Polyarteritis Nodosa (PN) Complicated with Unilateral Exophthalmos

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A 58-year-old woman suddenly developed right exophthalmos. A CT scan of her orbit revealed an increase in volume and density of extraocular muscles and intraorbital soft tissues that resembled exophthalmos in Graves' disease. The exophthalmos gradually improved without treatment. Two months later she developed mononeuritis multiplex in her limbs, and then showed a sudden onset of swelling of her right calf. Sural nerve biopsy was performed and the diagnosis of polyarteritis nodosa (PN) was established from the histological findings. A rare case of PN with exophthalmos is herein reported with a review of the literature.

Key words: mononeuritis multiplex, sural nerve biopsy, Wegener's granulomatosis, Graves' disease

Introduction

Exophthalmos is a symptom frequently associated with Graves' disease (1). However, the pathogenesis of exophthalmos in Graves' disease has not been clarified (1). Vasculitic syndrome may be associated with exophthalmos, but occurs rarely (2-4) except for Wegener's granulomatosis (5, 6). Here we report a case of unilateral exophthalmos prior to necrotizing vasculitis accompanied by mononeuritis multiplex.

Case Report

The patient was a 58-year-old woman with a history of subarachnoidal hemorrhage five years earlier and hypertension for eight years. She had been followed at the Division of Neurosurgery without medications for several months. In June 1990, she recognized right eyelid swelling and exophthalmos without any pain (Fig. 1). She consulted an ophthalmologist at the hospital. An exophthalmometer revealed an obvious protrusion of her right eye. Her left eye was normal. Visual acuity, visual field, retinography and eye movement were normal on both sides. Computed tomography (CT scan) of her orbit revealed swelling and increased density of the right extraocular muscles and intraorbital soft tissues (Fig. 2). She received no treatment. However, her eye signs started to improve spontaneously. In August 1990, she developed dysesthesia, hypesthesia and muscle weakness of her limbs. She had difficulty in walking. She was admitted to Asahi General Hospital on August 23, 1990. On admission, blood pressure was 150/110mmHg, pulse rate was 84/min and regular. Body temperature was 35.7°C. The patient showed slight right exophthalmos with slight pigmentation, which appeared to have improved from two months earlier (Fig. 3). The vesicular sounds and heart sounds were normal. The liver, spleen and the kidneys were not palpable. On neurological examination, the cranial nerves were normal. Motor weakness was found in the upper and lower extremities with greater affection of the distal portions. The patient had dysesthesia, hypesthesia and hypalgesia in a gloves-stocking type distribution. However, the ulnar side of her left hand was only affected to a slight degree both in the motor weakness and sensory impairment. The deep tendon reflexes were diminished bilaterally in the distal portions of the extremities. The patient could not stand or walk without support. Laboratory studies on admission disclosed the following: erythrocyte, 461 × 10^6/mm^3; hematocrit, 42.3%; hemoglobin, 14.1 g/dl. The leukocyte count was 9300/mm^3 with a differential count of 18% eosinophil (1674/mm^3). Total protein.

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PN with Exophthalmos

is 7.2 g/dl and albumin was 4.1 g/dl. Creatinine was 0.6 mg/dl, blood urea nitrogen was 20 mg/dl and uric acid was 3.0 mg/dl. Liver function test included aspartate aminotransferase 101 U/l, alanine aminotransferase 61 U/l and lactate dehydrogenase 351 U/l. Creatine kinase was 641 U/l and serum electrolytes were within normal limits. Serological test for antinuclear antibody, rheumatoid factor, syphilis, hepatitis B surface antigen, anti-neutrophil cytoplasmic antibody (ANCA) and cross-reacting protein were all negative. Complement and immunoglobulin levels were within normal limits. The triiodothyronin was 1.2 ng/dl, the thyroxine was 14.3 µg/dl and the thyrotropin was 3.3 µU/ml. An X-ray film of her chest was normal and electrocardiogram revealed slight left ventricular hypertrophy. Urinalysis disclosed 1+ for blood on the dipstick but its microscopic study demonstrated no abnormality. The nerve conduction studies revealed a decrease of both the motor and sensory conduction velocity in the tibial nerve, and sensory conduction velocity in the median nerve. However in the left ulnar nerve, motor conduction velocity was normal and sensory conduction was only slightly decreased.

**Clinical Course**

On the seventh hospital day, she suddenly developed burning pain and swelling of the right calf. Magnetic resonance imaging (MRI-CT) of her calf revealed a high signal from the flexor muscles on T2-weighted image, but the vessels were not recognized clearly (Fig. 4). The symptoms in the right calf diminished without treatment in a few days. On the twelfth day, sural nerve biopsy was performed under lumbar epidural anesthesia. The sural nerve disclosed a marked loss of myelinated fibers with severe axonal degeneration (Fig. 5). Inflammatory cells were infiltrated in and around the epineurial vessels (Fig. 6A). Arterioles and small or middle-sized arteries were most severely affected. Some arterial lesions were accompanied by fibrinoid necrosis of the vessel walls (Fig. 6B). There was no infiltration of eosinophils in the biopsy specimens. Therefore, we assumed that the neurological involvement, which was mononeuritis multiplex in the clinical features, was caused by necrotizing vasculitis. She had no history of drug use or respiratory infection before the onset of exophthalmos and peripheral neuropathy. On the basis of the histological findings and medical history, we diagnosed polyarteritis nodosa (PN). Sixty milligrams prednisolone (PSL) was administered. Eosinophil count normalized rapidly, but other laboratory studies did not change. The muscle strength gradually recovered with rehabilitation. Hypesthesia and dysesthesia in the hands and feet remained. She could walk by herself when she was discharged after three months.
Fig. 4. Magnetic resonance T2-weighted image of her calf on the seventh hospital day. Swelling and high signal intensity of muscles, especially flexor muscles, were noted.

Fig. 5. Sural nerve biopsy. There was marked loss and degeneration of myelinated fibers with formation of myelin ovoids (A). Teased nerve fibers showed active axonal degeneration (B). (A: Toluidine blue stain, ×400, B: osmium stain, ×200).

Fig. 6. Vasculitis observed in the sural nerve biopsy. Inflammatory cells infiltrated in and around small and middle-sized arteries in the epineurium, but infiltration of eosinophils was not recognized (A). Fibrinoid necrosis of small artery and destruction of the internal elastic lamina was observed (B). (A: HE stain, ×240, B: Elastica van Gieson stain, ×400).
PN with Exophthalmos

Discussion

In 1866, Kussmaul and Maier first described “periarteritis nodosa” as a disease involving systemic arteries (7). Afterward, many authors reported cases of vasculitis with various clinical features; such as allergic granulomatous angiitis (AGA), Wegener’s granulomatosis (WG) and hypersensitivity angiitis (HS) (8). In addition, the limited form of vasculitides, such as cutaneous PN (9), renal PN (10) and nasal WG (11) was no longer supported. Moreover, in 1981, Wees et al (12) reported 11 patients with PN diagnosed by sural nerve biopsy in which only 3 patients had renal complication. In recent years, some cases were reported to share clinical features of many vasculitic syndromes as “polyangiitis overlap syndrome (13)”. Although our patient had cosinophilia and exophthalmos, AGA and WG were ruled out because of histological findings and clinical features. We did not make a diagnosis of HS because she had no history of drug use and no cutaneous lesions. Moreover there was no evidence of infection that could induce vasculitis. On the grounds mentioned above, although the clinical features were different from those of “classical” PN described by Kussmaul and Maier (7), the patient was diagnosed as having PN involving the peripheral nerves, right orbit and right calf. This diagnosis is compatible with the report by Wees et al (12).

Exophthalmos is a rare complication in patients with vasculitis except for WG. In cases of WG, necrotizing invasive granuloma may destroy orbital walls and sometimes have accompanying exophthalmos (5, 6). The CT scan of the orbit in the present patient revealed increased density and volume of extraocular muscles and intraorbital soft tissues, but no destructive lesions. It is noteworthy that these features resemble those of Graves’ disease (14). Inoue (15) reported that enlargement of both extraocular muscles and soft fatty tissues increase introrbital pressure resulting in exophthalmos in Graves’ disease. Maki et al (16) studied extraocular muscles histologically in dysthyroid (hyperthyroid) ophthalmopathy and reported inflammatory cells infiltrating around vessels in the acute phase of one patient. This may suggest the vasculitic mechanism of exophthalmos in Graves’ disease.

Van Wien and Merz (2) reported a case of PN with exophthalmos. They performed orbital biopsy and found both periarteritis and periphlebitis in the specimen. Sale and Patterson (17) reported a case of AGA with bilateral exophthalmos in recurrence. The present patient developed exophthalmos two months prior to the onset of mononeuritis multiplex. Moreover, the swelling of her right calf which developed after admission surprisingly resembled the feature of exophthalmos. Swelling in both the leg and the eye, as well as mononeuritis multiplex, were assumed to be caused by vasculitis. The lesion in the peripheral nerves caused irreversible functional disorder. However, those in the orbit and calf were reversible. We speculate that the difference was due to the vessels attacked as described in the pathological study by Van Wien and Merz (2). In the orbit and calf, the symptoms were mainly due to phlebitis and subsequently congestive change occurred. Therefore, they improved spontaneously with development of bypass venous return. However, the symptoms in peripheral nerves were assumed to be caused by arteritis, in other words by irreversible ischemia. The ischemia caused axonal degeneration of the nerve, followed by a loss of nerve fibers. Although corticosteroid therapy would have suppressed active inflammation of arteritis, loss of the nerve fibers due to axonal degeneration did not recover rapidly because axonal regeneration is very slow.

Exophthalmos is a very rare symptom in PN, but it sometimes precedes other symptoms as demonstrated in the present case. Six cases of PN with exophthalmos have been reported since 1956 (2-4, 18-20). However, they were not complicated by mononeuritis multiplex as that reported here. The similarities in the CT findings of exophthalmos between our PN case and Graves’ disease suggest the presence of a common mechanism ‘vasculitis’ in the development of exophthalmos. This is supported by the finding that corticosteroid was reported to be effective against severe ophthalmopathy of Graves’ disease (21).

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References