Granulomatous lipophagic panniculitis and temporal arteritis in a patient with cryptogenic chronic active hepatitis

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Abstract

An elderly woman receiving long term treatment with prednisone and azathioprine for cryptogenic chronic active hepatitis developed granulomatous lipophagic panniculitis and temporal arteritis. The lymphoplasmahistiocytic inflammatory reaction pattern is common to this patient's three diseases. It is suggested that an aberration of the defence mechanisms, immunological or otherwise, is responsible for this unusual occurrence. The triple association of chronic active hepatitis, granulomatous panniculitis and temporal arteritis has not been reported previously.

A patient who had been treated for 16 years with low doses of prednisolone and azathioprine for chronic active hepatitis was referred for the evaluation of panniculitic skin lesions and unilateral amblyopia. Investigations showed temporal granulomatous arteritis and granulomatous lipophagic panniculitis. To the best of our knowledge, this association has not been previously described in chronic active hepatitis.

Case report

The patient, an 80 year old woman, was admitted to hospital because of a sudden deter-

ioration of her sight in the left eye. Funduscopy examination showed a pale and swollen optic disc. Symptoms and signs consistent with polymyalgia rheumatica or tenderness of the temporal arteries were not present. The erythrocyte sedimentation rate was 63 mm/hour. The clinical diagnosis of temporal arteritis was confirmed by a biopsy sample. Examination showed numerous small reddish nodules in the skin of her calves.

Sixteen years before this admission, cryptogenic chronic active hepatitis was diagnosed on clinical, laboratory, and histological grounds. Repeated tests for hepatitis B surface antigen, antibodies to hepatitis virus A, B, and C and antibodies to nuclear antigens, mitochondria, and smooth muscle were negative. The patient was treated with prednisone and azathioprine for two years. Discontinuation of treatment was shortly followed by a severe deterioration in liver function tests. Reinstitution of the drugs normalised the tests. As the withdrawal of the two drugs was repeatedly followed by markedly increased liver enzymes, treatment was continued until this admission to hospital, at which time she was taking 10 mg prednisone and 50 mg azathioprine daily. Hepatic changes were not observed in a liver biopsy sample obtained seven years previously. The liver function tests had been normal for several years. Drugs were continued as it has been suggested that under these circumstances this treatment should be maintained for life.¹

The patient recalled having had several skin nodules on her calves two years previously. The nodules resolved spontaneously within a month. She noticed the reappearance of similar skin lesions three weeks before this admission. The patient was in good general health, and had a temperature of 37.0–38.4°C. The temporal arteries were not tender but were moderately indurated. The liver and spleen were normal. The skin of her calves showed some tiny, brownish scars, which the patient related to the previous episode, and a dozen non-tender, raised, pink nodules, measuring up to 10 mm in diameter. Except for an erythrocyte sedimentation rate of 87 mm/hour, other laboratory tests, including those for liver enzymes, immunoglobulins and autoantibodies, were negative or within the normal range. Following an increase of the prednisone dose to 60 mg per day, there was no further deterioration of her sight, and the skin lesions slowly faded. The last determined erythrocyte sedimentation rate was 12 mm/hour. The patient died after a cerebrovascular accident two months after discharge.

Figure 1 Biopsy sample of a temporal artery showing the severely thickened and inflamed intima with a few necrotic foci (appearing dark in the reproduction). The residual lumen is pinpoint. Haematoxylin and eosin stain.

Figure 2 Biopsy sample of a panniculitic calf lesion. The epidermis is acanthotic and hyperkeratotic. In spite of mild perivascular lymphocytic cuffing, the dermis is normal. The subcutaneous septa are slightly thickened and chronically inflamed. The lobules of the panniculus adiposus are partly replaced by fibrosis and granulomatous inflammation. Haematoxylin and eosin stain.

Figure 3 Higher magnification micrograph of the inflamed panniculus adiposus. The adipocytes are partly replaced and separated from each other by fibrous tissue and a lymphocytic, plasmacytic, and histiocytic infiltrate admixed with foreign body and Touton-type giant cells. Haematoxylin and eosin stain.

MICROSCOPIC FINDINGS

The first liver biopsy sample showed chronic active hepatitis. The distended portal tracts contained a heavy lymphoplasmacytic infiltrate. There was piecemeal necrosis and moderate lobular inflammation.

There was extreme mural thickening of the temporal artery, the residual lumen being pinpoint. The intimal layer occupied most of the width of the arterial wall; it was fibrotic, contained increased amounts of acid mucopolysaccharides, and was heavily infiltrated by lymphocytes, plasma cells, histiocytes, and rare eosinophils. A few irregular foci of recent necrosis were scattered throughout (fig 1). The inflammatory infiltrate extended into the media and adventitia. A giant celled granulomatous response related spatially to the fragmented and reduplicated internal elastic membrane.

The epidermis was mildly acanthotic and hyperkeratotic. Except for mild perivascular lymphocytic cuffing, the dermis was normal. The subcutaneous septa were chronically inflamed and fibrotically thickened. The lobules of the panniculus adiposus were partly replaced by a chronic inflammatory infiltrate and fibrosis (fig 2), the latter being of the reticulin fibre type. The lipocytes varied in size; they were reduced in number and separated from each other by lymphocytes and plasma cells, but mostly by foamy macrophages, foreign body and Touton-type giant cells (fig 3). In addition, there were several foci of membranous fat tissue necrosis (fig 4). Vascular lesions were not observed.

Discussion

The emergence of several, not commonly encountered, disease entities in the same patient may be fortuitous, or may be the expression of shared underlying pathogenetic mechanisms. Our patient presented with cryptogenic chronic active hepatitis, temporal arteritis, and granulomatous lipophagic panniculitis.

Chronic active hepatitis without an overt cause is classified as the cryptogenic variant of the disease.^{2 3} Although cryptogenic and 'auto-immune' chronic active hepatitis are used synonymously by some workers,⁴ others emphasise their clinical and histological similarities and their similar response to treatment with prednisone and azathioprine.⁵ Thus it is the absence of nuclear and smooth muscle autoantibodies which characterises cryptogenic chronic active hepatitis.^{2 3} By these criteria, our patient's liver disease is consistent with the latter diagnosis.

Giant celled granulomatous inflammation of the medium sized elastic arteries in elderly patients is the anatomical correlation of a symptom complex comprising polymyalgia rheumatica, ischaemic disturbances, and constitutional manifestations.^{6 7} Our patient sought medical help because of a sudden deterioration of her sight. The ischaemic optic neuritis and increased erythrocyte sedimentation rate indicated temporal arteritis,⁸ the diagnosis of which was confirmed histologically.

The patient's cutaneous disorder was charac-

Figure 4 Membranous fat tissue necrosis characterised by crenulated, deeply eosinophilic, hyaline linear structures.¹⁸ The two foci of membranous fat tissue necrosis are spatially related to the fibrotic and inflamed panniculus adiposus. Haematoxylin and eosin stain.

terised by multiple small subcutaneous nodules which left depressed scars after healing. Mild chronic septal and severe granulomatous lipophagic panlobular panniculitis dominated the histology.⁹⁻¹⁰ The association of granulomatous lipophagic panniculitis with chronic active hepatitis has been described previously in two patients.¹¹⁻¹²

Temporal arteritis and granulomatous lipophagic panniculitis have not been reported previously in a patient with chronic active hepatitis. The lymphocytic, plasmacytic, and histiocytic inflammatory infiltration, resulting in tissue destruction, is common to these three diseases. The presence of multinucleated giant cells is not discriminative of one disease process or another as they are variants of histiocytes, reflective of macrophagic 'frustration'.

Temporal arteritis and granulomatous lipophagic panniculitis are not sequelae of chronic hepatitis, which, in our patient, was inactive for many years. They are not distant organ mani-

festations of chronic active hepatitis.¹³⁻¹⁴ Instead, the association of chronic active hepatitis, temporal arteritis, and granulomatous lipophagic panniculitis may constitute three different organ manifestations of the same underlying aberration of the defence mechanisms, whether immunological, genetic, or otherwise.⁴⁻⁹⁻¹⁵⁻¹⁶

At first sight it is surprising that temporal arteritis and granulomatous lipophagic panniculitis evolved in a patient treated with prednisone and azathioprine. It is well known, however, that patients with polymyalgia rheumatica who are adequately treated with 10–15 mg of prednisone daily may develop temporal arteritis.¹⁷ Similarly, temporal arteritis and granulomatous lipophagic panniculitis appeared in our patient treated with low dose prednisone and azathioprine.

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