Eosinophilic Fasciitis Complicated with Peripheral Polyneuropathy

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Peripheral polyneuropathy and the complication of eosinophilic fasciitis (EF) is rare; only 2 such cases have been described previously. A 40-year-old woman suffered from swelling of the extremities after strenuous exercise and complained of bilateral paresthesia on the soles of her feet. The diagnosis was EF according to clinical symptoms, peripheral eosinophilia, and histological examination of the fascia. Nerve conduction tests also revealed sensory disturbance as mononeuritis multiplex. After administration of prednisolone, the swelling and tenderness of the extremities improved immediately but the neuropathy lasted for 6 months. (Internal Medicine 37: 417–420, 1998)

Key words: hypereosinophilic syndrome, eosinophilia-myalgia syndrome, mononeuritis multiplex, polyneuropathy, major basic protein

Introduction

Eosinophilic fasciitis (EF), first described as an entity in 1974 (1), is characterized by inflammation and thickening of the deep fascia, hypergammaglobulinemia, and peripheral blood eosinophilia; it is not associated with other connective tissue diseases. The condition occurs abruptly after exceptional exertion, responds favorably to corticosteroid therapy, and usually does not involve internal organs (2), e.g., the nervous system. We treated a case of EF accompanied with peripheral polyneuropathy, which as far as we are aware is the third reported case of this rare association (3, 4).

Case Report

In October 1996, a 40-year-old woman first noted a dull pain and swelling on her left lower thigh after strenuous aerobic exercise. Ten days later, the sizable, painful swelling spread to her left calf and both feet, and from her right forearm to the hand (but not the fingers). At the same time, severe paresthesia on the soles of both feet annoyed her. On November 5, 1996, she was admitted to our hospital as her affliction became intolerable. The patient had not taken any medications or foods containing L-tryptophan. Diabetes, alcohol abuse, and nutritional deficiency were excluded; there was no history of Raynaud's phenomenon, arthralgia, or dysphagia. Examination showed

non-pitting edema and tenderness of the right wrist to the forearm, the left calf to the lower thigh, and both feet. Joint motion was limited in the right wrist, left ankle, and left knee; there was no sclerodactylia nor joint tenderness. On neurologic examination, the manual muscle testing revealed normal strength in the four limbs. Sensation to light touch and pinprick on both soles, especially on the right heel, and sensation to vibration on the right toes were decreased. Both median nerves were not involved. The Tinel sign was negative on both posterior tibial nerves. Deep tendon reflexes of the ankles were normal bilaterally. On laboratory examination, total white blood cell count was 11,500/mm³ (eosinophil count, 5,060/mm³), erythrocyte sedimentation rate was 15 mm/h, serum gammaglobulin was not elevated (0.87 g/dl), and the level of lactate dehydrogenase was slightly elevated (479 IU/l; normal <400 IU/l). However, aspartate aminotransferase, alanine aminotransferase, creatine kinase, and aldolase were within normal limits. Anti-nuclear antibodies and rheumatoid factor were negative.

Magnetic resonance imaging (MRI) of the left lower limb showed the hyperintensity area to be within the fascia (Fig. 1), but no abnormality was found in MRI of the right ankle. A muscle-fascia-skin biopsy from the left mid-calf revealed thickening of the fascia and pronounced infiltration of mixed inflammatory cells, including eosinocytes and histiocytes (Fig. 2). The epidermis, dermis, and muscle in this specimen were almost intact.

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Received for publication September 3, 1997; Accepted for publication January 6, 1998

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The patient was diagnosed as having EF and was treated with prednisolone (PSL, 30 mg/day). A few days after administration of PSL, swelling and tenderness of the extremities were ameliorated with reduction of the eosinophil count to a normal range, but the sensory disturbance in the feet persisted. The dose of PSL was tapered to 7.5 mg/day within 3 months and no recurrence of the disease was observed. The paresthesia and dysesthesia on both soles gradually improved during the ensu-

ing 6 months.

Before treatment with PSL, the levels of major basic protein (MBP) and thrombomodulin (TM) in the serum were elevated to 3,981 ng/ml (mean $\pm$ SD of normal subjects, 421 ± 56 ng/ml) and 26.3 U/ml (normal, 10.4–23.4 U/ml), respectively. The levels of MBP and TM decreased after treatment (Fig. 3). Serum levels of interleukin (IL)-3 and IL-5 were within normal limits throughout.

Figure 1. Magnetic resonance imaging axial scan through the mid-calf of the patient prior to treatment. A T2-weighted image shows the hyperintensity area to be within the fascia (arrows).

Figure 2. Biopsy of the fascia of left gastrocnemius. Many eosinophils and histiocytes are present within the thickened fascia. The number of eosinophils in the fascia is more than 120 cells in high-power field (HE stain, $\times 400$).

Figure 3. Clinical course of the patient with eosinophilic fasciitis complicated with peripheral polyneuropathy. After administration of oral prednisolone, swelling of the extremities and peripheral eosinophilia were rapidly improved. On the other hand, paresthesia and hypesthesia lasted for several months. EC: eosinophil count (/mm³), TM: thrombomodulin (U/ml), MBP: major basic protein (ng/ml), IL-3: interleukin-3 (pg/ml), IL-5: interleukin-5 (pg/ml).

The nerve conduction velocities and the nerve action potentials of both tibial nerves and sural nerves were measured at the time of admission and 10 weeks after the initiation of PSL (Table 1). Electrophysiologic study revealed a marked slowing in the conduction velocity of the right tibial nerve and the right sural nerve and a reduction in the amplitude of the muscle action potentials of both tibial nerves prior to treatment. From these results and the distributions of neural damage, her neuropathy was considered to be mononeuritis multiplex. The abnormalities in nerve conduction disappeared (i.e., nerve conduction reverted to normal) by 10 weeks after treatment.

Discussion

Polyneuropathy may complicate eosinophilia-related connective tissue diseases, such as hypereosinophilic syndrome (HES) (5-10), eosinophilia-myalgia syndrome (EMS) induced by L-tryptophan ingestion (11-15), and Churg-Strauss syndrome (CSS) (16-18). The incidences of neuropathy in HES, EMS, and CSS are reported to be 14% (10), 5 to 38% (12, 15), and 75 to 85% (17, 18), respectively. Two mechanisms of neural damage induced by eosinophils have been proposed. One is the direct neurotoxic effect by eosinophil products, such

as MBP, eosinophil-derived neurotoxin, and eosinophil cationic protein. The other is the neural damage related to vasculitic involvement of the *vasa nervorum*. The diffuse axonal neuropathy in patients with HES was suggested to be caused by the former mechanism (5, 6, 8, 9). On the other hand, mononeuritis multiplex in EMS and CSS was explained as a consequence of ischemia by small vessel vasculitis (11, 16-18).

Carpal tunnel syndrome due to tenosynovitic compression of the median nerve may occur in 20% of patients with EF (19-21). Similarly, compression of the posterior tibial nerve by the lacinate ligament that is continuous with the deep fascia of the calf, can result in tarsal tunnel syndrome (TTS). The distribution of neuropathies and the nerve conduction study of this case suggest multiple neuropathies and cannot be explained by TTS alone. Moreover, MRI of the right tarsal tunnel failed to show the evidence of tenosynovitic compression. Thus, TTS is not likely in this case. Peripheral polyneuropathy has not been described in patients with EF except in 2 cases (Table 2). One was a Japanese case reported by Seko et al (3) who reported on a patient showing mononeuritis multiplex of the left arm and leg; they speculated that the focal inflammation had injured the terminal branches of the sensory nerves around the involved fascia. In the other case, Satsangi and Donaghy (4) reported that

Table 1. Nerve Conduction Studies

Nerve	CV (m/s)		Amplitude sensory AP μ V		Amplitude muscle AP mV	
	before*	after*	before	after	before	after
rt Median (m) [†]	62.8	—	—	—	2.8 [‡]	—
rt Median (s) [†]	64.4	—	3.9	—	—	—
lt Median (m)	64.6	—	—	—	10.2	—
lt Median (s)	69.8	—	5.4	—	—	—
rt Tibial	34.9 [‡]	49.6	—	—	4.5 [‡]	7.2
lt Tibial	51.6	43.1	—	—	2.6 [‡]	8.2
rt Sural	25.1 [‡]	44.6	5.8	10.6	—	—
lt Sural	42.8	46.6	5.4	14.4	—	—

CV: conduction velocity, AP: action potential. *before and after: before treatment and 10 weeks after treatment. [†](m) and (s): motor component and sensory component. [‡]abnormalities when compared with age-matched controls.

Table 2. Peripheral Polyneuropathy in Patients with Eosinophilia

Authors	Disease	No.	Neuropathy	Eosinophil count (max.)
Seko et al (1988)	EF	1 (m 1)	MNM	493
Satsangi and Donaghy (1992)	EF	1 (m 1)	MNM	1,090
Present case (1997)	EF	1 (f 1)	MNM	5,060
Wichman et al (1985)	HES	7 (m 7)	PN	2,800-19,700
Burns et al (1994)	EMS	3 (m 2, f 1)	PN	3,920-19,200

EF: eosinophilic fasciitis, HES: hypereosinophilic syndrome, EMS: eosinophilia-myalgia syndrome, MNM: mononeuritis multiplex, PN: polyneuropathy.

sural nerve biopsy revealed lymphocytic cuffing of epineural arterioles. The peripheral neuropathies of the three EF patients (the two reported cases and the present case) were localized around the involved fascias. These distributions were distinct from those of HES which spread symmetrically over the extremities. Peripheral eosinophilia of HES patients usually continues for several months to years (5, 22), whereas peripheral eosinophilia in EF can be transient even without specific treatment (2). In HES, products are released into the circulation by huge numbers of eosinophils, whereas the secretion of cellular products is limited and released locally into tissues in EF. Differences in neuropathies between EF and HES may be explained by differences in the numbers of eosinophils and/or the duration of eosinophilia.

The ability of eosinophil products to cause neural damage has been described (22). Moreover, the deposition of MBP in the tissues affected by eosinophils, such as cardiac myocytes in eosinophilic myocardial disease (23), the skin in atopic dermatitis (24), the bronchi in asthma (25), and several tissues such as muscle, skin, lung, and bile duct in EMS (12), have been demonstrated. These suggest that the presence of eosinophils and their products is an integral component of tissue injury. Some authors also suggest that MBP probably damages the endothelium, whereas eosinophil cationic protein may be partially responsible for the thromboembolic phenomena (5, 22).

In the present case, the total eosinophil count was extremely high ($5,060/\text{mm}^3$) as in EF, and eosinophilic infiltration in the fascia was prominent. The number of eosinophils in the fascia was more than 120 cells in a high-power field in our case, whereas it was less than 5 cells per high-power field in 20 cases described earlier (21). No data were available concerning serum MBP in patients with EF, but the levels of MBP were reported as 100 to 1,352 ng/ml in 10 patients with EMS as compared to 158 ± 42 ng/ml in normal controls (12). Serum MBP in our case reached 3,981 ng/ml, more than nine times that of the mean of normal controls. In addition, the level of TM (a marker of intimal injury) was slightly elevated. These findings suggest that, in our case, products from large numbers of eosinophils infiltrated into the inflamed fascia and caused direct nerve damage or intimal injury of the *vasa nervorum*. The patient's neuropathy was relieved gradually over 6 months, since we started corticosteroids in the early stages of the disease.

EF is generally not involved in internal organs and has a favorable prognosis. However, the injurious effects of eosinophils can not be disregarded in EF patients presenting extreme peripheral eosinophilia or severe eosinophilic infiltration in the fascia.

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