CASE REPORT OLGU SUNUMU

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A Case of Granulomatosis with Polyangiitis Presenting with Multiple Pulmonary Nodules (Wegener's Granulomatosis)

Multiple Pulmoner Nodül ile Prezente Olan Granülomatözis Polianjiitis (Wegener Granülomatözü) Olgusu

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ABSTRACT Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is characterized by the simultaneous occurrence of vascular wall inflammation and peri- and extravascular granulomatous formations, constituting a form of necrotizing vasculitis. This pathology has the potential to affect any organ system, with the lungs and kidneys being the most commonly involved. Clinically, manifestations may include symptoms of upper respiratory tract involvement (such as sinusitis, otitis, nasal ulcers, subglottic stenosis), lower respiratory tract involvement (cough, hemoptysis, chest pain), and glomerulonephritis. A definitive diagnosis is established through biopsy. The primary goal of treatment is immunosuppression, with azathioprine and methotrexate being the most commonly used agents. In the differential diagnosis of bilateral nodules and cavitary lesions, it is important to consider GPA in addition to malignancy and metastatic cancer. This case presents a patient with GPA characterized by bilateral pulmonary nodules, accompanied by findings of mastoiditis and arthritis. This case aims to highlight the frequent ear, nose, throat involvement seen in granulomatous polyangiitis and remind that it can uncover this disease.

Keywords: Multiple nodules; granulomatosis with polyangiitis

ÖZET Granülomatözis polianjiitis (GPA) (eskiden Wegener granülomatözü olarak biliniyordu), vasküler duvar inflamasyonu ve peri- ve ekstravasküler granülomatöz oluşumların eş zamanlı ortaya çıkması ile karakterize edilen bir nekrotizan vaskülit formunu oluşturur. Bu patolojinin herhangi bir organ sistemini etkileme potansiyeli vardır; en sık etkilenenler akciğerler ve böbreklerdir. Klinik olarak üst havayolu tutulumu bulguları (sinüzit, otit, nazal ülserler, subglottik stenoz gibi), alt havayolu tutulumu bulguları (öksürük, hemoptizi, göğüs ağrısı gibi) ve glomerülonefrit görülebilir. Kesin tanı biyopsi ile konulur. Tedavide esas olarak immün sistemin baskılanması amaçlanır ve bu amaçla en sık azatioprin ve metotreksat kullanılır. Bilateral nodüller ve kaviter lezyonların ayırıcı tanısında, malignite ve metastatik kanserin yanı sıra GPA'nın da dikkate alınması gerektiğini vurgulamak istiyoruz. Bu olgu sunumunda, bilateral pulmoner nodüller, mastoidit ve artrit bulgularıyla birlikte görülen bir GPA olgusu sunulmuştur. Bu olguyu, GPA'da sık görülen kulak, burun, boğaz tutulumunu vurgulamak ve bu hastalığı açığa çıkarabileceğini hatırlatmak için açıklamaya çalışıyoruz.

Anahtar Kelimeler: Multiple nodüler; granülomatözis polianjiitis

Granulomatosis with polyangiitis (GPA), initially described in 1936 under the term "rhinogenic granulomatosis," represents a systemic, necrotizing, and granulomatous vasculitis, also known as Wegener's granulomatosis.[1,2] Its prevalence is 9.8 per million, with a higher incidence in middle-aged individuals, though it can manifest at any age.[3] The condition affects both genders equally. Therefore, it is considered one of the anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides, alongside eosinophilic GPA and microscopic polyangiitis. However, GPA is more commonly associated with cytoplasmic ANCA (c-ANCA) positivity, while the others are typically associated with perinuclear

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ANCA (p-ANCA) positivity. Clinically, it may present with symptoms of upper respiratory tract involvement (such as sinusitis, otitis, nasal ulcers, subglottic stenosis), lower respiratory tract symptoms (cough, hemoptysis, chest pain), and glomerulonephritis. A definitive diagnosis requires a biopsy.[4] The primary treatment objective is immunosuppression, for which azathioprine and methotrexate are most frequently employed.[4] In this study, we present a case of GPA featuring pulmonary and upper respiratory tract symptoms.

CASE REPORT

A 57-year-old male patient presented with recurring hospital visits due to fever, cough, sore throat, a sensation of fullness in the ear, eye redness, and joint pain that began 20 days ago, having received treatment under the preliminary diagnosis of upper respiratory tract infection. The patient had a history of using moxifloxacin and cefuroxime antibiotics for 14 days before presentation. During the physical examination, the patient was found to be in a moderate general condition, conscious, cooperative, with a body temperature of 38.2 °C, blood pressure of 120/80 mmHg, pulse rate of 110 bpm, and respiratory rate of 18 breaths per minute.

Examination of the respiratory system revealed coarse rales bilaterally at the basal areas. Complete blood count showed a leukocyte count of 12,900/uL, hemoglobin of 9.7 g/dL, eosinophils at 200/uL. Biochemical analyses indicated AST at 12 U/L, ALT at 16 U/L, BUN at 15.42 mg/dL, creatinine at 0.83 mg/dL, C-reactive protein at 139 mg/L, and erythrocyte sedimentation rate at 140 mm/hr.

Postero-anterior chest radiography revealed scattered cavitary lesions in both lungs (Figure 1A). Thoracic computed tomography showed multiple mass lesions, the largest being 3.5 cm in diameter, with most displaying central necrosis and a cavitary appearance, located in the parenchyma and subpleural areas of both lungs (Figure 2A). Due to a history of prior antibiotic use, empirical broad-spectrum antibiotic therapy with imipenem (3x500 mg) was initiated.

Diagnostic fiberoptic bronchoscopy was performed without observing any endobronchial lesions or signs suggestive of infection. Transbronchial lung biopsy and bronchial lavage samples were collected. Pathological examination reported benign cytological findings. The bronchial lavage culture was negative. Three sputum samples tested for acid-fast bacilli were negative for mycobacteria. At this point, the patient tested positive for c-ANCA (PR3): 88.8 and Rheumatoid Factor: 95.60. While the patient's diagnostic evaluations were ongoing, complaints of swelling and redness in the right knee were noted. A rheumatology consultation was requested to assess the patient for arthritis and other rheumatologic diseases.

An ear, nose and throat (ENT) consultation was requested for upper respiratory tract involvement. Paranasal sinus tomography revealed mucosal thickening with intermittent air densities in both maxillary sinuses at the anterior level. Additionally, mild thickening of the bilateral maxillary sinus walls was ob-

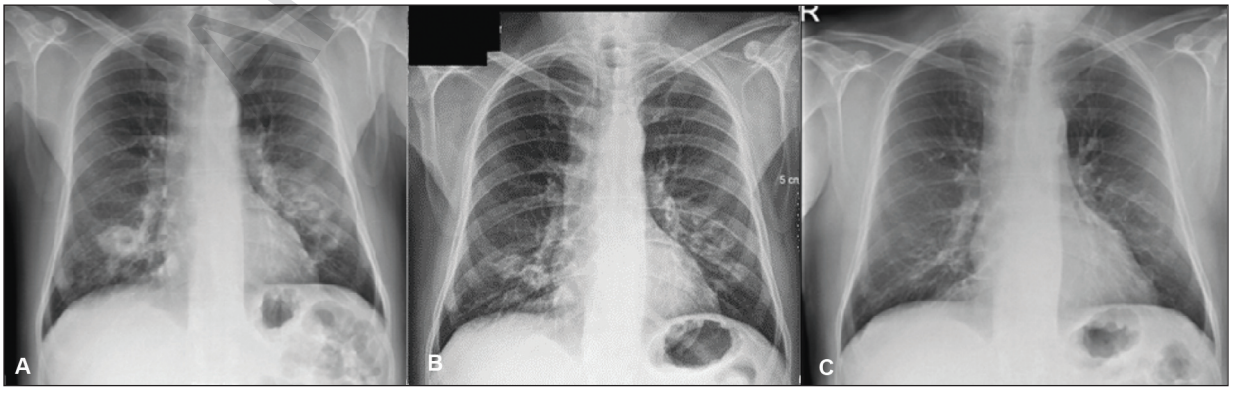

FIGURE 1: Before treatment **(A)** first month of treatment **(B)** and after five months of treatment **(C)**.

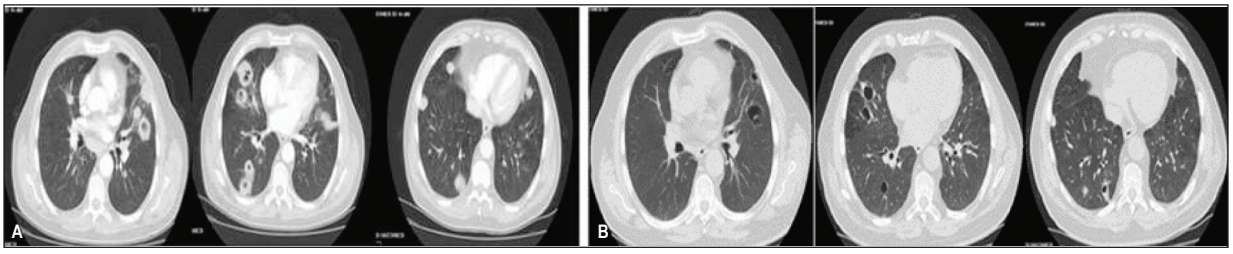

FIGURE 2: Cavitary mass lesions with central necrosis, up to 3.5 cm in diameter, scattered throughout the parenchyma and subpleural regions of both lungs **(A)**, and lesions regressed after 5 months of treatment **(B)**.

served (osteitis). Densities causing loss of aeration in the right mastoid cells were noted (automastoiditis).

A transthoracic tru-cut lung biopsy performed under ultrasound guidance reported necrosis, considered consistent with GPA. The patient was treated with methylprednisolone at a dose of 1 g/day for three days, followed by a maintenance dose of 1 mg/kg/day.

Considering the symptoms of upper and lower respiratory tract involvement, nodular and cavitary lesions, elevated erythrocyte sedimentation rate, and pathological findings, the diagnosis of GPA was made. Treatment continued with methylprednisolone (1 mg/kg/day), and the rheumatology department initiated azathioprine therapy. By the fifth month of treatment, radiological regression of lesions was observed, and treatment is still ongoing (Figure 1C, Figure 2B).

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from the patient included in the case report.

DISCUSSION

The annual incidence of GPA has been estimated as 4 to 12 cases per million.[5,6] Severe diffuse alveolar hemorrhage is an uncommon (<20%) complication of GPA, reflecting diffuse injury to the lung microvasculature (i.e., capillaritis) In this context, rapidly progressive glomerulonephritisis present in more than 90% of patients (Table 2).

In GPA, the most contributory histopathological findings to diagnosis are granulomatous inflammation, which, while largely suggestive of GPA, its absence does not definitively exclude the diagnosis. This is because GPA is diagnosed based on a clinicopathological context. ANCA-associated vasculitides are classified into Eosinophilic GPA, Microscopic Polyangiitis, and GPA.

The 2022 American College of Rheumatology/European League Against Rheumatism Classification Criteria and associated weights for GPA are detailed in Table 1. Following the exclusion of conditions mimicking vasculitis, a patient diagnosed with small or medium vessel vasculitis may be classified as having GPA if the cumulative score is 5 points or higher (Table 1).[7] In our case, the subject scored 2 points for the criterion of pulmonary nodules, 1 point for mastoiditis, and an additional 5 points for positive c-ANCA serology, accumulating a total of 8 points (Table 1).[7]

In GPA, nearly all patients experience upper respiratory tract involvement, while lung involvement occurs in about 90% of cases, and renal involvement is observed in approximately 80%. However, in our case, renal involvement had not yet been observed. Nasal and sinus disease is characterized by congestion and epistaxis due to mucosal friability, ulceration, and thickening. In our case, however, mastoiditis was present.[7] Musculoskeletal involvement abnormalities are observed in 4.7% to 67% of cases, with complaints typically involving polyarthralgia of the knees, hips, wrists, or ankles.[8,9]

Arthritis has been diagnosed in 28% of patients.[8] Hoffman et al. and Fauci et al. reported that joint deformities did not occur in their studies.[1,10,11] Joint symptoms are generally associated with disease activity.[9] In our case, arthritis was also present in the knee joint.

TABLE 1: Classification criteria for granulomatosis with polyangiitis.[7]

Clinical criteria	
Nasal involvement: bloody discharge, ulcers, crusting, congestion, blockage, or septal defect/perforation	
Cartilaginous involvement (inflammation of ear nose cartilage, hoarse voice or stridor, endobronchial involvement, or saddle nose deformity)	
Conductive or sensorineural hearing loss	
Laboratory, imaging, and biyopsy criteria	
Positive test for cytoplasmic-ANCA or antiproteinase 3 (anti-PR3) antibodies	+5
Pulmonary nodules, mass, or cavitation on chest imaging	+2
Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy	+2
Inflammation, consolidation, or effusion of the nasal/paranasal sinuses, or mastoiditis on imaging	+1
Pauci-immune glomerulonephritis on biopsy	+1
Positive test for perinuclear-ANCA or antimyeloperoxidase antibodies	-1
Blood eosinophil count ≥1x109/liter	-4

ANCA: Antineutrophil cytoplasmic antibodies.

TABLE 2: Organ systems affected by antineutrophil cytoplasmic antibodies-associated vasculitis.

Feature	Granulomatosis with polyangiitis (Wegener)	Microscopic polyangiitis eosinophilic	Granulomatosis with polyangiitis (Churg-strauss)
Upper airway disease	90%-95%	No	50%-60%
Pulmonary parenchymal disease	54%-85%	20%	30%
Alveolar hemorrhage	5%-15%	10%-50%	<3%
Glomerulonephritis	51%-80%	60%-90%	10%-25%
Gastrointestinal tract	<5%	30%	30%-50%
Eyes	35%-52%	<5%	<5%
Nervous system	20%-50%	60%-70%	70%-80%
Heart	8%-16%	10%-15%	10%-15%
Skin	33%-46%	62%	50%-60%
Eosinophilia	Rare	Rare	Yes
Asthma	No	No	Yes
Granulomatous inflammation	Yes	No	Yes

Although the exact cause of the disease is not fully understood, levels of ANCA against proteinase 3 and myeloperoxidase are generally high in these patients and are associated with disease activity.[12] In our case, the absence of p-ANCA steered us away from a diagnosis of Eosinophilic GPA.

There are studies indicating that cyclophosphamide and rituximab demonstrate similar efficacy for remission induction in the treatment of GPA.[13] In our case, remission was achieved with methylprednisolone (1 mg/kg/day), and the rheumatology department initiated azathioprine.

While Microscopic Polyangiitis cases often involve renal impairment, upper respiratory tract involvement is rare; however, our case prominently featured upper respiratory symptoms and pulmonary involvement. GPA, with its potential for multiple system involvement, can be confused with a variety of pathologies. The differential diagnosis of nodular, cavitary lesions, and mass lesions mimicking malignancy should also consider GPA. This case aims to highlight the frequent ENT involvement seen in granulomatous polyangiitis and remind clinicians that it can reveal this disease. As seen in our case, early and accurate diagnosis and treatment can reduce mortality rates.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

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