Lung-Limited Seronegative Granulomatosis With Polyangiitis Successfully Diagnosed via a Multi-Disciplinary Diagnosis: A Case Report

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A 74-year-old man presented with a persistent cough, peripheral blood leukocytosis, and lung opacities. No lesions were identified in the upper airways or kidneys, and the anti-neutrophil cytoplasmic antibodies (ANCA) were negative. The initial clinical presentation was relatively mild and compatible with post-infectious organizing pneumonia; however, the presence of multinucleated giant cells, microabscesses, small granuloma-like lesions, and focal fragmentation/disruption of the vascular elastic laminae, in conjunction with organizing pneumonia in the lung parenchyma, were suggestive of granulomatosis with polyangiitis (GPA). A multi-disciplinary diagnosis, integrating clinical, radiological, and pathological findings, is useful for the early diagnosis of ANCA-negative, lung-limited GPA, which may later recur and require intensive immunosuppressive therapy.

Key words: Anti-neutrophil cytoplasmic antibody, Diagnosis, Granulomatosis with polyangiitis, Lung

INTRODUCTION

Granulomatosis with polyangiitis (GPA) is a disease that systemically involves small- and medium-sized blood vessels [1]. The disease is clinically characterized by lesions in the upper and lower respiratory tracts and kidneys. Pathologically, necrotizing granulomatous inflammation is often observed within these organs and vessels [1]. The American College of Rheumatology has established diagnostic criteria for GPA, which include the presence of red blood cell casts or five or more red blood cells per high-power field in urine sediment, abnormal findings on chest radiographs, oral ulcers or rhinorrhea, and granulomatous inflammation on biopsy [2]. When two or more of these four criteria are met, the sensitivity and specificity are 88% and 92%, respectively. The treatment of GPA involves the systemic administration of corticosteroids in conjunction with immunosuppressants, such as cyclophosphamide or rituximab [3].

GPA develops in association with anti-neutrophil cytoplasmic antibodies (ANCA), especially proteinase 3 (PR3)-ANCA, in Western countries, whereas myeloperoxidase (MPO)-ANCA is positive in about half of the patients with GPA in Japan [4, 5]. However, 10–20% of patients with GPA are ANCA-negative, with disease predominantly localized to one or two organs [6]. Regarding pulmonary lesions, alveolar hemorrhage with or without acute respiratory failure is observed mostly in patients with ANCA-positive GPA, whereas multiple or solitary nodular or mass lesions with cavities are observed in both patients with ANCA-positive and -negative GPA [7, 8].

Here, we report a case of ANCA-negative, lung-limited GPA that initially exhibited mild clinical presentation. The patient was successfully diagnosed via multi-disciplinary diagnosis (MDD) among clinicians, radiologists, and pathologists.

CASE PRESENTATION

A 74-year-old man with a smoking history of 37 pack-years and a 40-year history of asthma presented with dry cough for two weeks. The patient had no fever, rash, arthralgia, or neurological symptoms. Physical examination revealed fine crackles audible upon auscultation of both lower lung fields. Although no signs of active synovitis were observed, the proximal and distal interphalangeal joints were deformed. Laryngoscopy revealed no upper airway abnormalities. Peripheral blood tests showed leukocytosis (12,100/μL) with neutrophilia (9,632/μL) and modest eosinophilia (399/μL), but neither anemia nor thrombocytosis was present. Serum concentrations of C-reactive protein (CRP) IgG4, and soluble interleukin-2 receptor were increased to 4.2 mg/dL, 119 mg/dL, and 1196 U/mL, respectively. Renal function and urine findings were normal. Tests for PR3-ANCA, MPO-ANCA, and other autoantibodies associated with collagen vascular

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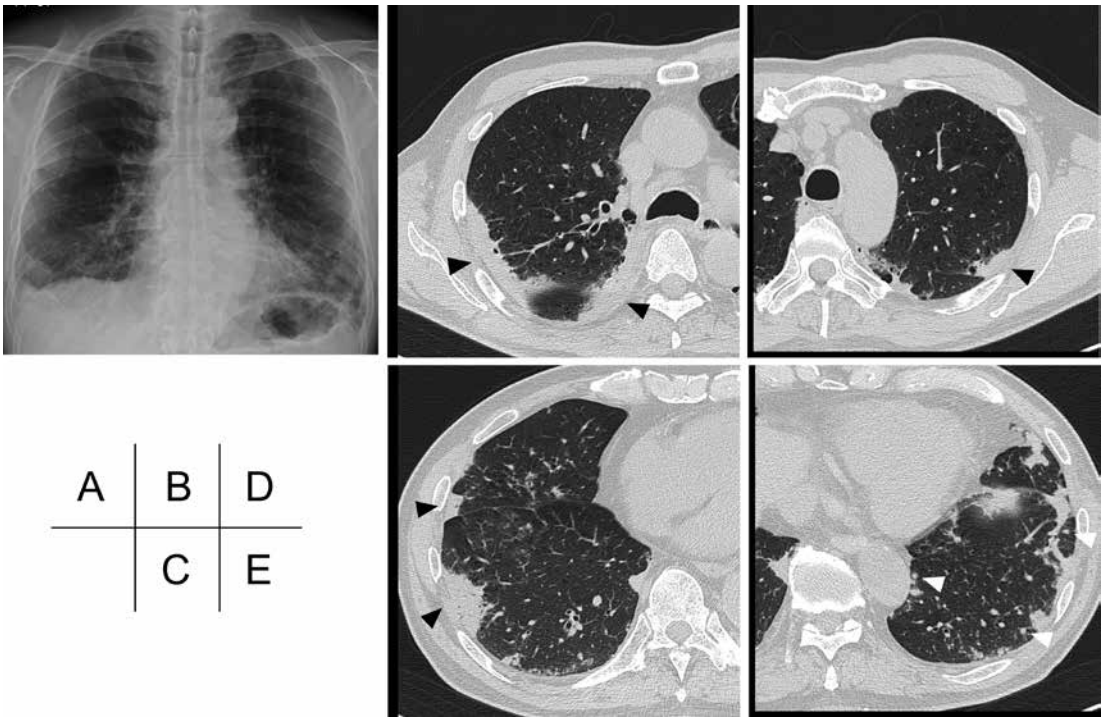

Fig. 1 Chest radiography and computed tomography findings at the first visit
Chest radiograph (A) showed opacities in the right upper and bilateral lower lung fields. Thin-section axial CT images with 1 mm slice thickness (B–E) showed multifocal bilateral pulmonary consolidations (arrow heads, B–D) and nodules (arrow heads, E) predominantly in the peripheral regions of the lungs.

disease were negative. Chest radiography revealed opacities in the right upper and bilateral lower lung fields (Fig. 1A). Thoracic computed tomography (CT) revealed multifocal consolidations and nodules, predominantly in the peripheral regions of both lungs (Fig. 1B–E).

Antibiotic therapy did not result in clinical improvement. Analyses of the bronchoalveolar lavage fluids demonstrated differential cell counts of macrophages 88%, lymphocytes 8%, neutrophils 2%, eosinophils 1%, and basophils 1%. Bacterial cultures were negative. Because transbronchial lung biopsy specimens revealed non-specific findings, a video-assisted thoracoscopic lung biopsy of the left upper lobe was performed. Pathological examination of the resected lung tissue revealed inflammatory lesions in the parenchyma with multinucleated giant cells, microabscesses, small granuloma-like lesions, and destruction of the vascular elastic laminae, in conjunction with organizing pneumonia (Fig. 2A–C). Ziehl–Neelsen and Grocott methenamine silver/Periodic acid-Schiff staining were negative. Pleuritis accompanied by pleural thickening and fibrin deposition was also observed.

An MDD involving pulmonologists, rheumatologists, radiologists, and pathologists was performed. Eosinophilic granulomatosis with polyangiitis, infectious granulomatous diseases, or hypersensitivity pneumonitis were excluded based on clinical features, laboratory data, radiologic patterns, and histopathology. The clinical course was compatible with post-infectious organizing pneumonia; however, the multiple nodular lesions in the bilateral lower lobes were atypical for organizing pneumonia. Although vascular damage was observed pathologically, a definite diagnosis of vasculitis could not be established because the vascular lesions were limited to areas with severe parenchymal inflammation. A provisional diagnosis of ANCA-negative GPA limited to the lungs was established.

Although serum CRP levels decreased to 0.62 mg/dL and bilateral lower lung field opacities improved within 3 months without active treatment, the patient's cough evolved from dry to productive, and opacities in the right upper lung field persisted. Oral administration of prednisolone (PSL; 1 mg/kg/day) was initiated. Respiratory symptoms and lung opacities improved promptly after initiating PSL; however, lung opacities and cough recurred when PSL was tapered to 2.5 mg on alternate days. The PSL dose was then increased to 20 mg/day.

Another worsening of cough and lung opacities, accompanied by erythematous plaques on the skin of the back and extremities, appeared 6 months later when PSL was tapered to 5 mg/day. Serum CRP levels were increased to 19.0 mg/dL. A skin biopsy demonstrated leukocytoclastic vasculitis with infiltration and fragmentation of neutrophils, lymphocytes, and plasma cells around the small vessels in the dermis. Corticosteroid pulse therapy with 1 g of methylprednisolone for three days, followed by 60 mg/day of PSL and intravenous cyclophosphamide every two weeks temporarily improved the pulmonary and cutaneous lesions. However, the patient developed high fever and hypotension one month later, accompanied by markedly elevated serum CRP levels (47 mg/dL) and a new opacity in the right upper lung field. Antibiotic therapy partially improved the patient's condition; however, low-grade inflammation and lung opacities in the right upper and bilateral lower lobes remained unresolved.

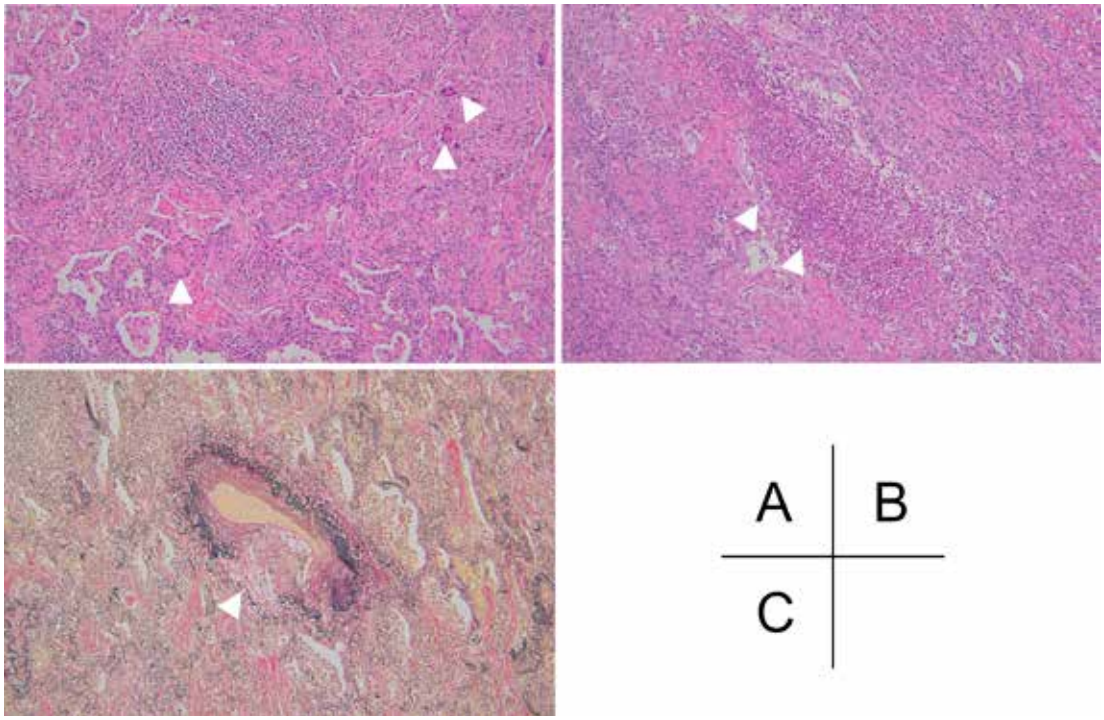

Fig. 2 Pathological findings of the resected lung tissue
(A) Multinucleated giant cells (arrow heads), with focal histiocyte aggregation forming small granuloma-like lesions, suggestive of a granulomatous-type inflammatory reaction but not well-formed granulomas, and (B) microabscesses (arrow heads), inflammatory lesions of the lung parenchyma (Hematoxylin–eosin staining, x100). (C) Focal fragmentation/disruption of vascular elastic laminae (arrow heads) adjacent to organizing pneumonia suggestive of vascular wall injury, although it is not sufficient for definite diagnosis of vasculitis (Elastica van Gieson staining, x100).

Rituximab was administered but was discontinued after two doses due to infection. The patient's condition finally stabilized when methotrexate was added; serum CRP levels normalized to 0.05 mg/dL, and lung opacities improved even when PSL was tapered to 10 mg/day.

DISCUSSION

The diagnosis of GPA is not difficult if combined involvement of the upper and lower airways and renal lesions is present, especially when PR3- or MPO-ANCA are positive [2]. However, the diagnosis in the present case was challenging at the initial presentation because extrapulmonary lesions were absent and the ANCA test was negative. Even the pathological examination of the specimen obtained from surgical lung biopsy lacked a definite diagnosis; therefore, MDD involving pulmonologists, rheumatologists, radiologists, and pathologists was essential for the diagnosis of GPA. Patients with ANCA-negative GPA tend to exhibit milder disease and are less likely to experience recurrence than those with ANCA-positive GPA [5]. Initially, the patient responded relatively well to corticosteroid therapy alone; however, the disease was repeatedly exacerbated and became refractory to treatment.

The diagnosis of GPA limited to the lungs is often difficult, not only because of the lack of symptoms suggestive of systemic vasculitis and specific serological markers, such as PR3- and MPO-ANCA, but also because of the atypical presentation of lung lesions on chest CT. In the present case, chest CT demonstrated multiple opacities without cavitary lesions, which are characteristic of GPA. Furthermore, the initially mild clinical presentation, partial spontaneous resolution of consolidations, and CT pattern suggested post-infectious organizing pneumonia. However, the presence of multiple micronodular shadows in the peripheral lungs, which are non-specific, but less common in organizing pneumonia [9], prompted us to proceed with pathological examination via surgical biopsy, which revealed inflammatory lesions in the lung parenchyma with multinucleated giant cells, microabscesses, small poorly-formed granuloma-like lesions, and destruction of the vascular elastic laminae. However, these findings did not satisfy the pathological criteria for GPA due to lack of necrotizing granuloma and/or destruction of vascular elastic lamina in the non/less-inflamed tissues [10]. Pathological diagnosis has a limitation as it can only examine the biopsied tissue. In the present case, the lung biopsy was performed in the left upper lobe where peripheral consolidation was dominant, whereas peripheral nodules observed on HRCT were mostly present in the lower lobes. Therefore, an MDD using a clinical–radiological–pathological approach was crucial in determining that the coexistence of multiple peripheral micronodules and the atypical histologic features was unlikely to be attributable to organizing pneumonia alone, and instead raised a strong suspicion for ANCA-negative, lung-limited GPA in this case.

The second challenge was to determine the optimal treatment strategy. ANCA-positive GPA exhibits a poor prognosis due to life-threatening complications of systemic vasculitis without intensive immunosuppressive therapy [3]. However, the optimal treatment for

ANCA-negative, localized GPA has not yet been established. American College of Rheumatology/Vasculitis Foundation guideline conditionally recommends methotrexate plus glucocorticoids over glucocorticoid monotherapy for active, non-severe GPA and emphasize the importance of close monitoring if glucocorticoid monotherapy was used [11]. On the other hand, some patients with lung-limited GPA have shown no long-term recurrence after resection of pulmonary lesions without receiving immunosuppressive therapy, thereby avoiding the adverse effects of intensive treatment [4, 12]. In a prospective cohort that employed a step-up immunosuppressive treatment approach for patients with localized GPA based on disease activity and treatment response, relapse and progression to systemic disease occurred in 46% and 10% of the patients, respectively [13]. The presence of necrotizing granulomatous inflammation or vasculitis at diagnosis is a risk factor for seroconversion from ANCA-negative to -positive GPA with higher disease severity and recurrence rates [5]. Because of the absence of these risk factors and the patient's advanced age, we shared decision-making with the patient and chose to avoid intensive immunosuppressive therapy. Although the patient responded well to the initial corticosteroid therapy without severe adverse effects, remission could not be maintained. Therefore, it is important to diagnose patients with GPA in the early stages and provide them with appropriate therapeutic interventions or careful observation.

There is a limitation in ANCA testing of this case: although MPO- and PR3-ANCAs were negative, indirect immunofluorescence-based ANCA testing was not performed, and thus, presence of atypical ANCA positivity cannot be excluded.

In conclusion, this case report demonstrates the importance of MDD in the early diagnosis of ANCA-negative, lung-limited GPA. MDD is not necessarily required for the diagnosis of typical cases of GPA, however, it can be crucial when there are no decisive components for the diagnosis either in clinical features, radiologic patterns, or histopathology. Furthermore, this case illustrates that ANCA-negative, lung-limited GPA may present with an apparently mild, organizing pneumonia–like phenotype without necrotizing granulomatous inflammation or vasculitis at diagnosis, yet still follow a relapsing course that ultimately requires escalation from glucocorticoid monotherapy to combination immunosuppressive therapy, underscoring the importance of early MDD-based diagnosis, vigilant monitoring for recurrence, and flexible adjustment of treatment intensity according to dynamic disease behavior.

REFERENCES

1) Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, *et al*. 2012 revised International Chapel Hill consensus conference nomenclature of vasculitides. Arthritis Rheum 2013; 65: 1–11.
2) Robson JC, Grayson PC, Ponte C, Suppiah R, Craven A, Judge A, *et al*. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. Ann Rheum Dis 2022; 81: 315–20.
3) Hellmich B, Sanchez-Alamo B, Schirmer JH, Berti A, Blockmans D, Cid MC, *et al*. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Ann Rheum Dis 2024; 83: 30–47.
4) Iau Graca Ribeiro LM, Ind PW. Lung-limited granulomatosis with polyangiitis: managed without immunosuppression. QJM 2019; 112: 685–8.
5) Casal Moura M, Falde S, Sethi S, Fervenza FC, Specks U, Baqir M. Granulomatosis with polyangiitis with and without antineutrophil cytoplasmic antibodies: a case-control study. Rheumatology (Oxford) 2024; 63: 3279–88.
6) Falk RJ, Jennette JC. ANCA small-vessel vasculitis. J Am Soc Nephrol 1997; 8: 314–22.
7) Miloslavsky EM, Lu N, Unizony S, Choi HK, Merkel PA, Seo P, *et al*. Myeloperoxidase-antineutrophil cytoplasmic antibody (ANCA)-positive and ANCA-negative patients with granulomatosis with polyangiitis (Wegener's): Distinct patient subsets. Arthritis Rheumatol 2016; 68: 2945–52.
8) Puechal X, Iudici M, Pagnoux C, Cohen P, Hamidou M, Aouba A, *et al*. Comparative study of granulomatosis with polyangiitis subsets according to ANCA status: data from the French Vasculitis Study Group Registry. RMD Open 2022; 8: e002160.
9) Cherian SV, Patel D, Machnicki S, Naidich D, Stover D, Travis WD, *et al*. Algorithmic approach to the diagnosis of organizing pneumonia: a correlation of clinical, radiologic, and pathologic features. Chest 2022; 162: 156–78.
10) Ambrogi E, Cavazza A, Smith ML, Graziano P. Pulmonary pathology in vasculitis. Pathologica 2024; 116: 93–103.
11) Chung SA, Langford CA, Maz M, Abril A, Gorelik M, Guyatt G, *et al*. 2021 American College of Rheumatology/Vasculitis Foundation guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheumatol. 2021; 73: 1366–83.
12) Kanda R, Nakano K, Nawata A, Iwata S, Nakayamada S, Tanaka Y. Remission of granulomatosis with polyangiitis only after resection of a pulmonary nodule. Intern Med 2022; 61: 2803–8.
13) Holle JU, Gross WL, Holl-Ulrich K, Ambrosch P, Noelle B, Both M, *et al*. Prospective long-term follow-up of patients with localised Wegener's granulomatosis: does it occur as persistent disease stage? Ann Rheum Dis 2010; 69: 1934–9.