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Case report

Elephantiasis neuromatosa

A light, immunohistochemical and electron microscopic study

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Summary. An example of elephantiasis neuromatosa, an unusual variant of neurofibromatosis, coexistent with lipomatosis is presented. This dual cell population produced a diffuse swelling of the gluteal sulcus of a young female. The neurogenous origin of the spindle cell component was substantiated by immunoreactivity for S-100 protein as well as by the fine structural observation of a regular basement membrane coating and a profusion of Luse bodies. As far as can be ascertained, this is the first reported immunohistochemical and ultrastructural study of this particular variant of peripheral nerve sheath lesion.

Key words: Elephantiasis neuromatosa – Neurofibromatosis – Electron microscopy – Immunohistochemistry – S-100 protein

Tumours of peripheral nerve sheath origin usually present as rather circumscribed masses (Harkin and Reed 1969). Diffuse swelling of a sizeable portion of the body is a less common manifestation and has mostly been dealt with in clinically oriented articles (Anzinger 1931; Hudson and Cox 1956; Shereff et al. 1980) under the labels "elephantiasis neuromatosa" and "elephantoid hypertrophy".

This paper concerns the morphological features of such a deep-seated peripheral nerve sheath growth, coexistent with lipomatosis which exhibited an insidious invasion of the gluteal muscle of a young female.

Case history

A 17-year-old female complaining of a swelling below the right buttock which had gradually increased in size over a period of three years, was referred to the Department of Plastic Surgery. The swelling was cosmetically embarrassing but otherwise asymptomatic. The patient's previous health record was good and, with particular reference to von Recklinghausen's disease,

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there was no predisposition to either familial or hereditary disorders. She had been an enthusiastic horsewoman since she was nine years old and rode for up to an hour a day.

Examination revealed a soft swelling measuring 4 × 11 cm in the right gluteal sulcus. There was no pulsation and the overlying skin was normal in appearance. The tumour was mobile in relation to the skin and the underlying bone and resembled an intramuscular lipoma. Pelvic X-ray showed no bony abnormality. Haemoglobin, serum creatinine and sedimentation rate were normal. Surgical exploration exposed a thickened area of the right gluteus maximus muscle. This area was not discrete and the borderline between it and the normal muscle tissue so poorly defined that radical excision was impossible. Perioperative frozen section gave no definite diagnosis. Continuity with nerve trunks was not identified. The postoperative period was uncomplicated, the patient being discharged on the fifth day and referred to the out-patient clinic for follow-up. At the six month follow-up no further abnormal growth was observed.

Morphologic techniques

Tissue for this study was obtained at the time of surgery. For light microscopic examination, pieces of tissue were fixed in 10% neutral formaldehyde and processed by standard methods. Sections were stained with haematoxylin-eosin, Fontana Masson and Luxol fast blue.

Immunohistochemical reactions were performed on sections of paraffin-embedded tissue. The sections were deparaffinized and incubated with hydrogen peroxide to eliminate endogenous peroxidase activity. After preincubation with normal swine serum, specific rabbit antiserum (rabbit anticow S-100 protein (Dacopatt, Copenhagen); 1:250 dilution) was applied and incubated for $\frac{1}{2}$ an hour at room temperature, followed by application of peroxidase – conjugated swine – antirabbit IgG (Dacopatt, Copenhagen; 1:20 dilution). Following reaction with 3-amino-9-ethylcarbazole the slides were mounted. Control sections were prepared by substituting the specific antiserum with normal rabbit serum.

For *electron microscopic examination,* 1 mm cubes of tissue were fixed in 3% phosphate-buffered glutaraldehyde, post-fixed in 2% osmium tetraoxide, dehydrated in graded ethanols and embedded in epon 812. Ultrathin sections were cut on an ultramicrotome and stained with uranyl acetate and lead citrate. The sections were examined in a Philips 201 electron microscope.

Pathology

The gross specimen, which measured 7 × 4 × 3 cm, had a pale gray-yellowish hue and a rather soft consistency. On cut section, an enhanced fascicular appearance of the muscle was seen.

Light microscopy. The most conspicuous finding was a diffuse infiltration of fusiform, finely wavy cells, splitting up the substance of striated muscle (Fig. 1), whose fibers occasionally displayed atrophic changes. The invading cells were arranged in parallel bundles and had oval, comma-shaped nuclei with single small nucleoli. The cytoplasm was pale and eosinophilic. A special search for dense intracytoplasmic inclusions on the Luxol fast blue preparations revealed nothing. Melanin could not be demonstrated. Rounded Verocay bodies frequently formed (Fig. 2). Mitotic activity was not observed, nor was necrosis a feature.

Accompanying this spindle cell growth was a prominent fatty component of mature lipocytes. Chondroid and osseous metaplasia were not apparent.

Immunohistochemistry. The immunohistochemical study showed positive reaction for S-100 protein, the reactionsproduct being localized to the nuclei and cytoplasm of the spindle cell component. The intensity of the nuclear staining exceeded that of the cytoplasm (Fig. 3). The control sections were negative (not shown).

Electron microscopy. The spindle cell component had oval, irregularly contoured nuclei, whose chromatin formed clumps beneath the nuclear membrane. From the relatively scanty perinucle-

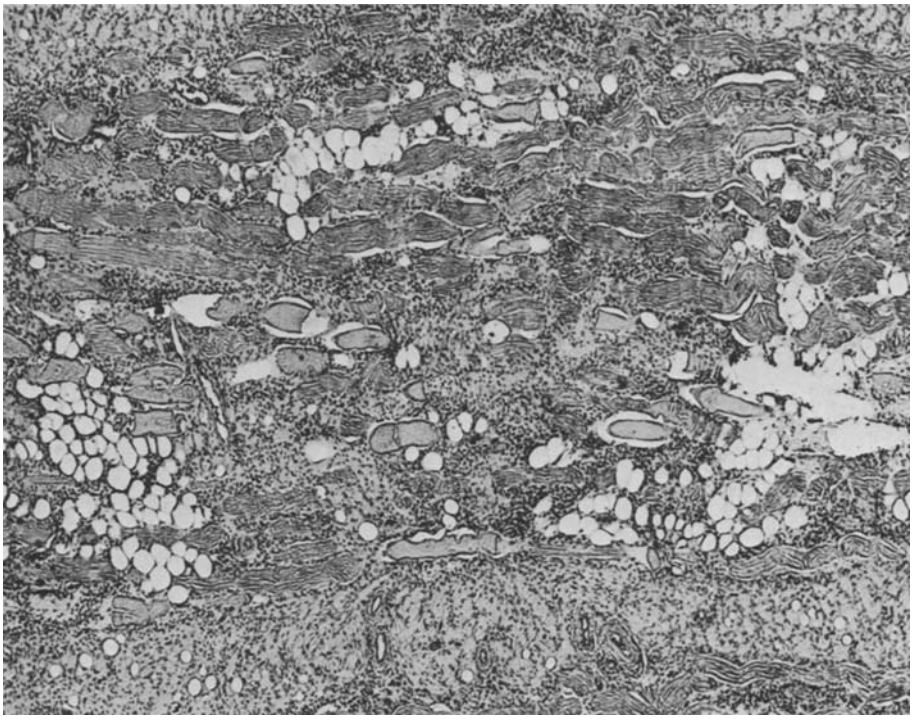

Fig. 1. Low power view demonstrating muscle bundles spread apart by a proliferation of spindle cells and lipocytes. (Hematoxylin eosin, ×46)

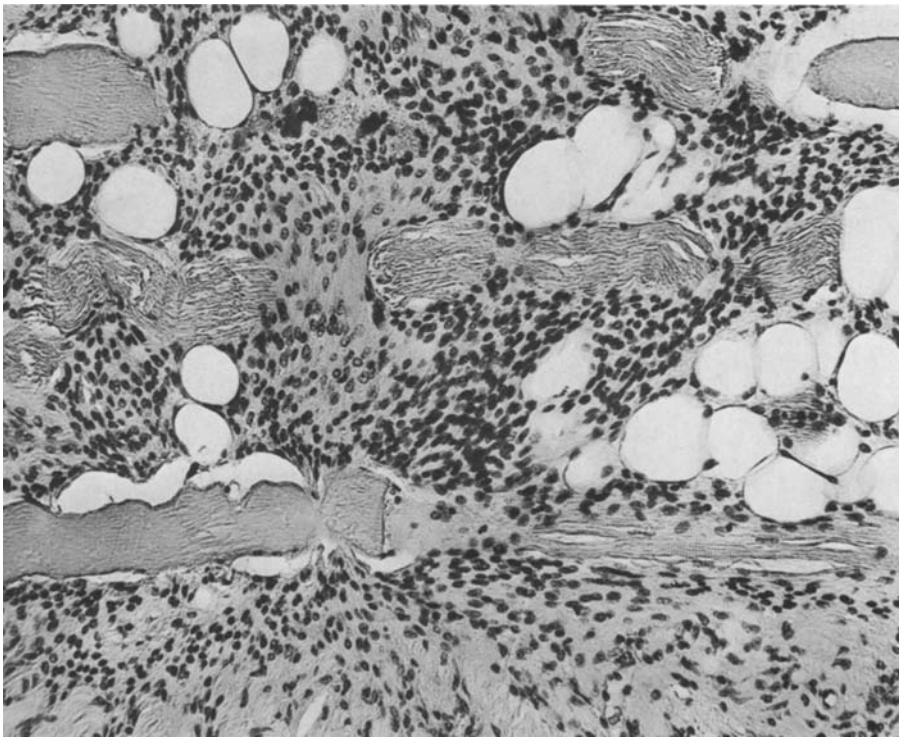

Fig. 2. This is a close-up view of the lower mid portion of Fig. 1, showing Verocay bodies below, alternating with more cellular zones above. The entrapped muscle fibers display degenerative changes. (Hematoxylin eosin, ×184)

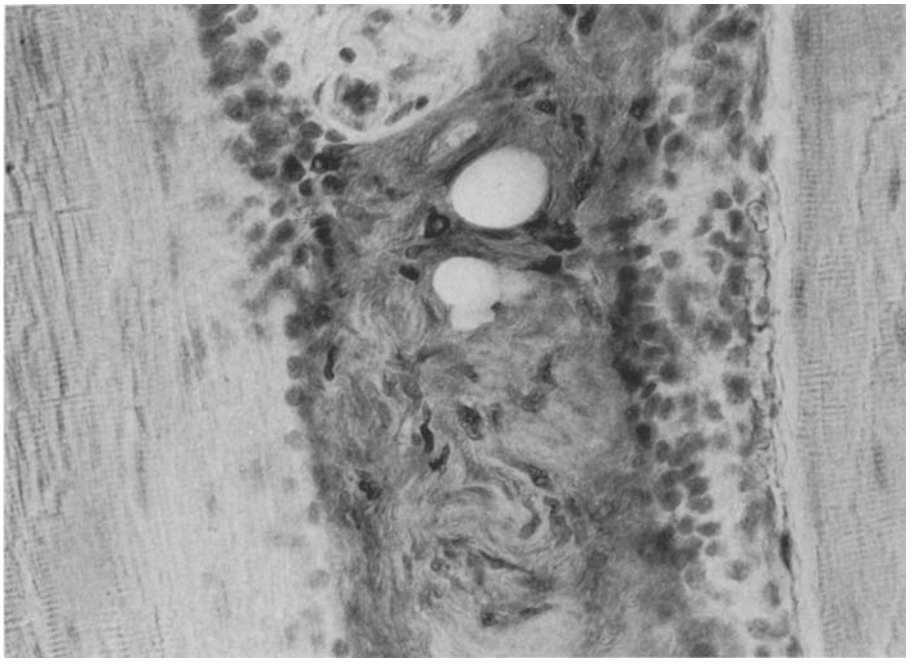

Fig. 3. Immunostaining for S-100 protein showing positive nuclear and cytoplasmic reaction of the spindle cell component (center of the field). The striated muscle fibers are none reacting. (Immunoperoxidase without counter stain, ×460)

ar cytoplasm, very long, often thread- thin extensions emanated. In places, these cell processes were arranged in parallel bundles, corresponding to the central portions of Verocay bodies. Cytoplasmic organelles, comprising scattered short strands of ribosome-studded membranes, poorly developed Golgi complexes and small rod-shaped mitochondria, were largely concentrated in the perinuclear portion of the cell. Micropinocytotic vesicles were sometimes conspicuous. Notably absent were neurotubules, filaments and dense-core vesicles. A conspicuous, non-disrupted basement membrane coated both the central cell body and its extensions (Fig. 4). Reduplication of basement membrane material was not observed.

Within the intercellular matrix abundant segments of fibrous long-spacing collagen, so-called Luse bodies, with a periodicity of approximately 100 nm formed (Fig. 5). These strands consistently merged with basement membranes.

Interspersed between the spindle elements were rounded cells with large fat vacuoles and eccentric nuclei.

Discussion

The clinico-morphological picture of the present case resembled elephantiasis neuromatosa, an uncommon variant of neurofibromatosis, briefly mentioned by Abell et al. (1970), in their review article on tumours of the peripheral nervous system. Several case reports on this condition are at hand, discussing the clinical features (Hudson and Cox 1956; Shereff et al. 1980), whereas the morphological aspects, to our knowledge, only have received cursory attention.

Clinically, this entity typically produces a conspicuous swelling of a

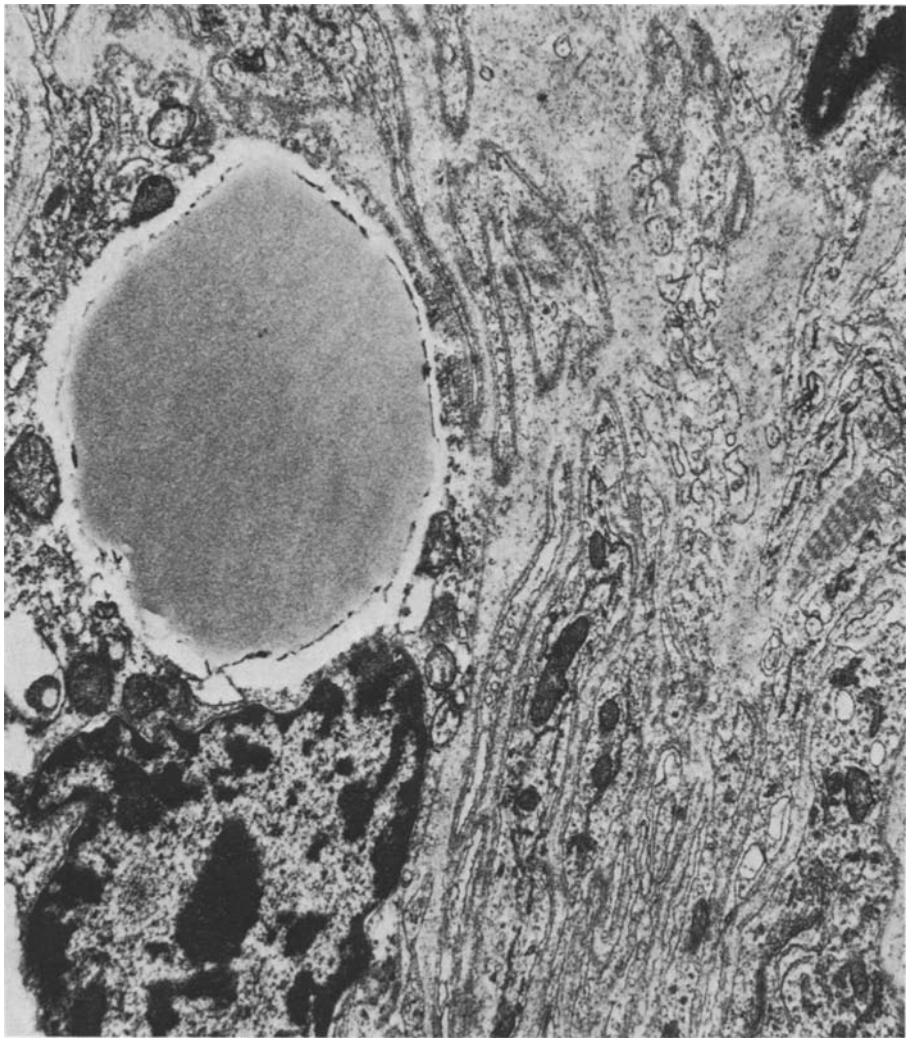

Fig. 4. This field illustrates portion of a lipocyte (left) adjacent to neurogenous cell processes (right). Basement membrane material parallels the course of the cell border. (Uranyl acetate and lead citrate ×13.725)

portion of the body; in the current case a thickening of the gluteal muscle was noticed. No skeletal lesion coexisted in our patient as is sometimes observed. Nor were other stigmata of von Recklinghausen's disease apparent. In the present case there was a history of a mild mechanical injury to the affected region; yet we hesitate to imply a causative interrelationship between this trauma which was of repeated nature and the evolution of the tumour.

The lesion was confined to skeletal muscle which was diffusely infiltrated with spindled cells and lipocytes creating a vague checkerboard effect. Such a composite pattern of neurogenous and lipomatous structures occassionally

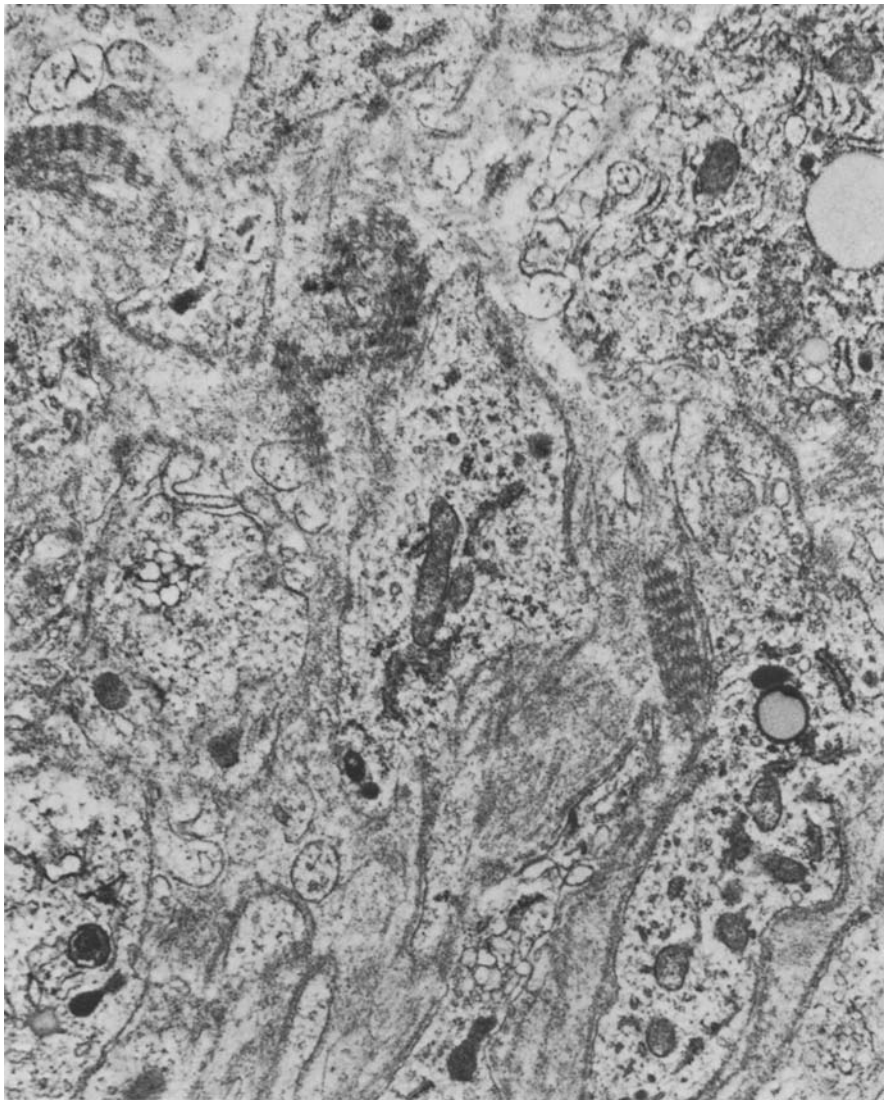

Fig. 5. The intercellular matrix contains straight and curved Luse bodies in contact with basement membranes. (Uranyl acetate and lead citrate, × 18.150)

appears. Thus, a similar intimate admixture of nerve cell elements and lipocytes has been described in cutaneous tumours, labelled neurofibrolipomatosis (Harkin and Reed 1969). Other neural crest derived lesions, such as intradermal nevi may also, on occasion, coexist with fatty elements (lever and Schaumburg-Lever 1983).

The fine structure of elephantiasis neuromatosa has, to the best of our knowledge, not previously been reported. The salient findings were fusiform cells with very long and thin cell processes encased by basement membranes,

conforming to a neurogenous lesion. The occurrence of so-called Luse bodies have been considered diagnostic of neurogenous tumours (Sobel et al. 1973) but has, though rarely, been observed in other tissues as well (Banfield et al. 1973). Lamellar bodies, as described in some benign and malignant schwannomas (Hwang and Benediktsson 1982) were not identified.

Whereas the presence of pinocytotic activity is reportedly more in keeping with a perineural origin (Erlandson and Woodruff 1982; Lazarus and Trombetta 1978), the positive immunostaining with anti-S-100 protein (Nakazato et al. 1982) and the fine structural observation of non-disrupted basement membranes (Lazarus and Trombetta 1978) supported a schwannian origin of the spindle cell growth.

Regarding the natural history of the lesion, little information is available. Extensive infiltration by a peripheral nerve sheath tumour has been construed as signifying malignancy, despite paucity of mitoses (Trojanowski et al. 1980). We are reluctant to adopt such a view for the present variant of nerve sheath lesion. Furthermore, the regular basement membrane investment, demonstrated herein, clearly differs from the disrupted and sometimes inconspicuous or absent basement membrane frequently seen in malignant schwannomas (Averback 1978; Conley et al. 1976; Vuia O (1972). In fact, some investigators have taken an incomplete basement membrane coating of schwannian cells as presumptive evidence of malignancy (Ursell et al. 1982). However, the growth pattern depicted above, which shared some features with fibromatosis, indicates a locally aggressive behaviour. Our case is a recent one, but we do anticipate local recurrences.

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