Xanthoma and paraproteinaemia: a spot diagnosis

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DESCRIPTION

A 48-year-old woman was referred to the immunology clinic in pursuit of a unifying diagnosis for long-standing polyarthralgia, widespread cutaneous erythematous/yellow papules/plaques as well as subcutaneous nodules and xanthomas around her eyes (see figure 1). Prior to our review, she received various therapeutic trials. She was intolerant of methotrexate, while azathioprine, etanercept and adalimumab failed to control her disease. She developed immediate hypersensitivity to abatacept. Ciclosporin appeared to halt progression of skin disease, but her arthralgia persisted.

Further investigations revealed the presence of an IgG kappa paraprotein measuring 5 g/L, hypocomplementaemia (C4, 0.11 g/L; reference range 0.14–0.42 g/L). All relevant autoimmune serology was negative. C-reactive protein and erythrocyte sedimentation rate were persistently normal despite debilitating arthralgia. By contrast, positron emission tomography (PET) scan suggested inflammatory polyarthritis with subtle erosions of sternoclavicular joints, 18F-fluorodeoxyglucose (FDG)-avid subcutaneous nodules on both feet as well as bilateral pulmonary ground-glass changes that exhibited increased FDG uptake. Bone marrow

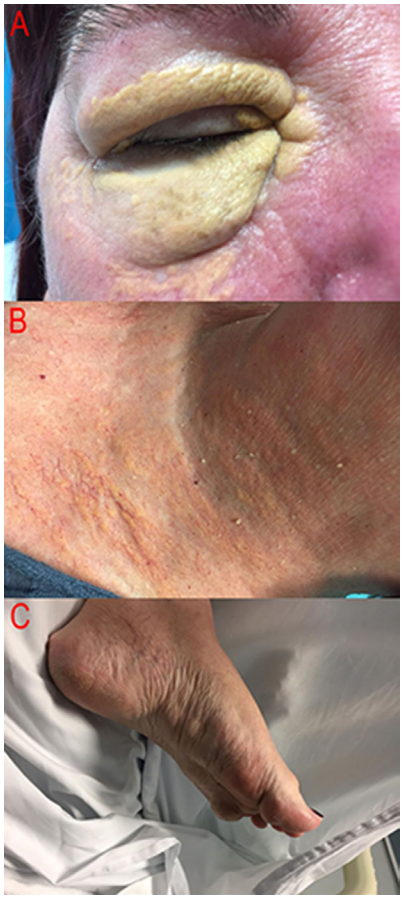

Figure 1 (A) The patient's xanthoma. (B) Yellow plaque on her neck/chest. (C) The patient's foot nodules.

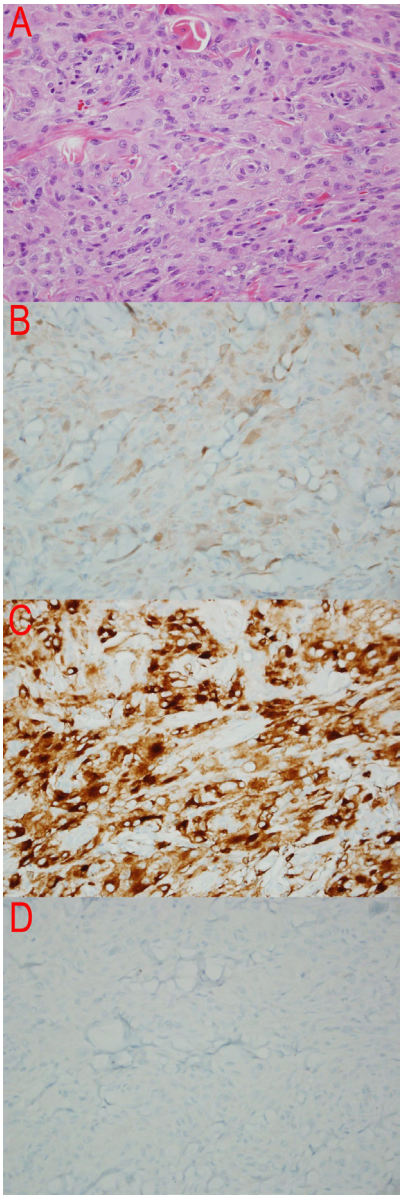

Figure 2 Left-arm skin biopsy with various staining on the dermis. (A) H&E staining, original magnification ×400—high-power microscopic view showing heavy infiltrate of epithelioid histiocytes. (B) Factor XIIIa staining, original magnification ×400 power—histiocytes demonstrate moderate patchy cytoplasmic staining. (C) CD68 staining, original magnification ×400—histiocytes demonstrate heavy cytoplasmic staining. (D) CD1a staining original magnification ×400 power—there was no staining on the histiocytes.

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biopsy revealed reactive changes but plasma cells were normal in number and appearance.

A papule on her left forearm was biopsied (see figure 2). Epithelioid histiocytes with abundant eosinophilic cytoplasm with round to oval nuclei were identified within the dermis. These cells were positive for CD68 and factor XIIIa but negative for Langerhans cell histiocyte marker CD1a. The canonical *BRAF* mutation encoding a valine 600 to glutamic acid substitution (V600E) was not detected.

Taken together, these findings make the diagnosis of non-Langerhans cell histiocytosis (NLCH). The spectrum of NLCH associated with periorbital xanthomas includes Erdheim-Chester disease, a systemic disease with cutaneous papules and plaques, with lesions in lungs, long bones and central nervous system[1] and is associated with *BRAF* V600E mutations in 50%–70% of cases.[1 2] Necrobiotic xanthogranuloma (NXG) is associated with xanthomas, and skin changes show characteristic palisading necrobiotic granulomas. Both are associated with paraproteins, hypocomplementaemia and an increased risk of haematological malignancy. Our patient is somewhat intermediate between these phenotypes, with insufficient systemic features to fulfil Erdheim-Chester disease (ECD), and an absence of typical palisading granulomas on skin biopsy.

She received a trial of low-dose oral chlorambucil and made a partial response with normalisation of serum complement but experienced persistent musculoskeletal symptoms. Pamidronate did not produce sustainable response. Thalidomide was trialled at low dose but was curtailed because of severe bradycardia. Despite slow disease progression, since her initial symptoms onset at the age of 33, the patient has declined a trial of lenolidomide or more intensive cytotoxic therapy. She remains on prednisolone.

NLCH encompasses a heterogeneous group of diseases. Due to its rarity, and incomplete understanding of pathogenesis, the optimal treatment has not been determined. Paraprotein and complement abnormalities are useful for distinguishing this entity from xanthomas related to dyslipidaemia. Recognition is important because of the association with an increased risk of malignancy.[3]

Learning points

- Periorbital xanthoma, monoclonal gammopathy and hypocomplementaemia point to the possibility of non-Langerhans cell histiocytosis.
- Testing for *BRAF* mutation (V600E) is important for diagnosis and treatment but is largely limited to the systemic variant (Erdheim-Chester disease).
- The diagnosis should prompt investigation for underlying plasma cell dyscrasia or other haematological malignancy.

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