Case Report

Dantrolene and pleural effusion: case report and review of literature

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Study design: Single-subject case (a quadriplegic female, 56 years).

Objectives: To describe a new case of eosinophilic pleural effusion induced by dantrolene chronic administration.

Setting: Physical medicine and rehabilitation unit in a teaching hospital, France.

Methods: Diagnosis of an eosinophilic pleural effusion induced by dantrolene without any respiratory symptoms, except a decrease of breath sounds on the right lung base.

Results: Chest radiograph revealed a right-sided pleural effusion, and blood cell count a significant peripheral eosinophilia. Thoracentesis contained 85% of eosinophils. The other explorations eliminated other causes of pleural effusion. The diagnosis of drug-induced effusion was almost sure and led us to discontinue the dantrolene. After 3 months, she had completely recovered. These characteristics, similar to the eight other cases described in the literature, are essential for the diagnosis of pleural effusion induced by dantrolene.

Conclusion: Dantrolene, a long-acting skeletal muscle relaxant, is well known to induce liver side effects but it can also induce pleural pericarditis. The pathogenesis is still not clearly identified, but similarities of chemical structures of dantrolene and nitrofurantoin make us think that it could be the same mechanism. The association between dantrolene and nitrofurantoin may have contributed to the expression of the pleural effusion.

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Keywords: pleural effusion; eosinophilia; spinal cord injury; spasticity; dantrolene; nitrofurantoin

Case report

A 56-year-old woman was admitted to the physical medicine and rehabilitation unit (PM&R) from May to December 1998 with an incomplete traumatic quadriplegia (ASIA A: Motor level C4 on the right, C5 on the left, sensory level C5), which occurred on April 1998. At 4 months after the accident, she was treated with baclofen (60 mg daily) for spasticity and 2 months later dantrolene sodium was prescribed (225 mg daily). She went back home in December 1998.

Owing to a urinary tract infection in March 1999, nitrofurantoin (150 mg daily) was administered for 20 days. A few days later, she was admitted in the PM&R unit for a decreased functional performance and pain related to an increase in spasticity (FIMTM score = 65).

On examination she was afebrile. She had no respiratory complaints, but breath sounds were decreased in the right lung base. Chest radiograph showed a right-sided pleural effusion. Arterial blood gas

measurements revealed: oxygen saturation 95.9%, PaO_2 73 mmHg and $PaCO_2$ 37 mmHg. The respiratory vital capacity was evaluated at 2 l. White blood cell count was normal ($8.060/mm^3$), but there was significant eosinophilia ($1.840/mm^3$) that did not exist before. There was no inflammatory syndrome (CRP was 10 mg/l and the erythrocyte sedimentation rate was 22 mm/h). On 21st April, a diagnostic and therapeutic thoracentesis yielded more than 1 l of serosanguinous fluid with $13\,160/mm^3$ erythrocytes, $2140/mm^3$ leukocytes (85% of eosinophils). The pleural fluid protein concentration was 43 g/l. Aerobic, anaerobic, fungal and mycobacterial cultures of the fluid as well as the cytological evaluation for malignant cells were negative. Liver function tests were normal, serum rheumatoid factor and serum antinuclear antibody were negative. An isotope ventilation–perfusion lung scan ruled out pulmonary embolism. Electrocardiogram and echocardiogram did not show pericarditis.

This clinical and paraclinical presentation led us to suspect a drug-induced pleural effusion. Therefore, the primary drug responsible was dantrolene sodium, which was prescribed to the subject from 7 months. It was immediately discontinued. After 7 days the peripheral

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eosinophilia had resolved, and the respiratory vital capacity had increased to 2.7 l. Chest radiographs were normal in June 1999. Improvement of pulmonary function was associated with decreasing spasticity and pain. The dose of baclofen was decreased to 90 mg daily and pain medications were discontinued. The patient was able to walk again with an ankle foot orthosis and a rollator as far as 40 m. She went back home in June 1999 (FIMTM score = 73). The patient is regularly examined by a PM&R doctor, has never had new respiratory dysfunction and dantrolene has not been reintroduced. For the spasticity, baclofene and botulinum toxin injection were prescribed.

Review of the literature

We searched the MEDLINE database with 'dantrolene and pleural effusion' as keywords and found eight cases reported from 1979 to 2002. The incidence is rare but probably underestimated. Mahoney and Bachtel¹ mention 19 other cases of pleural effusion, without any clinical description, since dantrolene has been used (1967). Sahn² also refers to five other cases mentioned by Light. Table 1 describes the characteristics of the eight cases from the literature and our patient. Some similarities can be noticed: onset after chronic administration of dantrolene (>60 days); association with peripheral and pleural fluid eosinophilia; disappearance of symptoms after discontinuation of the drug; absence of other causes to explain the effusion. All the patients had a disease of the central nervous system without any respiratory dysfunction (normal chest radiograph) before the initiation of the treatment with dantrolene. Respiratory or cardiovascular symptoms have always been reported, such as coughing, shortness of breath, chest pain, tachycardia or fainting. As for the patient described here, who presented none of these symptoms, systematic clinical examination only led us to diagnose the pleural effusion. A low-grade fever (temperature 38–38.5°C) is often noticed,^{3–5} except for one patient who had a temperature of 39°C.⁵ Liver function tests were always normal. An elevated immunoglobulin E concentration (50.4 µg/l) is reported only by Mahoney and Bachtel.¹ Three pleural tissue biopsies revealed non-specific inflammation. The chest radiograph always showed a pleural effusion, sometimes bilateral, sometimes with associated pericarditis, but never with any other pleural or pulmonary disease. Lung scan, ventilation-perfusion lung scintiscan or other examinations ruled out other etiology. No infection, pulmonary thromboembolic disease, malignancy or connective tissue disease were discovered. In only two cases, antinuclear antibodies were weakly positive with a titer of 1:10, which is not significant for lupus.^{4,5} All rheumatoid factor tests as well as tuberculin skin tests were negative. As a result, for all the authors, the diagnosis that came to mind was dantrolene-induced pleural effusion. Each time, the treatment consisted in discontinuing dantrolene, and for one case, in adding orally steroid therapy for 2 weeks (prednisone 40 mg

Table 1 Review of the literature data

References	Gender	Age (years)	Delay before treatment	Daily dose (mg)	Onset	Nitrofurantoin	Disease	Clinical manifestation	Peripheral eosinophilia (mm ⁻³)	Pleural eosinophilia (%)
Petusevsky (1979)	F	53	NR	225	2 months	NR	Paraplegia	Left pleural effusion	1198	66
	M	38	12 years	400	3 years	NR	Multiple sclerosis	Left pleural effusion	485	37
	M	23	2 years	400	6 months	Yes (3 months before effusion)	Quadriplegia	Right pleural effusion	375	46
	M	20	6 months	300	3 months	Yes (3 months before effusion)	Quadriplegia	Right pleural effusion + pericarditis	602	36
Miller DH (1984)	F	43	10 years	100	3 months	NR	Multiple sclerosis	Bilateral effusion + pericarditis	1500	NR
Mahoney (1994)	M	35	NR	100	12 years	No	Quadriplegia	Pleuropericarditis	1314	70
Dohen (2000)	M	72	5 years	300	27 months	NR	Stroke	Left pleural effusion	658	55
Felz (2001)	M	22	NR	400	5 years	NR	Quadriplegia	Right pleural effusion	1496	64
Present case	F	56	7 months	225	5 months	Yes (1 month before effusion)	Quadriplegia	Right pleural effusion	1840	85

M = male; F = female; NR = no reported

daily) because of an early recurrence.⁶ After several months of follow-up, no case of relapse was noted and none of the patients were rechallenged with dantrolene. Sometimes, residual costophrenic angle blunting persisted on the chest radiograph, without any clinical repercussions.^{3,5} For one of the patients, spasticity was treated with diazepam and baclofen⁶ as for the other patients, the treatment was not reported. Our patient's spasticity is adequately controlled with baclofen (90 mg daily) and botulinum toxin injections.

Discussion

Medications are a rare etiology of pleural effusions, even though 15 drugs at least can induce them. Pleuritis occur more often with methysergide or other antimigraine agents. Eosinophilic pleural effusion (EPE), defined as containing more than 10% eosinophils and frequently associated with peripheral eosinophilia, represent 1–9% of all pleural exudates.⁷ A cause is identified in only 25% of EPE cases.⁸ The precise mechanism of drug-induced pleural disease is not entirely elucidated.

Dantrolene sodium is the only drug against spasticity that acts directly on the long-acting skeletal muscles, without any modification of the nervous conduction or neuromuscular transmission. It inhibits the movements of intracellular calcium, preventing it from getting out of the sarcoplasmic reticulum and therefore inducing a dissociation of the excitation–contraction coupling. It is used to treat spastic neurological disorders and malignant hyperthermia during anesthesia. Severe liver insufficiency is a definite contraindication to dantrolene sodium. The risks of toxicity on the liver range from asymptomatic transaminase elevation to fatal hepatitis,⁹ and are dose-dependent. Several cases of dantrolene-induced diseases are reported, but with no certitude about their pathogenesis.

An immunologic mechanism such as immediate-type hypersensitivity is suggested by the clinical presentation and the pleural and peripheral eosinophilia, but anti-dantrolene IgE is never found because of the chemical structure of the drug. Moreover, performing a radioallergosorbent test (RAST) is technically impossible.³ An immune complex reaction can be considered, but immunofluorescent studies of pleural tissue disclose only nonspecific inflammation with deposition of IgG and IgA, and no evidence of granular immune complex deposition.⁵

In summary, an allergic mechanism is strongly suspected because of the peripheral eosinophilia, the onset after chronic administration of the drug, the recovery after treatment discontinuation and the lack of other explanations despite extensive clinical and paraclinical evaluation.^{1,6} Obviously, a recurrence of the effusion after a new administration of the drug would be a powerful argument for an allergic reaction, but no such cases are reported.

It is interesting to note some similarities in chemical structure between nitrofurantoin and dantrolene.¹⁰

Nitrofurantoin is a urinary antimicrobial agent commonly implicated in pulmonary or hepatic allergic reactions. Many cases of acute pleuropneumonitis with eosinophilia are reported with nitrofurantoin use, and have been identified as a drug-induced allergic reaction.^{11,12} More recently, hepatic injury from nitrofurantoin frequently associated with autoantibodies and hyperglobulinemia has been described, without any correlation between the dose and the severity of the disease, in contrast to hepatotoxicity from dantrolene.¹⁰ Different immunologic mechanisms are proposed. There was evidence of *in vitro* lymphocyte sensitivity to nitrofurantoin in a few cases of acute pneumonitis and systemic lupus erythematosus induced by this agent.^{12,13} It is assumed that the pulmonary reactions are mediated by antigen–antibody complexes and studies on IgG and IgM antibodies and lymphocyte transformation tests have produced conflicting results.¹¹ Cell-mediated and cytotoxic immune mechanisms can also be implicated.¹⁴ Thus, chemical structural similarities reinforce the hypothesis for an allergic basis to dantrolene-induced pleurisy, even if efforts to detect *in vitro* lymphocyte sensitization to dantrolene were unsuccessful.⁵ Three reasons may explain this failure: the testing was performed in only two cases; there was an important delay between the discontinuation of the drug and the *in vitro* testing; or the reaction involves a toxic metabolite or a short-lived by-product of dantrolene. So, even though the most frequent side effects are different (dantrolene and hepatotoxicity; nitrofurantoin and pulmonary disease), the association of these two medications could have precipitated the apparition of EPE in our patient.

In conclusion, even if its pathogenesis is uncertain and its incidence rare, dantrolene sodium-induced pulmonary toxicity must be recognized and recalled when unexplained pleural effusion or pleuropericarditis occurs. In fact, recovery is linked to the discontinuation of treatment, which should be done as soon as possible. Dantrolene is commonly used, and frequently associated with nitrofurantoin, in neurological patients. Systematic, regular and careful clinical examination is therefore recommended, especially for those patients who can have an atypical clinical presentation. Monitoring of pulmonary auscultation must be systematic and frequent when dantrolene sodium is administered for over 60 days, particularly when associated with nitrofurantoin.

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