

## Testicular Infarction and Pulmonary Embolism Secondary to Nonasthmatic Eosinophilic Granulomatosis With Polyangiitis: A Case Report

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J Invest Allergol Clin Immunol 2020; Vol. 30(5): 380-381  
doi: 10.18176/jiaci.0566

**Key words:** Eosinophilic granulomatous vasculitis. Testicular infarction. Pulmonary embolism.

**Palabras clave:** Vasculitis granulomatosa eosinofílica. Infarto testicular. Embolismo pulmonar.

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is a rare systemic vasculitis of unknown etiology. It is characterized by eosinophil-rich granulomatous inflammation and small to medium-sized blood vessel vasculitis with eosinophilia [1]. However, larger vessels can also be affected by vasculitis, leading to the rare and severe complication called thromboembolism [2]. We report an uncommon presentation of both testicular infarction and pulmonary embolism in a man who was diagnosed with EGPA. To our knowledge, this is the first such case reported in the literature.

The patient was a 57-year-old man with no history of asthma or allergic rhinitis. His right testicular discomfort had been present for a month, and the pain had worsened in the previous 20 hours. Scrotal examination revealed painful and slight swelling after his first admission. Laboratory tests showed elevated C-reactive protein (CRP) of 100 mg/L, an erythrocyte sedimentation rate (ESR) of 82 mm/h, and a slightly elevated D-dimer value of 2.3 mg/L. There was a multifold increase in eosinophils (62.3% in the differential leukocyte count) with an absolute eosinophil count of  $10.67 \times 10^9/L$ . The total number of leukocytes was  $17.12 \times 10^9/L$ . The urine dipstick test revealed 1+ proteinuria and 2+ microscopic hematuria. Serum creatinine was  $52 \mu\text{mol/L}$ , and the glomerular filtration rate was  $112.52 \text{ mL/min/1.73 m}^2$ . The results of other biochemical tests were within normal limits. Complement fractions C3 and C4 were normal, and the result of antinuclear antibody (ANA) testing was negative. The result of the antineutrophil cytoplasmic antibody (ANCA) immunofluorescence assay was positive with perinuclear staining (P-ANCA), and the enzyme-linked immunosorbent assay demonstrated antimyeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) ( $89.2 \text{ U/mL}$  [reference <20]). The computed tomography (CT) scan of the whole body

revealed a nonfixed scattered shadow in the right lung and left lower-middle lung. Nerve conduction studies revealed severe axonal sensorimotor polyneuropathy with a symmetrical acral distribution. No torsion was found during surgery, and the right testicle was black and faint purple (Supplementary Figure, A). A diagnosis of testicular infarction was confirmed. A biopsy of the right testicle showed necrotizing vasculitis with prominent eosinophilic infiltration in interstitial tissue (Supplementary Figure, B and C).

The patient was diagnosed with EGPA, which we treated with methylprednisolone, initially intravenously at 1.5 mg/kg/d. Even though the 5-factor score developed by the French Vasculitis Study Group was 1, intravenous cyclophosphamide (1 g) was administered to improve prognosis because of multiple organ dysfunction affecting the lungs, kidneys, and peripheral nervous system. At discharge, oral prednisone was decreased to a maintenance dose of 1 mg/kg/d. The patient was followed up regularly and received a second and third course of cyclophosphamide as an outpatient in May and June, respectively. Moreover, oral prednisone was slowly tapered to 0.6 mg/kg/d in June.

The patient was readmitted with a 1-month history of recurrent chest pain, as well as generalized fatigue and weakness. Physical examination revealed a blood pressure of 116/74 mmHg and oxygen saturation of 92% in room air. Laboratory tests revealed that eosinophils, ESR, and CRP were within normal limits. MPO-ANCA and P-ANCA had both become negative, and ANA and anticardiolipin antibody were negative. Creatine kinase, cardiac troponin T, and urine sediment were normal. There was a striking increase in D-dimer to 5.9 mg/L. CT pulmonary angiography revealed an unexpected finding of a filling defect in the right pulmonary artery, thus indicating pulmonary emboli (Figure, A). High-dose methylprednisolone (500 mg/d) was administered for 3 days, as was a fourth course of intravenous cyclophosphamide (1 g), since EGPA remained active. In addition, systemic anticoagulation was commenced with inpatient heparin infusion and outpatient warfarin therapy, with a target prothrombin time–international normalized ratio

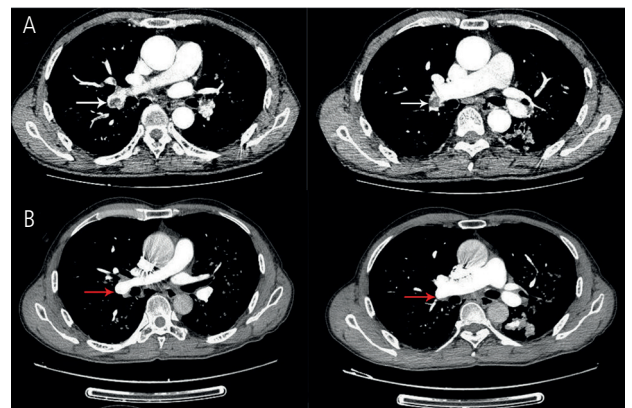


Figure. A, Computed tomography pulmonary angiography revealed an unexpected finding of a filling defect (white arrows) in the right pulmonary artery (July 2019). B, Follow-up computed tomography pulmonary angiography showed that the pulmonary emboli had disappeared (red arrows).

of 2-3. The patient was followed up regularly, with no relapses during the following 2 months. The pulmonary embolism had disappeared on follow-up CT pulmonary angiography (Figure, B).

The 1990 American College of Rheumatology (ACR) classification criteria for EGPA include asthma, eosinophilia >10%, mononeuropathy, polyneuropathy, nonfixed pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophils as the most accepted compatible findings [3]. In the present case, the patient presented with a history of blood and testicular tissue eosinophilia, refractory peripheral neuropathy, and pulmonary infiltrates, thus fulfilling 4 of these criteria and leaving no doubt that he had EGPA. However, the patient did not have a history of asthma. Although asthma has been considered a central clinical feature of EGPA and almost all patients (>90%) have a history of bronchial asthma, nonasthmatic forms of EGPA have been reported [4,5].

Thromboembolism in the setting of EGPA due to altered indices of coagulation and fibrinolysis is less well described. The few case reports in the literature involve deep vein thrombosis [6], pulmonary emboli [7], and cerebral infarction [8]. Testicular infarction in EGPA is an exceedingly rare phenomenon, with few reported cases. In this report, the patient had both testicular infarction and pulmonary embolism at the first admission, although his prognosis gradually improved. The nature of these thrombotic diseases obliges us to ask why there is such a high prevalence of thromboembolism in EGPA?

The condition could be due to a unique set of biochemical and molecular abnormalities. On the one hand, eosinophil granules release several proteins, such as eosinophilic cationic protein, eosinophilic peroxidase, and major basic protein, which play an essential role in thrombosis. Moreover, major basic protein and eosinophilic peroxidase are able to activate platelets and thus facilitate thrombosis [9]. On the other hand, strikingly enhanced levels of tumor necrosis factor  $\alpha$ , interleukin 1, and interleukin 6 mitigate the antithrombotic role of thrombomodulin. In addition, high expression of CD40 ligands on eosinophils amplifies inflammatory processes involving the initiation and progression of thrombosis [10]. Furthermore, high blood viscosity caused by long-term high-dose corticosteroids also contributes to thrombosis.

Given the presumptive mechanism discussed above and the involvement of eosinophils in pathogenesis, eosinophilic inflammation should be managed prior to effective anticoagulation in EGPA. Currently recommended therapy for EGPA includes corticosteroids and immunosuppressive agents. Cyclophosphamide has been widely shown to improve prognosis. In the present case, the patient was diagnosed with EGPA and testicular infarction on his first admission. Effective and aggressive treatment with corticosteroids and cyclophosphamide reduced the number of eosinophils to normal levels. Unfortunately, the patient had a pulmonary embolism on his second admission. Given the limited anticoagulative effects of corticosteroids and immunosuppressants, it is highly recommended to apply systemic anticoagulation to reduce the frequency of thromboembolism. Standard anticoagulation treatment should consist of parenteral anticoagulation with low-molecular-weight heparin over the first 5-10 days,

followed by oral medication with warfarin and rivaroxaban. The duration of anticoagulation should cover at least 3 months, aiming for an international normalized ratio of 2.0-3.0.

#### Funding

The authors declare that no funding was received for the present study.

#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Manuscript received January 19, 2020; accepted for publication April 24, 2020.

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