CLINICOPATHOLOGICAL CASE CONFERENCE

Lymphoma, paraproteinaemia, and neuropathy

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Case presentation

In 1984 a 55 year old former nurse developed anaemia (haemoglobin 6.4 g/dl), palpitation, haemoglobinuria, and splenomegaly. Investigations showed an erythrocyte sedimentation rate (ESR) > 140 mm/h, white blood cell count 4×10^9 g/l, platelets 97×10^9 g/l, reticulocytes 2.2%, direct Coombs test negative, anti-S antibody present; IgG 4.9 (7-19) g/l, IgA 0.6 (0.8-5) g/l, IgM 14.5 (0.5-2) g/l, IgM lambda paraprotein. Bone marrow biopsy showed a non-Hodgkin's lymphoma predominantly composed of B cells. A chest radiograph and abdominal CT showed no lymphadenopathy. Her lymphoma was treated with prednisolone and chlorambucil (4 mg daily) and she received blood transfusions. Despite this treatment, her haematological indices worsened and in February 1985 she received one cycle of cyclophosphamide, vincristine (2 mg/mm²), and prednisolone. In June 1985, steroids were replaced with azathioprine and she was maintaining a haemoglobin of 11 g/dl.

In January 1985 she developed "sciatica pains" down her right leg followed by a numb patch on the dorsum of her right foot. In June 1986 she developed "needle pains" in her right thumb, index, and middle fingers followed by gradual numbness and coldness of these fingers. In May 1987 a numb patch appeared suddenly on her right lower lip and submental region. In August 1987 a right carpal tunnel decompression failed to relieve the finger pains. Right T8 dermatome shingles developed in October 1987. In 1988 she developed burning sensations and patchy loss of pain and temperature sensation in both hands and feet, worse on the right side. She noted that painless burns had affected her right index finger, and had to wear a glove because of hypersensitive skin on the right hand. Her bowel habit became erratic and she developed nocturia.

The neurological examination in 1988 showed that muscle bulk, power, tendon reflexes, vibration, and joint position sensations were normal. There was impaired pin prick and temperature sensation in the left submental region, the first to third fingers of the right hand, and the dorsum of the right foot. Blood pressure was 100/70 mm Hg lying and 70/60 mm Hg standing.

Investigations included nerve conduction studies. Sensory nerve action potentials were: right median 0 µV, left median 10 µV, left ulnar 6 µV, right sural 2 µV. Right posterior tibial nerve motor conduction velocity was 48 m/s, distal motor latency 5.8 ms, and F wave

latency 53 ms. Right sural nerve biopsy showed myelinated fibre loss, no vasculitis. Congo red staining was negative. The ECG RR interval ratio (inspiration/expiration) was 1.08. Blood glucose, vitamin B12, antinuclear factor, and chest radiography were normal.

A diagnostic investigation was performed.

Discussion

Dr John H J Wokke

This patient had a raised ESR, low white blood cells and platelets, and an IgM lambda paraprotein. These abnormalities are in favour of a gammopathy and therefore the first diagnostic procedure is a bone marrow biopsy to analyse the nature of the gammopathy. May we review the pathological studies of this biopsy?

Dr J Morris

The bone marrow trephine (fig 1) showed marrow diffusely infiltrated by tumour composed largely of lymphoplasmacytoid cells that marked immunocytochemically as B cells. Many of the tumour cells also marked with IgM and lambda light chain. A diagnosis of non-Hodgkin's lymphoma, B cell type was made.

Dr Wokke

In 1984 a B cell non-Hodgkin's lymphoma was diagnosed and the patient received immunosuppressive and cytostatic therapy. However, during this treatment her neurological condition gradually worsened as she developed sciatica of the right leg which resulted in numbness of the right foot in January 1985; in June disturbance of sensation of fingers of the right hand developed. Two years later disturbance of sensation in an area of the right mandibular nerve occurred. She had an intercurrent reinfection with the *Varicella zoster* virus in 1987. In 1988 symptoms of a small fibre neuropathy became manifest with a somewhat asymmetric distribution. In addition, orthostatic hypotension and erratic bowel habit pointed to failure of the autonomic nervous system. The neurological examination was inconclusive as there was no proof of symmetric polyneuropathy. Superficial sensation was only disturbed in restricted nerve areas. However, the nerve conduction studies gave more proof of neuropathy, but again asymmetric and compatible with axonal loss. The amplitudes of sensory action potentials were low in the right sural nerve and absent in the right median nerve. Studies of motor nerves

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Presented at the Conference
of the Association of British
Neurologists and
Nederlandse Vereniging voor
Neurologie, Avimore,
4-6 May 1994.

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Received 5 October
and in revised form
18 January 1996
Accepted 24 January 1996

Figure 1 Microscopic illustration of the bone marrow trephine. There is extensive infiltration of lymphoid and lymphoplasmacytoid cells and displacement of many of the other marrow elements that is most easily appreciated by the absence of the multinucleate megakaryocytes that produce platelets. Haematoxylin and eosin $\times 250$.

were normal. In addition, the RR interval ratio of the ECG had decreased. At this stage a biopsy of the affected sural nerve was justified to demonstrate deposits of the M protein on myelin sheaths, deposits of amyloid, or alternatively to look for signs of vasculitis. Can we see the sural nerve biopsy?

Dr Morris

The sural nerve biopsy showed only moderate diffuse loss of myelinated fibres of all diameters. No abnormalities were seen in the blood vessels and no amyloid was seen on Congo red stains either in the walls of blood vessels or within the endoneurium. Electron microscopy was not performed. The teased preparation showed only occasional degenerating axons, a finding consistent with the diffuse loss of myelinated axons seen in the wax embedded material.

Dr Wokke

The neurological diagnosis is a small fibre sensory neuropathy in a patient with B cell lymphoma with IgM paraproteinaemia and secondary immunodeficiency. There are many causes of small fibre sensory loss, the first being hereditary sensory and autonomic neuropathy (HSAN). There are five types of this disease,¹ but usually they become manifest in childhood and lead to acral mutilation in an early stage. Other accompanying features such as deafness and mental retardation may be present.

Sensory neuropathy may occur in the course of Tangier disease, which is a very rare disorder of plasma lipid transport characterised by hypocholesterolaemia and absence of high density lipoprotein.² Painful neuropathy is of course a sign of X linked Fabry disease; carriers may have a peripheral neuropathy.³ Other features of this disease are a characteristic maculopapular rash and disturbance of renal function. Due to absence of

specific abnormalities neither of these conditions can be diagnosed in the present case.

In lepromatous leprosy asymmetric sensory neuropathy is characterised by skin abnormalities,⁴ which were absent in this patient. Painful sensory neuropathy may develop in the course of diabetes mellitus, which was excluded by laboratory tests.

Finally, both the superficial sensory loss and the disturbance of autonomic function are in favour of primary amyloidosis. Amyloid is a sticky substance, which, once there, cannot be removed due to its physicochemical properties. It consists of linear, non-branching aggregated fibrils with a width of 7.5 to 10 nm and indefinite length.⁵ Each fibril consists of two to five filaments and is arranged in an antiparallel configuration, the so-called cross β pleated sheet. The protein resists proteolytic digestion and hampers normal tissue function.

Amyloid can be demonstrated with the light microscope as homogeneous and amorphous pink deposits with haematoxylin and eosin staining and it stains metachromatically with methyl violet. The diagnostic test for demonstration of amyloid is staining with Congo red and viewing with polarised light; it then shows an apple green birefringence. In addition, specific antisera make accurate identification of types of amyloid fibrils possible. Using the electron microscope deposition of amyloid fibrils can be accurately demonstrated in various tissues. Amyloidosis often causes peripheral neuropathy and sometimes myopathy.⁶ There are different clinical forms of amyloidosis, which are characterised by distinct types of amyloid. Amyloidosis in gammopathy is called primary amyloidosis and the amyloid fibril shows homology to the N terminal region of the variable fragment of an immunoglobulin light chain.⁵ The major protein components are therefore kappa or lambda light chains. In primary amyloidosis the male:female ratio is 2:1 and 97% of patients are aged over 40.

Many have organomegaly and macroglossia may be seen. Many also have orthostatic hypotension and peripheral neuropathy.⁷ Patients with primary amyloidosis or lymphoma are among those with the worst prognosis in IgM gammopathy: 50% die after two years.⁸ The neuropathy may manifest as two distinct clinical syndromes: firstly, a carpal tunnel syndrome caused by thickening of the transverse carpal ligament after deposition of amyloid; secondly, a symmetric sensory and autonomic neuropathy which is characterised by a loss of feeling, dysaesthesiae, and pain, and by orthostatic hypotension, bowel dysfunction, impotence, and disturbance of sweating. Muscle weakness may develop late in the disease.⁷ Primary amyloidosis may be a likely explanation in the present case, but the affected sural nerve did not show amyloid deposition.

Therefore we must first consider other causes of the polyneuropathy leading to axonal degeneration and characterised by a clinical and neurophysiological asymmetric distribution. Of course, many causes of neuropathy may be detected by a careful clinical work up.⁹ Asymmetric neuropathy may be a manifestation of necrotising vasculitis, which may occur systematically or, rarely, isolated in the peripheral nervous system,¹⁰ or associated with cancer.¹¹ Usually the first manifestation is that of mononeuritis multiplex followed by asymmetric polyneuropathy, evolving to symmetric polyneuropathy. Pain is a frequent symptom as are motor abnormalities when ischaemic lesions of nerve segments cause axonal degeneration. Neuropathy caused by vasculitis is therefore a serious condition and the prognosis is influenced by involvement of other organs and response to immunosuppressive treatment. The hallmark of the diagnosis is demonstration of vasculitic changes in biopsies of affected tissues, which were absent in the sural nerve biopsy of the present case.

One of the laboratory abnormalities in the patient which must be discussed separately is the presence of anti-S antibodies. These are directed against the MNS system and sometimes occur after maternal-fetal immunisation in pregnancy or after haemotransfusion.¹² It is not clear whether this patient had been pregnant in the past; neither whether she had received blood transfusions for anaemia in 1984. If so, she might have been infected with HIV. All types of neuromuscular manifestations may be associated with HIV type 1 infection and in as many as 50% of patients,¹³ the painful sensory neuropathy which occurs is usually symmetric, and based on distal axonal degeneration from an unknown pathogenetic mechanism. Direct viral invasion of the axons has been postulated. Mononeuropathy multiplex also occurs in patients with HIV-1 infection both with and without AIDS.¹³ the cause may be cytomegalovirus infection or again vasculitis. The clinical syndrome in the present case and the sural nerve biopsy findings make HIV-1 infection an unlikely explanation.

Another cause of sensory disturbances of the peripheral nervous system may be infec-

tion with *Borrelia burgdorferi*,¹⁴ which is usually characterised by intermittent distal limb paraesthesiae; however, sometimes these have a more patchy distribution. Sensory loss, if present, is only mild and autonomic dysfunction has not been described. As other manifestations of Lyme disease were absent, infection with *B burgdorferi* can be excluded.

A relation between the neuropathy and the non-Hodgkin's lymphoma should also be considered. Association of lymphoma and subacute large fibre sensory neuropathy has been reported, but it is extremely rare.¹⁵ This condition is a more frequent paraneoplastic manifestation of small cell lung cancer; anti-neuronal, so called anti-Hu antibodies which are directed against neuronal nuclear antigens, may be demonstrated.¹⁶ The neuropathy is characterised by sensory ataxia. Direct infiltration by lymphocytic cells which may explain subacute neuropathy could not be demonstrated in the sural nerve biopsy.

As all causes seem to have been excluded, can chronic idiopathic axonal polyneuropathy (CIAP) be diagnosed? We have recently performed a prospective clinical study in a cohort of 75 patients with CIAP and have concluded that this condition does not take a rapid or incapacitating course¹⁷; although the symptoms may at onset be asymmetrically distributed, the syndrome shows symmetric abnormalities after one to two years. The legs tend to be more seriously involved and autonomic failure is not seen.

Therefore I must return to the possibility of an association between the presence of the gammopathy and neuropathy. Three explanations should be examined. Firstly that of a direct relation between the paraprotein and the neuropathy. The relation of paraproteinaemia and neuropathy is well established.^{8,18} The neuropathy usually has a symmetric distribution and is slowly progressive over years. Patients have both sensory and motor abnormalities leading to unsteadiness, and autonomic features are not prominent.¹⁹ Of the patients with IgM paraproteinaemia about 50% have serum antibodies against the myelin associated glycoprotein. Neurophysiological testing shows signs of demyelination and of axonal degeneration. In sural nerve biopsies deposition of IgM on myelin sheaths can be regularly shown; there is a predominant reduction of large diameter myelinated nerve fibres. In a five year follow up study of 32 patients rapid deterioration was seen in five patients; in three of these non-Hodgkin's lymphoma was diagnosed; the other two had features of chronic inflammatory demyelinating polyneuropathy.¹⁹ This first explanation does not seem to solve the problem of the present case.

The second explanation may be cryoglobulinaemia. Cryoglobulins are serum proteins which precipitate when cooled and dissolve when heated again. There are three types; cryoglobulins type I are composed of isolated monoclonal immunoglobulins (IgG, IgM, IgA, or monoclonal light chains), type II are mixed (two or more immunoglobulins, including one monoclonal immunoglobulin), and

type III are polyclonal without an M component.²⁰ Cryoglobulinaemia is associated with lymphoma or collagen diseases and is often accompanied by peripheral neuropathy. Sensory asymmetric neuropathy has been seen in cryoglobulinaemia type II,²⁰ and neuropathy may precede skin manifestations of cryoglobulinaemia. Sural nerve biopsies show features of axonal degeneration and abnormalities of endoneurial microvessels ranging from overt vasculitis to thickening of the vessel wall and redundant basal lamina formation.^{20–21} Recently it has been suggested that precipitation of cryoglobulins within the vascular lumen may cause occlusive microangiopathy.²² No evidence in support of cryoglobulinaemia was found.

Finally, we must return to the first diagnosis of primary amyloidosis, which had to be rejected after the negative biopsy of the affected sural nerve. Evidence in favour of a diagnosis of primary amyloidosis includes the clinical syndrome of small fibre neuropathy and autonomic failure, the presence of an IgM monoclonal protein, and the absent reaction on treatment and rapid deterioration leading to death of the patient six years later. Cranial neuropathy, as occurred in the present patient, does not exclude the diagnosis.²³ We must now consider the possibility of a false negative sural nerve biopsy. It is of course possible that amyloid depositions may have been present but beyond the limit of detection. Another explanation may have been the presence of amyloid in a proximal segment of the sural nerve, which could not be taken for biopsy. Proximal abnormalities of peripheral nerves leading to distal axonal degeneration have been hypothesised in vasculitic neuropathy. We have recently diagnosed amyloid deposits in the sural nerve biopsy of a patient with IgM paraproteinaemia and small fibre sensory neuropathy and autonomic failure neuropathy; deposits were very small and only sporadically

present in longitudinal sections. In another patient with IgG paraproteinaemia and polyneuropathy the first sural nerve biopsy showed only axonal degeneration. When the situation of this patient deteriorated after one year despite immunosuppressive treatment, and orthostatic hypotension pointed to autonomic failure the other sural nerve was biopsied and amyloid depositions were clearly present. Results of biopsies from different tissues or organs may vary,^{7–24} and even affected sites are not always positive.⁷ Abdominal fat and the rectum have been optimally analysed in this respect and biopsies are not very invasive.

In conclusion, in my opinion all evidence in this patient is in favour of neuropathy associated with primary amyloidosis. The diagnostic procedure should be a rectal biopsy.

Pathology discussion

Dr Morris

As Dr Wokke deduced, the diagnostic investigation was indeed a rectal biopsy (fig 2). It showed a normal appearing bowel mucosa but a large deposit of amorphous and finely fibrillar faintly eosinophilic material in the lamina propria. The material stained with Congo red and polarisation showed the focal apple green birefringence diagnostic of amyloid. Immunocytochemical staining showed the presence of epitopes of IgM and lambda light chains together with the amyloid A protein. These findings demonstrate the systemic deposition of a paraprotein derived amyloid and support the diagnosis of amyloid neuropathy despite the inability to demonstrate amyloid in the sural nerve biopsy.

As was noted in the protocol the patient died some two years after the rectal biopsy was performed. At necropsy, death was shown to be due to pulmonary oedema without evidence of pulmonary infection. Micro-

Figure 2 Part of the rectal biopsy. The rectal glands are normal, but there are masses of amorphous amyloid deposited in the hypocellular lamina propria. Haematoxylin and eosin $\times 125$.

Figure 3 Section from one of the intradural spinal roots showing a nodule of amyloid on one of the small arteries. Haematoxylin and eosin $\times 50$.

scopically, there was amyloid deposition in both the blood vessels of the lung and in the walls of the alveoli which might well have contributed to the development of the pulmonary oedema.

In the remainder of the systemic examination, there was para-aortic and thoracic lymphadenopathy that on microscopic examination proved to be a result of amyloid deposition in the lymph nodes rather than lymphoma. No residual lymphoma was detected either macroscopically or microscopically. The other systemic organs had a normal macroscopic appearance but microscopic examination of the kidney showed amyloid in the walls of some of the interlobular arteries and in the perinephric fat. Variable amounts of vascular amyloid were also present in some of the other viscera, notably the heart, where

there was some extension into adjacent myocardium with amyloid surrounding some of the individual myocytes. As with the rectal biopsy, immunocytochemistry on the post-mortem material showed staining for IgM, lamda light chain, and amyloid A protein.

Turning to the nervous system, the brain weighed 1430 g and both it and the spinal cord had an entirely normal appearance on external examination, brain slices, and microscopic study. As would be expected in a systemic amyloidosis, no amyloid was seen in any of the cerebral or spinal vessels with the exception of the intradural spinal roots where some of the small arteries within the spinal roots had amyloid deposited in their walls (fig 3). Although, as described, amyloid was clearly present and easy to find in the systemic organs, there was also extensive amyloid depo-

Figure 4 Section of vagus nerve taken at necropsy. Congo red stain shows very extensive perivascular amyloid deposition with extension into adjacent endoneurium. Congo red $\times 50$.

sition in muscle and peripheral nerve (fig 3). The muscles sampled were intercostal, sternomastoid, posterior belly of the digastric, tongue, psoas, and quadriceps. With the exception of the sternomastoid, all these muscles showed amyloid deposition in the walls of blood vessels with, in most cases, some additional amyloid deposition in the adjacent connective tissue.

Sections of popliteal and femoral nerve showed focal deposits of amyloid in vessels and the endoneurium, and the vagus nerve showed massive amyloid deposition in blood vessel walls associated with the nerve and in the endoneurium as well as adjacent epineurial tissue (fig 4). Curiously, in view of the considerable amount of amyloid in the other peripheral nerves that were sampled, the sural nerve that had not been biopsied was entirely free of amyloid deposits, although, as with the biopsied sural nerve, there was some axonal degeneration that presumably reflected more proximal axonal damage from vascular and endoneurial amyloid deposition. As was noted by Dr Wokke, the amyloid deposits in the sural nerve can be very scattered and inconspicuous, but it is interesting that, unlike the patient he referred to, in whom the contralateral sural nerve contained amyloid a year after a negative biopsy, in this patient there was still no amyloid in the remaining sural nerve at necropsy more than two years later.

Diagnosis

- (1) Non-Hodgkin's lymphoma, with IgM paraproteinaemia
- (2) Amyloid neuropathy, IgM-lambda type.

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