

Teaching Point

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The transplanted patient who suffered from excruciating lower limb pain and developed nodular skin lesions

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A 57-year-old man was admitted in May 1998 with a 15-day history of moderate fever and tender subcutaneous nodules and plaques on both thighs and legs. In 1967 he underwent successful renal transplantation for end-stage renal disease (ESRD) due to chronic glomerulonephritis. No rejection episode occurred. Maintenance immunosuppression included azathioprine and prednisolone. In January 1998 liver transplantation was performed for hepatocellular carcinoma complicating hepatitis C virus (HCV)-related cirrhosis. Tacrolimus was added to the immunosuppressive regimen. Two months later, intense HCV replication required a transient tapering of the immunosuppression. In May 1998 he developed fever up to 38°C; nine blood cultures grew no organisms and CMV antigenaemia was negative. A few days later multiple painful erythematous subcutaneous plaques appeared on both thighs (Figure 1) and extended progressively to the legs. On admission (D1), treatment included tacrolimus 2 mg o.d, prednisolone 8 mg o.d, isradipine 2.5 mg o.d and furosemide 120 mg o.d.

Physical examination revealed moderate ascites that was known since the time of liver transplantation. The rest of the examination was normal.

Laboratory tests showed: haemoglobin 12.3 g/dl, white blood cell count $13.92 \times 10^9/l$ (91.8% neutrophils), platelets $243 \times 10^9/l$ and a normal coagulation screen, urea 154 mg/dl, creatinine 147.8 µmol/l, CRP 3.2 mg/dl, fibrinogen 247 mg/dl, serum iron 28 µg/dl, ferritin 833 ng/ml, triglycerides 257 mg/dl, cryoglobu-

lin 0.06 mg/dl, ASAT 118 IU/l, and ALAT 222 IU/l. CD4/CD8 ratio was <1. Serological investigations for bacterial (Salmonella, Yersinia Enterocolitica, Rickettsia, Chlamydia), parasitic (Toxoplasma) and viral (HSV 1-2, HZV, HHV6, Parvovirus B19, HBV, HIV) infections were negative.

Skin lesion biopsy performed on D1 disclosed a lobular panniculitis with fat necrosis and infiltrating histiocytes, many of which had ingested red blood cells and lymphocytes. Epidermis and superficial dermis were normal. This picture is pathognomonic of the so-called cytophagic histiocytic panniculitis (Figure 2) (1).

Progressively, nodules on the right ankle turned to ecchymotic vesicles and then became ulcerated. Skin lesions became more and more painful and required morphine administration. Methylprednisolone 125 mg/day was given in association with ceftriaxone 1 g/day (D9). The patient progressively lost consciousness, grand-mal seizures occurred and he died on D 13.

A second skin lesion biopsy performed on day 9, available after patient's death, revealed massive *Cryptococcus neoformans* fungi invading dermis and subcutaneous fat. Autopsy further disclosed the presence of *C. neoformans* within the skin, prostate, meninges, cerebral ventricles and cortex. Retrospective analysis of the first skin biopsy also revealed the presence of Cryptococci on some histological sections (Figure 2).

Cytophagic histiocytic panniculitis associates fever and subcutaneous nodules or plaques which may progressively become ecchymotic and ulcerated. Diagnosis relies on histological features of fat infiltration by benign-appearing histiocytes which have phagocytosed lymphocytes and erythrocytes [1,2]. Such pattern differentiates it from malignant histiocytosis and Weber-Christian disease: in the former situation, malignant histiocytes infiltrate the skin whereas in the

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Fig. 1. Erythematous subcutaneous plaque of the thigh.

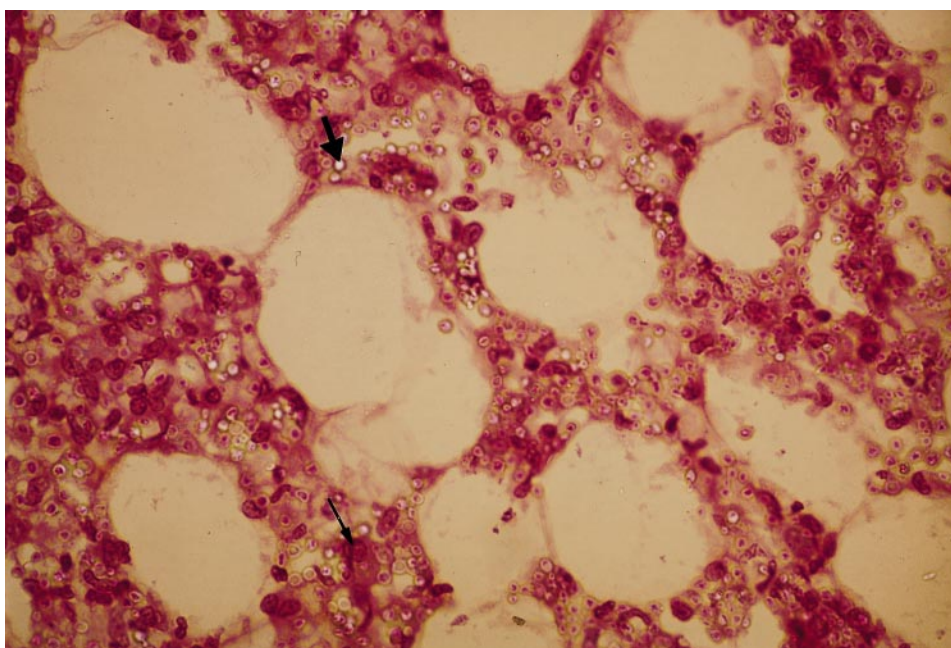


Fig. 2. Skin biopsy performed on day 1 (haematoxylin eosin stain, $\times 100$) showing fat necrosis with infiltrating histiocytes (thin arrow). Cryptococci (thick arrow) are also present (see text for details).

latter, lipophagocytosis (but not erythro- and lymphophagocytosis) is present. In addition, staining with specific antibodies is necessary to rule out hypodermic lymphoma. The outcome of cytophagic histiocytic panniculitis is usually fatal due to haemorrhagic complications, liver failure or to the underlying disease [2]. Occasionally, in the absence of associated disease,

favourable outcome has been described under cytostatic or immunosuppressive therapy [3].

Cytophagic histiocytic panniculitis may occur either isolated or as a cutaneous manifestation of the haemophagocytic syndrome [4]. The cause of cytophagic histiocytic panniculitis often remains elusive and its pathophysiology is ill-defined. It has been reported in

immunocompromised patients with lymphoma, AIDS or SLE [4]. To the best of our knowledge, this is the first description of *C. neoformans*-associated cytophagic histiocytic panniculitis after organ transplantation.

Teaching point

Cytophagic histiocytic panniculitis is a rare and often fatal form of panniculitis. The occurrence of excruciating limb pain in association with nodular ulcerated lesions in a kidney graft recipient should promptly lead to a skin biopsy in order to recognize this entity. A thorough work-up should include a search for mycotic infection within the skin lesions, so that a specific antifungal therapy can be early initiated.

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