Cryptococcal Pleural Effusion in a Patient with Chronic Renal Failure Receiving Long-term Corticosteroid Therapy for Rheumatoid Arthritis

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A 52-year-old woman with a seven-year history of rheumatoid arthritis (RA) was transferred to our department with chronic renal failure to undergo hemodialysis. She had been treated with prednisolone for a long time, and had renal amyloidosis secondary to RA. During her hospitalization, a left pleural effusion developed. Pleural fluid cultured positive for *Cryptococcus neoformans* (CN), and the CN antigen was detected in both pleural fluid and serum. Chest computerized tomography revealed an infiltrate shadow in the left lower lung field suggestive of CN infection. This was successfully treated with anti-fungal agents. Pleural effusion is an unusual manifestation of pulmonary cryptococcosis. We should consider a diagnosis of CN infection when pleural effusion is observed in compromised patients such as those receiving a long-term corticosteroid treatment. (Internal Medicine 37: 534–537, 1998)

Key words: *Cryptococcus neoformans* (CN), compromised host, secondary amyloidosis, antigen test

Introduction

Cryptococcal pulmonary infection rarely occurs in healthy or compromised persons (1–10). *Cryptococcus neoformans* (CN) infection associated with pleural effusion is uncommon, even in patients with acquired immunodeficiency syndrome (AIDS) (4, 6–10). Here, we report a rare case of pleural effusion due to CN that developed in a patient with chronic renal failure receiving long-term corticosteroid treatment for rheumatoid arthritis (RA).

Case Report

A 52-year-old woman was transferred to our department on December 3, 1996 to receive hemodialysis treatment for chronic renal failure. She had been treated with prednisolone (PSL) (maintenance dose of 10 mg/day) for rheumatoid arthritis (RA) since she was 45 years old. At 50 years of age, she had undergone a left nephrectomy due to renal cell carcinoma, and was diagnosed with renal amyloidosis. Since then, non-steroidal anti-inflammatory drugs (NSAID) had been avoided to guard the renal function. Her RA state had been stable and was stage III and class 2 according to Steinbrocker's classification (11). On admission, her serum creatinine (Cr) level was 4.4 mg/dl,

and she had gained 10 kg in weight. Chest roentgenograms revealed pulmonary congestion and bilateral pleural effusion. She underwent hemodialysis twice weekly from December 5, and thereafter the bilateral pleural effusion resolved and her general condition improved. However, ileus occurred in mid-January 1997, and a loop colostomy was carried out on January 23 in the Department of Surgery. Later, her ileus proved to be paralytic due to intestinal amyloidosis. After surgery, disseminated intravascular coagulation (DIC) occurred which was triggered by postoperative infection, and she was transferred back to our ward on January 29.

On the same day (1/29), laboratory data (Table 1) showed thrombocytopenia ($3.5 \times 10^4/\mu\text{l}$), enhanced coagulation activity, and raised C-reactive protein (CRP) (15.7 mg/dl). Following treatment with antibiotics and gabexate mesilate (FOY), her platelet counts and CRP returned to normal levels, $40.2 \times 10^4/\mu\text{l}$ and 0.3 mg/dl, respectively (2/10). However, her fever returned on February 11 and her CRP was elevated to 9.9 mg/dl on the Feb. 17. Chest roentgenograms (2/17) (Fig. 1) revealed a left pleural effusion. The next day, thoracentesis was carried out and *Cryptococcus neoformans* was cultured (Table 2). The CN antigen was also detected in both pleural fluid and serum. No signs of meningitis were observed. Chest computerized tomography (CT) (Fig. 2) revealed an infiltrate shadow in the left

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Table 1. Laboratory Data on Day of Transfer from the Surgical Department (1/29)

White blood cells	8,620/ μ l (8,600)*	anti-HIV antibody	(-)
neutrophils	77.4%	HBs antigen	(-)
lymphocytes	15.0%	anti-HCV antibody	(-)
monocytes	6.3%		
eosinophils	0.9%	Prothrombin time	77.9%
basophils	0.3%	Fibrinogen	498 mg/dl
Red blood cells	204×10^6 / μ l (298)	FDP	6.9 μ g/ml
Hemoglobin	6.1 g/dl (8.6)	AT-3 activity	51.2%
Platelet	3.5×10^4 / μ l (3.0)	D-dimer	3.1 μ g/ml
ESR	75 mm/h	Urinalysis	
C-reactive protein	15.7 mg/dl	protein	(+++)
RAHA	$\times 640$	sugar	(++)
		occult blood	(+)
Total protein	4.7 g/dl	cast	(+)
Albumin	53.0%	bacteria	(-)
α_1 -globulin	4.5%		
α_2 -globulin	12.2%	Blood culture: bacteria	(-)
β -globulin	8.5%		
γ -globulin	21.8%	Arterial blood gas (room air)	
Aspartate aminotransferase	8 IU/l	PH	7.386
Alanine aminotransferase	1 IU/l	PaO ₂	66.8 torr
Lactate dehydrogenase	263 IU/l	PaCO ₂	28.2 torr
Na	141 mEq/l (139)	HCO ₃	16.9 mEq/l
K	5.0 mEq/l (4.3)		
Cl	111 mEq/l (106)	PPD skin test:	negative
Blood urea nitrogen	39 mg/dl (20)		
Creatinine	3.8 mg/dl (1.4)		

*Parentheses indicate data following hemodialysis. Body weight was reduced by 1.5 kg following hemodialysis. ESR: erythrocyte sedimentation rate, FDP: fibrinogen degradation product, HIV: human immunodeficiency virus, AT-3: antithrombin 3, HCV: hepatitis C virus, PPD: purified protein derivative of tuberculin, RAHA: rheumatoid factor.

Table 2. Characteristics of Pleural Effusion (2/18)

Color: yellow, turbid	
Lymphocyte-predominant	4,320/ μ l
Specific gravity	1.020
Total protein	2.5 (4.9)* g/dl
Albumin	1.4 (2.3) g/dl
Lactate dehydrogenase	364 (248) IU/l
Glucose	110 mg/dl
Adenosine deaminase	27.8 IU/l
Culture: <i>Cryptococcus neoformans</i> (+)	
<i>M. tuberculosis</i> (-)	
Cytology: class II	

*Parentheses indicate serum levels on the same day. Hemodialysis was not performed on this day.

Figure 1. Chest roentgenograms on readmission (2/17) revealed a left pleural effusion.

lower lung field suggestive of CN infection. No mediastinal or hilar lymphadenopathy was observed. The serum level of adenosine deaminase (ADA) was not high enough to strongly suspect the *M. tuberculosis* infection. Pleural effusion due to RA also appeared to be unlikely, because the activity of RA was stable clinically and the level of glucose in the effusion was not low (110 mg/dl). Anti-fungal therapy was begun on Feb. 21 (Fig. 3). She was first treated with amphotericin B (AMPH) intravenously (div), and then intrapleurally (ipl).

Culture of pleural fluid for CN became negative (2/28), CN antigen titer decreased from 1:64 (3/3) to 1:16 (4/14) (Table 3), and the left pleural effusion and parenchymal shadow were resolved by the end of May. Since the serum CN antigen remained positive, flucytosine (5-FC) and fluconazole (FCZ) were continued orally. She was discharged from the hospital on June 18, and has since been treated with PSL at a daily dose of 5 mg, FCZ at 100 mg and 5-FC at 2 g twice weekly following hemodialysis at the outpatient clinic.

Figure 2. Chest CT scan (3/7) revealed a parenchymal infiltrate shadow in the left lower lung field suggestive of CN infection and a left pleural effusion.

Discussion

Cryptococcus neoformans infection rarely occurs in healthy or compromised persons. As for pulmonary manifestations of CN infection, parenchymal nodules are common in the case of healthy persons. Conversely, diffuse interstitial infiltrates, alveolar consolidation, ground glass shadow, and mediastinal or hilar lymphadenopathy are most commonly seen in cases of compromised persons with a disease such as AIDS (4, 6–10). In the present case, a localized interstitial infiltrate shadow was observed on the chest CT (Fig. 2), but was not considered typical of CN infection, probably due to the fact that our case was not an AIDS patient.

Among the parenchymal, nodular, and pleural abnormalities, pleural abnormality is reported to be the most uncommon pulmonary manifestation of CN infection. The frequencies of patients with pleural effusion due to CN infection are reported

Figure 3. Clinical course.

Table 3. Characteristics of Pleural Effusion following Treatment with AMPH

AMPH*	2/18 div	2/28	3/3	3/17	3/25 ipl	4/1	4/7	4/14	4/17
TP (g/dl)	2.5	2.4	2.5	2.5	1.9	2.5	2.6	2.5	2.8
ALB (g/dl)	1.4	1.4	1.4	1.3	1.1	1.3	1.4	1.3	1.3
LDH (IU/l)	364	147	141	134	133	274	283	273	486
WBC (/μl)	4,320	858	594	232	144				
Culture	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
CN antigen titer		(+)	1:64					1:16	

*Amphotericin B (AMPH) was administered intravenously (div) from 2/21 to 3/24, and intrapleurally (ipl) from 3/25 to 4/21.

to be 0/10 (4), 1/12 (8), and 3/14 (9). In Japan, Taguchi et al (5) reported such a case with impaired cellular immunity secondary to human T-lymphocyte virus type 1 (HTLV-1) infection. In 1980, Young et al (3) reviewed 30 cases with cryptococcal pleural effusions based on the English literature. Probably, around 50 such cases have been documented to date, but this is still very few. They stated that treatment with corticosteroid and/or immunosuppressive drugs was the most common predisposing condition for such cases. The present case had also undergone treatment with PSL over a long period, and her chronic renal failure itself may also have been immunosuppressive. The characteristic of pleural effusion in our case was exudate and lymphocyte predominancy, and these findings were in agreement with the reports of several investigators (3, 6). According to the review literature (3), positive rates for cryptococci in pleural fluid are not so high; only 11 out of 26 cases were shown to be positive. Salyer and Salyer (2) reported that negative cultures might be due to the fact that the effusion results not from the growth of organisms, but rather from the release of antigen into the pleural fluid, just as occurs in *M. tuberculosis*. In fact, they had identified subpleural nodule as a part of the primary pulmonary lymph nodal complex in 6 out of 7 autopsy cases with pleural cryptococcosis. In the present case, the effusion seemed to result from the growth of the organism in the pleural cavity.

The cryptococcal antigen was positive in both the fluid and serum in our case. The cryptococcal antigen test is reported to be a useful adjunct in confirming a diagnosis and in assessing the response to treatments (3). Diamond and Bennett (12) showed that patients with cryptococcal meningitis who had relapsed had persistently high posttreatment titers of cryptococcus antigen in their serum or cerebrospinal fluid. They warned that there is a high possibility of relapse in patients who continue to receive daily corticosteroid therapy at doses of over 20 mg of PSL after undergoing antifungal therapy. The cryptococcal antigen in the serum is still positive in our case, so

we will continue to administer antifungal drugs orally for a certain period.

Although cryptococcal pleural effusion is uncommon, this disease should be considered in patients who have serious underlying diseases, especially when they have been receiving corticosteroid for a long period of time. We think it is important to include the cryptococcal antigen test or culture in the evaluation of pleural effusion in such patients.

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