Case Report: A 64-Year-Old Man with 10-Year History of Eosinophilic Granulomatosis with Polyangiitis with Bronchiectasis and Severe *Klebsiella pneumonia*

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Patient: Male, 64-year-old
Final Diagnosis: Eosinophilic granulomatosis with polyangiitis
Symptoms: Cerebral infarction • eosinophilia • pneumonia • polyneuropathy • rhinosinusitis • severe bronchial asthma
Medication: —
Clinical Procedure: —
Specialty: Pulmonology

Objective: Unusual clinical course
Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare and severe progressive disease with multiple clinical manifestations and organ damage. Usually, it requires long-term monitoring of the state of many organs due to the gradual character of its manifestations.

Case Report: We report a case of a long-term follow-up of a patient with eosinophilic granulomatosis with polyangiitis with emphasis on specific clinical features in this patient. A 64-year-old man was being followed up for 10 years. The initial diagnosis was allergic bronchial asthma; however, as new clinical signs and symptoms developed, the diagnosis of EGPA became obvious. A positive treatment response was seen, mainly manifested as reduced polyneuropathy. Meanwhile, bronchial asthma remained uncontrolled and bronchiectasis and *Klebsiella pneumoniae* colonization developed despite the combination treatment with prednisolone and methotrexate. Furthermore, the patient suffered a cerebral ischemic infarction. During the last hospital admission, severe uncontrolled bronchial asthma complicated with pneumonia resulted in the patient’s death.

Conclusions: This clinical case shows the gradual development of EGPA with multiple-organ involvement, including respiratory manifestations and peripheral and central nervous system damage. Immunosuppressive treatment combined with complications of EGPA could have contributed to severe pneumonia development and death of the patient.

Keywords: Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis • Churg-Strauss Syndrome • Bronchiectasis • Klebsiella Infections

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**Background**

Systemic vasculitides are difficult to diagnose due to the heterogenous clinical manifestations requiring a wide differential diagnostic search. One of the most uncommon vasculitis types is eosinophilic granulomatosis with polyangiitis (EGPA), or Churg-Strauss syndrome [1,2]. This vasculitis is associated with the presence of antineutrophil cytoplasmatic antibodies (ANCA) and is characterized by necrotizing inflammatory lesions of mainly small vessels, as well as eosinophilic and granulomatous inflammation in various organs. Bronchial asthma and eosinophilia are the most common clinical manifestations of EGPA [1-3]. In 2012, according to the current classification of systemic vasculitides, Churg-Strauss syndrome was renamed “Eosinophilic Granulomatosis with Polyangiitis” (EGPA) and classified into the ANCA-associated vasculitides group [3].

EGPA is a rare ANCA-associated vasculitis. The incidence rate is 0.5-6.8 new cases/year per million populations in Europe [2]. Prevalence is higher in northern latitudes compared to southern Europe [4]. The disease occurs most commonly in people 40-60 years of age [2,5]. No sex predominance has been clearly demonstrated [4].

The pathogenesis of the disease is still not completely clear, but the key role is attributed to autoimmune inflammation with the participation of eosinophils, CD8+, and CD4+ lymphocytes (predominantly Th-2) and their proinflammatory cytokines: interleukin (IL)4, IL5, and IL13 [2,5]. Elevation of immunoglobulin (Ig)E, IgG4, and eotaxin-3 is common in EGPA patients [2,5]. The frequent (in 30-40% of cases) detection of ANCA (mainly antibodies to myeloperoxidase) also suggests the autoimmune nature of the disease. ANCA-positive patients are more frequently diagnosed with glomerulonephritis and mononeuritis, whereas the ANCA-negative ones more frequently demonstrate endocardial, myocardial, and pulmonary eosinophilic infiltrates [1,2,5,6].

There are 3 phases in the development of EGPA (these phases partially overlap and may not appear in sequence):

- the allergic phase, distinguished by allergic upper respiratory tract inflammation (rhinosinusitis, allergic rhinitis) and bronchial asthma;
- the eosinophilic phase, manifested with severe eosinophilia in combination with multiple eosinophilic infiltrates in various organs (most often in the lungs and gastrointestinal tract);
- the vasculitis phase, with small- and medium-vessel inflammation of different organs, which can often be life-threatening [5,6].

Respiratory manifestations of EGPA include allergic rhinitis, sinusitis, nasal polyposis and, in more than 95% of patients, poorly controlled bronchial asthma [5]. Chest radiography findings include transient and migratory opacities, ground-glass opacity, focal consolidation, and small peribronchial and centrilobular nodules or masses [7]. Computed tomography reveals bronchial abnormalities, most commonly thickened wall and dilatation with secondary bronchiectasis formation, leading to frequent infections [7,8]. Pleural effusions and alveolar hemorrhages are uncommon manifestations of EGPA [1,5,7,8].

A characteristic neurological manifestation seen in 75% of patients with EGPA is peripheral neuropathy (mononeuritis multiplex) [1,5]. Upper-limb symptoms due to neuropathy, as well as vasculitis in epineurial vessels, were more frequently reported in the ANCA-positive group [9]. Eosinophil-associated tissue damage and vascular occlusion leading to ischemia are more specific in ANCA-negative patients [9]. Also, the tissue damage caused by eosinophils may be associated with IL-5 concentration [10]. Brain hemorrhage, subarachnoid hemorrhage, and ischemic brain infarction are rare [1,5,6].

The main drugs for the treatment of EGPA are glucocorticoids. In organ- or life-threatening manifestations, the recommended starting dose of prednisone is 1 mg/kg/day with a maximal daily dose of 80 mg for 2-3 weeks, with tapering to a minimal supporting dose selected individually to control the symptoms and minimize the adverse effects of treatment. Methylprednisolone (7.5-15 mg/kg/day) can be used as a pulse therapy for life-threatening manifestations [11,12]. Most patients need prolonged or lifelong steroids. In the case of organ- or life-threatening manifestations, glucocorticoids in combination with cyclophosphamide are prescribed [11,12]. The combination of glucocorticoids and methotrexate or mycophenolate is required to induce remission in mild or moderate disease [11,12]. Mepolizumab (a humanized monoclonal antibody targeting IL-5) has been used for EGPA treatment [11]. For ANCA-positive patients with renal involvement or refractory disease, rituximab can be considered [3, 11].

Due to the rare occurrence of EGPA and the variety of its clinical manifestations, the diagnosis and treatment of this disease can be challenging. Currently, reports of long-term observations with the detailed patient follow-up are of great interest. The aim of our case report is to present rare manifestations of EGPA, such as bronchiectasis and stroke. We also focused on the infectious complications of immunosuppressive treatments. Thus, we would like to present a 10-year observation of a patient with EGPA.

**Case Report**

The male patient, born in 1953, was first hospitalized in the Pulmonary Department of our clinic in 2007 due to exacerbated...
asthma. The patient’s history was remarkable for multiple allergies (to house dust, cat and dog epidermis, and plant pollen) as well as nonsteroidal anti-inflammatory drugs intolerance (manifested as bronchospasm). The patient denied unhealthy habits and occupational hazards (he worked as a driver). His family history was not remarkable. The patient has had allergic rhinitis since adolescence. The first asthma symptoms appeared at the age of 18 while serving in the army. At the age of 22, an allergist diagnosed him with bronchial asthma. The patient had annual exacerbations (1-2 times a year) due to cold or allergen exposure, and acute respiratory viral infections. At the age of 42, polyloid rhinosinusitis was found, and a polypectomy was performed. Since 2006, the patient had been on controller treatment with salmeterol/fluticasone inhaler (25/250 mg, respectively) 2 doses 2 times a day.

In late 2009, extremely elevated eosinophils (53%) and total IgE (1000 IU/L) were found for the first time. Also, since 2009, the patient has had transient lung opacities, which usually disappeared after treatment with prednisolone 30 mg per day.

In August 2010, the patient noticed numbness on the back surface of the left foot, which spread to the entire left lower leg in 1 month, as well as numbness of the right foot and lower leg. Later, the patient started having tingling, twisting, and burning sensations aggravated by touching in the feet and lower legs. Also, the weakness in the distal parts of the legs developed, and he started having difficulties moving around on his own and falling while walking, and he was subsequently hospitalized in our clinic due to exacerbated asthma. On laboratory testing, high eosinophils (53%) and gamma-globulins (27.9%) were found in November 2010. The chest radiography showed emphysema and consolidation in the middle lobe of the right lung. A Neurology consult confirmed asymmetrical distal sensory-motor polyneuropathy demonstrated by lower distal asymmetrical paraparesis with decreased muscle strength in the foot flexors and extensors, more severe on the left side, low tone of the shin muscles, hypoactive Achilles reflexes, and reduced leg sensitivity starting from the middle of the shin and below, more severe in the peroneal nerve innervation area. The patient also demonstrated abnormal coordination (heel-to-knee, Romberg) test results and bilateral steppage gait with knee overextension. Electroneuromyography showed axonal lesion of all distal leg nerves and secondary myelinopathy. Thus, EGPA was suspected. The ANCA (anti-myeloperoxidase) titer was 30 U/ml (normal reference below 20 U/ml).

Allergic bronchopulmonary aspergillosis and other causes of hypereosinophilia were consistently ruled out. IgE and IgG for Aspergillus spp. and Aspergillus spp. in sputum were not found.

Thus, the presence of severe bronchial asthma, rhinosinusitis, high and persistent eosinophilia, transient pulmonary opacities, and polyneuropathy suggested EGPA (5 out of 6 clinical criteria of American College of Rheumatology present). Based on the clinical presentation and increased ANCA titer, the patient was diagnosed with EGPA. Systemic steroid treatment (prednisolone 300 mg intravenously and 30 mg orally) was prescribed, and 5 plasmapheresis sessions were performed. Later, prolonged combination immunosuppression (prednisolone 10 mg/day and methotrexate 25 mg/week) and controller asthma treatment (fluticasone propionate/salmeterol 250/25 µg 4 doses/day, tiotropium bromide 18 µg per day) were prescribed. After 1 month on prednisolone and methotrexate, there was a significant neurological improvement: the motor and sensory disturbances decreased, and the patient was able to move around on his own. Further on, polyneuropathy completely resolved on the combination treatment. His asthma remained uncontrolled despite the combination treatment: he had frequent (3 times a year) severe exacerbations requiring hospitalization. In 2015, newly-emerged copious purulent sputum associated with frequent infection-related asthma exacerbations was noted. In January 2016, a patient underwent chest computed tomography (CT), which showed generalized bronchiectasis. Stenosis of the proximal bronchi was ruled out also by fibrobronchoscopy. The bronchial secretion microbiology revealed Klebsiella pneumoniae growth (10³ colony-forming units).

In November 2016, during the asthma exacerbation, the patient suffered a cerebral ischemic infarction involving the right occipital lobe, confirmed by CT (Figures 1, 2).

On March 2, 2017, the patient was admitted to our hospital due to severe respiratory failure caused by pneumonia in the left upper lobe and severe asthma exacerbation.

The complete blood count showed high WBCs (15.2×10⁹/l) with left shift. The IgE level was 144.0 IU/l, C-reactive protein was 48.8 mg/dL. Clinical chemistry was remarkable for urea nitrogen 18.4 mmol/l and creatinine 1.55 mg/dL. The sputum microbiology demonstrated 100 WBCs and 160 RBCs per vision field, 48.8 mg/dL. Clinical chemistry was remarkable for urea nitrogen 18.4 mmol/l and creatinine 1.55 mg/dL. The sputum microbiology demonstrated 100 WBCs and 160 RBCs per vision field, and no eosinophils were revealed. A chest CT revealed Klebsiella pneumoniae growth (10³ colony-forming units).

The patient was prescribed intravenous antibiotics (ceftriaxone 2 g/day and ciprofloxacin 800 mg/day replaced by cefoperazone 4 g/day and amikacin 1 g/day after 3 days due to low efficacy), bronchodilator and anti-inflammatory therapy (nebulized ipratropium bromide, fenoterol, and budesonide 2000 µg per day, prednisolone intravenously 150 mg and orally 30 mg). Despite the aggressive treatment, the respiratory failure progressed, and on day 6 of hospitalization the patient was transferred to the Intensive Care Unit and intubated. On day 7, the patient died. On autopsy, the EGPA diagnosis was confirmed, signs of ischemic infarction in the occipital lobe of the brain.
were found, and left upper lobe pneumonia with abscess formation and generalized bilateral bronchiectases were revealed.

**Discussion**

Based on the long follow-up period and careful interpretation of signs and symptoms, typical laboratory abnormalities, the diagnosis was clear. Among the most commonly used diagnostic criteria of EGPA are the American College of Rheumatology (ACR) classification criteria, Lanham’s criteria, and the Chapel Hill Consensus Conference criteria. The presence of 4 or more ACR classification criteria, including bronchial asthma, eosinophilia (more than 10%), paranasal sinus abnormalities, migratory or transient eosinophilic pulmonary infiltrates, extravascular eosinophil infiltration on biopsy, and mono- or polyneuropathy, has a sensitivity of 85% and a specificity of 100% [2,5,6]. We identified 5 out of 6 American College of Rheumatology clinical criteria present in our patient.

**Figure 1.** Brain multi-spiral computed tomography performed in 2016 showing ischemic brain damage in the right occipital lobe.

**Figure 2.** (A–C) Chest computed tomography of patient showing large left upper lobe pneumonia and bronchiectasis in lower lobes.
This clinical case shows gradual development of EGPA with multiple-organ involvement (see Figure 3). The disease onset was characterized by respiratory manifestations and suspicion of EGPA appeared only after the development of polyneuropathy (after 39 years) with hypereosinophilia. Polyneuropathy was noted at the age of 57, which is slightly later than the average age of onset reported in the literature [13]. Notably, the patient was ANCA-positive and his long-term neurological manifestation (mononeuritis) was quite typical for ANCA vasculitis [5,6,8,13]. The diagnosis became obvious after comprehensive assessment of the disease history with its gradually evolving signs and symptoms and laboratory abnormalities. Almost all manifestations of the disease seen in the patient were typical except for stroke, which is an exceptional feature for this case [1,5,6]. Neurological involvement manifested as ischemic stroke is an uncommon complication of EGPA (seen only in 5.2% of all patients) [1]. Thus, the patient demonstrated both peripheral and central nervous system involvement, which is unusual and life-threatening in EGPA.

This clinical case of EGPA also attracted our attention due to severe respiratory manifestations. While typical respiratory manifestations such as rhinosinusitis, asthma, and transient lung infiltrates are well documented in the literature, EGPA-associated bronchiectasis is rarely mentioned [14]. Bronchiectasis in the patient was detected by CT at the age of 63. The patient was a nonsmoker, and no other cause of bronchial abnormalities and airflow obstruction could be identified. Stenosis of the proximal bronchi was ruled out by fibrobronchoscopy and CT. The diagnosis of allergic bronchopulmonary aspergillosis was not confirmed. Klebsiella pneumoniae colonization was found during the last 2 years of the patient’s life. Klebsiella pneumoniae is a typical pathogen causing bronchiectasis [15]. It should be noted that aspergillosis and mycobacteriosis are common complications of bronchiectasis [15], but neither was identified in our patient.

The patient was treated for a long time with a combination of prednisolone and methotrexate. There was a significant positive effect on polyneuropathy, but uncontrolled bronchial asthma persisted. This treatment regimen complies with current recommendations [3,11]. Patients with life-threatening and/or organ-threatening manifestations (including lesions of the central nervous system and severe peripheral neuropathy) require therapy with a combination of a glucocorticoid and a cytostatic [3,11].

The use of immunosuppressive drugs in patients with ANCA-associated vasculitis significantly increases the risk of infection and mortality [16-18]. Prednisone and methotrexate use were found to be significant predictors of hospitalization for pneumonia. Frequent infections (more than 1 episode) are reported in patients with ANCA-associated vasculitis during the first year of diagnosis and initiation of therapy [18]. We assume that bronchiectasis complicated by bacterial colonization and bronchial obstruction in combination with immuno-suppression led to severe pneumonia and death of the patient.

Conclusions

The present case report demonstrates a long-term follow-up of a patient with EGPA. Both common and rare manifestations of EGPA have been described in the patient, such as central nervous system damage and bronchiectasis. Immunosuppressive treatment probably contributed to Klebsiella infection development. Thus, long-term complications of EGPA in combination with adverse effects of medications could have caused the severe pneumonia and death of the patient.
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