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Case report

IgM cryoglobulin deposits in the peripheral nerve

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Summary. In a patient with Waldenström's macroglobulinaemia and peripheral neuropathy, direct immunofluorescence of a peripheral nerve revealed the presence of abundant IgM and kappa light chain deposits in the endoneurium. Electron microscopic examination showed the microtubular structure of these endoneurial deposits, which strongly suggested the presence of cryoglobulin; this was then found in the serum.

Key words: Waldenström's macroglobulinaemia – Cryoglobulin – Peripheral neuropathy

Introduction

Cryoglobulins have been classified into three types (Brouet et al. 1974): those composed of an isolated monoclonal immunoglobulin (type I), those corresponding to mixed cryoglobulins with a monoclonal component (type II), and the mixed polyclonal cryoglobulins (type III). Reports on peripheral neuropathies (PN) with cryoglobulinaemias mainly concern types II and III (Nemni et al. 1988; Vital et al. 1988). There are only two reports in the literature of PN associated with type I cryoglobulinaemia. The case reported by Vallat et al. (1981) had an IgG cryoglobulinaemia associated with multiple myeloma, and the patient reported by Lippa et al. (1986) had an IgM kappa monoclonal cryoglobulin. So far, endoneurial cryoglobulin deposits have been observed only once in the literature by Vallat et al. (1981). We report the findings in a patient suffering from PN associated with Waldenström's macroglobulinaemia in whom the cryoglobulin was first identified by ultrastructural examination of the peripheral nerve biopsy.

Case report

An 82 year old man had paraesthesia in the hands and feet for 5 months with Raynaud's syndrome. Neurological examination revealed hypoaesthesia of both hands and feet, with absence of ankle jerk. Nerve conduction velocities were normal, but the amplitude of all sensory responses was reduced. Routine laboratory values were normal except for the erythrocyte sedimentation rate which was 131 mm/h. Serum protein immunoelectrophoresis revealed a monoclonal IgM kappa, and bone marrow biopsy showed cellular infiltration by atypical plasma cells (30%). A peripheral nerve biopsy was performed and electron microscopic examination suggested a cryoglobulinaemia, which was then identified in the serum as a monoclonal IgM kappa. Detection of anti-myelin-associated glycoprotein (anti-MAG) activity in the serum was negative (courtesy of Dr A. Steck).

A neuro-muscular biopsy was performed on the antero-external surface of one leg. Muscle fragments were paraffin-embedded. The nerve fragment was divided into three portions. Standard techniques were used on paraffin sections. Direct immunofluorescence microscopy was performed on transverse cryostat sections of the second portion, using anti-IgA, anti-IgG, anti-IgM, anti-IgE sera, anti-kappa and anti-lambda light chain sera (Behring, Marburg, FRG). The third fragment was immediately fixed in 5% glutaraldehyde and postfixed in 1% osmium tetroxide. Epon-embedded semithin and ultrathin sections were prepared for light and electron microscope examination.

After removal of the supernatant, the serum cryoprecipitate was fixed in 5% glutaraldehyde and prepared for electron microscope examination.

Results

No lesion could be detected by light microscopic examination of paraffin-embedded fragments; in particular, there was no vasculitis in either the muscle or the nerve fragments.

Direct immunofluorescence microscopy revealed the presence of abundant IgM and kappa light chain deposits in the endoneurium of three fascicles (Fig. 1); these deposits were totally absent in two other fascicles. Examination of semithin sections confirmed the great variation from one nerve fascicle to another. Three fascicles were extensively involved, with abundant amorphous deposits present in the endoneurium and a dramatic loss of myelinated fibres. In other fascicles, endoneurial deposits were slight or absent and there was a less severe reduction of myelinated fibres. At ultrastructural study, endoneurial deposits consisted of straight or slightly curved aggregated tubular structures with a very small

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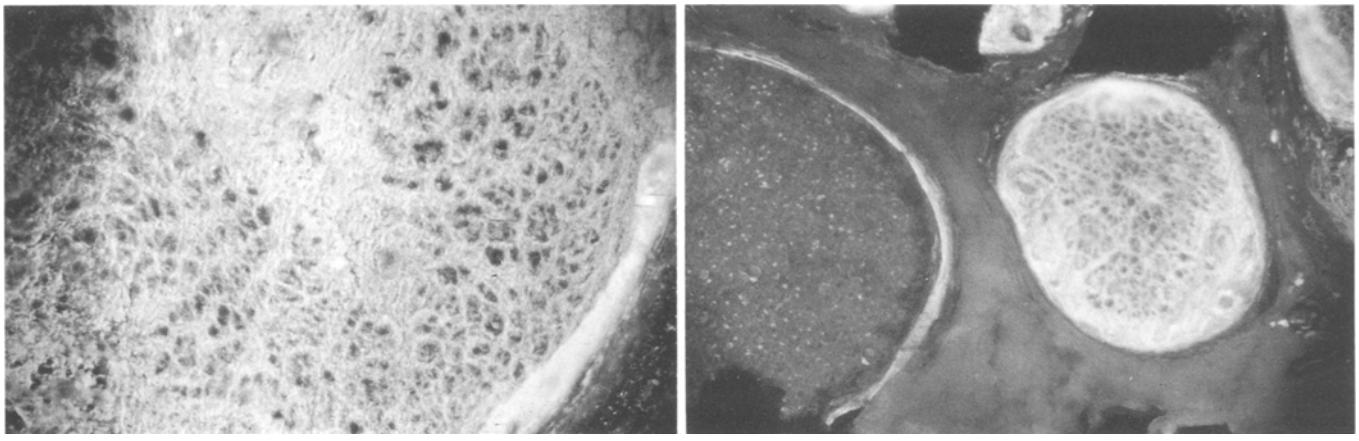
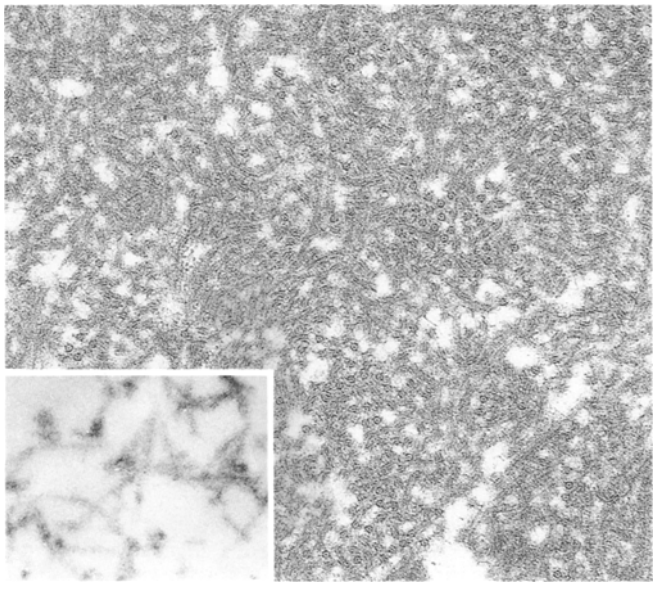


Fig. 1. Direct immunofluorescence microscopy shows abundant IgM (*left*) (×180) and kappa light chain deposits (*right*) (×112) in the endoneurium of some fascicles



central spot (Fig. 2). The diameter of the tubules was 50 nm. Such structures were strongly suggestive of cryoglobulin. In three of the fascicles examined, these deposits were very abundant and compressed the nerve fibres. The walls of the endoneurial capillaries were thickened by tubular aggregates, but none could be seen in their lumen (Fig. 3, left). In the more affected fascicles, lesions of nerve fibres were severe, consisting of numerous ovoids and bands of Büngner, associated with intra-axonal organelle accumulations in myelinated and unmyelinated fibres (Fig. 3, right). Features of segmental demyelination were few, and no widened myelin lamellae were observed.

Fig. 2. Endoneurial deposits consist of straight or slightly curved aggregated tubular structures with a very small central spot. *Inset*: The serum cryoprecipitate has a similar ultrastructure. Acetate uranyl, lead citrate, ×32000

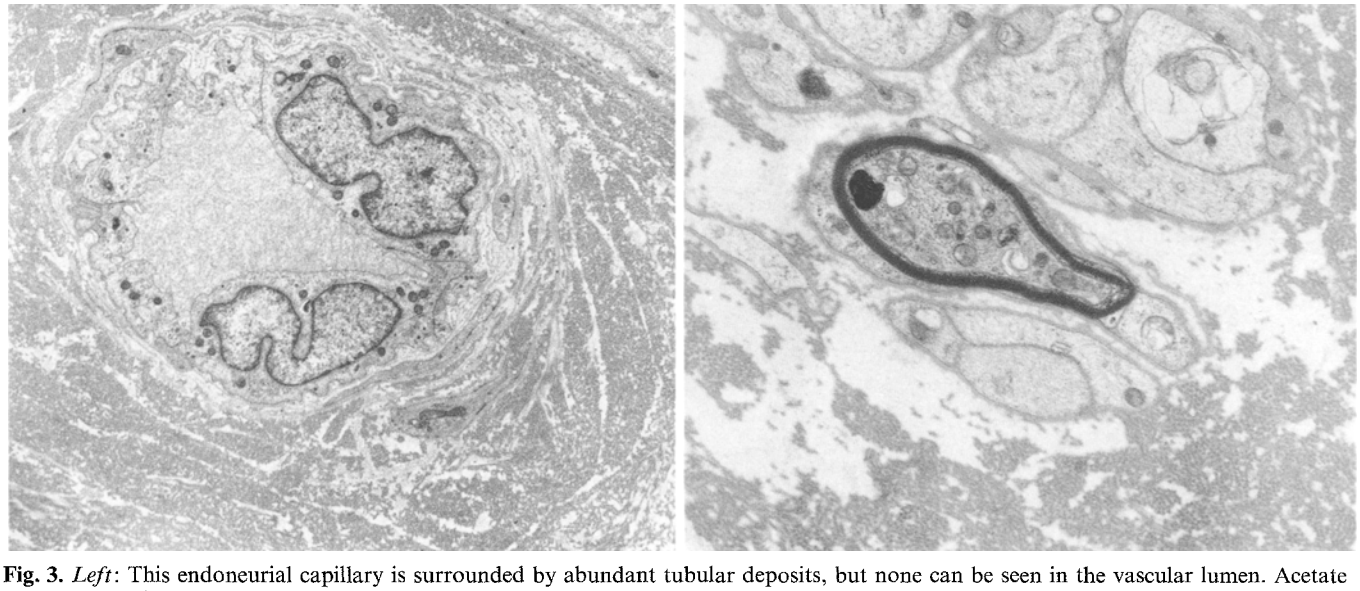


Fig. 3. *Left*: This endoneurial capillary is surrounded by abundant tubular deposits, but none can be seen in the vascular lumen. Acetate uranyl, lead citrate, ×4000. *Right*: Unmyelinated and myelinated fibres are altered; there is intra-axonal organelle accumulation in this myelinated fibre. Acetate uranyl, lead citrate, ×10000

Ultrastructural examination of the serum cryoprecipitate revealed a similar tubular structure (Fig. 2, inset).

Discussion

Cryoglobulins with monoclonal components (type I and type II) may be deposited in the tissues, as previously reported in the bone marrow (Kalderon et al. 1977), and in skin and kidney (Feiner 1988). So far, endoneurial cryoglobulin deposits have been observed only once in the literature by Vallat et al. (1981) in a patient with an IgG cryoglobulinaemia corresponding to multiple myeloma; ultrastructural examination of the peripheral nerve biopsy in this case revealed the tubular structure of these endoneurial deposits. We found endoneurial deposits in our case with Waldenström's macroglobulinaemia; at direct immunofluorescence examination on frozen sections, these deposits were identified as IgM and kappa light chains. In the case of Vallat et al. (1981) these deposits were also seen in the lumen and the walls of the endoneurial capillaries, thus suggesting an ischaemic mechanism due to a single component-monoclonal cryoglobulin occluding the lumina of the vasa nervorum. In our case, none could be seen in the vascular lumina despite abundant perivascular deposits. However, the structural identity between the serum cryoprecipitate and the tissue deposits provides further evidence that the deposits represent the circulating cryoglobulin. Differences in the ultrastructure of monoclonal and mixed cryoglobulins have been documented in serum specimens (Stoebner et al. 1979).

In previously reported cases of PN with mixed cryoglobulinaemia (type II and III), peripheral nerve biopsies showed lesions of vasculitis in the epineurium (Nemni et al. 1988; Vital et al. 1988). Such lesions of vasculitis in the epineurium are probably partly responsible for ischaemic nerve fibre lesions in mixed cryoglobulinaemia. As in the two previously reported cases of PN associated with cryoglobulinaemia type I (Vallat et al. 1981; Lippa et al. 1986), no vasculitis was observed in the present case. The nerve fibre lesions were different in the patient reported by Lippa et al. (1986) with an IgM kappa monoclonal cryoglobulin; both axonal degeneration and segmental demyelination were present. This suggested to these authors that single component monoclonal immunoglobulins are more likely to be associated with demyelination and microcirculatory occlusion, whereas mixed cryoglobulins have a greater propensity of being associated with vasculitis. In fact, features of segmental demyelination were scanty in our case and were not significant in our opinion. Moreover, neither in the case of Lippa et al. (1986) nor in our present case was any widening of the myelin lamellae observed. This is characteristic of certain cases of polyneuropathy associated with an IgM monoclonal gammopathy corresponding to Waldenström macroglobulinaemia, and with IgM monoclonal gammopathy of unknown significance (Vital et al. 1989). In such cases, there is generally an anti-MAG antibody on serum IgM, and this was absent in the case of Lippa et al. (1986) and in our present case. When both widening of myelin lamellae and anti-MAG activity are present in patients with IgM monoclonal gammopathy, direct immunofluorescence study usually reveals IgM binding to the myelin sheaths. This IgM binding to the myelin was absent in the present case, but IgM and kappa light chain deposits were abundant in the endoneurium. Endoneurial IgM deposits have been reported in cases of Waldenström macroglobulinaemia and in cases of IgM monoclonal gammopathy of unknown significance (Yee et al. 1989). However, such endoneurial deposits are granulo-fibrillar at ultrastructural examination and different from the tubular aggregates observed in the present case.

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