Respir Case Rep 2025;14(2):38-42 DOI: 10.5505/respircase.2025.74317

Two Cases of Granulomatosis with Polyangiitis: Common Features with Tuberculosis and Differential Diagnosis

Granülomatöz Polianjitis Tanısı Alan İki Olgu: Tüberküloz ile Ortak Özellikler ve Ayırıcı Tanı

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Abstract

Granulomatosis with polyangiitis is a form of vasculitis that affects the kidneys and the lower and upper respiratory tracts, and progresses with pathologically necrotizing granulomatous inflammation. Patients can present with such nonspecific symptoms as malaise, fever, weight loss and hemoptysis. Diagnosis is based on radiological, pathological and laboratory examinations. Lung involvement usually presents in the form of bilateral nodules, and cavitary lesions and pulmonary infiltrates may also be seen. Tuberculosis and granulomatosis with polyangiitis share common clinical symptoms, radiological findings and immunopathological features. In our country, where the incidence of tuberculosis (TB) is high, necrotizing granulomatous inflammation are often evaluated initially as TB. We present here two cases of nodular lung disease to draw attention to the need for careful differential diagnosis between granulomatosis with polyangiitis and tuberculosis.

Keywords: *Granulomatosis with Polyangiitis, necrotizing granulomatous inflammation, tuberculosis, c ANCA.*

Öz

Granülomatöz polianjiitis, böbrekleri, alt ve üst solunum yollarını etkileyen, patolojik olarak nekrotizan granülomatöz inflamasyonla seyreden bir vaskülittir. Hastalar, halsizlik, ateş, kilo kaybı ve hemoptizi gibi nonspesifik semptomlarla başvurur. Tanı kriterleri arasında, radyolojik, patolojik ve laboratuvar incelemeler yer almaktadır. Akciğer tutulumu genellikle bilateral nodüller olarak karşımıza çıkar. Bunun yanında kaviter lezyonlar ve pulmoner infiltrasyonlar da görülebilmektedir. Tüberküloz ve Granülomatöz polianjiitis klinik bulgular, akciğer görüntülemeleri, immünopatolojik olarak ortak özelliklere sahiptir. Tüberküloz insidansının yüksek olduğu ülkemizde nekrotizan granülomatöz inflamasyon ilk olarak tüberküloz lehine değerlendirilmektedir. Granülomatozis polianjiitis ve tüberküloz arasında dikkatli bir ayırıcı tanıya ihtiyaç duyulduğuna dikkat çekmek için burada, nodüler akciğer hastalığı olan iki olgu sunuyoruz.

Anahtar Kelimeler: *Granülomatöz polianjiitis, nekrotizan granülomatöz inflamasyon, tüberküloz, c ANCA.*

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Submitted (Başvuru tarihi): 21.01.2025 ***Accepted (Kabul tarihi):*** 08.05.2025

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Granulomatosis with polyangiitis (GPA), known formerly as Wegener's granulomatosis, is a rare autoimmune systemic disease characterized by small vessel vasculitis and pathologically necrotizing granulomatous inflammation affecting the kidneys and the lower and upper respiratory tracts. Mortality is as high as 90% in untreated cases (1). Patients mostly present to hospital with nonspecific symptoms, including malaise, fever, loss of appetite and weight loss (2,3). Diagnosis is based primarily on the evaluation of radiologic, pathologic, and laboratory findings, as the presence of granulomatous vasculitis in a biopsy alone is not sufficient for diagnosis. The similarity of the clinical, radiologic and even histopathologic features of GPA with those of tuberculosis make differential diagnosis difficult (2,4). We present here the cases of two GPA patients who were initially diagnosed with tuberculosis to highlight the potential difficulties encountered in the differential diagnosis of granulomatous diseases and tuberculosis, and the importance of early treatment.

CASE

Case-1: A 54-year-old woman diagnosed with diabetes mellitus and hypertension presented with complaints of loss of appetite, weight loss, weakness and pain in the knees. Thoracic computed tomography (CT) revealed nodular lesions in both lungs, after which a Tru-Cut biopsy was performed under CT guidance. The pathology result indicated "granulomatous inflammation with caseous necrosis", and recommended evaluation for miliary tuberculosis. The patient was duly diagnosed with smear negative tuberculosis and treatment was started. In the second month of treatment, urea and creatinine were found to be elevated by the health center to which she presented with respiratory distress. A diagnosis of acute kidney injury (AKI) was made, based on which, she was admitted and started on fluid therapy. No hemodialysis was performed as her urine output and urea and creatinine values had returned to normal. At this stage, she was referred to our center for re-evaluation of the tuberculosis diagnosis and for our opinion on the continuation or discontinuation of the anti-tuberculosis treatment.

A review of previous test results and the results of a positron emission tomography (PET CT) revealed bilateral multiple nodules and a lesion with a maximum diameter of 3 cm in the paravertebral area of the lower lobe of the left lung with SUV (Figure 1). The patient was a nonsmoker, and no lung malignancy was considered. The patient was evaluated for granulomatous diseases, especially GPA, and for ear, nose and throat (ENT) and ophthalmologic diseases. Paranasal sinus CT showed atrophy of the nasal turbinates and sinus mucosal thickening, while a nasal biopsy indicated nonspecific ulcerous inflammation. Proteins were detected in a urinalysis. Abdominal ultrasound was normal. The Tru-Cut biopsy samples obtained from the referring center were re-examined in the pathology unit of our hospital. Acid-fast bacillus (AFB) was negative, while findings compatible with GPA were identified, and the diffuse anti-neutrophil cytoplasmic antibody (c-ANCA) obtained from the patient was positive. The patient was referred to the rheumatology department and started on steroid and cyclophosphamide treatment based on the diagnosis of GPA. Upon clinical and radiological improvement, the patient was followed up and treated in the rheumatology outpatient clinic.

Case-2: A 38-year-old woman presented to the outpatient clinic with complaints of cough, chest pain, weakness, nausea, occasional vomiting and generalized arthralgia for 1 month. She had no known disease and did not smoke. The following test results were obtained: urea in blood biochemistry: 53 mg/dl; creatinine: 2.11 mg/dl; and sedimentation: 67 mm/h. A diagnostic CT-guided needle biopsy was performed on the diffuse bilateral nodular lesions identified on thorax CT, the largest of which was 2.1 cm in size (Figure 2). Pathological findings indicated necrotizing granulomatous inflammation. Her young age pointed to tuberculosis, however, her anamnesis suggested no contact with tuberculosis patients, and she reported no sputum production, night sweats or weight loss. A tuberculin skin test (TST) result was 0 mm, and a deep tracheal aspirate (DTA) smear was negative for AFB. The patient was subsequently examined for granulomatous lung diseases, especially GPA. Blood tests were positive for c-ANCA, but negative for myeloperoxidase (MPO) ANCA, antinuclear antibody (ANA) and rheumatoid factor (RF). Urine tests revealed protein 3(+) and erythrocyte 2(+). Her abdominal ultrasound was normal. Paranasal sinus CT revealed hypertrophy of the bilateral inferior nasal turbinates and a mucosal thickening of the walls of the maxillary and ethmoid sinuses. A subsequent examination by the ENT department revealed bilateral hearing loss and sinusitis. The patient was then referred to the rheumatology outpatient clinic where, based on her GPA diagnosis, she was started on steroid and rituximab treatment. Follow-up tuberculosis cultures showed no growth and thorax CT after treatment revealed regression in the lesions (Figure 3). The patient continues to be followed up by the rheumatology outpatient clinic.

DISCUSSION

GPA, known previously as Wegener's disease, was first described by Klinger in 1931 as a variant of polyarteritis nodosa. Godman and Churg determined the clinical and pathologic features of the condition in 1954 and coined the term GPA to indicate the presence of granuloma, necrotizing vasculitis and glomerulonephritis (known also as Wegener's triad) in the upper respiratory tract (3). According to the Chapel Hill Consensus criteria, the

presence of small- and medium-sized vasculitis and granulomatous inflammations involving the respiratory tract confirms a diagnosis of GPA, while ANCA positivity is excluded from the criteria (1). The American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) published the GPA classification criteria in 2020, which have high sensitivity and specificity in support of diagnosis. The criteria comprise a total of 10 items related to clinical, laboratory, histologic and radiologic findings, and a total of at least 5 points is required for a diagnosis of GPA. The ACR/EULAR classification criteria are presented in Table-1 (5).

The incidence rate between sexes is equal, and although it is most common in those aged 40–55 years, any age group can be affected (3,6). The incidence rate is estimated to be 2.1 per million with a reported 5-year survival rate of 74–91% (7,8). The mortality rate associated with untreated GPA is as high as 90% (1).

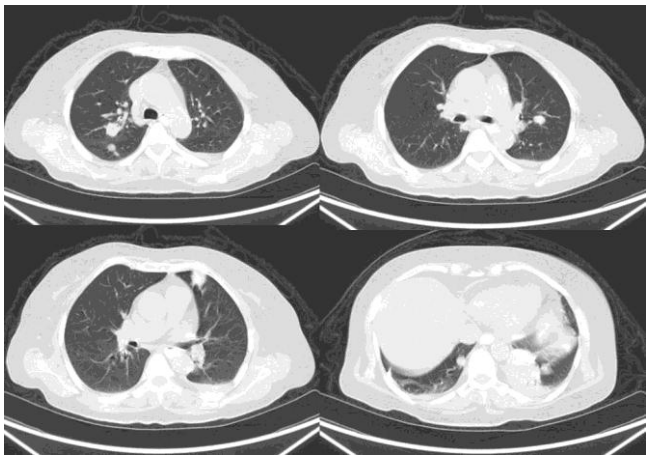

Figure 1: Bilateral multiple pulmonary nodules and a mass in the left lung

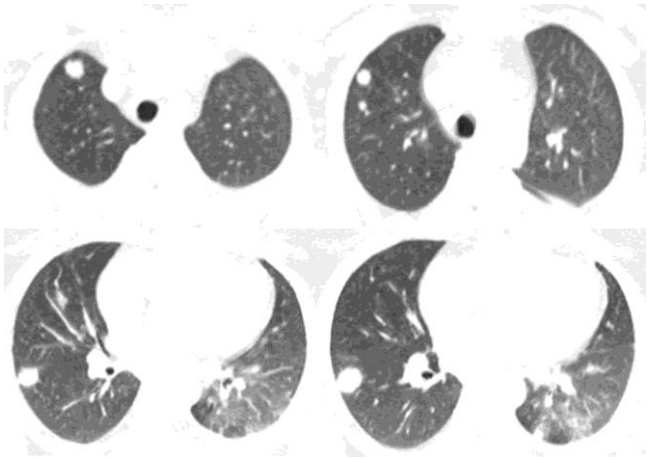

Figure 2: Pre-treatment thorax CT

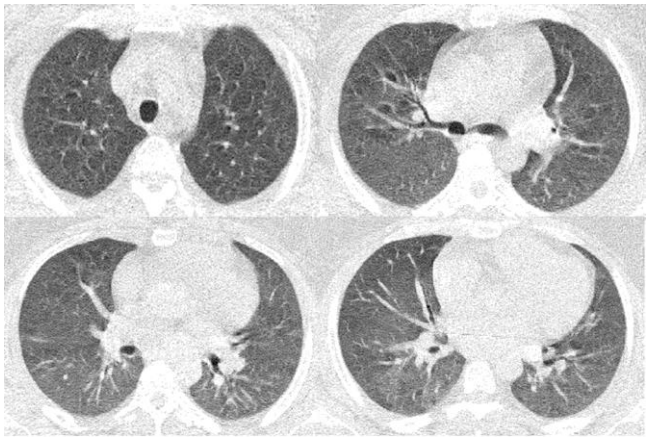

Figure 3: Post-treatment thorax CT

Table 1: 2022 ACR/EULAR Classification Criteria for Granulomatosis with Polyangiitis

Domain	Item	Points
Clinical	Nasal passage involvement (e.g., bloody discharge, ulcers, crusting, congestion, blockage, or septal defect/perforation)	+3
	Cartilaginous involvement (e.g., saddle-nose deformity, subglottic stenosis)	+2
	Conductive or sensorineural hearing loss	+1
Laboratory	PR3-ANCA (or C-ANCA) positivity	+5
	MPO-ANCA (or P-ANCA) positivity	-1
	Serum eosinophil count ≥1000/μL	-4
Histological	Granulomatous inflammation on biopsy	+2
	Pauci-immune glomerulonephritis	+1
Radiological	Nodules, cavities, or fixed infiltrates on chest imaging	+2
	Sinus opacification or bony destruction	+1

Patients usually present with such nonspecific symptoms as malaise, fever, loss of appetite and weight loss, although hemoptysis, nosebleeds and skin rashes may also be present. The upper and lower respiratory tract and kidneys are most common areas of involvement, although at the time of diagnosis, more than half of all patients have lung involvement, increasing to 85% in the more advanced cases (6,9). It usually appears as bilateral nodules measuring 2–3 cm and rarely as masses reaching 10 cm. Cavitary nodules, alveolar hemorrhage, and pulmonary infiltrations may also be observed among radiologic findings (6,10). The thorax CT findings of GPA may mimic those of several other diseases. Due to the similarity of radiologic findings – such as lung nodules, masses and cavities – differentiating between pulmonary tuberculosis, malignancy and bacterial, viral or fungal infections can be challenging (11). Li et al. (12) reported that 52% of patients diagnosed with GPA with thorax CT findings are

misdiagnosed, and suggested the need for biopsy for a definitive diagnosis.

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* that, similar to GPA, presents with symptoms such as fever, loss of appetite, weight loss and hemoptysis. Radiologically, the pulmonary infiltrations, nodules and cavitary lesions seen in the two conditions are similar. Tuberculosis, however, may present with different radiologic appearances (13). The upper lobe apical and posterior segments and the lower lobe superior segments of the lung are the most commonly involved regions, and any calcification in pulmonary nodules and lymph nodes is also useful in for diagnosis (14). In GPA, pulmonary involvement is mostly bilateral and there is no specific zone involvement (11).

GPA and tuberculosis have common histopathologic and immunologic features, and the release of cytokines and chemokines is the main mechanism of granuloma formation in both diseases. The lesions in cases with GPA may vary pathologically, from typical granulomatous vasculitis to such findings as nonspecific chronic inflammation (4). In cases with tuberculosis, caseous necrosis typically develops in the center of granulomas (13). In GPA, more than 90% of patients test positive for c-ANCA and pr3-ANCA (9). That said, ANCA positivity may also be observed in tuberculosis (4,15).

In Case-1 presented here, pathology indicated caseous inflammation, which initially pointed to tuberculosis due to its high incidence in this country. A subsequent paranasal CT of the patient, who had been identified with pulmonary nodules and a mass on imaging and granuloma on biopsy, was compatible with inflammation, indicating GPA based on ACR/EULARACR classification criteria. The second case was diagnosed based on the presence of nodular lesions, granulomatous inflammation on biopsy, and c-ANCA positivity.
It has been reported that reaching a concrete diagnosis can take up to a year as pulmonary and renal symptoms are faint at the time of first admission, and the disease has a slow course (16). The most important factor affecting prognosis is renal involvement. Rapid diagnosis in cases with GPA is crucial for prognosis due to the potential for rapid remission under immunosuppressive treatment regimens, thereby reducing the morbidity and mortality associated with the disease (17,18). Remission has been achieved through treatment in more than 90% of patients without renal damage (3). Treatment is generally rituximab, cyclophosphamide and methotrexate used in combination with steroids, and cyclophosphamide/rituximab has been reported to be effective in GPA patients with nodules, cavities and infiltration (9,19,20).
In conclusion, tuberculosis and GPA have common clinical findings, and their similar lung imaging, pathologic and even immunologic features can lead to misdiagnosis and inappropriate treatment, and cases of miliary tuberculosis due to misdiagnosis of GPA have been reported (21). Furthermore, delays in the diagnosis of GPA reduce the chance of dialysis-free survival (2). Although pathology is of great importance in the diagnosis of GPA, patients should always be subjected to a comprehensive evaluation.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - Z.G., G.K., F.D.Ü., O.K.; Planning and Design - Z.G., G.K., F.D.Ü., O.K.; Supervision - Z.G., G.K., F.D.Ü., O.K.; Funding - Z.G., G.K., F.D.Ü., O.K.; Materials - Z.G., G.K., F.D.Ü., O.K.; Data Collection and/or Processing - Z.G., G.K.; Analysis and/or Interpretation - Z.G., G.K.; Literature Review - Z.G., G.K.; Writing - Z.G., G.K.; Critical Review - Z.G., G.K., F.D.Ü., O.K.

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