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CASE REPORT

Cavitary lung lesion in a patient with systemic lupus erythematosus: an unusual manifestation of cytomegalovirus pneumonitis

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Abstract We report a 35-year-old female patient with systemic lupus erythematosus (SLE). She was admitted due to deterioration of lupus nephritis and received treatment with a high dose of steroid and cyclosporine. Approximately 1 month after admission, the patient was also treated for cytomegalovirus (CMV) infection because she was found to have CMV antigenemia. Although a cavitary lesion was shown by chest computed tomography (CT), its cause could not be clarified by blood examination, smears or cultures, or by bronchoscopy. We considered that this lesion may have been caused by CMV pneumonitis because it was resolved during the treatment for CMV infection. It is known that CMV causes opportunistic infections in patients with collagen vascular diseases (CVD) who are receiving immunosuppressive therapy. However, it is extremely rare for a cavitary lesion to be formed as a result of CMV pneumonitis. Here we describe the details of this interesting case.

Keywords Cavitary lung lesion · Systemic lupus erythematosus (SLE) · Opportunistic infection · Cytomegalovirus · Compromised host

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Introduction

Differential diagnosis of cavitary lung lesions is very important. Patients with collagen vascular disease (CVD) are at increased risk of opportunistic infections because of the condition itself and treatments with corticosteroids or immunosuppressive agents. Therefore, patients with CVD often have cavitary lung lesions complicated by opportunistic infections such as fungal or bacterial infections, or tuberculosis. Here we present a patient with systemic lupus erythematosus (SLE) who had a cavitary lesion in the lung, but its cause could not be determined due to difficulty with the differential diagnosis. However, we considered that CMV pneumonitis might be one possible cause, as the patient had CMV antigenemia, and the cavitary lesion was resolved by anti-CMV treatment. CMV is known to be a typical agent responsible for opportunistic infections, such as pneumonitis, gastroenteritis or colitis, and retinitis in compromised hosts, such as patients with acquired immunodeficiency syndrome (AIDS), organ transplant recipients, and patients with CVD. While the major radiographic appearances of CMV pneumonitis are reportedly ground-glass attenuation, dense consolidation and so on [1–4], cavitary lesions are rarely found. We consider that the present cavitary lung lesion was due to CMV pneumonitis, and here we describe the clinical course with reference to the literature.

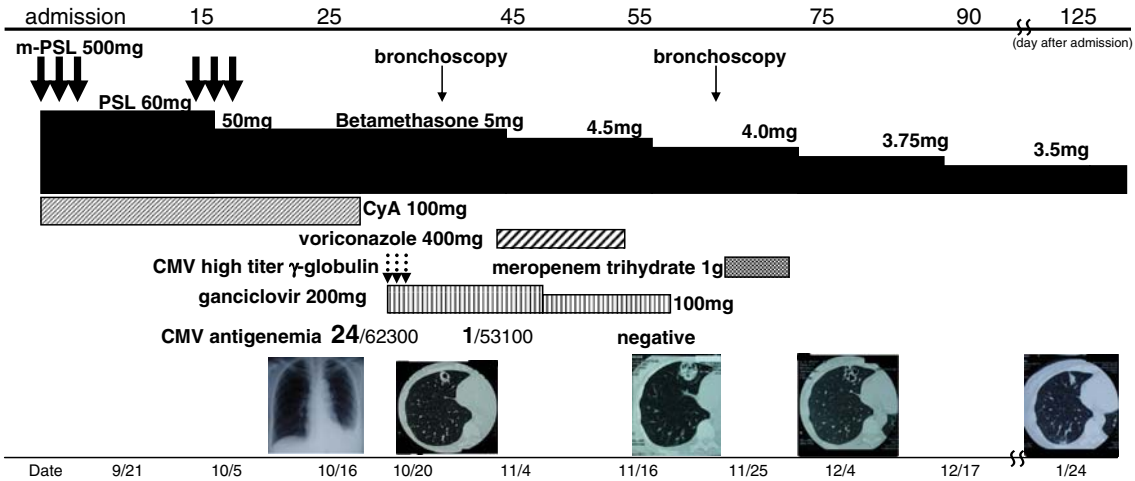
Case report

The patient, a 35-year-old woman, had been diagnosed as having SLE complicated by lupus nephritis [World Health Organization (WHO) class IV], arthritis, leukocytopenia and positivity for anti-nuclear-antibody and

anti-DNA-antibody 13 years prior to presentation. Her medical history included no other condition besides SLE. Although her condition had been stable on a daily dose of 5 mg of prednisolone (PSL), her renal function had gradually worsened since August 2006, and edema had appeared in the lower part of both thighs. Despite an increase in the dose of PSL to 30 mg/day, her condition was not improved. She was hospitalized on 21 September 2006 because of the renal failure caused by recurrence of the lupus nephritis.

On admission, slight anemia was evident in the conjunctiva, and edema was present in both lower thighs. The patient's blood pressure was 156/96, and laboratory studies showed increases in the levels of blood urea nitrogen (BUN) and serum creatinine to 82.2 and 4.0 mg/dl, respectively, and a decrease of serum albumin to 2.2 g/dl. Although the titers of SLE-related factors such as compliment and anti-DNA antibody were improved when the dose of PSL was initially increased, lupus nephritis nephritic syndrome was exacerbated, and the urinary protein level became 7.9 g/day (Fig. 1). Her SLE disease activity index (SLEDAI) score was 23 points. A plain chest X-ray on admission showed no abnormal shadows in the lung fields, excluding bilateral pooling of pleural effusion (Fig. 2a).

Immediately after admission, the patient received 500 mg of methylprednisolone for 3 days followed by oral prednisolone 60 mg/day (which was changed to betamethasone 1 month later) and cyclosporine A, 100 mg/day. However, hypoalbuminemia due to nephrotic syndrome continued, and the lower extremity edema and pooling of pleural effusion worsened. Furthermore, leukocytopenia and thrombocytopenia became evident. We considered that the cytopenia had been drug-induced, but there was no improvement even when several of the drugs were changed or withdrawn. There was no evidence of diseases that have cytopenia as a complication, such as hemophagocytic syndrome (HPS), thrombotic thrombocytopenic purpura (TTP), idiopathic thrombocytopenic purpura (ITP) (platelet-associated IgG (PA-IgG) was negative) and disseminated intravascular coagulation syndrome (DIC). Therefore, a CMV antigenemia test for differential diagnosis was conducted on the 26th day after admission. The test showed positivity for CMV antigenemia, and the patient was diagnosed as having CMV infection. At this time, the IgG value and lymphocyte count decreased to 261 mg/dl and 195/μl, respectively, and the patient was in a state of strong immunosuppression. Ganciclovir was administered for 4 weeks from days 29 to 47 after admission, and was withdrawn when negativity for CMV



Date	9/21	10/5	10/16	10/20	11/4	11/16	11/25	12/4	12/17	1/24
WBC	15500	14800	6500	2100	9300	7200	13400	9000	7100	7000
Lym	775	888	195	462	1395	720	938	990	1704	1190
Plt	27.7	13.2	8.3	5.5	20.2	20.6	17.2	25.7	21.8	20.4
CRP	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	13.2	<0.3	<0.3	<0.3
Alb	2.4	2.2		2.1	2.0		2.7	2.6		3.2
IgG	568	279	261	594	386	366		327	419	611
DNA-Ab	33.7	<2.0			<2.0			<2.0		<2.0
CH50	23	26			32			43		50
IC	3.7	<1.5			<1.5			<1.5		<1.5
U-Pro	7.9	6.0		5.4	2.0	2.8	4.0	2.2	2.6	0.5

Fig. 1 The clinical course after admission. *m-PSL* methylprednisolone, *PSL* prednisolone, *CyA* cyclosporine A, *CMV* cytomegalovirus, *WBC* white blood cell (/μl), *Lym* lymphocyte (/μl), *Plt* platelet (10^4/μl), *CRP* C-reactive protein (mg/dl), *Alb* serum albumin (g/dl), *lgG* immunogloblin G (mg/dl), *DNA-Ab* anti-DNA-antibody (IU/ml), *CH50* 50% hemolytic unit of complement (U/ml), *IC* immune complex (μg/ml), *U-Pro* urine protein (g/day)

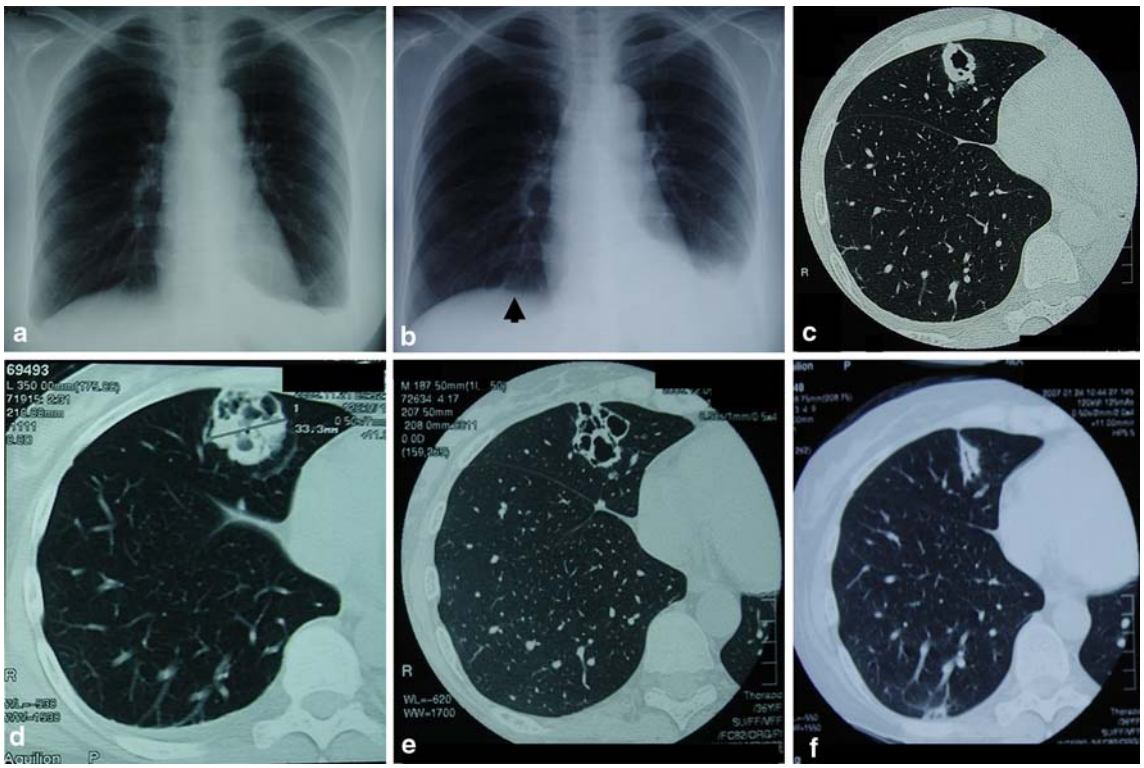


Fig. 2 Plain chest X-ray film obtained on admission (**a**). No abnormal shadows are present in the lung fields, excluding bilateral pooling of pleural effusion. Plain X-ray film obtained on day 20 after admission (**b**). A small mass lesion is evident in the right lower lung field. Chest CT films obtained on days 34 (**c**) and 62 (**d**) after admission. The cavitary lung lesion is evident in the right middle lobe. Chest CT films obtained on days 76 (**e**) and 127 (**f**) after admission. The cavitary lesion resolved without any special treatments

antigenemia was confirmed. After administration of ganciclovir and CMV high-titer γ-globulin agent, the patient's blood parameters gradually improved.

The chest CT on day 34 after admission for evaluation of the pleural effusion revealed a cavitary lesion in the right middle lobe of the lung (Fig. 2c). No consolidations or reticular shadows were found in other parts of the lung field. A small mass lesion was retrospectively confirmed in the right lower lung field on a plain X-ray film that had been taken on day 20 after admission (Fig. 2b). The patient did not have any respiratory or infectious symptoms such as cough, sputum, hemosputum or hemoptysis, dyspnea or fever during the period when the cavitary lesion was evident. There was also no evidence of an inflammatory reaction, including elevation of the plasma C-reactive protein (CRP) level. We initially considered that the most likely cause of the cavitary lesion was lung tuberculosis. However, smears of sputum and gastric juice for *Mycobacterium* were negative as well as polymerase chain reaction (PCR) for *M. tuberculosis*. A fungus infection was considered as another possible cause, but blood tests including β-D-glucan and fungal antigen (*Aspergillus*, *Cryptococcus* and *Candida*) gave negative results. C-ANCA, a marker of Wegener's granulomatosis (WG), was also negative. Bronchoscopy examination was therefore conducted twice (on days 37 and 65 after admission). Since the patient's condition was not good, simple bronchoalveolar lavage (BAL) and brush cytology were performed for only a short time. BAL fluid (BALF) staining and culture for *Mycobacterium*, fungus, and bacteria all gave negative results. BALF PCR for *M. tuberculosis* and atypical mycobacteria, including *M. avium* and *M. intracellulare*, was also negative. BALF and brush cytology showed no malignant cells. Thus, even bronchoscopy failed to reveal the cause of the cavitary lesion. Since we were unable to completely rule out the presence of a fungal infection, an antimycotic drug (voriconazole) was administered to the patient during 2 weeks from days 45 to 58 after admission. However, it was discontinued because of liver function abnormality. As the second bronchoscopy confirmed fever and an inflammatory reaction, an antibiotic (meropenem trihydrate) was administered. No antituberculous agent was administered because the possibility of tuberculosis seemed very low. Thereafter, the cavitary lesion was carefully monitored without any special treatment, and after a while it showed obvious signs of resolution. Chest CT on day 76 after admission (Fig. 2e) showed that the cavity wall had become thin and that the

activity of the lesion had clearly decreased. CT on day 127 after admission (Fig. 2f) showed that the cavity was no longer present and that only a funicular shadow remained.

Discussion

The presence of a cavitary lesion in the lung can be a significant sign in compromised hosts, such as CVD patients who are being treated with steroids or immunosuppressive agents, and therefore differential diagnosis of such lesions is extremely important. Lung carcinoma, tuberculosis, and fungal and bacterial infections are diseases that typically form cavities in the lung. As for CVD, WG is known to form cavitary lesions in the lung. However, in the present case, it was considered unlikely that WG would have been developed under high-dose steroid treatment for SLE. Also the possibility of a cancerous lesion, either primary lung carcinoma or a metastatic lung tumor, seemed low because BALF and brush cytology were negative, and the lesion resolved without any special treatment. In the same way, tuberculosis seemed the least likely cause, because smears, cultures and PCR for tuberculosis were all negative, and the lesion resolved without any anti-tuberculosis therapy. However, bacterial infection could not be ruled out. Although both smears and cultures gave negative results, there was a possibility that the antibiotic used in the second bronchoscopy had a therapeutic effect on the lesion. Realistically, however, the possibility of bacterial infection seemed very low. Similarly, we were unable to rule out a fungal infection because the patient was administered an antimycotic drug. Irrespective of whether the cause was a bacterial or a fungal infection, the lack of any sign of inflammation, such as a rise in the CRP level, was unexplainable. It is conceivable that the high dose of steroid administered to the patient might have masked the symptoms and any inflammatory reaction. However, we believe that the possibility of fungal infection was also very low because there was no exacerbation of the lesion after treatment with the antifungal agent had been discontinued, and treatment for fungal infection generally requires continuous long-term administration of an antimycotic drug.

We propose that CMV pneumonitis was the cause of the cavitary lesion in this case, because the only evidence of a likely causative agent we obtained was that of CMV. CMV antigenemia was positive at almost the same time when the mass shadow appeared on chest X-ray films, and the cavitary lesion began to improve after CMV antigenemia had become negative. Although the improvement began to be evident shortly after the end of treatment for CMV, it is generally not unusual for improvement of imaging findings to occur after disease activity decreases. Najjar et al. [5] reported two patients with SLE who were receiving corticosteroids and immunosuppressive agents and had a cavitary lesion caused by CMV infection. In case 1, neither bronchoscopy nor CT-guided transthoracic lung biopsy revealed the cause of the cavitary lesion. CMV pneumonitis was diagnosed by thoracoscopic and surgical lung biopsy. Similarly, in case 2, the lesion was diagnosed not by bronchoscopy, but by surgical lung biopsy. CMV pneumonitis was reportedly improved by administration of ganciclovir and immunoglobulin in both cases. Ayyappan et al. [6] reported multiple cavitary masses caused by CMV pneumonitis in a patient who was receiving corticosteroids and cyclophosphamide for rheumatoid arthritis-related interstitial lung disease. In this case, CMV pneumonitis was diagnosed by PCR of BALF and transbronchial lung biopsy samples and was ameliorated by ganciclovir. Karakelides et al. [7] reported an immunocompetent host with CMV pneumonitis that formed a cavitary lesion similar to a lung cancer. In this case, the patient was a smoker, but not an immunocompromised host. Although CMV pneumonitis was diagnosed by transbronchial biopsy, wedge excision was performed via a thoracotomy, because it was believed that CMV could not cause any cavitary lung mass in this immunocompetent patient. The lesion reportedly improved, even though no treatment for CMV was given. In both of these reported cases, the CT images of the cavitary masses were not specific and had none of the characteristics that are often found in CMV pneumonitis, and therefore differential diagnosis from bacterial or fungal infection, tuberculosis, and malignancy was necessary. Unfortunately, in our patient, CMV pneumonitis was not considered as a cause of the cavitary lesion because this condition rarely forms a cavity, and therefore PCR for CMV in BALF was not examined, nor was CT-guided or surgical lung biopsy conducted in consideration of the patient's condition. In light of these previous reports and the features of the present case, it is suggested that patients with cavitary lesions of CMV pneumonitis may have a good prognosis if their condition is correctly diagnosed as CMV pnumonitis and treated appropriately. Our experience with the present case suggests that it is unnecessary to continue treatment for CMV until the cavitary lesion disappears if the clinical symptoms are stable, the appearance of the cavitary lesion suggests that it is resolving, and CMV antigenemia is absent.

CMV pneumonitis is a serious complication in immunocompromised patients, such as those who have received bone marrow [8] or solid organ transplants, or patients with AIDS [9, 10]. Also for patients with CVD who are on corticosteroids or immunosuppressive agents, CMV pneumonitis can be a fatal complication. The radiographic appearance of CMV pneumonitis includes interstitial infiltrates, ground glass attenuation, consolidation and

pulmonary nodules [1–4], but reports describing the formation of cavitary lesions have been few. Aviram et al. [11] reported that 3 of 20 AIDS patients with cavitary lung lesions were diagnosed as having CMV pneumonitis: 1 patient had CMV infection only, and the other 2 were complicated by bacterial infection, although the details were not described. The authors considered that the primary causes of the cavitary lesions were single or mixed bacterial infections. McGuinness et al. [12] reported CT findings of CMV pneumonitis in 21 patients with AIDS. In their report, the major CT findings of CMV pneumonitis were described as ground-glass attenuation, dense consolidation, nodules or masses, and mixtures of these patterns. As for masses, 12 patients had either single or multiple nodules, or masses that were between 1 and 3 cm in size, and in 3 of these 12 patients, masses were not associated with air spaces or interstitial infiltrates. Although these patients seemed similar to our patient, only one of them had a cavitary lesion with a thick wall. Franquet et al. [13] reported CT findings in 32 cases, comprising 30 immunocompromised patients with CMV pneumonitis who underwent organ transplantation and 2 patients on long-term corticosteroid therapy, not including patients with AIDS. They reported that CT findings of CMV pneumonitis usually consisted of a mixture of patterns such as ground-glass attenuation, areas of consolidation and small nodules smaller than 10 mm in diameter. Leung et al. [14] reported radiographic findings of pulmonary infections after bone marrow transplantation. The primary causes were reportedly CMV and *Aspergillus* after bone marrow transplantation, and the radiographic findings of CMV pneumonitis consisted of parenchymal opacification and innumerable nodules smaller than 5 mm, most of the masses and nodules being ascribable to aspergillosis. These reports suggest that cavitary and mass lesions in CMV pneumonitis tend to form more frequently in AIDS patients than in transplantation patients. It is necessary to accumulate more of these reports because there have been few published details of radiographic images of CMV pneumonitis in patients with CVD.

We have described a patient with SLE in whom a cavitary lesion formed in the lung and was suspected to be caused by CMV pneumonitis. However, as CMV pneumonitis has not been known to form any cavitary lesion, diagnosis of this lesion was very difficult. It should be recognized that CMV pneumonitis may form cavitary lesions in the lungs of immunocompromised hosts such as CVD patients who are being treated with immunosuppressive agents.

Conflict of interest All of the authors confirm that there is no conflict of interest with regard to this work.

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