ratio CD4/CD8 = 0.3; absolute number of CD4 lymphocytes: 0.03 × 10^9/l) confirmed by repeated investigations during follow-up and sharply decreased titres of immunoglobulins G, A and M [3.14 g/l (normal range 6.9–14.0), 0.46 g/l (0.7–4.1) and <0.21 g/l (0.34–2.4)], these abnormalities possibly related to a malabsorption syndrome of more than 10 years duration suspected on indirect clues (hyperlipidaemia, hypoalbuminaemia, hypocalcaemia and low blood iron). Blood tests for HIV-1 and -2 were repeatedly negative. Biopsies of pubis nodules and thigh lesions revealed a deep infiltration of skin (including subcutaneous fat), fascia and muscle (for the infiltrated plaque of the thigh) by large lymphoid expressing CD4, CD5, CD8, CD30 but not CD1a, CD3, ALK1, EMA, EBV markers or CD56, consistent with PCALCL of T phenotype. No dominant clonal T-cell clone was detected in lesions. An extensive staging procedure including chest, abdominal and pelvis CT scan showed no evidence of visceral dissemination or lymph node involvement. Bone marrow biopsy was normal. A right lower limb MRI confirmed the deep infiltration of subcutaneous tissues extending to fat, fascia and muscles (Fig. 4a). An F-18-fluoro-deoxy-glucose positron emission tomography showed hypermetabolism of sites clinically involved by the tumour (Fig. 4b). Six cycles of CHOP chemotherapy associated with radiotherapy on the thigh nodule yielded limited results with disappearance of pubis nodules, but persistence of lower limb deep infiltration and development of additional cutaneous nodules on the thigh during the last courses of chemotherapy; a second-line, cisplatin-based
Fatal primary cutaneous anaplastic large cell lymphomas

chemotherapy was subsequently implemented with a poor clinical result and a rescue treatment with five courses of alemtuzumab (anti-CD52 monoclonal antibody although the expression of CD52, a glycoprotein widely expressed on all normal and most malignant B- and T-lymphocytes, by neoplastic cells had not been specifically tested in our patient) (10) was also unsuccessful. The patient died of sepsis 13 months after the initial diagnosis.

DISCUSSION

According to the 4th World Health Organization (WHO) 2008 lymphoma classification blue book (11), case 1 developed a CD30+ PCALCL, corresponding to a primary cutaneous post-transplant lymphoproliferative disorder (PCPTLD). Case 2 developed a CD30+ PCALCL occurring in a setting of CD4+ T-cell lymphocytopenia, entity not stated in this new classification. These two CD30+ PCALCL cases are exceptional regarding their poor clinical behaviour, which contrasts sharply with the usually favourable outcome of this subset of primary cutaneous lymphomas in immunocompetent patients (12).

In both cases, the clinical pattern was very similar and highly unusual, with a disease localized to an anatomical region and marked by a prominent involvement of deep skin structures and fascia (and underlying muscles in one case). To the best of our knowledge, this situation is unique and has never been described in this subset of cutaneous lymphomas. The absence of both visceral and lymph node involvement and ALK1 expression by neoplastic cells is theoretically not consistent with a secondary cutaneous involvement of a systemic ALCL, even though our observations might represent an intermediate entity between the usual forms of PCALCL and their systemic counterpart, especially when considering the outcome.

Another relevant point was the fact that these two deeply infiltrating PCALCL developed in an immunocompromised background: 11 years after a kidney transplantation in one patient and in a setting of immunodepression with lymphocytopenia of unknown aetiology and duration in another one. However, a link between chronic lymphocytopenia and malabsorption syndrome remains possible, since such a relationship has already been documented in coeliac disease (13). From this perspective, it is of interest to point out that the occurrence of PCALCL in a setting of CD4+ T-cell lymphocytopenia whatever its origin (probably chronic idiopathic CD4+ lymphocytopenia with humoral immunodeficiency in our patient) has never been previously reported, although the distinction between cause and consequence is quite debatable.

Both patients had EBV-negative tumours, which is an important fact since the presence of EBV markers has been previously identified as a poor prognosis factor in PTLD by Leblond et al. (14). The lack of dominant clonal T-cell receptor gamma gene rearrangement in case 2 skin tumour, although rare, is possible in about 10% in PCALCL (15). Conversely, the rare T/null-cell type immunophenotype displayed by our first patient, together with the presence of a dominant clonal T-cell receptor gamma gene rearrangement has been described previously (16, 17). Cutaneous T-cell lymphomas account for 30% of post-transplant primary cutaneous lymphomas (18), whereas most of them are B-cell lymphoma most often EBV-induced. Only 26 cases of primary cutaneous T-cell PTLDs have been published so far (8, 19). PCALCL occurring in a renal transplant recipient was first described by Seçkin et al. (1) and 11 cases (without present case 1) of PCPTLDs of the ALCL subset have been reported in literature review series so far (7, 8), all of them in transplant recipients and more specifically in renal transplant recipients (75%). The mean interval between transplantation and the diagnosis of lymphoma in these patients is close to 6 years, a delay that is not significantly different from the first patient’s chronology. As previously noticed in short series (5, 7, 18, 20–22), the overall course of PCALCL is usually indolent in immunocompetent patients, with a 95% disease-specific survival rate at 5 years in localized forms (but decreasing to 50% in extensive forms) (12), whereas their outcome seems significantly less favoura-

Fig. 4. Case 2: (a) MRI of the right thigh showing tumoural infiltration of the hypodermis, muscle and fascia (T1 Gadolinium fat-saturation signal hyperintensity). (b) F-18-fluoro-deoxy-glucose positron emission tomography showing elevated uptake of the tumour in the inner part of the right thigh and the pubic area.

Acta Derm Venereol 89
ble in immunocompromised patients (7, 8). Our patients illustrated these data, since both cases died of disease-related complications, 30 and 13 months, respectively, after the onset of the lymphoma, which matches the mean delay of 14.6 (range: 6–22) months between diagnosis and death in the 6 patients who experienced a fatal outcome available in the literature. These data must be taken into account when considering the therapeutic strategy, and systemic therapies should probably be preferred as first choice after the initial diagnosis of PCALCL in an immunocompromised patient with such clinical presentation, even though their adequacy in immunocompromised patients, prone to infectious complications, is questionable.

The unusual clinical aggressiveness of these two PCALCL suggests that this peculiar subset of PCALCL with deep structures involvement might be characterized by a poor prognosis, especially in immunocompromised patients, a fact that should be taken into consideration when making therapeutic choices.

ACKNOWLEDGEMENT
No sources of funding were used to assist in the preparation of this case report.

The authors declare no conflict of interest.

REFERENCES