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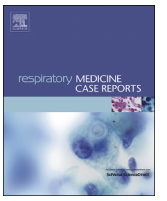

Case Report

# Eosinophilic pleural effusion due to *Staphylococcus epidermidis* infection: A case report

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ABSTRACT

Eosinophilic pleural effusion is rare, and the cause is often obscure. A 73-year-old man with no relevant medical history presented with exertional dyspnea. Chest imaging revealed left-sided pleural effusion, and pleural fluid examination revealed eosinophilic pleural effusion. Blood tests revealed an increased peripheral blood eosinophil count and elevated Immunoglobulin E levels. *Staphylococcus epidermidis* was detected in pleural specimens collected via thoracoscopy. Antimicrobial therapy targeting *Staphylococcus epidermidis* resolved the eosinophilic pleural effusion and elevated peripheral blood eosinophil count. *Staphylococcus epidermidis* infection may be considered as a cause of eosinophilic pleural effusion when the diagnosis is difficult.

## 1. Introduction

Eosinophilic pleural effusion (EPE) is defined as pleural effusion with >10 % eosinophils [1]. EPE is rare, and the cause is often obscure. EPE may be idiopathic, drug-induced, or caused by diverse conditions including malignancy, infection, autoimmune disease, and chest trauma, with infection being the trigger in 10–20 % of cases [1,2]. EPE may be caused by infection with mycobacteria, parasites, fungi, viruses, and rarely bacteria [1,3]. Here, we report the first case of EPE caused by *Staphylococcus epidermidis* infection.

## 2. Case presentation

A 73-year-old afebrile man first presented to our hospital with exertional dyspnea for the past 3 months. He had no relevant medical history, including respiratory, allergic, or skin diseases. On examination, his vital signs and physical findings were unremarkable. Chest radiography and computed tomography revealed left-sided pleural effusion (Fig. 1). Table 1 shows the findings of blood tests and pleural-effusion characteristics at the time of the initial examination. The peripheral blood eosinophil count was increased, and nonspecific immunoglobulin E (IgE) levels were elevated; however, the C-reactive protein level was not elevated. The pleural effusion was exudative with a predominance of eosinophils and lymphocytes. No pathogens or malignant cells were detected in the pleural fluid. For the next 4 months, the pleural effusion continued to increase, requiring drainage of approximately 1 L of fluid every 2 weeks. Multiple pleural-fluid tests were performed during the course of the disease; however, no findings other than exudative EPE were observed. Since the cause of the EPE was unknown, no systemic treatment including steroids, antimicrobials, or antiparasitic drugs was administered.

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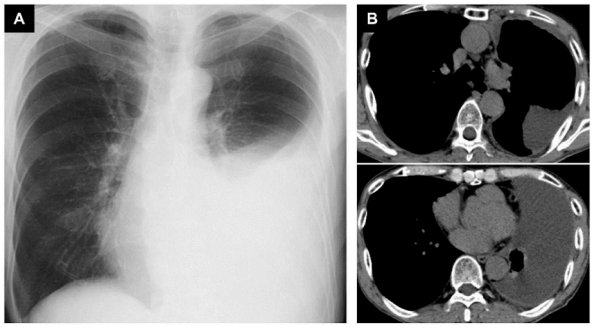


**Fig. 1.** Imaging at the initial examination
Chest radiograph (A) and computed tomography images (B) showing left pleural effusion.

**Table 1**
Laboratory tests on initial examination.

| | | | | | |
|---|---|---|---|---|---|
| **Complete blood cells** | | | Anti-nuclear antibody | negative | |
| White blood cells | 6300 | /μL | Anti-cyclic citrullinated peptide | negative | |
| Neutrophils | 70.2 | % | PR3-ANCA | negative | |
| Lymphocytes | 13.8 | % | MPO-ANCA | negative | |
| Eosinophils | 9.4 | % | Anti-parasitic antibodies | negative | |
| Red blood cells | $4.87 \times 10^6$ | /μL | T-SPOT | negative | |
| Hemoglobin | 15.2 | g/dL | β-D-Glucan | <6.0 | pg/mL |
| Hematocrit | 45.2 | % | IgE RIST | 3400 | IU/mL |
| Platelets | $20.4 \times 10^4$ | /μL | **Pleural fluid findings** | | |
| **Blood biochemistry** | | | Lactate dehydrogenase | 113 | IU/L |
| C-reactive protein | 0.3 | mg/dL | Total protein | 4.9 | g/dL |
| Blood urea nitrogen | 14 | mg/dL | Albumin | 2.2 | g/dL |
| Creatine | 0.69 | mg/dL | Glucose | 104 | mg/dL |
| Total protein | 7 | g/dL | Adenosine deaminase | 32.8 | IU/L |
| Albumin | 3.6 | g/dL | Triglyceride | 13 | mg/dL |
| Total bilirubin | 1 | mg/dL | Hyaluronic acid | 5060 | ng/mL |
| Aspartate transaminase | 24 | IU/L | Total cell count | 1952 | /μL |
| Alanine aminotransferase | 16 | IU/L | Neutrophils | 0 | % |
| Lactate dehydrogenase | 177 | IU/L | Lymphocytes | 72.0 | % |
| **Serum immunology** | | | Eosinophils | 16.5 | % |
| Rheumatoid factor | negative | | Monocytes | 1.5 | % |

PR3-ANCA: proteinase 3-*anti*-neutrophil cytoplasmic antibodies, MPO-ANCA: myeloperoxidase-*anti*-neutrophil cytoplasmic antibodies, IgE: immunoglobulin E.

Thoracoscopy performed to determine the cause of effusion revealed a multifocal pleural effusion consisting of septa and thickened mural pleura in the left thoracic cavity (Fig. 2). Therefore, intrapleural lavage and curettage were performed, with no complications or worsening of the patient's condition. Gram staining of pleural specimens and pleural fluid revealed gram-positive cocci; therefore, the patient was treated with vancomycin (750 mg every 12 h) intravenously from postoperative day 1, which was 4 months after the initial visit. After initiating the antimicrobial therapy, the peripheral blood eosinophil count reduced to the normal range (Fig. 3). The collected pleural specimen and effusion were cultured on sheep blood agar [Try/Soy Blood Agar (Sheep) No.2, Kyokuto Pharmaceutical Industrial, Tokyo, Japan]. The cultured colonies were identified as *Staphylococcus epidermidis* using the automated identification ID/AST MicroScan WalkAway Microbiology System (DxM 1096; Beckman Coulter, Sacramento, CA, USA) with gram-positive panel (Pos Combo 16; Beckman Coulter). Based on the drug sensitivity for the detected *Staphylococcus epidermidis*, after 1 week of vancomycin treatment, the antimicrobial agents were switched to oral minocycline (100 mg every 12 h). After completion of the antimicrobial therapy for a total of 2 months, no increase in the peripheral blood eosinophil count or recurrence of pleural effusion was observed (Fig. 4). No systemic treatment other than antimicrobials was administered after the patient's initial visit.

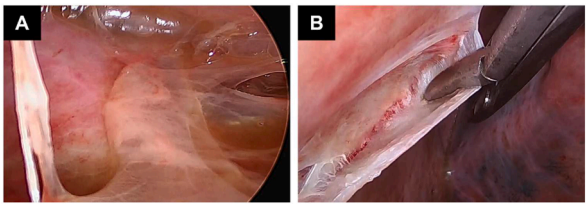


**Fig. 2.** Intrathoracic findings on thoracoscopy
Thoracoscopy shows a multifocal pleural effusion consisting of septa (A) and a thickened mural pleura (B).

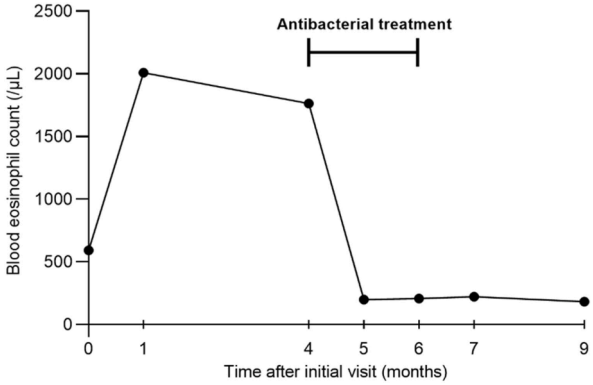


**Fig. 3.** Dynamic monitoring of blood eosinophil count and its timeline
Decreased blood eosinophil count indicates the clinical response to antibacterial treatment.

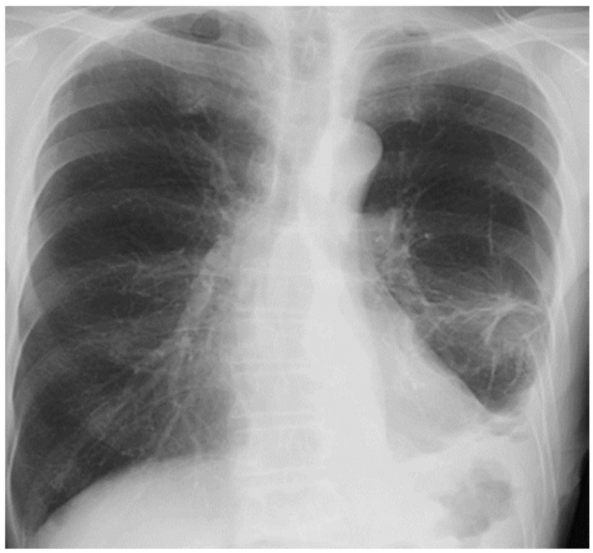

**Fig. 4.** Imaging after treatment.
Chest radiograph showing reduction in the left-sided pleural effusion after treatment.

## 3. Discussion

Our study presents a case of eosinophilic pleural effusion due to *Staphylococcus epidermidis* infection. The causes of eosinophilic pleural effusion are diverse, including infection (bacterial, fungal, parasitic, and tuberculous), malignancy, autoimmune disease, drug-induced, chest trauma, and idiopathic, with malignancy, idiopathic, and infection accounting for more than half of all the causes [2,3]. There is no established diagnostic procedure for EPE, but various tests including pleural fluid test are performed in expectation of these causative diseases [4]. In our case, multiple pleural fluid tests performed prior to thoracoscopy failed to detect the bacteria. One possible reason for the failure of detection could be attributed to the generally low detection rate of bacteria in pleural fluid samples during pleural fluid infections [5–7]. Pleural biopsy has a higher rate of bacterial detection than pleural fluid or blood culture [8]. In addition, the pleural effusion in this case was multifocal, which may have prevented the collection of a valid pleural fluid specimen for bacterial detection.

*Staphylococcus epidermidis* is a coagulase-negative bacterium [9] that is less pathogenic than *Staphylococcus aureus* but occasionally causes infections such as catheter infections and endocarditis [10]. In a previous study, *Staphylococcus epidermidis* caused pyothorax [11]. In the present case, *Staphylococcus epidermidis* caused pleural infection with no evidence of pyothorax, such as neutrophil infiltration and decreased glucose level in the pleural fluid. Furthermore, no fever or elevated C-reactive protein levels were observed. These findings could be attributed to the low virulence of *Staphylococcus epidermidis*. Moreover, the encapsulated pleural effusion infected with *Staphylococcus epidermidis* may have contributed to the lack of systemic inflammation.

*Staphylococcus epidermidis* is a common bacterial colonizer of the skin [12]. In this case, no trauma or skin disease was reported, and no intravascular device was inserted; therefore, the route of entry into the body was unclear. As pneumonia did not occur during the course of the disease, invasion of the thoracic cavity by the lung infection was unlikely. The possibility of contamination of the pleural fluid with *Staphylococcus epidermidis* due to multiple thoracenteses for pleural fluid examinations was also considered.

However, because the pleural fluid remained eosinophilic with no increase in the neutrophil count or decrease in the glucose level from the initial examination, the possibility of *Staphylococcus epidermidis* contamination caused by thoracentesis was considered low. Moreover, the improvement in the blood eosinophil count after antimicrobial therapy suggested that *Staphylococcus epidermidis* was the cause of EPE rather than contamination.

In a previous study, *Staphylococcus aureus* directly activated eosinophils, whereas *Staphylococcus epidermidis* did not [13]. Therefore, we speculate that the EPE in this case was due to cytokine-mediated activation of eosinophils. It has been reported that *Staphylococcus epidermidis* infection release several cytokines such as tumor necrosis factor-α (TNF-α) and C-X-C motif chemokine ligand 8 [14], which cause eosinophil activation and migration. In addition, pleural mesothelial cells stimulated by TNF-α secrete eotaxin, a potent chemotactic factor for eosinophils [15]. Mesothelial cell-derived eotaxin is speculated to be one of the causes of EPE [16] and may have contributed to its development in this case. Mice infected with *Staphylococcus epidermidis* have been reported to have increased serum interleukin-33 levels [17], which causes type 2 (eosinophilic) inflammation [18]. In the present case, *Staphylococcus epidermidis* infection may have caused eosinophil activation and migration through cytokine release, leading to EPE. The fact that antimicrobial therapy targeting *Staphylococcus epidermidis* resulted in a decrease in blood eosinophil count also supports this hypothesis. However, this hypothesis was not proven because cytokine levels in the pleural fluid were not measured in this case.

The patient had no allergic diseases, such as asthma or atopic dermatitis. In addition, the eosinophil count did not increase after completion of antimicrobial therapy, suggesting that *Staphylococcus epidermidis* itself caused type 2 inflammation and that *Staphylococcus epidermidis* infection did not enhance pre-existing type 2 inflammation.

The pathogenesis of EPE caused by bacterial infection remains poorly understood. Further studies are required to determine the effects of *Staphylococcus epidermidis* infection on type 2 inflammation during EPE.

## 4. Conclusions

To the best of our knowledge, this is the first report of EPE caused by *Staphylococcus epidermidis*. *Staphylococcus epidermidis* infection can be considered a differential diagnosis in patients with EPE, and pleural effusion caused by *Staphylococcus epidermidis* infection improves with appropriate antimicrobial therapy.

## Data availability

Data are available in the article or upon a reasonable request to the corresponding author.

## Ethical approval and consent for publication

This study was approved by the Ethics Committee of the National Defense Medical College (approval numbers: 5017). Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

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## CRediT authorship contribution statement

**Koki Ito:** Data curation, Formal analysis, Investigation, Visualization, Writing – original draft. **Takunori Ogawa:** Conceptualization, Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. **Tomomi Tanigaki:** Investigation, Supervision, Writing – review & editing. **Koji Kameda:** Supervision, Writing – review & editing. **Hiroshi Hashimoto:** Supervision, Writing – review & editing. **Akihiko Kawana:** Project administration, Writing – review & editing. **Yoshifumi Kimizuka:** Project administration, Supervision, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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