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Eosinophilic Pleurisy Induced by Dantrolene

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A 70-year-old male developed eosinophilic pleurisy fifteen years after dantrolene sodium had been started for his spastic paraplegia due to spinocerebellar degeneration. Drug lymphocyte stimulation test (DLST) for dantrolene was positive. After discontinuance of dantrolene, pleural effusion gradually decreased and inflammatory reaction improved. During two-year observation, we have found no relapse of pleurisy without special medication. We present this case and compare this case with other 10 reported cases.

Key words: dantrolene sodium, eosinophilic pleurisy, drug lymphocyte stimulation test (DLST), spastic paraplegia, spinocerebellar degeneration

INTRODUCTION

Dantrolene is used to treat spastic neurological disorders and malignant hyperthermia during anesthesia. It is well known that dantrolene has dose-dependent toxicity on the liver. The risks range from asymptomatic transaminase elevation to fatal hepatitis [1]. On the other hand, the side effect on respiratory system is not common. Only 10 cases of dantrolene-induced pleurisy have been reported to date. We experienced a case with eosinophilic pleurisy induced by dantrolene sodium, fifteen years after chronic administration of dantrolene.

CASE PRESENTATION

A 70–year-old male was suffered from spastic paraplegia due to spinocerebellar degeneration since 1984. He had been treated with dantrolene sodium (150 mg daily) and eperisone hydrochloride (150 mg daily) for spasticity, pindolol (15 mg daily) for hypertension, and dihydroergotamine mesylate (2 mg daily) for migraine since August 1988. On March 23, 2003 he began to have cough, sputum, fever and dyspnea. He visited our emergency unit complaining of development of the symptoms four days after the onset.

On physical examination, the patient was alert, height was 165 cm, weight was 60 kg and body temperature was 39.2°C. The blood pressure was 164/98 mmHg. The pulse was 88 beats per minute, respiratory rate was 20 breaths per minute. Respiratory sound was decreased in the right lung base. Heart sound was normal. No edema was found on the extremities. Chest radiograph revealed a right-sided massive pleural effusion (Fig. 1). Arterial blood gas revealed severe hypoxemia with respiratory alkalosis (Table 1). Laboratory data on admission indicated inflammatory reaction, normal liver function and normal renal function (Table 1). Antinuclear antibody (ANA) was negative. Rheumatoid factor (RF) was negative. Diagnostic thoracenthesis was performed. Pleural fluid was bloody. Cell count of pleural fluid was 1,400/μl (neutrophil 2%, lymphocyte 56%, histiocyte 12%, eosinophil 27%, and atypical lymphocyte 2%). Protein concentration was 4.7 g/dl, albumin concentration was 2.6 g/dl and lactate dehydrogenase concentration was 473 IU/l. The concentration of adenosine deaminase (ADA) was 11.8 IU/l (normal

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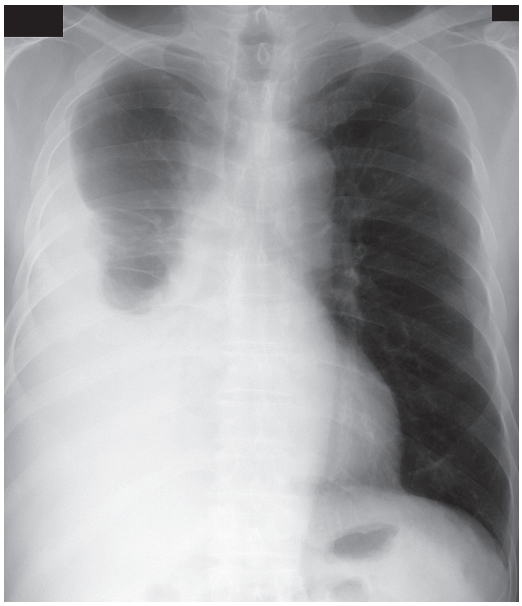

Fig. 1 Chest radiograph on the admission, right-sided massive pleural effusion is noticed.

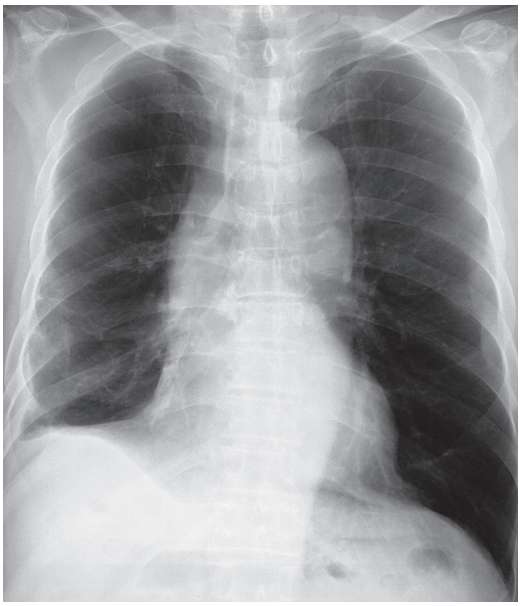

Fig. 2 Chest radiograph, 2 years after discontinuance of dantrolene, the right-sided costophrenic angle persisted blunt as the scar of inflammation.

Table 1 Laboratory data on admission

Arterial Blood Gas (O_2 5 l/min)		Biochemistry	
pH	7.508	Urea nitrogen (mg/dl)	12
$PaCO_2$ (Torr)	25.5	Creatinine (mg/dl)	1.1
PaO_2 (Torr)	90.2	Aspartate aminotransferase (IU/l)	19
$[HCO_3^-]$ (mmol/l)	19.8	Alanine aminotransferase (IU/l)	3
		Lactate dehydrogenase (IU/l)	329
Complete blood count		Total protein (g/dl)	6.7
WBC (per μl)	3,800	Albumin (g/dl)	3.3
Hematocrit (%)	34.6	Creatine kinase (IU/l)	38
Hemoglobin (g/dl)	11.5	Sodium (mmol/l)	135
Platelet (per μl)	117,000	Potassium (mmol/l)	4.2
		Plasma glucose (mg/dl)	117
Differential Count		CRP (mg/dl)	9.89
Neutrophil (%)	66		
Lymphocyte (%)	25		
Monocyte (%)	5		
Eosinophil (%)	3		
Basophil (%)	1		

range 6.8-18.2). Aerobic, anaerobic, fungal and mycobacterial culture of the fluid were negative. Cytological evaluation for malignant cells were negative. Drug induced pleurisy was suspected because of eosinophilic pleural effusion. Drug lymphocyte stimulation test (DLST) was performed and DLST for dantrolene was positive. We diagnosed the eosinophilic pleural effusion as dantrolene-induced pleurisy and discontinued dantrolene. After discontinuance of dantrolene, pleural effusion gradually decreased (Fig. 2) and inflammatory reaction improved.

DISCUSSION

We excluded the possibility of hydrostatic etiology, because cardiac, renal and liver function and nutritional status were normal. We also excluded the possibility of the infection, malignancy and collagen disease because aerobic, anaerobic, fungal, mycobacterial culture, cytological evaluation for malignant cells of the pleural fluid, ANA and RF were all negative. We suspected that some kind of drug-induced pleurisy in this case because eosinophil count in pleural fluid was remarkably high. We concluded that this pleurisy was induced by dantrolene because DLST for dantrolene was positive and the discontinuance of this drug improved the pleurisy.

We found that 10 cases with dantrolene-induced pleurisy had been reported by 2004 [3, 4, 7-10, 12]. We can find some characteristics of the 10 cases. Onset after chronic administration is common. Mean duration after administration of dantrolene is 31 months (from 2 months to 12 years). The duration of our case was fifteen years, which was the longest. Respiratory symptom such as cough and dyspnea has been reported in nine cases. Only one case had no respiratory symptoms [7]. A fever over 38°C was often noticed. The chest radiograph usually showed unilateral pleural effusion (right-sided; 5 cases, left-sided; 3 cases, and bilateral; 2 cases). Moderate eosinophilia is common in reported 10 cases, mean eosinophil count is 1060 per μl (from 375 per μl to 1840 per μl). Our case did not show significant eosinophilia (114 per μl). The mean rate of eosinophil count in pleural fluid of reported cases was 58% (from 36 % to 85 %). Toxicity on the liver is the common side effect of dantrolene, but all 10 cases showed normal value in liver function test. Rheumatoid factor of all 10 cases was negative. Only 2 cases showed weakly positive in antinuclear antibody, which is not significant for systemic lupus erythematosus and lupus syndrome.

The treatment was discontinuing the drug except one case, in which steroid was added because of recurrence [4].

The pathogenesis of dantrolene induced pleurisy is unknown. An immunologic mechanism is suggested by the peripheral and pleural eosinophilia.

It is known that some drug induce pleurisy or plural effusion without pulmonary disorder. Methotrexate possibly induces pleural effusion without any pulmonary injury even after single administration [11]. Procainamide sometimes induces the lupus syndrome followed by pleural effusion with or without pulmonary injury [5]. Methysergide is known as the drug sometimes induces pleural effusion [6]. Nitrofurantoin has similar chemical structure to dantrolene and is well-known as the drug which induces pulmonary fibrosis and/or pleural effusion [2].

In conclusion, eosinophilic pleurisy is rare side effect of dantrolene sodium, so clinicians should suspect drug-induced pleurisy when the etiology of pleurisy is unknown. The treatment for dantrolene-induced pleurisy is discontinuance of drug without special medication and the prognosis is good.

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