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Pathological findings in three non-japanese patients with the POEMS syndrome

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Summary. The pathological features of three European patients with plasma cell dyscrasia, osteosclerosis and a multisystem disorder, most frequent in Japan, that includes polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes (POEMS syndrome), are reported. The material was obtained from biopsies (peroneal nerve, lymph node) and general autopsy, including hypophysis, in one case. The most salient findings were: peripheral nerve lesions, including both segmental demyelination and axonal degeneration, with so-called uncompacted myelin lamellae (UML); angiofollicular lymph node hyperplasia (AFLNH); and non inflammatory vascular changes. Though not specific, it appears that UML and AFLNH may be contributive findings in atypical cases of POEMS syndrome (incomplete forms, lack of underlying malignant plasma cell dyscrasia or circulating monoclonal immunoglobulin). Among the various autopsy findings we emphasize the skin thickening which was secondary to a hyaline sclerosis of the papillary dermis, and the presence in adenohypophysis of numerous cells showing positive reactions with the anti-alpha MSH antibody. Though immunological, vascular and hormonal disturbancies have been implicated at the origin of several manifestations of the disorder, the pathogenesis of the POEMS syndrome remains obscure.

Key words: POEMS syndrome – Peripheral neuropathy – Angiofollicular lymph node hyperplasia – Osteosclerotic myeloma

Introduction

Peripheral neuropathy is observed in 30–50% of patients with osteosclerotic myeloma and may be accompanied by a multisystem disorder that includes skin changes (hyperpigmentation, skin thickening, hypertrichosis), oedema (peripheral and generalized type), endocrinopathy (hypogonadism, amenorrhoea, gynaecomastia, hypothyroidism, diabetes mellitus), organomegaly (lymphadenopathy, hepato-splenomegaly) and finger clubbing (Kelly 1985; Meier 1985; Gherardi et al. 1988). First described by Crow in 1956, the disorder was subsequently recognized as a separate clinical syndrome by japanese investigators and appears in the literature under the term POEMS syndrome, for "Polyneuropathy, Organomegaly, Endocrinopathy, M protein, Skin changes" (Bardwick et al. 1980), Takatsuki syndrome (Driedger and Pruzanski 1980), or Crow-Fukase syndrome (Nakanishi et al. 1984). This rare condition has been reviewed by Nakanishi et al. (1984) who compared 102 japanese patients with 52 cases published outside Japan.

Pathological data concerning the POEMS syndrome are fragmentary in the English literature. Most reports mention trivial alterations or are dealing with features exceptionally observed in the syndrome, although some authors have recently focused on the ultrastructural evidence of "uncompacted myelin lamellae" in peripheral nerve (Berguouignan et al. 1987) and "Castelman-like" lesions in lymph nodes (Nakanishi et al. 1984; Bitter et al. 1985). Knowledge of contributory lesions is of importance since POEMS syndrome is frequently misdiagnosed, especially in pauci-symptomatic patients or when circulating monoclonal gammopathy or malignant plasma cell dyscrasia is lacking (Gherardi et al. 1988).

The pathogenesis of the syndrome remains obscure. An hypothalamo-hypophyseal origin of the endocrine disturbancies has been hypothesized (Meier et al. 1986) but we were not able to find an immunocytochemical study of the adenohypophysis in POEMS patients in the literature.

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Table 1. Clinical features

	Sex/ Age*	Polyneuropathy	Organomegaly	Endocrinopathy	M-protein	Skin changes	other signs
Case 1	F/46	low MNCV High CSF protein (1,13 g/L) Argyll-Robertson papilledema	Liver Spleen Lymph nodes	Diabetes	IgA lambda osteosclerosis	Thickening Hypertrichosis Hyperpigmentation Raynaud phenomenon	edema anasarca arteriopathy thrombocytosis renal failure
Case 2	M/72	Low MNCV High CSF protein (2,67 g/L) papilledema	Liver Lymph nodes	–	IgG lambda mixed osteosclerosis and lysis	–	edema anasarca
Case 3	M/39	Low MNCV High CSF protein (1,32 g/L) papilledema	Liver Lymph nodes	Hypothyroidism Hypocorti-solemia Hypogonadism Gynecomastia	Lambda mixed osteosclerosis and lysis	Thickening Hypertrichosis Hyperpigmentation	edema anasarca steatorrhea finger clubbing

Case 1: nerve biopsy 70260, general autopsy A5425
Case 2: nerve biopsy 149422
Case 3: nerve biopsy and lymph node biopsy 182882

* age at onset of neurologic symptoms

MNCV: motor nerve conduction velocities; CSF: cerebrospinal fluid

The aim of this paper is to report the pathological findings that we have observed in 3 European patients with the POEMS syndrome and to discuss their diagnostic value and pathogenetic significance.

Material and methods

Three patients with the systemic signs of the POEMS syndrome and osteo-sclerotic myeloma were studied. The relevant clinical data are presented in Table 1. The material consisted of biopsy and autopsy samples. The peroneal biopsies in all patients, the node biopsy in patient 3 and the samples removed at post-mortem examination of patient 1 were formalin fixed, paraffin embedded and stained with haematoxylin and eosin, Masson's trichrome, PAS and Congo red.

The adenohypophysis removed at autopsy of patient 1 was conventionally studied using Herlant's tetrachrome, P.A.S., orange G and Wilder's silver impregnation. Immunocytochemical study was also performed using indirect immunoperoxidase on paraffin sections. Details concerning the antibodies applied in the study are listed in Table 2.

Direct immunofluorescence on nerve fragments in patient 2 and 3 was performed on cryostat sections using anti-IgA, IgG, IgM, Kappa, Lambda, C3 and C1q sera. The remainder of the peroneal nerve biopsies in patients 2 and 3 was processed as follows: fixation by 2.5% glutaraldehyde in 0.1 M cacodylate buffer pH 7.4 for 24 h, post-fixation in 2% osmium tetroxyde for 1 h, deshydratation in ethanol, embedding in Epon 812, semithin sections (2 μm thick) stained with toluidine blue, ultrathin sections stained with uranyl acetate and lead citrate.

A morphometric study of nerve biopsy was performed in case 2 and 3. The size and density of myelinated fibers (MF) per mm^2 of endoneurial area were determined directly from the semithin sections using the semi-automatic analyzer ASM Leitz. The density and size of unmyelinated axons (UA) were calculated from electron micrographs at ×10000 magnification. The results were compared with previously published data of normal controls (Gherardi et al. 1986).

Teasing preparation was done in patient 3: a part of the nerve sample was osmicated for 3 h after fixation and 100 consecutive single myelinated fibers were dissected.

Table 2. Results of immunoperoxidase staining on adenohypophysis

Antigen	Source of antibodies	Labelling
Prolactin	anti h PRL (Pr. Dray, C. Rougeot, I. PASTEUR)	absent
Growth hormone	anti h GH (Pr. Girod, Lyon)	normal
Gonado-tropin	anti h CG total (C. Tramu, Lille)	normal
ACTH	anti ACTH 1–24 (id)	normal
α MSH	anti α MSH (M.P. Dubois, Nousilly, INRA)	present
β Endorphin	anti β endorphin (id)	normal
TSH	anti h TSH β (Niam D.D. USA – A.F. Parlow	normal
FSH	anti h FSH β (id)	normal
LH	anti h LH β (id)	normal

Results

Paraffin-embedded fragments from the three peroneal nerve biopsies showed occasional mononu-

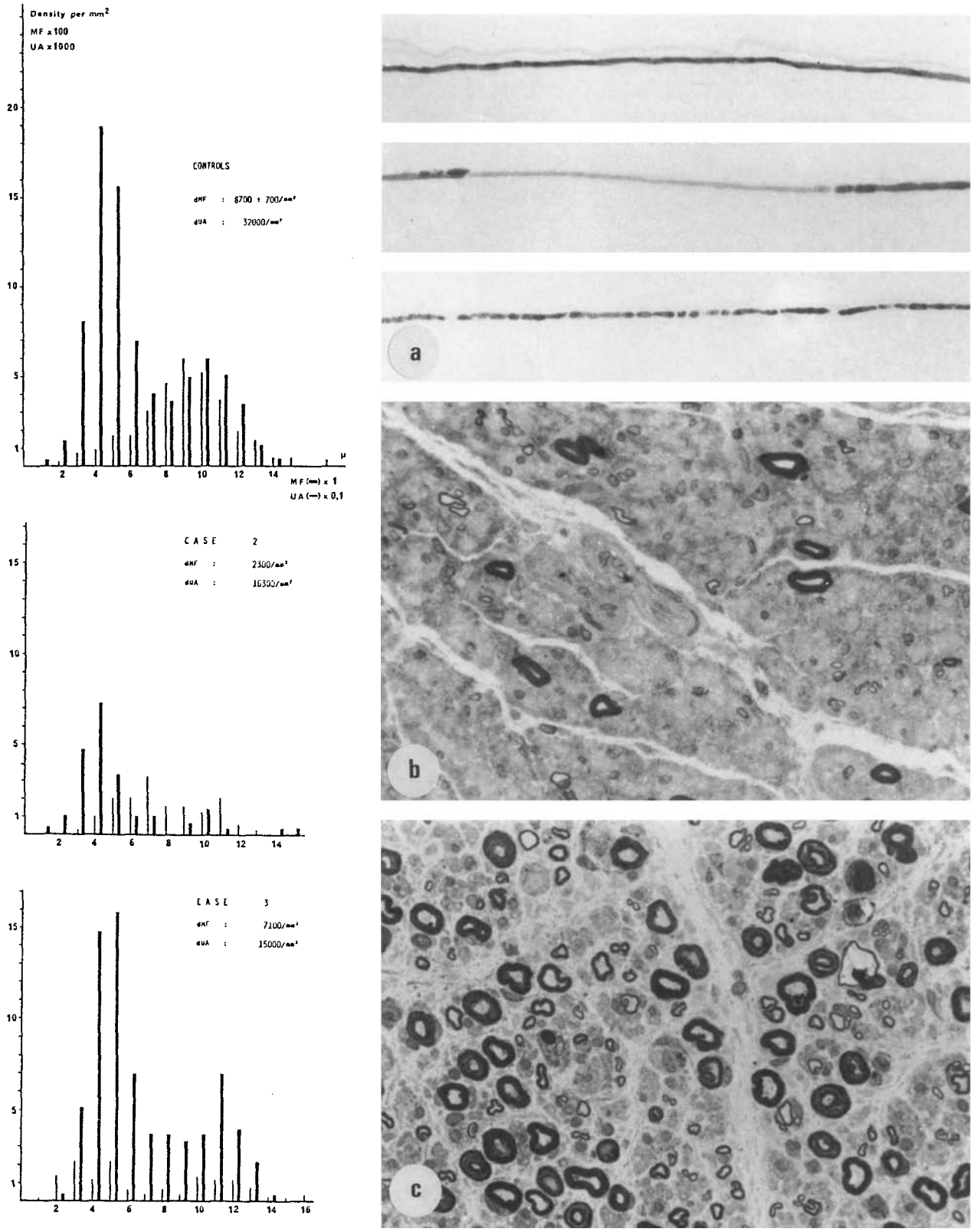

Fig. 1. (a) Isolated myelinated fibers showing respectively normal myelin sheath, segmental demyelination and Wallerian degeneration (case 3, teasing preparaton); **(b)** and **(c)** peroneal nerve transverse sections showing marked to moderate myelinated fiber loss assessed by diameter histograms, and clusters of small regenerating myelinated fibers (cases 2 and 3, semithin sections, toluidine blue, ×1600)

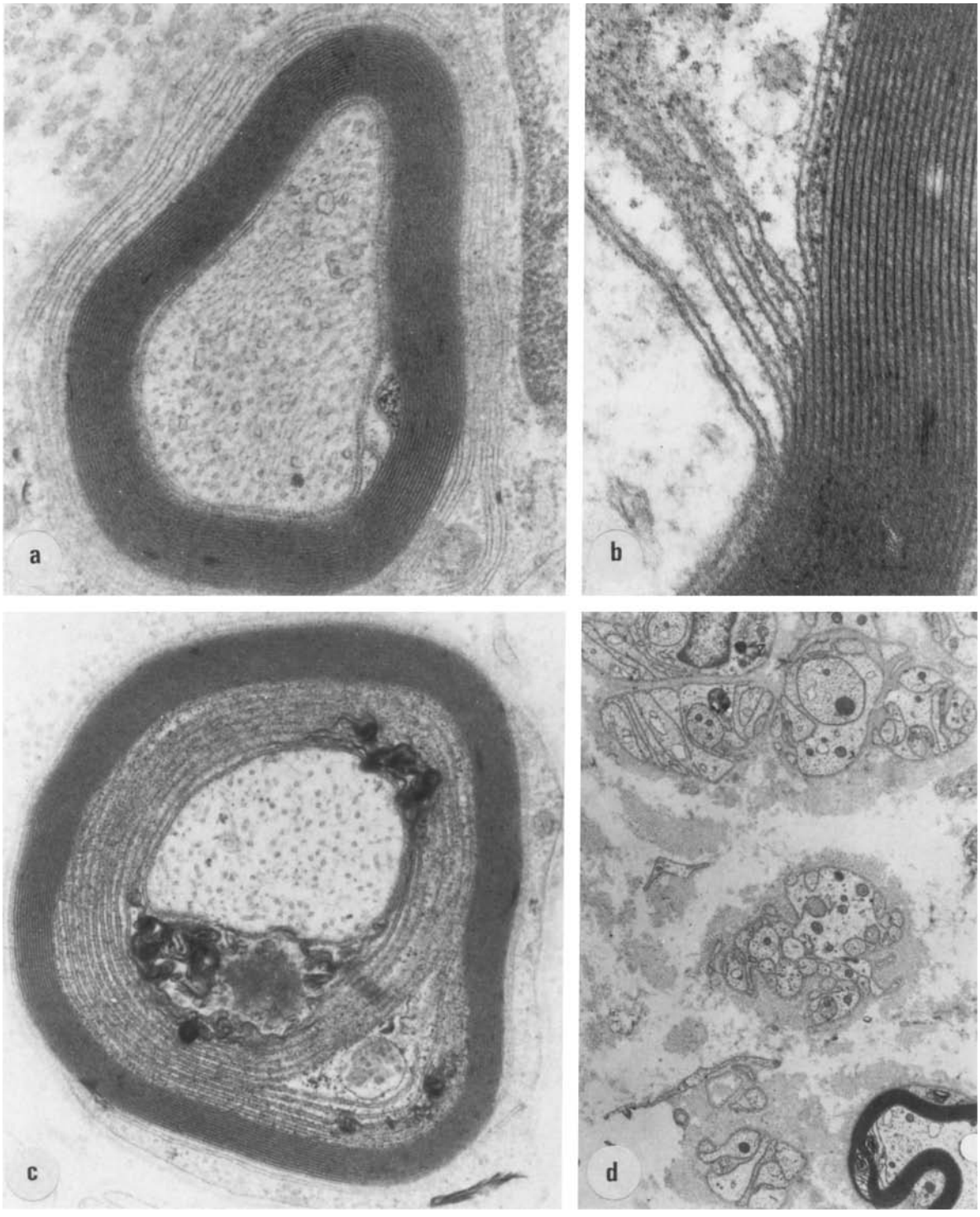

Fig. 2. (a) and **(c)** Uncompacted myelin lamellae in the outer or inner portion of the myelin sheath (case 2, electron microscopy, ×3150); **(b)** Uncompacted myelin lamellae are secondary to the division of the major dense line of myelin (case 2, electron microscopy, ×80000); **(d)** Schwann cells showing either flat processes devoid of axons (*up left*) or multiple peripheral axon sprouts (*center*) (case 3, electron microscopy, ×10000)

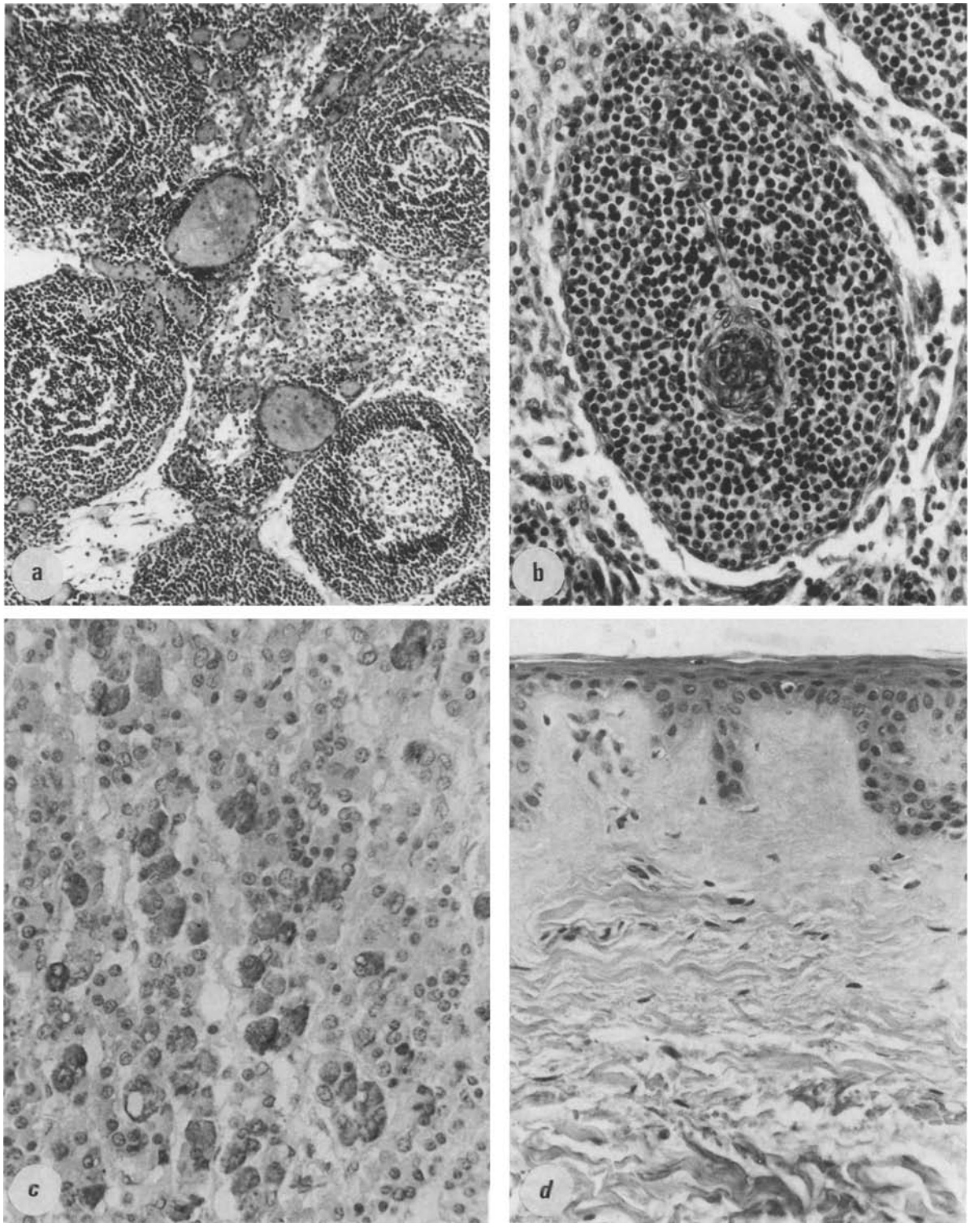

Fig. 3. (a) Lymph node showing angiofollicular hyperplasia: follicle centers of various sizes are coated with concentrically arranged lymphocytes, and interfollicular areas show vascular proliferation and sinusal histiocytosis (case 1, H & E, ×400); **(b)** small follicle showing a central thick-walled vessel and a capillary penetrating the coat of lymphocytes (case 1, H & E, ×1000); **(c)** immunostaining of adenohypophysis showing numerous cells positive with the anti-alpha MSH antibody (case 1, immunoperoxidase, ×1200); **(d)** skin showing hyaline sclerosis of the papillary dermis (case 1, H & E, ×600)

clear cells in epineurium and no amyloid deposits. Endoneurial oedema and mild vascular abnormalities, i.e. concentric thickening of small vessels walls in epi- and endoneurium and plump endothelial cells, were observed in case 3. Direct immunofluorescence study showed diffuse endoneurial positivity with IgG and lambda anti-sera (case 2) and lambda anti-serum (case 3). Immunostaining was not observed in myelin sheaths, perineurium and vessel walls.

Moderate to marked myelinated fiber (MF) loss was observed in the 3 cases. The morphometric study of case 2 and 3 (Fig. 1) gave the following data:

– the biopsy of case two contained 2300 MF per mm^2 and that of case three 7100 MF per mm^2 (controls = 8700 +/− 700). In both cases MF size distribution was bimodal.

– the density of unmyelinated axons (UA) was moderately decreased in case 2 and 3 (respectively 16300 and 15000 UA per mm^2, control = 32000). UA size histograms showed abnormal, roughly bimodal, patterns of distribution.

Teasing preparations in case 3 revealed 40% of MF with no myelin abnormality, 32% at various stages of wallerian degeneration and 28% with segmental abnormality of myelin sheaths including segmental demyelination and remyelination (Fig. 1).

Semithin sections revealed pictures of acute myelino-axonal degeneration and clusters of regenerating MF (Fig. 1). The ultrastructural study showed, in addition, Büngner's bands, Schwann cells with flattened processes devoid of axons and occasional immature axon sprouts at their periphery (Fig. 2). Onion bulb formation was not prominent. The picture of uncompacted myelin lamellae (UML) secondary to the division of the major dense line of the myelin sheath was observed in both cases (Fig. 2). The involved MF accounted respectively for 8% and 1% of the entire MF population. UML were either located in the inner or outer portion of the myelin sheaths. No widening of myelin lamellae secondary to division of the minor dense line was found.

Almost all cervical, mediastinal and abdominal lymph nodes removed at autopsy of patient 1 showed large irregularly shaped follicles consisting of whorled structures with a central arborizing hyalinized vessel. The concentric rings of mature lymphocytes were penetrated by capillaries issued from the follicle's center. The interfollicular areas showed marked vascular proliferation, sinusal histiocytosis and sheets of mature plasma cells. These features were consistent with a diffuse angiofollicular lymph node hyperplasia (Fig. 3). Abundant whorled follicles were also observed in spleen.

Axillary lymph node biopsy in case 3 showed reactive hyperplasia and 3 concentrically arranged follicles with a central vessel.

The other lesions found at autopsy of case 1 included an increased number of plasma cells in bone marrow consistent with myeloma, left pleural and pericardial effusions, and generalized skin thickening due to hyaline sclerosis of the pars papillaris of the dermis. Here a band-like area showing homogenization of collagen, a decreased number of fibroblasts, but no inflammatory cell infiltrate was present immediately beneath a thin and hyperpigmented epidermis (Fig. 3). The sclerosis surrounded and extended along the hair sheaths. A similar juxta-epithelial sclerosis was observed in the chorium of the oesophagus. A systemic non-inflammatory arteriopathy with medial hyperplasia and fibrous endarteritis and moderate arteriolosclerosis was seen. Splenomegaly (500 g) with splenic infarction, hepatomegaly (2600 g) with moderate portal mononuclear inflammation but neither hepatocytic degeneration nor architectural abnormality, severe chronic interstitial nephritis, and a micro-vesicular adenoma in the thyroid gland were also observed. An unusual immuno-cytochemical pattern was seen in the adenohypophysis (Table 2). The neurohypophysis was normal and the adenohypophysis was architecturally normal. Small P.A.S. positive colloid cysts were present and foci of interstitial fibrosis were observed. Neither cellular infiltrates nor vascular changes were detected. Immunocytochemical study revealed a lack of prolactin cells and fairly numerous cells reacting positively with the anti-alpha MSH serum (Fig. 3). The remainder of the study showed no abnormality. The central nervous system was unremarkable.

Discussion

The 3 patients reported here suffered from plasma cell dyscrasia, with osteosclerotic lesions on skeletal X-rays and a multisystem disorder. The clinical features were consistent with those previously reported in the POEMS syndrome. The M-proteins, when detectable, were almost all IgG or IgA with lambda light chains (Bardwick et al. 1980). Osteosclerotic myelomas have been detected in up to 69% of POEMS cases (Solomons 1982). The association of the syndrome with myeloma is more frequent in non-Japanese than in Japanese cases (Nakanishi et al. 1984). It is noteworthy that monoclonal pro-

teins cannot be found in about 25% of patients with osteosclerotic myelomas (Kelly; Kyle et al. 1983) and that incomplete forms of the syndrome are common outside Japan: 60% of the non-japanese cases reviewed by Nakanishi et al. (1984) had less than 5 manifestations of the disorder.

The most significant pathological findings were peripheral nerve lesions with "uncompacted myelin lamellae" (case 2 and 3) and angiofollicular lymph node hyperplasia (AFLNH) (case 1 and 3).

According to previous literature, the neuropathological alterations of the peripheral nervous system included both axonal degeneration and segmental demyelination (Iwashita et al. 1977; Ohnishi 1984; Ohi et al. 1985; Semble et al. 1986; Bergouignan et al. 1987). Axonal involvement was an important feature in the neuropathy, as assessed by several findings including major MF loss without abundant onion bulb formation despite a long-standing history of neuropathy in case 2, numerous clusters of regenerating MF, and some involvement of unmyelinated fibers (case 2 and 3). This was consistent with the results of Ohi et al. (1985) who concluded, on grounds of the pattern of demyelination on teased fibers, that segmental demyelination was secondary to axonal attenuation in osteosclerotic myeloma patients.

Uncompacted myelin lamellae (UML) were observed in both cases with electron microscopy study. This distinctive alteration of the myelin sheath has been recorded rarely (Vital and Vallat 1987). The picture is due to the division of the major dense line and has to be distinguished from the "widening of myelin lamellae" frequently observed in IgM neuropathies which consist of the division of the intraperiodic line (King and Thomas 1984). It was first reported in man by Ohnishi and Hirano (1981) in three cases of dysglobulinaemic neuropathy, including two with the POEMS syndrome, and was subsequently observed in over half the cases with the POEMS syndrome studied by Ohnishi (1984), involving 3 to 8% of MF on transverse sections, and in the 3 cases reported by Bergouignan et al. (1987), with a frequency ranging from 1 to 16%. The lesion is not specific since it has been described in other disorders including inflammatory demyelinating polyneuropathies without dysproteinaemia (King and Thomas 1984). It seems likely, however, that high incidence of UML may be predominantly encountered in the field of dysglobulinaemic polyneuropathies (Vital et al. 1983).

Angiofollicular lymph node hyperplasia (AFLNH) was observed in the 2 patients in which histological examination of lymph nodes was performed. Diffuse AFLNH may be found in many different clinical settings, including genetically determined and acquired immunodeficient states, various auto-immune diseases, and an apparently idiopathic condition called multicentric Castelman's disease (Frizzera 1984). In POEMS syndrome, lesions reminiscent of Castelman's disease, plasma cell type, have been found in 19/30 lymph node specimen obtained from Japanese cases (Nakanishi et al. 1984). Similar lesions have been reported in non-Japanese patients (Bitter et al. 1985; Bergouignan et al. 1987; Case Record 1987). It has been stated that although AFLNH and POEMS syndrome may be related, the two disorders are not identical: idiopathic AFLNH may indeed be associated with systemic manifestations but only some of these belong to the POEMS syndrome (Case Record 1987). Nevertheless, we suggest that the finding of AFLNH may trigger evaluation for a possible POEMS syndrome and that node biopsy constitutes a potentially valuable diagnostic procedure in the incomplete forms of the disease (Gherardi et al. 1988).

Among the other pathological features, we emphasize the thickening of arteriolar walls found in the peripheral nerve (case 3) and the generalized arteriopathy found at the autopsy of case 1 together with a splenic infarct. Arteriopathy was mentioned by Amiel et al. (1975). Vascular changes described as "bland medial thickening" and endothelial proliferation of the small arterioles were reported by Trentham et al. (1976). Systemic non-necrotizing vascular changes, affecting both capillaries and arterioles predominantly in muscle, nerve and spleen were observed by Semble et al. (1986). Microangiopathic glomerulopathy may also be observed (Fam et al. 1986; Viard et al. 1988). Finally, vascular changes, especially arteriosclerosis, seem rather common in the disease (Semble et al. 1986). Splenic infarct, in the pathogenesis of which thrombocytosis had probably also played a role, has been already recorded by Bergouignan et al. (1987).

Previously reported pathological features such as nodular regenerative hyperplasia of the liver (Zea-Mendoza et al. 1984) or osseous mastocytosis (Lapresle et al. 1986), presumably exceptional in the syndrome, were not observed.

The pathogenesis of the disease remains unknown. Attempts to demonstrate a seric auto-antibody activity directed against an antigen of the peripheral nervous system have failed. Endoneurial deposition of the paraprotein without fixation on myelin sheaths was detected in case 2 and 3 by direct immunofluorescence, but the feature seems

non-specific. It is likely that the deposition of immunoglobulins alone is an insufficient cause of nerve fiber degeneration in the syndrome (Ohnishi 1984). King and Thomas (1984) have partly reproduced UML in rat sciatic nerves soaked with hypotonic solutions and the hypothesis that peripheral nerve lesions could be related to increased endoneurial pressure subsequent to oedema has been proposed recently (Viard et al. 1988). A similar mechanism possibly accounts for the skin thickening, which appeared secondary to a papillary dermis sclerosis (case 1) resembling that of post-oedema skin sclerosis (Fanti et al. 1984).

An hypothalamo-hypophyseal origin of the endocrine disturbancies has been repeatedly hypothesized (Bardwick et al. 1980; Meier et al. 1986). The immunocytochemical study of the adenohypophysis in case 1 evidenced a conspicuous number of positive cells with the anti-alpha MSH antibody. Since positive reactions with anti-alpha MSH are inconstantly observed in adults (5/15 in the series of Nieuwenhuyzen Kruseman and Schroder-Van der Elst 1976), some relationship between this finding and the skin hyperpigmentation frequently observed in the POEMS syndrome seems possible. An immunological mediation has been recently suggested by Meier et al. (1986) who have detected a seric antibody activity directed against hypophysis in one patient, but this fact needs substantiation.

The relationships between AFLNH and POEMS syndrome are puzzling (Gherardi et al. 1988). One may consider the possibility that the lymph node lèsions in the POEMS syndrome are due to the plasma cell dyscrasia since improvement of polyadenopathies together with other symptoms may occur following local treatment of the plasma cell tumour (Kelly 1985; Meier 1985). However, plasma cells in AFLNH, which are usually polyclonal, may become neoplastic (Nagai et al. 1986) giving rise to an extra-medullary plasmocytoma occasionally thought to underlie a POEMS syndrome (Nakanishi et al. 1984). Finally, by analogy with the other Castelman's disease-like processes, it seems likely that AFLNH in POEMS syndrome is related to an abnormal immunoregulation (Frizzera 1984). However, it remains unclear whether the plasma cell dyscrasia is the cause of abnormal immunoregulation or not: dysglobulinaemia may represent an epiphenomenon produced by an unknown inciting agent, possibly toxic (Bardwick et al. 1980; Nakanishi et al. 1984) that affects multiple organs, directly or through immunological, hormonal or vascular disturbancies (Case Record 1987).

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