Xanthoma disseminatum

G P Ford MB MRCP
R D Eady MB MRCP
A J Freemont MD MRCP
The Skin Hospital, Manchester and Department of Rheumatology, University of Manchester, Manchester

Xanthoma disseminatum with its distinctive clinical features, is considered by many to be a specific entity, though an apparent overlap between xanthoma disseminatum and histiocytosis X is frequently commented on (Mishkel *et al.* 1977, Sonnex *et al.* 1981). We report a patient with xanthoma disseminatum and the findings of cell marker studies undertaken in an attempt to clarify the histogenesis of the disorder.

Case report

A 47-year-old lady presented in October 1983 with a 3-month history of increasing numbers of yellowish xanthomatous papules appearing in her antecubital fossae, her axillae, on the sides of her neck and on the buccal mucosa (Figure 1). In addition, she complained of polyuria and polydipsia of a similar duration. She had no symptoms of upper airway involvement and further examination, including assessment of her visual fields, was normal.

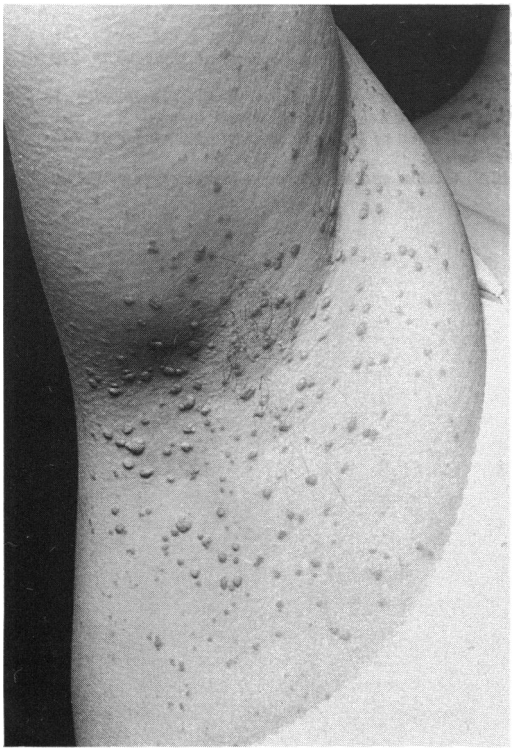

Figure 1. Axillary xanthomata

Urea and electrolytes, liver function tests, an oral glucose tolerance test, thyroid function tests, fasting lipids and lipoprotein electrophoresis were normal. Her 24-hour urinary output was around 8–9 l. Paired urine and plasma osmolalities were 85 and 299 osmol/kg water respectively.

A short water deprivation test carried out some months after she presented was suggestive of mild diabetes insipidus. Skull, pituitary fossa and chest X-rays were normal as was a CT scan of the head. Though compulsive water drinking could not be excluded, it was felt that this lady had mild, intracranial diabetes insipidus and, subjectively, this responded well to intranasal desmopressin.

Routine histology revealed that the lesions were xanthomata, the dermal infiltrate consisting of histiocytes, foam cells, Touton giant cells and an inflammatory infiltrate.

Monoclonal antibody studies were undertaken on snap-frozen, air dried and acetone-fixed sections with the following reagents: OKM1 (myeloid and monocyte specific), MO_2 (monocyte), OKT6 (thymocytes and Langerhans' cells) OKT4 (T_H cells), B1 (B-lymphocytes), OKT_8 (T_S and cytotoxic lymphocytes) and OKT_9 (reactive, proliferating cells). The large, histiocytoid cells in the dermal infiltrate stained with OKM1, MO_2 and OKT_9. They did not stain with OKT_6. The lymphocytic infiltrate staining revealed a mixture of helper and suppressor/cytotoxic T-lymphocytes.

The histiocytoid cells in the dermal infiltrate stained strongly positive for non-specific esterase; no Langerhans' cell granules were seen within these cells on electron microscopy.

Discussion

Xanthoma disseminatum is a rare disorder consisting of the triad of widespread normolipaemic

xanthomata, xanthomata involving the mucous membranes of the upper respiratory tract and mild, transient diabetes insipidus. The histology of the early lesion reveals predominantly histiocytic proliferation. Subsequently, there is apparent secondary accumulation of lipid within the histiocytes, and the mature lesion consists of a mixture of histiocytes, foam cells, Touton giant cells and inflammatory cells within the dermis (Lever & Schaumburg-Lever 1983).

The clinical features and laboratory findings, i.e. normolipaemic, predominantly flexural xanthomata, xanthomata involving the upper respiratory tract and mild, transient, intracranial diabetes insipidus, permit xanthoma disseminatum to be distinguished from other disorders associated with xanthomata such as type II hyperlipoproteinaemia, diabetes mellitus, normolipaemic plane xanthomata and xanthogranuloma in adults. The prognosis of xanthoma disseminatum is good. The flexural xanthomata shows a tendency to resolve spontaneously, though this may take some years. The associated intracranial diabetes insipidus is mild and transient. Xanthoma disseminatum cannot, however, be considered a wholly benign disorder. The xanthomata commonly involve the upper respiratory tract (Altman & Winkelmann 1962), often producing symptoms such as hoarseness and, occasionally, airways obstruction. Altman & Winkelmann (1962) reported on 46 cases of xanthoma disseminatum collected from a review of the world literature plus seven cases from the Mayo Clinic. Out of 53 cases, five required tracheostomy because of laryngeal or tracheal xanthomatosis.

While most authorities consider xanthoma disseminatum to be a distinct entity, possibly due to a reactive proliferation of histiocytes which later accumulate lipid (Altman & Winkelmann 1962), others suggest that it 'is possibly a variant of the histiocytosis X group of disorders' (Mishkel *et al.* 1977). Xanthomata and diabetes insipidus can be found in both xanthoma disseminatum and histiocytosis X; however, there are significant dissimilarities which indicate that the two disorders are distinct entities. Xanthoma disseminatum is predominantly a disorder of adulthood, unlike histiocytosis X; is commonly associated with xanthomata involving the upper respiratory tract, a feature not seen in histiocytosis X; and unlike histiocytosis X, it is rarely associated with bony lesions. Only one case of xanthoma disseminatum with bony lesions has been described (Mishkel *et al.* 1977).

The monoclonal antibody, histocytochemistry and electronmicroscopy studies undertaken in this case indicate that xanthoma disseminatum is a disorder of histiocytes/macrophages. No 'markers' of Langerhans' cells were noted. The positive staining with the monoclonals OKM1 and MO_2 indicates that the cells of the dermal infiltrate are macrophage derived. The cells did not react with the Langerhans' cell marker OKT6, unlike those of the Langerhans' cell derived histiocytosis X group of disorders (Harrist *et al.* 1983).

The strong positive staining of these cells for non-specific esterase is in keeping with their presumed macrophage/histiocyte origin and against any relationship with Langerhans' cells (and histiocytosis X) which would stain only weakly, if at all (Rosai 1981).

The presence or absence of Langerhans' cell granules must be the most decisive factor in discriminating xanthoma disseminatum from the histiocytosis X group of disorder. Electron microscopy failed to reveal Langerhans' cell granules in our case. Of five previously reported cases of xanthoma disseminatum in which electronmicroscopy was undertaken, Langerhans' cell granules were not found in four cases (Ferrando & Bombi 1979, Kumakiri *et al.* 1981, Sonnex *et al.* 1981). In the one case in which Langerhans' cell granules were reported to be present (Perrot *et al.* 1972), it is possible that the actual diagnosis was histiocytosis X.

On the basis of the presently available evidence, xanthoma disseminatum appears to be a distinct entity unrelated to the histiocytosis X group of disorders. As stated by Altman & Winkelmann (1962), it appears to be the result of a reactive proliferation of histiocytes which later become xanthomatous.

References

Altman J & Winkelmann R K
(1962) *Archives of Dermatology* **86**, 582–596
Ferrando J & Bombi J A
(1979) *Archives of Dermatological Research* **266**, 143–159
Harrist T J, Bhan A K, Murphy G F *et al.*
(1983) *American Journal of Clinical Pathology* **79**, *294–300*
Kumakiri M, Sudoh M & Miura Y
(1981) *Journal of the American Academy of Dermatology* **4**, 291–299
Lever W F & Schaumburg-Lever G
(1983) Histopathology of the Skin, 6th edn. J B Lippincott Co, Philadelphia; pp 396–397
Mishkel M A, Cockshutt W P, Nazir D J *et al.*
(1977) *Archives of Dermatology* **113**, 1094–1100
Perrot H, Thivolet J, Hermier C *et al.*
(1972) *Bulletin de la Société Française de dermatologie et de syphiligraphie* **79**, 674–675
Rosai J
(1981) In: Ackerman's Surgical Pathology, 6th edn. Ed. Rosai J. St Louis, C V Mosby Co; p 1161
Sonex T S, Ryan T J & Dawber R P R
(1981) *British Journal of Dermatology* **105** (Suppl 19), 79–81