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CASE REPORT

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Dextromethorphan for neuropathic pain with Churg–Strauss syndrome

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Abstract A 48-year old man who had been treated with prednisolone, aminophylline, and pranlukast, a leukotriene-receptor antagonist, was diagnosed with Churg–Strauss syndrome based on the findings of asthma, eosinophilia, mononeuropathy, and extravascular eosinophils. Intractable neuropathic pain of the legs was successfully controlled with an N-methyl-D-aspartate receptor antagonist, dextromethorphan. We suggest that dextromethorphan receptor antagonists may be a useful treatment for the pain of neuropathy caused by vasculitis syndrome.

Key words Churg–Strauss syndrome · Dextromethorphan · Neuropathy · Pain · Pranlukast

Introduction

Churg and Strauss initially reported the cases of 13 patients with a systemic vasculitic disease involving the lungs, kidneys, skin, liver, and peripheral nervous system.[1] Peripheral neuropathy, usually mononeuritis multiplex, is found in many patients with Churg–Strauss syndrome (CSS). Although this symptom is not life-threatening, painful dysesthesia from peripheral neuropathy means that patients are extremely disabled.[2] The N-methyl-D-aspartate (NMDA) receptor complex is widely distributed throughout the central nervous system and is associated with many physiological functions, including learning and memory, neuronal plasticity, and pain.[3] We report the case of a patient with CSS experiencing intractable neuropathic pain which was successfully controlled with an N-methyl-D-aspartate receptor antagonist, dextromethorphan.

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Case report

A 48-year-old man who had been treated for asthma visited our hospital because of painful swelling and purpura of the legs. On admission, he was treated with prednisolone at a dose of 20 mg/day, aminophylline at a dose of 400 mg/day, and pranlukast, a leukotriene-receptor antagonist, at a dose of 450 mg/day, which gave good control of his respiratory symptoms. Physical examination showed that the patient's height was 164 cm and his weight was 60 kg. His pulse rate was 90/min, blood pressure 104/76 mmHg, and body temperature was 36.7°C. Neither anemia nor jaundice was observed. No abnormal cardiopulmonary findings were noted. He experienced pain and swelling in his legs, and purpura was observed on his feet. Asymmetrical muscle weakness and sensory loss of limbs were observed in a distal-dominant fashion. Muscular atrophy was not recognized. Although decreased deep-tendon reflexes were observed in his left arm, deep-tendon reflexes could not be examined in his legs because of extremely severe pain.

Laboratory examinations (Table 1) revealed a white blood cell count of 25100/mm^3, eosinophilia of 45%, an erythrocyte sedimentation rate (ESR) of 79 mm/h, a C-reactive protein (CRP) concentration of 8.10 mg/dl, a serum alanine aminotransferase concentration of 279 U/l, a serum aspartate aminotransferase concentration of 229 U/l, a blood urea nitrogen concentration of 18.2 mg/dl, a serum creatinine concentration of 1.4 mg/dl, and a serum creatine phosphokinase concentration of 538 U/l. Urinalysis revealed no abnormality. Occult blood was absent from the stool. Hepatitis B virus surface antigen, antihepatitis B core antibody, antihepatitis C antibody, and antinuclear antibody were all negative. Rheumatoid factor was positive. Serum immune complex determination was within normal limits. Antineutrophil cytoplasmic antibodies and anticardiolipin antibodies were absent. The plasma IgE

Table 1. Laboratory data on admission

Hematology		
	WBC 25100/mm^3	
	RBC 495 × 104/mm^3	
	Platelet 29.4 × 104/mm^3	
Urinalysis		
	Nothing particular	
ESR	79 mm/h	
Coagulation tests		
	PT	139%
	HPT	100%
	APTT	22.9 s
	TAT	1.5 ng/ml
	FDP	≤10 μg/dl
Biochemical examination		
	AST	229 U/l
	ALT	279 U/l
	LDH	1690 U/l
	ALP	1099 U/l
	Total protein	7.7 g/dl
	Albumin	3.2 g/dl
	CRP	8.10 mg/dl
	BUN	18.2 mg/dl
	Creatinine	1.4 mg/dl
Immunological examination		
	IgA	383 mg/dl
	IgM	245 mg/dl
	IgG	2090 mg/dl
	C_3 (72–144)	176 mg/dl
	C_4 (10–40)	29 mg/dl
	CH_{50}	54 U/ml
	Immune complex	2.4 μg/ml
	RF	(+)
	HBs-antigen	(−)
	Anti-HBc Ab	(−)
	Anti-HCV Ab	(−)
	Anti-nuclear Ab	(+)
Homogeneous × 320		
	Anti-DNA Ab	
		ds (−)
		ss (−)
	Anti-Ul RNP Ab	(−)
	Anti-Sm Ab	(−)
	p-ANCA	(−)
	c-ANCA	(−)
	Anticardiolipin Ab IgG	(−)

WBC, white blood cells; RBC, red blood cells; ESR, erythrocyte sedimentation rate, PT, prothrombin time; HPT, hepaplastin test; APTT, activated partial thromboplastin time; TAT, thrombin–antithrombin complex; FDP, fibrin degradation product; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CRP, C-reactive protein; BUN, blood urea nitrogen; Ig, immunoglobulin; C, complement; RF, rheumatoid factor; Ab, antibody; ANCA, antineutrophil cytoplasmic antibody

concentration was 2700 U/ml. A skin biopsy of the left foot revealed extravascular eosinophil infiltration (Fig. 1).

Following the 1990 American College of Rheumatology criteria,[4] the patient was diagnosed with CSS based on the findings of asthma, eosinophilia, mononeuropathy, and extravascular eosinophils. Chest X-ray, electrocardiography, esophagogastroduodenoscopy, and cardiac and abdominal ultrasonography revealed no abnormalities. Intravenous methylprednisolone pulse therapy (1000 mg/day), followed by oral prednisolone therapy (60 mg/day) were administered. WBC count, eosinophilia, serum CRP concentration, and ESR rapidly improved; however, severe painful paraesthesia of the legs continued. We examined the effects of analgesics to select effective agents for pain control. Because lidocaine provided partial relief of the intractable pain, we administered mexiletine, a structural analogue of lidocaine, at a dose of 300 mg/day. However, the effect was not sufficient. Ketamine, an NMDA receptor antagonist, was very effective, so we administered dextromethorphan, another NMDA receptor antagonist, at a dose of 90 mg/day, which sufficiently relieved the patient. Muscle atrophy progressed after the initiation of the treatment, although serum concentrations of CRP and ESR were normal. The prednisolone dose was tapered off, and 30 days after admission, the patient started physical training. Muscle weakness and atrophy then gradually improved. He was subsequently followed in our outpatient clinic without any sequelae.

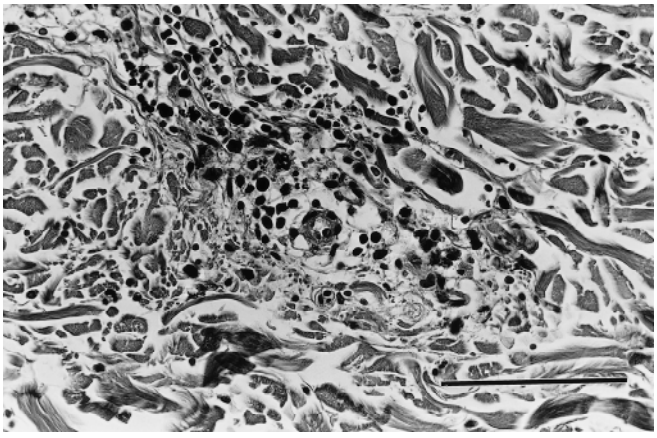

Fig. 1. Skin biopsy specimen showing extravascular infiltration, including eosinophils (hematoxilin–eosin stain, ×450, *Bar* = 100 μm)

Discussion

The present patient was diagnosed with CSS according to the American College of Rheumatology 1990 criteria for the classification of CSS[4] because of asthma, eosinophilia, multiple mononeuropathies, and extravascular eosinophils demonstrated by skin biopsy.

His onset of asthma was relatively late at the age of 41. At the onset of vasculitis, complete remission of the asthma was observed. Because cardiac, renal, or gastrointestinal involvement was not recognized, we chose the treatment of 1000 mg methylprednisolone for 3 days, followed by 60 mg prednisolone therapy without using cyclophosphamide. The most serious problem for the patient was painful dysesthesia of the lower limbs, and he could not sleep even after receiving nonsteroidal anti-inflammatory drugs and tranquilizers. Dextromethorphan has been used as a safe antitussive agent for more than 30 years.[5] It has been indicated that dextromethorphan reduces NMDA-mediated nocicep-

tive responses in the dorsal horn neurons.[6] NMDA receptor activation is essential for central sensitization, which increases the response to noxious stimuli and decreases the pain threshold after nociceptive stimulation, and is a key factor in the generation and maintenance of persistent pain states.[3] Recently, it was reported that an NMDA receptor antagonist was useful for treating painful diabetic neuropathy.[7] However, to our knowledge, there is no available data about the effects of the NMDA antagonist dextromethorphan for pain control of neuropathy induced by vasculitis syndromes. Dextromethorphan, an NMDA-receptor antagonist, was dramatically effective in the present patient, and it may be useful to relieve neuropathic pain in some other patients with vasculitis syndromes, including CSS.

Liver dysfunction immediately improved with the treatment, and tests for hepatitis B surface antigen and anti-HCV antibody were negative. Therefore, liver injury associated with CSS may be the most likely explanation for the abnormal liver function tests, because elevated liver enzymes are frequently found in vasculitis syndrome.[8]

Serum creatine phosphokinase concentration was elevated in this patient, and myositis has been observed in one-third of patients with CSS.[9]

Leukotriene-receptor antagonists are a new and effective approach for the treatment of asthma. Recently, zafirlukast has been reported to induce adverse effects similar to CSS.[10,11] One patient with CSS associated with pranlukast has been reported.[12] In most of these cases, CSS developed after the withdrawal of corticosteroids for asthma. In the present patient, CSS developed 1 year after the initiation of pranlukast. The frequency of patients with CSS associated with leukotriene-receptor antagonists is low.[12] Therefore, we think that some patients with severe asthma who depend on steroid and leukotriene antagonists may be known or potential patients with CSS, as suggested by Frosi et al.[13] Physicians should carefully observe patients with asthma who need complicated therapy, such as corticosteroids and leukotriene-receptor antagonists, for the possibility of CSS, especially whose onset of asthma is relatively late in life. Further analysis for an association between leukotriene-receptor antagonists and CSS is necessary.

In conclusion, pain control with an NMDA-receptor antagonist was very useful for relieving the neuropathic pain of a patient with CSS, and it should be considered as an optional treatment for neuropathic pain caused by vasculitis syndrome, including CSS.

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