Granulomatosis with polyangiitis (Wegener’s) rapidly developing multiple cavities in the lungs. Association with staphylococcal infection: a case report

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Abstract

- **Introduction** Granulomatosis with polyangiitis (Wegener’s) (GPA) is an inflammatory disease that frequently involves the lungs. Rapid deterioration of pulmonary GPA is often difficult to distinguish from intercurrent microbial infection. Pulmonary GPA may recur when infected by bacteria; however, *Staphylococcus aureus* is rarely isolated from the relapsed sites.

- **Case Presentation** A 54-year-old Japanese woman with nasal GPA was hospitalized because of a severe cough and fever. Four months before, three mass-like shadows emerged on a chest radiogram. Ten days earlier, airspace newly developed within each pulmonary lesion. The serum level of antiproteinases-3 antineutrophilic cytoplasmic antibody was also raised. The airspace had rapidly become large cavities with an air-fluid level by the time of admission. A biopsy specimen of the cavity wall revealed necrotic lung tissue, neutrophil infiltration, and colonies of gram-positive cocci. *S. aureus* was detected in a culture of bronchoalveolar lavage fluid. These findings led to a diagnosis as an acute relapse of pulmonary GPA with staphylococcal infection. Intensive immunosuppressive treatments in addition to antibiotics were required to achieve a remission of cavitary nodules. One year later, her illness recurred after withdrawal of cyclophosphamide. The pulmonary lesion consisted of histologically proven vasculitis and granulomas. *S. aureus* was again isolated from the bronchoalveolar lavage fluid.

- **Conclusion** The rapid progression of cavitary nodules can occur in patients with stable GPA. Prompt bronchoscopic examination should be needed to make a rapid diagnosis and therapeutic strategy. Staphylococcal superinfection may modulate the local immune responses in the pre-existing pulmonary involvements. The combination use of immunosuppressant agents and antibiotics is an appropriate approach in such a complicated case.

Key words; Granulomatosis with polyangiitis (Wegener’s), *Staphylococcus aureus*
Introduction
Granulomatosis with polyangiitis (Wegener’s) (GPA) is a systemic inflammatory disease that frequently involves the upper and lower respiratory tracts [1]. Major pathological findings in the lung biopsy specimen include parenchymal necrosis, vasculitis, and granulomatous inflammation [2]. More than 90% of patients with active GPA have various abnormalities on the chest radiogram [1, 3]. The most typical findings are bilateral multiple opacities, some of which accompany cavities [1, 3].

Rapid deterioration of pulmonary GPA is often difficult to distinguish from microbial infection [1-4]. In turn, bacterial superinfection may complicate the course of GPA [4, 5]. Chronic nasal carriage of Staphylococcus aureus constitutes a risk factor for the exacerbation of GPA [5, 6]. However, S. aureus has rarely been isolated from the relapsed lesions in the lungs [7]. We report an uncommon case of pulmonary GPA with staphylococcal infection, and discuss the pathologic relevance.

Case Presentation
A 54-year-old Japanese woman, who had GPA in the nasal sinus, presented with a severe cough and fever lasting 10 days. Her condition had been stable under treatment with low-dose corticosteroids. She was hospitalized for further evaluation. Physical examination revealed bilateral opthalmomcele and a saddle nose. Chest auscultation revealed wheezing and slight fine crackles. The white blood cell count was 18,430/μL. Serum C-reactive protein level rose to 18.6 mg/dL (normal; less than 0.3 mg/dL). No abnormalities were found in urinalyses and serum creatinine levels.

Four months before, a chest radiogram for the first time showed three mass-like shadows in the bilateral lung fields (Figure 1, left). Histological examination in those lesions revealed neutrophilic inflammation. The serum level of antiproteinases-3 antineutrophilic
cytoplasmic antibody (PR3-ANCA) was normal (less than 10 EU). She was asymptomatic, and yet the shadows remained unchanged on check-up radiograms.

Ten days earlier than the admission, just as she began to complain of respiratory symptoms, airspace newly developed within each nodule. Peripheral irregular infiltrates also emerged around the nodules (Figure 1, middle). The level of PR3-ANCA rose to 68 EU. By the time of admission, the airspace had rapidly become large cavities with an air-fluid level (Figure 1, right).

Chest computed tomography scans on admission revealed cavitary nodules in the bilateral upper lobes (Figure 2). They comprised thick-walls with irregular inner margins. The diameter of the largest cavity reached up to 8cm. Bronchoscopic examination revealed no stenosis or ulceration in the bronchus. Transbronchial biopsy specimen was taken from a proximal wall of the right cavity, showing parenchymal necrosis, neutrophil infiltration, and colonies of gram-positive cocci (Figure 3). Neither vasculitis nor granuloma was detected. A culture of bronchoalveolar lavage fluid revealed the growth of \textit{S. aureus}. Any fungi or mycobacterium was not isolated.

An acute relapse of GPA with staphylococcal infection was definitively diagnosed. Methylpredonisolone pulse (1000 mg daily) was initiated, followed by the combination of cyclophosphamide (50 mg daily) and predonisolone (50 mg daily). Cefepime dihydrochloride was concurrently administered. One week later, the dose of cyclophosphamide was doubled. The doses of predonisolone were then gradually tapered. Trimethoprim-sulfamethoxazole was intolerable because of hepatotoxic effects. These treatments led to rapid improvements of symptoms, chest X-ray findings and PR3-ANCA levels.

One year later, her illness recurred after withdrawal of cyclophosphamide. The pulmonary lesion consisted of histologically proven vasculitis and granulomas, even though confined to the left lower lobe. \textit{S. aureus} were again isolated from bronchoalveolar lavage fluid.
Discussion

Earlier recognition of relapse is vital for the management of GPA [1]. We experienced an uncommon case presenting with rapid progression of lung cavities. Prompt bronchoscopic examination revealed necrotizing inflammation with active infection by *S. aureus*. Intensive immunosuppressive treatments in addition to antibiotics were required to achieve the remission. Because the level of PR3-ANCA had already risen at the onset, the rapid cavity formation was mainly due to GPA. Staphylococcal superinfection could modulate the local immune responses in the pre-existing sites.

Cavity formation seen in GPA nodules may result from parenchymal necrosis or secondary infection [3]. We consider necrotizing processes to be predominant, because the rise in PR3-ANCA preceded the progression of cavitations. Most patients with active GPA have high levels of PR3-ANCA, which can predict future relapses [1, 5, 8]. The disease activity in the present case, therefore, might have increased in a greater extent than before. Pulmonary superinfection is prone to form necrotizing granulomas in the lungs rather than systemic vasculitis [4]. It is therefore not surprising that these processes readily appeared as rapid changes on the chest imaging. Likely mechanisms include acute tissue damage and air trapping with a check-valve mechanism. Of note, the cavitary nodules grew larger in combination with peripheral irregular infiltrates. Pulmonary hemorrhage due to alveolar capillaritis might correspond to these infiltrates [1-3].

Chest computed tomography scans in our case showed thick-walled cavities with irregular inner margins. As mentioned previously, this finding was unlikely to represent lung abscesses due to *S. aureus*. Staphylococcal abscesses are relatively small, commonly seen in the lower lobes with pleural involvements [9]. The most different point is the time to progression. Staphylococcal abscesses secondary to systemic disorders usually develop over 48 to 72 hours [10]. In our case, it took about 10 days for the cavities to progress.
Pulmonary GPA may deteriorate when infected by bacteria such as *Pseudomonas aeruginosa* and *Haemophilus influenzae* [3, 4]. *S. aureus* has rarely been isolated from the relapsed sites [3, 4, 7], even though associated with the pathogenesis of GPA [5, 6]. Chronic nasal carriers of *S. aureus* have higher levels of PR3-ANCA, more prone to relapse [5]. Little is known about the mechanisms by which *S. aureus* modulates ANCA-associated autoimmune phenomena. Staphylococcal superantigens may act as inducers for exacerbation [6].

**Conclusion**

The rapid progression of cavitary nodules can occur in patients with stable GPA. Prompt bronchoscopic examination is needed to make a rapid diagnosis and therapeutic strategy. Staphylococcal superinfection could modulate the local immune responses in the pre-existing pulmonary involvements. The combination use of immunosuppressive agents and antibiotics is an appropriate approach in such a complicated case.

**Abbreviations**

GPA: granulomatosis with polyangiitis (Wegener’s); PR3-ANCA: antiproteinases-3 antineutrophilic cytoplasmic antibody; *S. aureus*: *Staphylococcus aureus*

**Consent**

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.
Competing interests
The authors declare that they have no competing interests.

Authors' contributions
TS was a major contributor in writing the manuscript. YY revised the draft for intellectual content. NH, YK, SE, YM, SO, KS, and TO interpreted the data and images. YO supervised the manuscript preparation and gave final approval of the version to be submitted. All authors read and approved the final manuscript.

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References


**Figure legends**

**Figure 1.** Chest radiograms. Left panel; Four months before the admission. Middle panel; Ten days before the admission. Right panel; On admission.

**Figure 2.** Chest computed tomography scan at the level of the upper lobes.

**Figure 3.** Transbronchial biopsy specimen (Hematoxylin-eosin stain, × 40).