

Testicular infarction and Pulmonary embolism secondary to Non-asthmatic Eosinophilic Granulomatosis with Polyangiitis: a case report

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Eosinophilic granulomatosis with polyangiitis (EGPA), also formerly known as Churg-Strass syndrome (CSS), 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 as EGPA. To our knowledge, this is the first case reported in the literature.

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 past 20 hours. A scrotal examination revealed a painful and lightly swollen of his right scrotum after his first admission. Laboratory tests showed elevated C-reactive protein (CRP) of 100mg/L and erythrocyte sedimentation rate (ESR) of 82mm/h; slightly elevated D-Dimer of 2.3mg/L. There was a multifold increase in eosinophils (62.3% on differential leucocyte count) with an absolute eosinophil count of $10.67 \times 10^9/L$, and the total number of leukocytes is $17.12 \times 10^9/L$. The urine dip revealed 1+proteinuria and 2+ microscopic haematuria; normal serum creatinine level of 52umol/L and GFR 112.52ml/min.1.73m². Other biochemical tests were within normal limits. Complement fractions C3 and C4 were normal and antinuclear antibody (ANA) was negative. His anti-neutrophil 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) (89.2U/ml, reference <20). The computed tomographic (CT) scan of the whole body revealed no-fixed scattered shadow in right lung and left middle-lower lung. Nerve conduction studies revealed severe axonal motor-sensory polyneuropathy with symmetrical acral distribution. No torsion was found during surgical exploration and the right testicle presented black and faint purple (Supplementary figure a). The diagnosis of testicular infarction was confirmed. A biopsy of the right testicle showed necrotizing vasculitis with prominent eosinophilic infiltrating in interstitial tissue (Supplementary figure b and c).

The diagnosis of EGPA was established. We treated the patient with methylprednisolone, initially intravenously at 1.5mg/kg/day. Although five factor score which was developed by French Vasculitis Study Group was 1, intravenous cyclophosphamide (1g) was still

administered to improve prognosis because of multiple organ dysfunction including lung, kidney and peripheral nervous. Finally, the oral prednisone upon discharge was decreased to maintenance dose of 1mg/kg/day. The patient was followed up regularly and he received second and third course of cyclophosphamide as an outpatient in May and June, respectively. Moreover, the oral prednisone was slowly tapered to 0.6mg/kg/day in June.

He was readmitted due to recurrent chest pain for one month. He appeared generalized fatigue and weakness. Physical examination on readmission revealed a blood pressure of 116/74mmHg and oxygen saturation of 92% on room air. Laboratory tests on readmission were found that eosinophils, ESR and CRP were within normal limits. MPO-ANCA and P-ANCA were both transformed into negative, ANA and anticardiolipin antibody (ACA) were negative. CK, cTNT and urine sediment were normal. There was a striking increase in D-Dimer of 5.9mg/l. An unexpected finding of a filling defect in the right pulmonary artery, demonstrating pulmonary emboli by CT pulmonary angiography (Figure. a). High-dose methylprednisolone (500mg/d) for three days and fourth course of intravenous cyclophosphamide (1g) were administered considering the active EGPA. In addition, systemic anticoagulation was commenced with both heparin infusion and warfarin therapy as an in- and out-patient, respectively, with a target prothrombin time-international normalized ratio (PT/INR) of 2-3. The patient followed up regularly and no relapse occurred during next two months. The pulmonary embolism disappeared on follow-up CT pulmonary angiography (Figure. b).

The 1990 classification criteria for EGPA by the American College of Rheumatology(ACR) including asthma, eosinophilia>10%, mono-or poly- neuropathy, non-fixed pulmonary infiltrates, paranasal sinus abnormality and extravascular eosinophils has been the most accepted diagnostic criteria for the disease[3]. In this article, the patient presented with history of blood and testicular tissue eosinophilia, refractory peripheral neuropathy, pulmonary infiltrates, which fulfilled 4 of these criteria, leaving no doubt that our patient qualified for the diagnosis of EGPA. It should be noted that our patient did not have 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, non-asthmatic forms of EGPA had been reported [4,5].

Thromboembolism in the setting of EGPA due to altered indices of coagulation and fibrinolysis is less well described. There are only a few cases in the literature to report deep vein thrombosis[6], pulmonary[7] and cerebral infarction[8]. Testicular infarction in EGPA is exceedingly rare phenomenon with few reported case. In this report, the patient suffered both testicular infarction and pulmonary embolism since first admission and finally achieved better prognosis. Those thrombotic diseases raise a question: why there is high prevalence of thromboembolism in EGPA?

Some unique set of biochemical and molecular biology abnormality may account for this pathology. On one hand, the granules of eosinophils release several proteins, such as eosinophilic cationic protein (ECP), eosinophilic peroxidase (EPO) and major basic protein (MBP), which play an essential role in thrombosis. Moreover, the released MBP and EPO are able to activate platelets and then facilitate the thrombosis[9]. On the other hand, strikingly enhanced level of tumor necrosis factor α (TNF- α), interleukin-1 (IL-1) and interleukin-6 (IL-6) mitigate the anti-thrombosis role of thrombomodulin. In addition, high expression of CD40 ligands on eosinophils amplifies inflammatory process involving the initiation and progression of thrombosis[10]. Furthermore, high blood viscosity caused by long-term and high dose of corticosteroid also contributes to thrombosis.

Given the presumptive mechanism discussed above and involvement of eosinophils in the pathogenesis, the recommendations to reduce eosinophilic inflammation should be prior to the effectively anticoagulation in EGPA. Currently recommended therapy for the EGPA includes corticosteroids and immunosuppressive agents. Cyclophosphamide is the most studied agent to improve prognosis. In this case, the patient was diagnosed as EGPA and testicular infarction on first admission. After he received the effective and aggressive treatment of corticosteroids and cyclophosphamide, the number of eosinophils decreased to normal. Unfortunately, the patient had pulmonary embolism on the second admission. It is highly recommended to apply systemic anticoagulation to reduce the occurrence rate of thromboembolism considering the limited anticoagulative effects of corticosteroids and immunosuppressants. The standard anticoagulation treatment should consist of parenteral anticoagulation (low molecular weight heparin (LMWH)) over the first 5-10 days, then oral medication of warfarin and Rivaroxaban. The duration of anticoagulation should cover at least 3 months aiming for INR level of 2.0-3.0.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Figure

Figure. (a) An unexpected finding of a filling defect (white arrows) in the right pulmonary artery with CT pulmonary angiography in July 2019. (b) The pulmonary emboli disappeared (red arrows) on follow-up CT pulmonary angiography .

