

ACUTE SARCOID NEUROPATHY DEVELOPED 4 MONTHS AFTER THE OCCURRENCE OF A GASTROINTESTINAL STROMAL TUMOR (GIST)

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INTRODUCTION

Neurological manifestations occur in 5% of patients with sarcoidosis, and peripheral neuropathy (PN) is present in 1% (1). A few cases of real Guillain-Barré (GB) syndrome have been reported with a classic evolution and are generally considered as coincidental (2, 3). In a recent series of 4 cases with sarcoid neuropathy, one case with chronic inflammatory demyelinating polyneuropathy (CIDP) was initially considered as GB syndrome and a nerve biopsy was performed two years later (4). Said et al (5) have also reported a case presenting as a GB-like syndrome with lymphocytic reaction associated with elevated protein concentration in the cerebrospinal fluid (CSF) and whose muscle and nerve specimens exhibited noncaseated granulomas (NCG). We have recently observed such a patient, who is still suffering from motor difficulty, 11 months after the sudden onset of his neurological disease. Moreover, 4 months before his GB-like syndrome, our patient had removed a gastrointestinal stromal tumor (GIST). A possible relationship between this acute sarcoid neuropathy and such a rare tumor (6) deserves to be discussed.

CLINICAL SUMMARY

On January 1st 2008, an 80-year-old man was admitted to hospital due to sudden acute pain in both feet with bilateral weakness of the lower limbs predominately in the distal parts. No muscle atrophy was observed and tendon reflexes were absent at the ankles and decreased at the knees. Vibratory sense was abolished in the ankles and sensitivity to pinprick was reduced distally with a stocking distribution. In the upper limbs, weakness was observed bilaterally in the cubital area, predominating on the right side, and cranial-nerve functions were preserved. A diagnosis of GB syndrome was suggested but a lumbar puncture, performed the following day, showed a protein concentration at 1.2 g/liter with 114 lymphocytes/mm³. Weakness progressed for two weeks. Electrophysiologic study evidenced slowed motor nerve conduction velocities with conduction blocks in the lower limbs and the right cubital nerve, indicating a demyelinating process. Intravenous immunoglobulins (Ig) were ineffective and a spinal MRI revealed no abnormalities. A muscle and nerve biopsy was performed 77 days after the onset of the neurological symptoms and corticosteroid therapy was introduced as soon as nerve biopsy results were known. Search for other locations of sarcoidosis, especially in the mediastinal area, was negative. Progressive improvement of the neuropathy was observed. One month later, painful dysesthesia had disappeared and walking was possible with braces. In November, the patient was able to walk 1 kilometer without any walking stick.

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This patient had a renal insufficiency for 30 years which had recently worsened after the short Ig treatment. Vesical polyps without malignancy had been removed in June 2007, but at the end of August, he underwent the complete surgical resection of a GIST localized in the omentum. It was a nodular tumor, 9 x 8 x 6,5 cm in size, without any metastasis.

PATHOLOGICAL FINDINGS

Paraffin sections of the omental tumor exhibited proliferation of spindle cells with mitoses (five in 10 high power fields). Immunohistochemistry re-

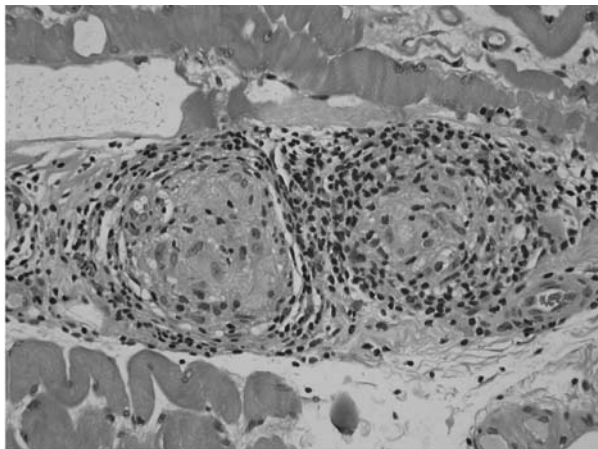


Fig. 1. Muscle biopsy. Two round NCG surrounded by numerous lymphocytes are located between muscle fibers (Hematoxylin-eosin x 80)

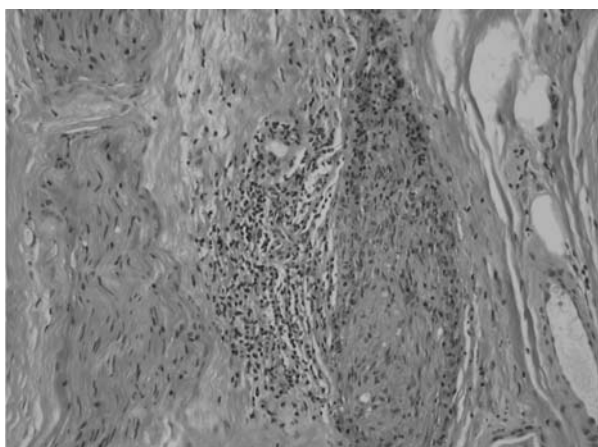


Fig. 2. Nerve biopsy. A large lymphocytic infiltrate close to a capillary is visible in the epineurium (Hematoxylin-eosin x 50)

vealed strong cytoplasmic staining for the C-kit (CD 117) and CD 34.

A neuromuscular biopsy was performed on the lower third of the antero-external surface of the right leg, as usual in our laboratory (4). Light microscopic examination of hematoxylin-eosin-stained paraffin sections of muscle specimens exhibited several NCG located between muscle fibers. These NCG were made up of epithelioid cells, a few multinucleated giant cells and lymphocytes visible at the periphery (Fig. 1). Paraffin section of the nerve specimen showed several perivascular lymphocytic infiltrates (Fig. 2) and a small NCG in the epineurium. On semi-thin sections there was severe myelinated fiber loss (Fig. 3), with red blood cells scattered in some fascicles, and a perivascular NCG visible in one fascicle (Fig. 4). On

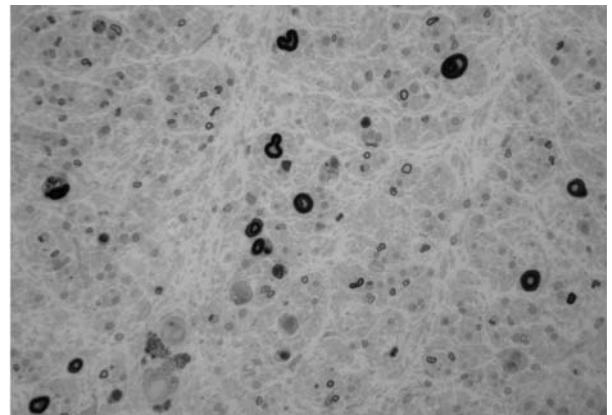


Fig. 3. Nerve biopsy. Semi-thin section. There is a severe loss of the myelinated fibers (Toluidine blue x 120)

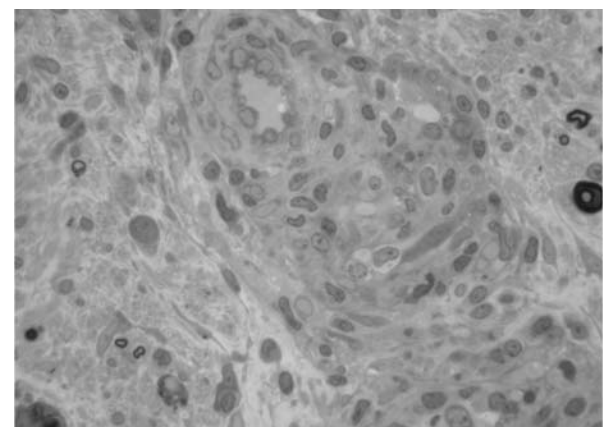


Fig. 4. Nerve biopsy. Semi-thin section. A small NCG made up of epithelioid cells (arrow) has developed around an endoneurial vessel (Toluidine blue x 150)

electron microscopic examination, several ovoids were observed and a severely damaged axon was visible without features of macrophage-associated demyelination.

DISCUSSION

A recent review of sarcoid PN with correctly examined nerve biopsy reported 38 cases, corresponding to 17 chronic sensorimotor PN, 13 mononeuropathy multiplex, 5 CIDP and 3 painful PN (4). The characteristic features of NCG were visible in the nerve, the muscle or both in 30 cases. In the remaining 8 cases, the histopathological diagnosis of sarcoidosis was provided by the biopsy from another parenchyma, mainly lung or lymph node. An additional case with mononeuropathy multiplex presenting active vasculitis on muscle and nerve specimens and NCG visible on the biopsy of a mediastinal lymph node has recently been reported (7). In six out of 40 cases, NCG were restricted to muscle, nerve specimens or both (4, 5, 9, 10), as for the case presented here. It is well known that neurological sarcoidosis may occur without any involvement of other organs (1, 11). It must be noted that NCG are more numerous and easier to identify in muscle specimens than in nerve samples (4, 5). The association of vasculitis and sarcoidosis in the nerve has already been underlined (4, 5, 7, 12, 13). Localized neuromuscular sarcoidosis may be compared with the nonsystemic vasculitic neuropathy reported by Dyck et al (14) and in which muscle is also frequently involved (15, 16). In most cases of sarcoid neuropathy, nerve specimens exhibit a loss of myelinated nerve fibers with features of axonal degeneration, but features of primary demyelination may be present (4, 5, 17), sometimes associated with conduction blocks in electrophysiologic studies (17, 18). In our case, demyelination was first evidenced by the electrophysiologic study but the nerve specimens, taken 77 days after the acute onset of the PN, exhibited only axonal lesions.

In the early 90's, cases of GIST were individualized and well differentiated from leiomyomas and schwannomas by their immunopositivity for CD34 and negativity for S100 protein (6). More recently, GIST have been selectively marked by CD117, the C-kit proto-oncogene product, whose positivity is

also found in the interstitial cells of Cajal, known to be neural-related and located through the muscular layer of the gastrointestinal tract (6). Although more than 95% of GIST are located along the gastrointestinal tract, a few of them develop in the mesentery or omentum, and in a series of 39 cases 3 extraGIST were located in the omentum (19).

The increased incidence of cancer in patients with sarcoidosis was emphasized by Brinker and Wilbek in 1974 (20), and other reports followed (21-23). However, the results presented by Reich et al (22) were contested about the criteria used to diagnose sarcoidosis (24). Another problem regards the necessary distinction between real sarcoidosis and the so-called sarcoid-like reaction (25, 26). Indeed, lymph nodes draining neoplasms are sometimes infiltrated by NCG but the reaction remains restricted to this area. Systemic sarcoidosis has been established in several cases in which cancer was located in remote areas, notably non-seminomatous testis cancer (25), lymphoma (27), carcinoma (28) and, more frequently, carcinoid in various locations (29-31). Cohen and Kurzrock recently reviewed several other cases and considered sarcoidosis as a real paraneoplastic disorder (32). Although sarcoidosis is not mentioned in recent reviews on paraneoplastic neurological syndromes (33, 34, 35), our case might be a paraneoplastic manifestation. Cohen and Kurzrock stated that a relationship between a malignant tumor and sarcoidosis can be considered when the discovery of cancer occurs within one year of the diagnosis of sarcoidosis and vice versa (32). In our case, it is likely that GIST had slowly developed for several months prior to its removal, and sarcoidosis had an acute presentation as has been seen in a few cases of this disease (1, 11).

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