CASE REPORT

Neurological Symptoms of Sarcoidosis-induced Small Fiber Neuropathy Effectively Relieved with High-dose Steroid Pulse Therapy

Hiroaki Saito¹, Tetsuo Yamaguchi², Yuta Adachi¹, Takaaki Yamashita¹, Yoko Wakai¹, Kazuhito Saito¹, Yoko Shinohara¹, Keiko Suzuki³, Soroku Yagihashi⁴, Jiro Terada⁵ and Koichiro Tatsumi⁵

Abstract

A 59-year-old woman was admitted to our hospital for an evaluation of a 10-day history of progressive pain and hypoesthesia of the right lower back associated with fever and constipation. Sarcoidosis was confirmed on mediastinal lymph node and skin biopsies. Although the neurological symptoms were suspected due to sarcoidosis-induced nerve dysfunction, nerve conduction studies and other routine examinations did not show any abnormalities. The intraepidermal nerve fiber density assessed on a skin biopsy was significantly reduced, suggesting small-fiber neuropathy (SFN). The patient was finally diagnosed with sarcoidosis-induced SFN, and her neurological symptoms were effectively relieved with high-dose steroid therapy.

Key words: sarcoidosis, small fiber neuropathy, steroid pulse

(Intern Med 54: 1281-1286, 2015) (DOI: 10.2169/internalmedicine.54.3702)

Introduction

Sarcoidosis is a multisystemic inflammatory disorder characterized by the presence of granulomas (1). Neurological complications of sarcoidosis occur in approximately 5% of patients and are well described to cause cranial nerve disorders (neurosarcoidosis) and peripheral neuropathy by affecting large nerve fibers (2, 3). Recently, small fiber neuropathy (SFN), a subtype of peripheral neuropathy that selectively involves thinly myelinated Aδ fibers and unmyelinated C fibers, has been recognized to be present in over 40% of patients with sarcoidosis (4). SFN results in potentially debilitating symptoms of neuropathic pain and autonomic dysfunction, although the precise pathophysiology remains unclear. Since nerve conduction studies and other routine examinations for the assessment of SFN are not available, the neuropathy may remain undiagnosed unless the symptoms are recognized by physicians and/or pulmonologists involved in the treatment of sarcoidosis. With regard to the treatment of SFN, no studies supporting the efficacy of steroid therapy for SFN have been reported to date. We herein describe a case of sarcoidosis-induced SFN that was effectively treated with steroid pulse therapy.

Case Report

A 59-year-old woman was referred to our hospital for an evaluation of a 10-day history of a high fever with pain and hypoesthesia of the right lower back. She had never smoked and had no remarkable family or past medical history. Since the symptoms persisted and a thoracic CT scan revealed swelling of the mediastinal and abdominal lymph nodes, the patient was admitted to our hospital for a further evaluation of the unidentified disease.

On admission, a physical examination demonstrated a
Table 1. Laboratory Findings on Admission.

| Peripheral blood | Biochemistry | Serology                      |
|------------------|--------------|-------------------------------|
| WBC 4.910×10^9/μL | TP 7.9 g/dL  | CRP 0.2 mg/dL                 |
| Neut. 56.0%      | Alb 3.9 g/dL | HbA1C(NGSP) 6.2%              |
| Lym. 31.4%       | BUN 16.0 mg/dL | IgG 2,009 mg/dL            |
| Mono. 12.0%      | Cr 0.67 mg/dL | IgA 643 mg/dL                |
| Eos. 0.6%        | Na 136 mEq/L | IgE 34 IU/mL                  |
| Baso. 0.6%       | K 4.1 mEq/L | IgM 89.7 mg/dL               |
| RBC 461×10^12/μL | Cl 103 mEq/L | RF (-)                       |
| Hb 13.0 g/dL     | Ca 9.9 mg/dL | ANA 160<                     |
| Plt 23.7×10^11/μL | GOT 38 IU/L | anti-SS-A Ab 245 U/mL         |
| Urinalysis       | GPT 37 IU/L | anti-ss-B Ab (-)              |
| Prot. (-)        | ALP 170 IU/L | anti-ds-DNA Ab (+)            |
| Glu. (-)         | T-Bil 0.8 mg/dL | anti-Sm Ab (-)              |
| Ket. (-)         | CK 86 IU/L | anti-Scl-70 Ab (+)            |
| Occult Blood. (-) | AMY 170 IU/L | anti-centromere Ab (+)        |
| Bil. (-)         | Glu 126 mg/dL | anti-RNP,Ab (-)             |
|                 |              | anti-Jo-1 Ab (-)               |
| tuberculin reaction test | (-) | MPO-ANCA (-)                 |
|                 |              | PR3-ANCA (-)                  |
|                 |              | sIL-2R 3,430 U/mL            |
|                 |              | ACE 38.3 IU/L/37°C           |
|                 |              | Lysozyme 20.6 μg/mL          |

blood pressure of 153/99 mmHg, pulse rate of 100 beats/min, pulse oximetry of 96% on room air and body temperature of 37.5°C. Mild tenderness in the right hypochondrium and central line of the abdomen was noted on abdominal palpation, and protuberant nodes ranging in size from small beans to the tip of the thumb were observed on both knees and elbows. Papillary light reactions, ocular movement and all other cranial nerve functions were normal; however, hypoesthesia was noted along the right L4 and right Th5-Th11 dermatomes. The deep tendon reflexes in the upper extremities, Achilles tendon reflex and patellar tendon reflex were bilaterally normal. On laboratory studies, the levels of antinuclear antibodies, anti-SS-A antibodies, immunoglobulin (IgG and IgA), soluble IL-2 receptors, angiotensin-converting enzyme (ACE) and lysozyme were elevated (Table 1). In addition, chest X-rays showed bilateral swelling of the hilar lymph nodes (Fig. 1A), while a CT scan disclosed swelling of the mediastinal, hilar and abdominal paraaortic lymph nodes (Fig. 1B) and gallium scintigraphy demonstrated abnormal accumulation in the hilar and mediastinal lymph nodes (Fig. 1C). No angiogenesis in was observed the mucous membrane of the trachea or bronchus on bronchoscopy. Meanwhile, the bronchoalveolar lavage fluid (BALF) (left B5) exhibited a cell count of 2.3×10^7 cells/mL, with a differential cell count showing 67% of the cells to be lymphocytes and 33% of the cells to be macrophages, no neutrophils, monocytes, eosinophils or basophils. Among the lymphocytes, CD4 cells comprised 73.2% of the T cell population, while CD8 T cells comprised 21.7%, making the CD4/CD8 ratio 3.37. An endobronchial ultrasound-guided transbronchial needle aspiration biopsy of a subcarinal lymph node (#7) and skin biopsies revealed noncaseating epithelioid granulomas. Although the anti-SS-A antibody titer was elevated, the patient did not display either dry eyes or mouth. Additionally, since the biopsy specimens of the minor salivary glands demonstrated infiltration with very few lymphoid cells, the possibility of Sjögren’s syndrome was excluded. Based on the above findings, a diagnosis of histological sarcoidosis was made.

After hospital admission, the patient’s pain and hypoesthesia continued and she suffered from severe constipation. Five days after hospitalization, she developed a feeling of pressure in both sides of her back as well as worsening constipation and the onset of a feeling of numbness in the limbs with allodynia in the back (touch-evoked pain), which subsequently caused insomnia. Pregabalin was administered for the feeling of numbness in addition to mosapride citrate, magnesium oxide and sennosides for the constipation; however, the improvements were only temporary. On hospital day 11, the patient complained of difficulty urinating and she experienced difficulty walking due to dizziness upon standing, with continued allodynia in the back. She also became depressed as a result of the uncontrolled autonomic and sensory nervous symptoms and loss of sleep described above. At that time, the neurological motor function and deep tendon reflexes in the upper extremities remained normal, as did light touch and vibratory senses. However, the Achilles tendon reflexes and patellar tendon reflexes were mildly decreased bilaterally, and the pin-prick sensation was slightly reduced in the distal portion of the extremities; Romberg’s test was negative and Babinski’s sign was absent. An examination of the cerebrospinal fluid revealed a slight increase in the protein level and cell count, although the ACE level was not increased. Brain and spinal cord
magnetic resonance imaging showed no apparent abnormalities, and the nerve conduction velocity was only slightly reduced in the tibia, with no apparent damage to the large fibers (Table 2). The coefficient of variation of the R-R intervals (CVR-R) on the electrocardiogram was low at 1.24, suggesting the presence of an autonomic disorder.

Although the possibility of the coexistence of a large nerve fiber disorder was also considered, the main cause of the patient’s neurological symptoms was suspected to be small nerve fiber damage based on her mixed symptoms (sensory disturbances and autonomic dysfunction), low CVR-R and the lack of predominant abnormalities in large nerve fibers. Therefore, punch biopsies (3 mm diameter) were taken from skin on the lower leg (10 cm proximal to the lateral malleolus) and thigh (20 cm distal to the anterior iliac spine). PGP9.5 immunohistochemical staining was performed, and the intraepidermal nerve fiber density (IENFD) was calculated according to indirect immunofluorescence with confocal microscopy (Carl Zeiss, Tokyo, Japan) (Fig. 2) (5). On evaluations of IENFD using 50-μm sections, a reduction was observed in the intraepidermal nerve fiber density (5.8/mm in the lower leg and 17.3/mm in the thigh), and thus small fiber damage was pathologically identified in the lower leg. Increased extra branching of the intraepider-

**Table 2. Result of Nerve Conduction Study.**

| CMAP    | Amp | MCV | Lat | Proximal | Distal | Proximal |
|---------|-----|-----|-----|----------|--------|----------|
| R-Median| 52.6| 13.1| 13  | 3.7      | 7.5    |
| L-Median| N.D.| 9.7 | 9   | 2.7      | 6.0    |
| R-Ulnar | 57.6| 9.7 | 9   | 2.7      | 6.0    |
| L-Ulnar | N.D.| N.D.| N.D. | N.D.     | N.D.   |
| R-Tibial| 37.6| 11.5| 10.6| 3.2      | 12.5   |
| L-Tibial| N.D.| N.D.| N.D. | N.D.     | N.D.   |
| R-Peroneal | 42.4| 2.6 | 2.6 | 4.3      | 12.8   |
| L-Peroneal | 42.4| 2.6 | 2.9 | 3.7      | 12.2   |

| SNAP    | Distal | Lat | Proximal | Amp | SCV |
|---------|--------|-----|----------|-----|-----|
| R-Median| 2.6    | 27  | 53.8     | 6.2 | 15  |
| L-Median| N.D.   | N.D.| N.D.     | N.D.| N.D.|
| R-Ulnar | 2.2    | 28  | 54.5     | 5.4 | 17  |
| L-Ulnar | N.D.   | N.D.| N.D.     | N.D.| N.D.|
| R-Sural  | 2      | 11  | 50       |     |     |
| L-Sural  | 1.83   | 15  | 54.6     |     |     |

Amp: Amplitude (mV), N.D.: no data, Lat: Terminal Latency (msec/cm), CMAP: compound muscle action potential, SNAP: sensory nerve action potential, SCV: sensory nerve conduction velocity, MCV: motor nerve conduction velocity
mal nerve fibers in the lower leg was also observed, indicating pathomorphological peripheral neuropathy. These clinical, neurological and pathological features satisfied the diagnostic criteria for SFN proposed by Lacomis (6). Therefore, a diagnosis of sarcoidosis-induced SFN was made based on the above findings.

Steroid pulse therapy (1 g/day methylprednisolone for three days) was initiated on day 13 of hospitalization, followed by 40 mg/day prednisolone (PSL) in accordance with the recommended treatment for the severe form of neurosarcoidosis (7). The SFN screening list (SFNSL) was used to assess the treatment outcome. The SFNSL is a questionnaire that quantifies the intensity and frequency of SFN symptoms, such as numbness, and its score is useful for screening and evaluating SFN (8). The highest possible score is 84, and higher scores signify more intense symptoms. The patient’s SFNSL score was 41/84 just before the start of steroid pulse therapy and subsequently improved to 26/84 three days after the completion of the steroid pulse therapy (i.e., day 20), indicating that the treatment was effective. Furthermore, her subjective symptoms, including difficulty urinating, chest pain and dizziness upon standing, were ameliorated and the severe constipation was relieved, while the abnormalities in serological parameters, such as the lysozyme and ACE levels, were also improved.

Figure 2. Distribution of the intraepidermal nerve fibers (arrows) as observed in sections immunostained with anti-protein gene product 9.5 antibodies (PGP 9.5) on confocal microscopy. The nerve fibers were stained green (PGP 9.5) and the basement membrane and blood vessels were stained red (collagen IV). Quantification of the intraepidermal nerve fiber density (IENFD) (number of fibers penetrating the basement membrane to the epidermal layer per unit length) disclosed a marked reduction in the IENFD in the lower leg skin of the patient. There was also marked branching from a single nerve fiber ending in the leg skin, whereas the IENFD in the thigh was preserved.

Figure 3. The patient’s clinical course with respect to laboratory parameters and symptoms in response to treatment including steroid pulse therapy. PSL: prednisolone, mPSL: methyl PSL, SFNSL: small fiber neuropathy screening list.
sozyme and ACE levels, normalized (Fig. 3) and the sIL-2 receptor level decreased from 3,430 to 297 U/mL. Thereafter, the dose of PSL was reduced each month, with no recurrence of symptoms. The patient was consequently discharged on day 56, at which point her SFNSL score had improved to 5/84, and the dose of PSL was again further reduced after discharge. One year and six months after the diagnosis, the patient’s SFNSL score was 0/84, with no symptom recurrence at a PSL dose of 5 mg/day. Moreover, chest X-rays showed that the bilateral hilar lymph nodes had returned to their normal size, and the CVR-R on electrocardiograms normalized to 3.44.

**Discussion**

We herein presented a case of sarcoidosis-induced SFN treated with steroid pulse therapy within one month after the onset of neurological symptoms. The diagnosis of SFN in the present case was made based on the patient’s symptoms, electrophysiological data and pathological findings (6), and treatment with high-dose steroids was effective in improving her complicated neurological symptoms.

Neurological complications in sarcoidosis patients are well described, and the prevalence of clinical involvement of the nervous system, such as cranial nerve dysfunction and neuropathy of large fibers, is estimated to be approximately 5% (9-12). Recently, SFN has also been increasingly recognized to be a more common condition in sarcoidosis patients, as Hoitsma et al., reported that 31 of 70 patients (44%) with chronic severe sarcoidosis have SFN (4). In general, the symptoms of SFN include sensory disorders resulting from Aδ fiber damage (e.g., pain and feelings of numbness) as well as autonomic nervous disorders induced by C fiber damage (e.g., digestive symptoms, orthostatic ataxia, dysuria and hot flashes). The distribution of neurological symptoms has been reported to be non-length-dependent in cases of sarcoidosis-induced SFN (12), while generalized SFN sensory pain may present with a “stocking and glove” distribution depending on the nerve length (length-dependent SFN) or be distributed around the face, torso or ganglia (non-length-dependent SFN) (13, 14). Lacomis et al. (6) proposed the following criteria for diagnosing SFN: (1) symptoms of peripheral dysesthesia (typically pain), (2) an electrophysiologically normal nerve conduction velocity and needle electromyography results and (3) pathological findings (reduced intraepidermal nerve fiber density). The authors proposed that SFN may be present if the patient meets one criterion, the disease is likely present if the patient meets two criteria and the disease is definitively present if the patient meets all three criteria (6). The present patient demonstrated characteristics of sarcoidosis-induced SFN, including: 1) symptoms of a sensory disturbance (hyposthesia, pain and allodynia) and autonomic dysfunction (worsening constipation, difficulty urinating and a low CVR-R), 2) distribution with non-length dependence, 3) electrophysiological findings showing no objective evidence on nerve conduction studies or other conventional diagnostic procedures and 4) pathological findings of a reduction in the intraepidermal nerve fiber density. Hence, the present patient met all three criteria and was thus definitively diagnosed with SFN.

With regard to treatment for SFN, no studies published to date have shown steroids and/or methotrexate to be effective against sarcoidosis-induced SFN; rather, several studies have indicated that these drugs are not beneficial (12, 15, 16). A few reports have demonstrated anti-TNF-α agents (15), high-dose intravenous immunoglobulin (IVIG) (16) and ARA 290 (an erythropoietin derivative) (17) to be effective treatments for SFN. In the present case, we selected steroid pulse therapy based on the general treatment strategy for severe neurosarcoidosis and closely monitored her response to this therapy (7). Consequently, her symptoms, such as the feeling of back pressure, numbness, allodynia and constipation, clearly improved after the administration of pulse therapy, allowing us to gradually reduce the dose of steroids without the need to increase the dose of pregabalin or laxatives. We posit that the effectiveness of steroid treatment in this case of sarcoidosis-induced SFN was due to the administration pulse therapy. Additionally, the success of steroid pulse therapy may have also resulted from the initiation of treatment without waiting for pathological confirmation of small nerve fiber damage, as a recovery of the nerve function following heavy damage over time is highly unlikely.

Although all potential functional mechanisms of steroid pulse therapy (vs. the conventional use of steroid therapy) are not yet understood (18), it is known that pulse therapy is capable of transporting a sufficient amount of steroids to areas not easily accessed with non-pulse therapies and can induce the apoptosis of peripheral T-cells within 30 minutes after administration in vitro (19). The effects of steroid pulse therapy are so rapid that they cannot be explained by genomic mechanisms alone, and the pharmacological effects of this treatment are qualitatively different from those of non-pulse steroid therapy (18). This may be another reason why steroid therapy was effective in our patient, while conventional steroid administration was ineffective in previous cases.

The pathophysiology of sarcoidosis neuropathy involving large nerve fibers, characterized by granulomatous deposition around nerves and/or necrotizing vasculitic changes, is well described (3, 9). In contrast, the precise etiology of axon loss associated with sarcoidosis-induced SFN has yet to be fully clarified (12). Microangiopathy not due to granuloma formation is considered to be a possible cause (12, 20-22). Additionally, the involvement of signaling molecules (e.g., TNF-α) and immune-mediated mechanisms involving circulating immune complexes and autoantibodies has been postulated to be related to the development of sarcoidosis-induced SFN (15, 16). Although such mechanisms may have been associated with the patient’s neurological symptoms in the present case, the precise mechanism underlying the relief of her neurological symptoms with
high-dose steroid therapy remains unclear.

The possibility that the SFN improved due to the natural course of sarcoidosis cannot be excluded in the present case. However, we consider this possibility unlikely for the following reasons: 1) the patient’s symptoms were clearly progressing daily before the start of steroid pulse therapy and 2) the improvement in her neurological symptoms occurred too quickly for the relief to have been the result of resolution of the natural clinical course of sarcoidosis. Another possibility, that subclinical large nerve fiber involvement was coexistent with the SFN, should also be considered for a proper interpretation of the present findings, although nerve conduction studies, which are designed to evaluate large nerve fibers, did not show any obvious abnormalities in this case. In contrast, the patient’s decreased tendon reflex and hypesthesia of the right lower back cannot be fully explained by pure SFN. Nevertheless, since the symptoms, distribution and reduction in the intraepidermal nerve fiber density observed in the present case are consistent with the clinical characteristics of sarcoidosis-induced SFN, we concluded that the patient’s neurological symptoms were primarily due to SFN and subsequently mitigated by the high-dose steroid therapy.

We herein presented a case of sarcoidosis-induced SFN that was effectively treated with high-dose steroid therapy (steroid pulse therapy). Considering our patient’s clinical course, administering steroid pulse therapy prior to anti-TNF-α agents, high-dose IVIG and/or ARA 290 may be worthwhile in cases of sarcoidosis-induced SFN. However, careless steroid use should be avoided, as no other studies have shown steroid therapy to be beneficial for this disease, and long-term steroid use may actually cause SFN by inducing impaired glucose tolerance or worsening of diabetes.

The authors state that they have no Conflict of Interest (COI).

References

1. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 357: 2153-2165, 2007.
2. Lower EE, Weiss KL. Neurosarcoidosis. Clin Chest Med 29: 475-492, 2008.
3. Vital A, Lagueny A, Ferrer X, Louisset P, Canron MH, Vital C. Sarcoid neuropathy: clinico-pathological study of 4 new cases and review of the literature. Clin Neuroradiol 27: 96-105, 2008.
4. Hoitsma E, Marziniak M, Faber CG, et al. Small fibre neuropathy in sarcoidosis. Lancet 359: 2085-2086, 2002.
5. Lauria G, Comi BI, Johansson O, et al; European Federation of Neurological Societies. EFNS guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy. Eur J Neurol 12: 747-758, 2005.
6. Lacomis D. Small-fiber neuropathy. Muscle Nerve 26: 173-188, 2002.
7. Hoitsma E, Drent M, Sharma OP. A pragmatic approach to diagnosing and treating neurosarcoidosis in the 21st century. Curr Opin Pulm Med 16: 472-479, 2010.
8. Hoitsma E, De Vries J, Drent M. The small fiber neuropathy screening list: construction and cross-validation in sarcoidosis. Respir Med 105: 95-100, 2011.
9. Said G, Lacroix C, Planté-Bordeneuve V, et al. Nerve granulomas and vasculitis in sarcoid peripheral neuropathy: a clinicopathological study of 11 patients. Brain 125: 264-275, 2002.
10. Stern BI, Krumholz A, Johns C, Scott P, Nissim J. Sarcoidosis and its neurological manifestations. Arch Neurol 42: 909-917, 1985.
11. Hoitsma E, Faber CG, Drent M, Sharma OP. Neurosarcoidosis: a clinical dilemma. Lancet Neurol 3: 397-407, 2004.
12. Tavee J, Culver D. Sarcoidosis and small-fiber neuropathy. Curr Pain Headache Rep 15: 201-206, 2011.
13. Gorson KC, Herrmann DN, Thiagarajan R, et al. Non-length dependent small fibre neuropathy/ganglionopathy. J Neurol Neurosurg and Psychiatry 79: 163-169, 2008.
14. Gemignani F, Giovanelli M, Vitetta F, et al. Non-length dependent small fiber neuropathy. A prospective case series. J Peripher Nerv Syst 15: 57-62, 2010.
15. Hoitsma E, Faber CG, van Santen-Hoeufft M, De Vries J, Reulen JP, Drent M. Improvement of small fiber neuropathy in sarcoidosis patient after treatment with infliximab. Sarcoidosis Vasculitis Diffuse Lung Dis 23: 73-77, 2006.
16. Parambil JG, Tavee JO, Zhou L, Pearson KS, Culver DA. Efficacy of intravenous immunoglobulin for small fiber neuropathy associated with sarcoidosis. Respir Med 105: 101-105, 2011.
17. van Velzen M, Heij L, Niesters M, et al. ARA 290 for treatment of small fiber neuropathy in sarcoidosis. Expert Opin Investig Drugs 23: 541-550, 2014.
18. Sinha A, Bagga A. Pulse steroid therapy. Indian J Pediatr 75: 1057-1066, 2008.
19. Migita K, Eguchi K, Kawabe Y, et al. Apoptosis induction in human peripheral blood T lymphocytes by high-dose steroid therapy. Transplantation 63: 583-587, 1997.
20. Lauria G, Morbin M, Lombardi R, et al. Axonal swellings predict the degeneration of epidermal nerve fibers in painful neuropathies. Neurology 61: 631-636, 2003.
21. Ikedo Y, Yamaguchi T, Yamada Y, et al. Two sarcoidosis cases of small fiber neuropathy. Nihon Sarukoidoshitsu/Nikugesushikkan Gakkai Zasshi [The Japanese Journal of Sarcoidosis and Other Granulomatous Disorders] 24: 65-69, 2004 (in Japanese, Abstract in English).
22. Heij L, Dahan A, Hoitsma E. Sarcoidosis and pain caused by small-fiber neuropathy. Pain Res Treat 2012: 256024, 2012.