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A case of cardiac arrest and spontaneous renal hemorrhage in a male patient with persistent eosinophilia: highlighting the importance of early diagnosis of eosinophilic granulomatosis with polyangiitis

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Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare multi-system disease that presents significant diagnostic challenges due to its complexity and low incidence (White and Dubey, 2023). It affects males and females equally, though males may exhibit more active disease at diagnosis and often require more aggressive treatment (Liu et al., 2023). The hallmark features of EGPA include delayed-onset asthma, eosinophilia in tissues and blood, and vasculitis affecting small to medium-sized arteries (White and Dubey, 2023). EGPA falls under the category of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), whereas only about half of EGPA patients test positive for ANCA (Khoury et al., 2023).

Glucocorticoids remain the frontline drugs for EGPA treatment (Noth et al., 2003). In severe cases, especially those with endangered organ function, a combination of immunosuppressants and glucocorticoids is recommended (White and Dubey, 2023). The treatment strategy is guided by the Five-Factor Score (FFS), where patients at higher risk (FFS≥1) receive both immunosuppressants and glucocorticoids, while those with less severe disease (FFS=0) may be managed with glucocorticoids alone (Guillevin et al., 2011).

In this paper, we present a case of a 58-year-old man with persistent eosinophilia, whose condition was complicated by cardiac arrest and spontaneous renal hemorrhage (SRH). His medical history included a 10-year battle with asthma and idiopathic hypereosinophilic syndrome (I-HES) for one year, which was intermittently treated with glucocorticoids. His white blood cell count fluctuated between 20×10^9 and 30×10^9 L^{-1}, with approximately 30% eosinophils. Before referral to hematology, he was admitted to the intensive care unit (ICU) for dyspnea, melena, and hyperlactatemia. The vital signs showed a blood pressure of 178/103 mmHg (1 mmHg= 133.32 Pa), a heart rate of 124 beats/min, a respiratory rate of 29 times/min, and a temperature of 35.7 ℃.

Laboratory tests showed a white blood cell count of 55.8×10^9 L^{-1}, with 9.1% eosinophils and 72.4% neutrophils. Hemoglobin was significantly reduced to 54 g/L, while the platelet count was 348×10^9 L^{-1}. Coagulation tests indicated a prolonged prothrombin time of 20.9 s. Immunoglobulin E (IgE) was elevated at 1280 kU/L, C-reactive protein (CRP) was elevated at 32.1 mg/L, and whole blood lactate was elevated at 20 mmol/L, along with elevated lactate dehydrogenase (LDH) at 536 U/L and creatine phosphokinase (CPK) at 1178 U/L. Screening tests for ANCAs, antinuclear antibodies (ANAs), tumor markers, and chronic infectious diseases, including Epstein-Barr virus, tuberculosis, and viral hepatitis, were negative. Bone marrow analysis, including routine examination, biopsy, and immunophenotyping, demonstrated an increase in mature eosinophils. The karyotyping results were normal, and molecular tests were negative, including assessments for IgH and T-cell receptor (TCR) gene rearrangements, Fip1-like 1-platelet-derived growth

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factor receptor α (*FIP1L1-PDGFRα*) fusion gene, and fluorescent in-situ hybridization (FISH) for *PDGFRα*, *PDGFRβ*, fibroblast growth factor receptor 1 (*FGFR1*), and Janus kinase (*JAK*) gene abnormalities.

A cardiac ultrasound revealed mitral valve mucinous degeneration with a slight prolapse of the anterior lobe, raising concern for Loeffler endocarditis. A myocardial biopsy was planned but not performed because of the patient's low hemoglobin levels and the imminent risk of infection. At that time, the patient was diagnosed with I-HES and was continued on glucocorticoid treatment.

Seven months later, the patient was readmitted to the ICU with a 1-week history of back pain and subsequent cardiac arrest. Laboratory tests at admission showed a white blood cell count of 18.1×10^9 L^{-1}, with eosinophils at 4.4×10^9 L^{-1} and neutrophils at 10.2×10^9 L^{-1}. The white blood cell count later rose to 27.4×10^9 L^{-1}. Although this constituted a significant decrease compared with the first hospitalization, it was likely due to regular glucocorticoid use, which suppressed the proliferation of eosinophils and other inflammatory cells. It is also possible that more eosinophils had infiltrated the affected organs. Despite the reduction in the total white blood cell count, the patient's CRP level was elevated to 42.6 mg/L, indicating persistent inflammation and suggesting that the disease remained in its active phase. Initially, the hemoglobin level was 63 g/L but this progressively decreased. The platelet count (130×10^9 L^{-1}) remained within the normal range, and the prothrombin time (20 s) was relatively normal. Blood lactate was significantly elevated at 22 mmol/L. Cardiopulmonary resuscitation was applied, which successfully revived the patient.

Abdominal computed tomography (CT) revealed renal rupture and hemorrhage (Fig. 1). The patient underwent a right nephrectomy due to hemorrhagic shock. Postoperatively, he reported myalgia in the right upper limb and exhibited weakness on the right side of his body. Neurological evaluation revealed a positive Babinski sign in the right lower extremity and the complete loss of muscle strength, rated as 0 on the Medical Research Council (MRC) Muscle Scale for the right lower limb. Head imaging suggested ischemic changes, and a skin manifestation developed soon after (Fig. 2). One week later, a kidney biopsy revealed occlusive vasculitis with vascular wall destruction, accompanied by eosinophilic infiltration and eosinophilic abscess formation in the surrounding area (Fig. 3).

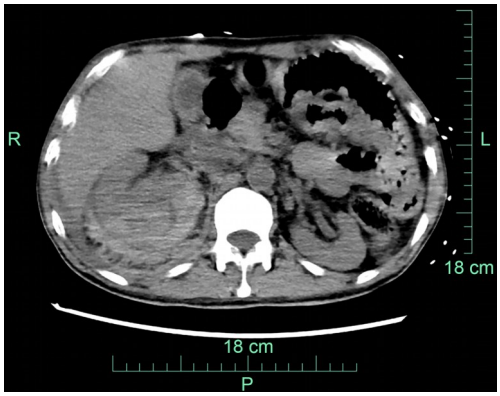

Fig. 1 Ruptured right kidney shown by abdominal computed tomography (CT). L: left; R: right; P: posterior.

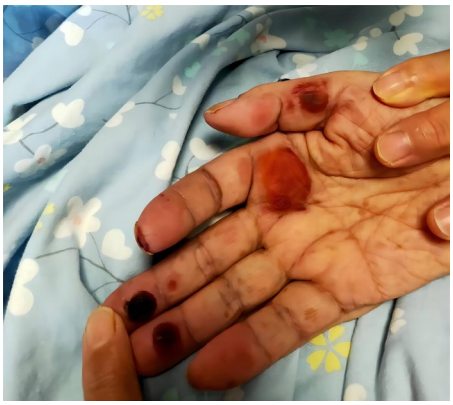

Fig. 2 Photograph of cutaneous bleeding on the patient's palm.

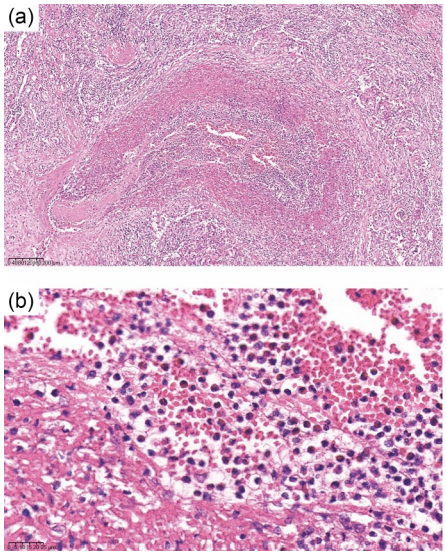

Fig. 3 Histological examination of kidney biopsy. (a) Haematoxylin and eosin (H&E) staining shows vascular occlusion and eosinophilic abscess formation. (b) H&E staining demonstrates eosinophilic infiltration. Scale bar: 200 μm (a) and 25 μm (b).

The clinical presentation and histological findings confirmed the diagnosis of EGPA. The patient was prescribed glucocorticoids and cyclophosphamide, resulting in complete resolution of the skin bleeding. Gradually, the patient regained sensation and mobility in the right lower extremity. After a cumulative dose of 4 g of cyclophosphamide was reached, the immunosuppressant was changed to mycophenolate mofetil (1000 mg daily). Five months after treatment and rehabilitation, the patient experienced significant improvement in overall well-being.

The rarity and diverse symptoms of EGPA make diagnosis challenging. The case discussed in this paper provides a comprehensive overview of the diagnostic journey and the life-threatening complications encountered in one patient with EGPA. There are currently no definitive diagnostic criteria for EGPA. As with other small-vessel vasculitides, diagnosis should rely on objective evidence of vasculitis, typically based on histological findings (Emmi et al., 2023). As some EGPA patients may lack definitive biopsy results, their clinical symptoms play a crucial role in diagnosis (Emmi et al., 2023).

Long before the renal pathology results, the patient exhibited a long-standing history of asthma, eosinophilia, and complications such as gastrointestinal bleeding and cardiac lesions. Adult-onset asthma is a key symptom affecting 95%–100% of EGPA patients and often appears years before other systemic symptoms (White and Dubey, 2023). The duration between the onset of vasculitis symptoms and the first episode of adult asthma varies among individuals (Khoury et al., 2023).

The patient of our case study was ANCA-negative and experienced life-threatening cardiac arrest during the second hospitalization. While the exact cause remains unclear, the cardiac arrest could have been triggered by hemorrhagic shock due to renal rupture and subsequent blood loss, or by EGPA-related cardiac complications such as Loeffler myocarditis, coronary artery vasculitis, or cardiomyopathy (Bond et al., 2022). Cardiac involvement is a recognized adverse prognostic indicator of EGPA, particularly in ANCA-negative patients (Bond et al., 2022). Previous case studies have reported EGPA-related cardiac arrest due to acute coronary vasospasm or atrioventricular block (Benallegue et al., 2016; Sakurai et al., 2023). The management of our patient's cardiac arrest included cardiopulmonary resuscitation (which was successful), followed by stabilization measures, while further interventional treatments or cardiac evaluations were limited, as the patient refused additional cardiac screening. A more comprehensive cardiac assessment during the first hospitalization, where echocardiography already indicated abnormalities, could have potentially prevented the severe complications observed later. Regular monitoring with noninvasive techniques such as magnetic resonance imaging (MRI) and cardiac emission computed tomography (ECT), which have high sensitivity for detecting early abnormalities in EGPA patients, might aid in the early detection and management of EGPA-related cardiac complications (White and Dubey, 2023; Zhao et al., 2023). In conclusion, the early recognition of cardiac involvement in EGPA patients, particularly those who are ANCA-negative, and timely intervention are critical for preventing severe outcomes like cardiac arrest (Garcia-Vives et al., 2021).

Renal involvement is uncommon in EGPA, occurring in about 25% of cases, and is typically associated with the ANCA-positive phenotype (Reggiani et al., 2023). SRH has been even less studied, with limited literature documenting its occurrence in EGPA, while SRH is more commonly associated with polyarteritis nodosa (PAN) (Ahn et al., 2018). In our case, although the patient was ANCA-negative, he developed severe SRH, which rapidly progressed to hemorrhagic shock. Given the urgency of the situation, conservative treatment or interventional embolization was deemed insufficient to control the extensive hemorrhage and stabilize the patient. Hence, the decision to perform a nephrectomy was made as the bleeding could not be controlled through less invasive means, and the patient's condition required immediate intervention to prevent further hemodynamic deterioration. Fortunately, the left kidney remained functional, allowing for nephrectomy as a life-saving measure. This also provided essential diagnostic information, as the pathological findings supported the diagnosis of EGPA. While nephrectomy offers diagnostic and life-saving benefits, we acknowledge that it poses potential long-term consequences for the patient's renal function, which will be monitored closely in follow-up care.

In severe EGPA cases, gastrointestinal symptoms may manifest as a precursor to the vasculitic phase (White and Dubey, 2023). Gastrointestinal involvement is also a poor prognostic indicator and can lead to potentially fatal complications (White and Dubey, 2023). Peripheral neuropathy occurs in 65%–75% of EGPA

patients (Noth et al., 2003), whereas central nervous system (CNS) involvement is relatively uncommon. While uncommon in EGPA, CNS involvement is linked to poor prognosis, with the most common type of lesion observed in this context being ischemia (Liu et al., 2021). Skin changes are observed in about 50% of EGPA patients (White and Dubey, 2023). Similar to granulomatosis with polyangiitis, EGPA patients with skin findings usually have more severe systemic disease, and in most cases, these findings appear either concurrently with or following systemic symptoms (Gibson, 2022).

The overlap between EGPA and I-HES presents a diagnostic challenge. Patients exhibiting systemic signs of hypereosinophilia, testing negative for ANCA and lacking the defining characteristics of either myeloid or lymphocytic variant HES, may have either ANCA-negative EGPA or I-HES (Khoury et al., 2023). Moreover, the consistent use of glucocorticoids has partially alleviated symptoms but has also masked the condition, complicating the diagnosis of EGPA.

In summary, diagnosing EGPA in our patient was particularly challenging. He was initially misdiagnosed with I-HES and was first hospitalized for respiratory distress, gastrointestinal bleeding, and hyperlactatemia. Despite regular glucocorticoid treatment, disease control was inadequate, leading to a second hospitalization due to SRH and cardiac arrest, followed by nervous system and skin involvement. While EGPA is a rare disease, the number of reported cases has been on the rise in recent years. However, the case discussed in this paper is set apart by the occurrence of both SRH and cardiac arrest, which are exceedingly rare complications in EGPA. Furthermore, both hospitalizations were life-threatening, yet the patient survived. Compared with previously reported cases, our case highlights the unusual progression and multisystem involvement, which makes early diagnosis and intervention critical. Given the diverse clinical manifestations and potential for multiple organ involvement in EGPA, multidisciplinary collaboration is crucial for optimal management. This case serves as a valuable reference, as the lessons learned emphasize the importance of early recognition, thorough evaluation, and timely treatment to prevent severe complications and improve patient outcomes.

Data availability statement

The data presented in this study are available from the corresponding author upon reasonable request.

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Author contributions

Jinya LIN, Rending WANG, Yuanyuan ZHU, Weijia HUANG, and Jie SUN provided clinical care for the patient. Rending WANG and Jie SUN made the diagnosis. Jinya LIN, Yuanyuan ZHU, Weijia HUANG, and Jie SUN collected the clinical data. Jinya LIN and Jie SUN wrote the original draft of the manuscript. Jinya LIN, Rending WANG, and Jie SUN edited the final manuscript. All the authors have read and agreed to the published version of the manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Jinya LIN, Rending WANG, Yuanyuan ZHU, Weijia HUANG, and Jie SUN declare that they have no conflicts of interest.

The study protocol was reviewed and approved by the Clinical Research Ethics Committee of The First Affiliated Hospital, School of Medicine, Zhejiang University (No. 20240637A), and all procedures were conducted in accordance with the institutional and national ethical standards and the principles of the Helsinki Declaration (1975, revised 2013). Informed consent was obtained from the patient to be included in the report. Additional informed consent was obtained from the patient for which identifying information is included and published in this article.

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