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## Sterile empyematous pleural effusion in a patient with systemic lupus erythematosus: a diagnostic challenge

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### Abstract

Herein we present a case of a patient with systemic lupus erythematosus (SLE) and a sterile empyematous pleural effusion, a complication not generally associated with SLE. A discussion of the diagnostic and treatment dilemmas follows the case presentation.

### Keywords

empyema; nephritis; systemic lupus erythematosus

### Case presentation

A 26-year-old woman from Cape Verde presented to the Beth Israel Deaconess Medical Centre with severe shortness of breath and chest pain. Several months prior to her presentation, the patient developed fever, progressive dyspnea on exertion, arthralgias, fatigue, weight loss (6 kg over 7 months) and a periorbital rash. One month prior to her presentation, she was found to have large bilateral pleural effusions and acute renal failure. Laboratory evaluation disclosed that she had positive anti-dsDNA antibodies and low complement levels; she was started on 60 mg oral prednisone daily. One week prior to admission to our hospital, she underwent left-sided thoracentesis in a hospital at Cape Verde. The laboratory tests from the pleural fluid demonstrated a glucose level less than 10 mg/dL, lactate dehydrogenase (LDH) of 2054 IU/L and a pH of 5.0 (Table 1). Bacterial cultures were negative. No antibiotics were administered.

Following this treatment the patient came to the United States for further care. Three days prior to presentation she stopped taking prednisone. Upon presentation to the BIDMC emergency department the patient complained of chest and left flank pain. On physical examination, she was tachycardic, tachypneic and had a temperature of 100.6 °F. She had mild periorbital erythema, dullness to percussion over both lung bases with decreased breath sounds bilaterally and tenderness to palpation over the right flank. She received one tablet of levofloxacin 750 mg for empiric treatment of pneumonia and was admitted to the hospital. Initial laboratory evaluations are shown in Tables 2 and 3. Chest X-ray and computed tomography revealed left greater than right pleural effusions with loculated air (Figure 1).

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On hospital day one, she underwent thoracentesis of her left-sided effusion and chest tube placement. Pleural fluid laboratory tests and cultures are shown in Table 1. The patient was empirically started on a 14-day course of intravenous Vancomycin 1000 mg every 12 h and piperacillin–tazobactam 4.5 g every 8 h after the procedure. She was also started on prednisone 60 mg, hydroxychloroquine 200 mg and lisinopril 5 mg daily. On hospital day two, she underwent thoracentesis of the right pleural effusion, which was consistent with lupus pleuritis (Table 1). On hospital day five, a renal biopsy was performed. Multiple blood cultures remained negative despite continued fevers on broad-spectrum antibiotics. On hospital day six, she underwent a video-assisted thoracoscopy with total pulmonary decortication.

## Differential diagnosis

Pleuritis is the most common manifestation of serositis in patients with systemic lupus erythematosus (SLE).<sup>1,2</sup> Pleural effusions in patients with SLE can also be secondary to renal failure, pulmonary embolism, infection or congestive heart failure. Lupus pleuritis in SLE is thought to result from immune complex deposition, complement activation and direct binding of anti-dsDNA antibodies to mesothelium.<sup>2-4</sup> Pleural effusions tend to develop during flares and are usually characterised by an exudate with either lymphocytic or neutrophilic predominance, and are often bilateral.<sup>1,2</sup> On occasion they can be refractory and difficult to treat.<sup>5</sup> Persistent pleural effusions are at risk for bacterial superinfection potentially leading to the development of empyema. Clinical suspicion of empyema thoracis warrants empiric antimicrobial treatment, especially given that patients with SLE have decreased antimicrobial vigilance and are often treated with immunosuppressive medications. Other causes of empyematous effusions include malignancies, pancreatitis, tuberculosis and rheumatoid arthritis (RA).<sup>4,6,7</sup> To our knowledge, although pleuritis is a common manifestation of SLE, culture-negative empyema has not been described in patients with SLE.

## Infectious workup of pleural effusion

Pleural fluid with empyematous characteristics including undetectable glucose, pH less than 7 and very elevated LDH, is highly suggestive of an infection.<sup>6,7</sup> However, this patient's blood, pleural fluid and tissue cultures were all negative. Broad-spectrum intravenous antibiotics did not abate spiking fevers for several days which would have been expected if the patient had a bacterial infection. It is unlikely that a single dose of levofloxacin 1 day prior to thoracentesis eliminated bacteria from the pleural fluid. It could have possibly influenced mycobacterial growth. Although tuberculosis does not usually present empyematous on pleural fluid sampling, it was certainly considered given the patient's origin and highly elevated adenosine deaminase (ADA) in her pleural fluid. However, mycobacterial PCR from pleural fluid and tissue as well as multiple pleural biopsies were unrevealing. In addition, the patient improved slowly on high dose immunosuppression (see later), which should have exacerbated tuberculosis.

## ADA elevation in pleural fluid

The enzyme ADA is involved in differentiation of lymphoid cells.<sup>8</sup> It is most abundant in lymphocytes, predominantly activated T cells (although the isoenzyme 2 is found mostly in monocytes/macrophages).<sup>8</sup> Total ADA levels greater than 70 IU/L in pleural fluid samples are highly suggestive of tuberculosis but can also be seen in bacterial empyematous effusions.<sup>8</sup> Other aetiologies of high pleural fluid ADA levels include malignancies, various other infections (including fungal) and RA.<sup>8</sup> None of these could be established as a cause in this patient. Importantly, an extensive workup for tuberculosis was negative as mentioned earlier. ADA levels in pleural fluid from patients with SLE have not yet been thoroughly studied. One report demonstrated levels below 50 IU/L in three patients with SLE (mean of 33.3 IU/L).<sup>9</sup> Another study established ADA levels around 15 IU/L in four SLE patients with patients when

examining the value of ADA in the diagnosis of tuberculous pleural effusions in young women in a region with high prevalence of tuberculosis.<sup>10</sup> We did not measure ADA in our patient's exudative (but non-empyematous), right-sided pleural effusion. We speculate that levels would have been considerably lower than in her highly abnormal left-sided effusion with empyematous characteristics and an ADA level above 100 IU/L. Remarkably, the ADA level in her left-sided effusion was only 4.3 IU/L 1 week prior to admission when examined in a hospital at Cape Verde. Little is known about sequential ADA levels over time in pleural fluids from patients with infectious or autoimmune diseases. Ongoing research on ADA and its isoenzymes (ADA-1 and ADA-2) will hopefully further clarify the usefulness of measuring ADA in various infectious and rheumatic diseases.

## Clinical diagnosis

SLE with lupus nephritis and sterile empyematous pleural effusion.

## Pathologic discussion

Histological examination of the pleural tissue revealed extensive granulation tissue with associated haemorrhage and fibrinopurulent exudates (Figure 2). Mixed inflammation comprised predominantly of neutrophils and lymphocytes was present without granulomata. Special stains (including Gomori-methenamine-silver and gram) performed were negative for microorganisms. PCRs for *Mycobacterium tuberculosis* done on pleural tissue were all negative.

The renal biopsy specimen contained 25 glomeruli all showing moderate mesangial proliferation and markedly thickened peripheral capillary loops with global and diffuse spike formation. In addition, 10 glomeruli showed segmental endocapillary proliferation and three had cellular crescents (Figure 2). Rare "hyaline thrombi" were also seen. There was minimal interstitial fibrosis and tubular atrophy. Vascular structures were unremarkable. Immunofluorescence studies demonstrated granular immune complex deposition within all glomeruli involving peripheral capillary walls and the mesangium. Several features of lupus nephritis were seen including presence of all immunoreactants including IgG, IgA, IgM, C3, kappa, lambda and C1q ('full-house' staining) within the glomeruli; immune complex deposition (IgG predominantly) within vessels and tubular basement membranes; and staining of tubular epithelial nuclei with IgG ('tissue ANA'). Ultrastructural examination revealed numerous electron dense deposits without substructure in the subepithelial, subendothelial and mesangial locations. Tubular reticular structures, also typical of lupus nephritis were noted.

## Anatomical diagnosis

1. Lupus nephritis, ISN/RPS Classification: mixed Class III (a) Focal Lupus Nephritis and V Membranous.
2. Fibrino-purulent haemorrhagic pleuritis without granuloma formation.

## Treatment course

Prednisone was continued at 60 mg daily orally. Lisinopril was increased to 10 mg daily but had to be discontinued during a hypotensive episode after her video-assisted thoracoscopy. She required transfer to the intensive care unit and brief administration of intravenous fluids. The patient was started on mycophenolate mofetil (MMF) 500 mg twice daily 2 weeks after admission when renal biopsy results revealed Class III/V lupus nephritis (Figure 2). Over the following week, her symptoms improved significantly. She completed an empiric 14-day course of intravenous vancomycin and piperacillin-tazobactam. Oral prednisone was slowly tapered to 35 mg daily during this hospital stay as MMF was increased to 1500 mg twice daily.

The patient was discharged on prednisone 35 mg daily and MMF 1500 mg twice daily with resolving pleural effusions, haemodynamic stability and resolution of urinary cellular casts but persistent nephritic range proteinuria.

## Discussion of treatment for lupus nephritis

Induction therapy for lupus nephritis with MMF is an attractive alternative to intravenous pulse cyclophosphamide following the NIH regimen, as suggested by recent clinical trials comparing these drugs with concomitant moderate- to high-dose glucocorticoid treatment.<sup>11-14</sup> MMF is associated with less infectious complications than cyclophosphamide.<sup>11-14</sup> MMF improves quality of life as perceived by patients when compared with cyclophosphamide.<sup>11,15</sup> Standard treatment with cyclophosphamide also requires frequent clinic visits for intravenous infusions which is inconvenient. On the basis of its improved safety profile over cyclophosphamide and at least equal efficacy, some investigators even suggest MMF as first-line induction therapy for proliferative lupus nephritis.<sup>11</sup> Our patient was certainly an excellent candidate for MMF given her preserved renal function, non-Caucasian or Asian background and young age with possible future pregnancy wishes.<sup>13</sup> Patients with different patient characteristics and more severely impaired renal function might still have been preferably treated with intravenous cyclophosphamide. Future studies and longer follow-up of this heterogeneous patient population will hopefully confirm the evolving advantages of MMF in the induction phase for lupus nephritis over more traditional, cytotoxic regimens. Our patient remains in remission on 1500 mg of MMF twice daily and currently 12.5 mg of daily oral prednisone (seven months after discharge). Further studies are also needed to address dosing and duration of glucocorticoids which remain an integral part of induction regimens and are a significant contributor to complications and adverse events.

## Final remarks on sterile empyematous pleural effusions

To our knowledge, culture-negative empyematous effusions have not been reported in patients with SLE. However, culture-negative empyema has been described to occur relatively frequently in children and is thought to be due to prior antibiotic exposure in most cases.<sup>16</sup> Highly sensitive *Streptococcus pneumoniae* is likely rapidly eliminated from the pleural fluid by the bacteriocidal action of cell wall inhibitors like penicillins. It is plausible that this can occur after only a brief course of antibiotics prior to fluid sampling. 16S ribosomal DNA PCR has been shown to increase the yield in paediatric culture-negative empyema.<sup>16</sup> Bacterial PCR may have been useful in this case to confirm a suspected infectious process.

On the other hand, sterile empyematous pleural effusions have been reported in RA, pancreatitis and malignancy as mentioned earlier.<sup>4,6,7</sup> Our patient certainly had systemic and local immunological activity consistent with active SLE given her systemic manifestations and very high ANA levels with low complement in both serum and pleural fluid. Measurement of pleural fluid ANA is usually not recommended as it contributes little additional information to serum levels that have been shown to correlate with pleural fluid levels.<sup>17</sup> However, absence of ANAs in the patient's left-sided pleural effusion would have excluded lupus-related pleuritis and supported an infectious process.<sup>17</sup>

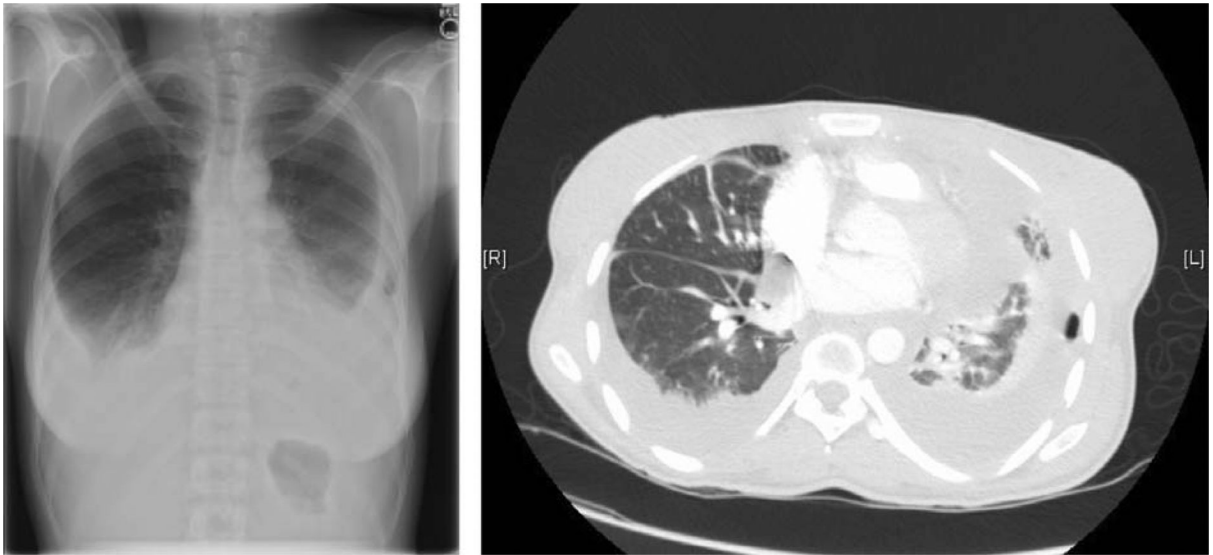
It remains unclear if the left-sided effusion was ever infected. Differentiation between infectious and purely inflammatory processes remains challenging in patients with autoimmune or autoinflammatory diseases, especially as infections can trigger flares in some cases. Improvements in the molecular detection of microbes as well as more specific tests for involvement of the various organs in systemic autoimmunity will be helpful in reducing these uncertainties in the future.

## Acknowledgements

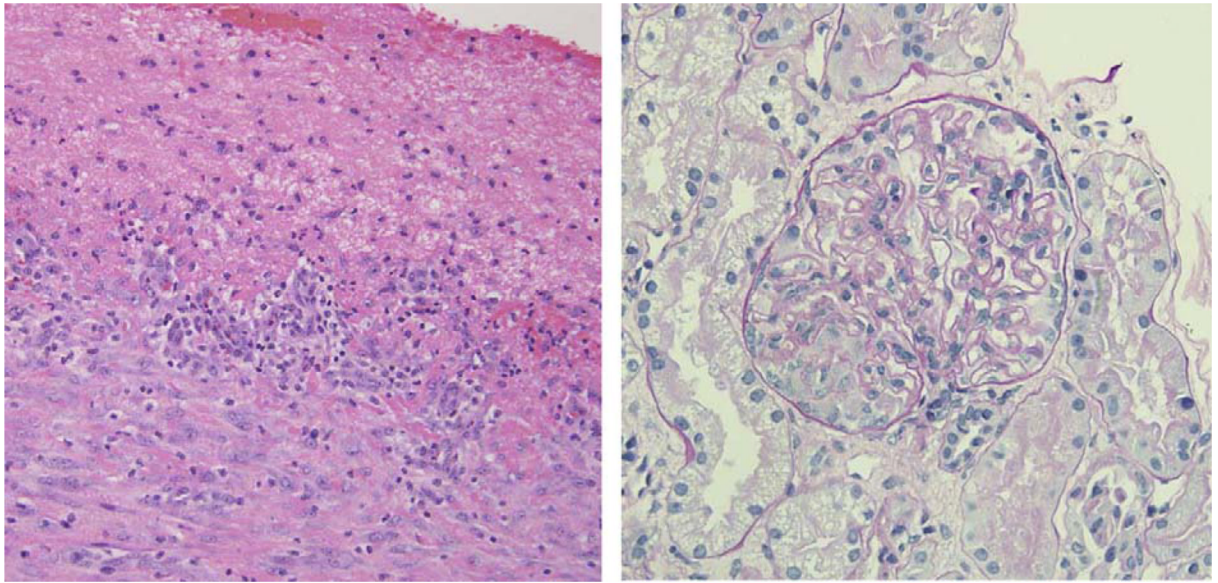
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**Figure 1.** Chest X-ray and contrast-enhanced computed tomography of the chest. Chest X-ray demonstrates moderate-sized bilateral pleural effusions, left greater than right, with associated atelectasis and left-sided loculation. Apical pleural thickening is noted bilaterally. Computed tomography demonstrates large, bilateral pleural effusions and small pericardial effusion. Multiple foci of air within the left-sided pleural effusion are noted. No rim enhancement present.



**Figure 2.** Microscopic images from pleural (left image) and renal (right image) biopsies. Pleural tissue histology reveals extensive granulation tissue with associated haemorrhage and fibrinopurulent exudates. The PAS stain from the renal biopsy shows a glomerulus with a cellular crescent and thickened peripheral capillary walls consistent with Class III/V lupus nephritis.

**Table 1**

## Pleural fluid results

Test (units)	Left-sided effusion <sup>a</sup> (1 week prior to admission)	Left-sided effusion (on admission)	Right-sided effusion (1 day after admission)
Volume (mL)	—	425	620
White blood count (cells/ $\mu$ L)	—	11,250	1400
Red blood cells (cells/ $\mu$ L)	—	2500	7250
Neutrophils (%)	—	91	74
Lymphocytes (%)	—	1	9
Monocytes (%)	—	2	17
Macrophages (%)	—	6	0
pH	5.0	6.83	7.24
Total protein (g/dL) <sup>b</sup>	3.1	4.5	4.1
Glucose (mg/dL)	<10	0	210
LDH (IU/L) <sup>a</sup>	2054	9850	417
Antinuclear antibodies	—	1:1280	1:1280
Total complement (U/mL)	—	<10	Not done
Gram-stain and cultures	Negative	Negative	Negative
Malignant cells	—	Negative	Negative
Adenosine deaminase (U/L)	4.3	105.0	Not done
Mycobacterial PCR	—	Negative	Negative

<sup>a</sup>Pleural fluid laboratory values from outside hospital at Cape Verde. — denotes that data not available.

<sup>b</sup>Serum protein level was 6.9 g/dL and serum LDH level was 198 IU/L.

**Table 2**

Results of blood and urine tests on admission

Test (units)	Value	Normal range
Hematocrit (%)	30.1	36–48
Haemoglobin (g/dL)	9.8	12.0–16.0
White blood cells (cells/ $\mu$ L)	8000	4000–11,000
Differential count (%)		
Neutrophils	71.7	50–70
Lymphocytes	23.2	18–42
Monocytes	4.1	2–11
Eosinophils	0.3	0–4
Basophils	0.6	0–2
Platelets (cells/ $\mu$ L)	294,000	150,000–440,000
Erythrocyte sedimentation rate (mm/h)	105	0–20
C-reactive protein (mg/L)	122	0–5
Urea nitrogen (mg/dL)	40	6–20
Creatinine (mg/dL)	0.9	0.4–1.1
Urinalysis		
Red blood cells (cells/hpf) <sup>a</sup>	3–5	0–2
White blood cells (cells/hpf)	11–20	0–6
pH	5.0	5–8
Protein (mg/dL)	>500	Negative
Glucose (mg/dL)	Negative	Negative

<sup>a</sup>hpf, high power field.

**Table 3**

## Serologic test results

Test (units)	Value	Normal range
Antinuclear antibodies (titre)	1:1280 (speckled pattern)	<1:80
Anti-dsDNA antibodies (U/mL)	1:80	Negative
Rheumatoid factor (IU/mL)	15	0–14
C1q (mg/dL)	<3.6	5.0–8.6
C3 (mg/dL)	31	90–180
C4 (mg/dL)	5	10–40
Smith antibody (units)	>8	<1
RNP antibody (units)	>8	<1
SS-A and SS-B antibodies (units)	>8	<1