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CASE BASED REVIEW

Testicular vasculitis in eosinophilic granulomatosis with polyangiitis: a case-based review

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Abstract

Testicular vasculitis (TV) develops when an organ is involved in systemic vasculitis. A 47-year-old man with eosinophilic granulomatosis with polyangiitis (EGPA) developed TV as the first clinical episode. The patient had bronchial asthma for 8 years and developed left testicular pain before developing arthralgia, abdominal involvement, and sensory polyneuropathy, which led to the diagnosis of EGPA. The induration of the affected testicle persisted even after initiating immunosuppressive therapy with corticosteroids and cyclophosphamide, raising concern for testicular neoplasm, while testicular pain and other symptoms resolved. The patient underwent inguinal orchiectomy, and a histology examination of the resected testicle revealed fibrinoid necrotizing vasculitis. Only three cases of biopsy-proven TV in patients with EGPA have been reported in our review of published English-language articles. Two of the three patients in the reviewed cases developed TV before being diagnosed with EGPA. Moreover, all patients underwent extirpation of the affected testicle, leading to a pathological diagnosis of TV. This report suggests that TV may develop and be the presenting condition in EGPA, although urogenital involvement is rare.

Keywords Eosinophilic granulomatosis with polyangiitis · Testicular pain · Testicular vasculitis

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a subgroup of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) with eosinophilic and granulomatous inflammation and fibrinoid necrotic vasculitis in small- to medium-sized arteries [1]. The complications of bronchial asthma and other allergic diseases differ from microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA). EGPA can involve many organs and systems, including the peripheral nerves, skin, musculoskeletal, respiratory, cardiovascular, gastrointestinal, and even the kidneys [2]. However, biopsy-proven glomerulonephritis is less common in EGPA than in GPA or MPA [3]. However, the manifestations of EGPA in the genital tract are rare. Herein, we present the case of EGPA in a patient who developed testicular vasculitis (TV) as an initial clinical episode. In addition, we reviewed previously published English-language articles to clarify the characteristics of TV in EGPA.

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Case presentation

A 47-year-old man with an 8-year history of eosinophilic pneumonia, allergic rhinitis, and bronchial asthma, who was treated with prednisolone (PSL) orally at the dose of 5 mg daily and inhaled steroids, developed left testicular pain. Despite receiving levofloxacin and minocycline at a nearby hospital for suspected epididymitis, the pain persisted for 2 weeks. The patient was admitted to our hospital after experiencing additional symptoms, such as numbness in his right hand and both feet, polyarthralgia, abdominal pain, and vomiting, over the previous week.

His body temperature and blood pressures were 37.6 °C and 131/94 mmHg, respectively. He presented with wheezing and crackles on pulmonary auscultation, a 92% oxygen saturation on pulse oximetry, and mild tenderness on the left lower abdomen with no guarding. Diffuse induration was observed on the left testicle, which was tender on palpation. Both shoulder joints and the femoral and crural muscles were tender with no other physical symptoms. No other abnormal neurological findings were observed except for sensory impairment. Urinalysis revealed no abnormalities and normal serum values for renal function, hepatic function, and creatine kinase. Other laboratory findings included an increases in the number of white blood cells (39,140/μL; normal, 3300–8600/μL), eosinophils (24,590/μL; normal, 20–860/μL), serum C-reactive protein (15.94 mg/dL; normal, < 0.01 mg/dL), immunoglobulin (Ig) E (5576 IU/mL; normal, 0–361 IU/mL), IgG4 (356 mg/dL; normal, < 134 mg/dL), C3 (175 mg/dL; normal, 73–138 mg/dL), and CH50 (56 U/mL; normal, 30–53 U/mL). Positive test results were obtained for rheumatoid factor (233 U/mL; normal, 0–14 U/mL) and myeloperoxidase (MPO)-ANCA (52.6 U/mL; normal, < 3.4 U/mL). The test results for antinuclear antibody (ANA), anti-cyclic citrullinated peptide, proteinase3-ANCA, angiotensin-converting enzyme, hepatitis B surface antigen, and hepatitis C virus antibody were negative. Serum human chorionic gonadotropin-β and alpha-fetoprotein levels were within the normal range. Neither (1,3)-β-D-glucan nor *Mycobacterium tuberculosis*-specific interferon-γ tests in the peripheral blood assays showed any infection. Contrast-enhanced computed tomography revealed rhinosinusitis, bronchial thickening, interstitial infiltrates in the lower lung fields, and a thickened jejunal wall with a partial contrast-filling defect (Fig. 1a). No evidence of erosion or ulceration was observed during colonoscopy. Mild high-density areas were partially observed in the left testicle (Fig. 1b). A peripheral nerve conduction study indicated a reduction in compound muscle action potential amplitude, suggesting axonal neuropathy. This patient was diagnosed with EGPA based on the current criteria [4], which included bronchial asthma, eosinophilia, mononeuropathy, pulmonary infiltrates, and paranasal sinus abnormality. PSL was orally administered at a dose of 60 mg daily after an intravenous infusion of methylprednisolone (1000 mg daily for 3 days), followed by an intravenous infusion of cyclophosphamide (IVCY) at a dose of 500 mg once, ultimately resulting in the immediate resolution of symptoms, including fever, respiratory signs, arthralgia, sensory impairment, abdominal pain, and vomiting (Fig. 2). Despite continuing antibiotic treatment with ceftriaxone sodium and clarithromycin after admission, the patient still had testicular induration without pain. Ultrasound examination of the left testicle revealed focal and interspersed hypoechoic lesions, in which increased blood flow was observed (Fig. 3). Testicular neoplasm was a concern given these findings and the poor response to immunosuppressive treatment. He underwent a left inguinal orchiectomy, and histology of the resected testicle revealed fibrinoid necrosis of small-sized arteries, with ruptured intimal elastic lamina, lymphoid cell infiltration, interstitial hemorrhage, and tubular necrosis. No granuloma formation or eosinophil infiltration was observed (Fig. 4). No evidence of testicular neoplasm was found. Remission was maintained when the PSL dose was reduced to 30 mg/day at hospital discharge.

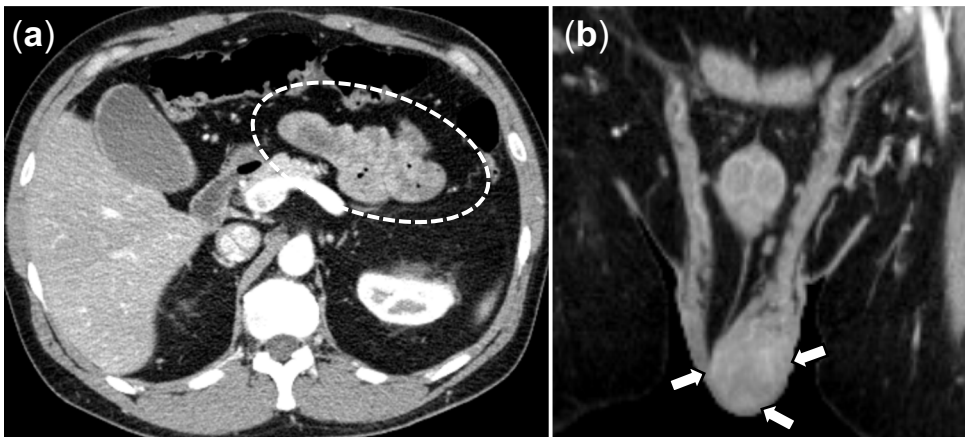

Fig. 1 Contrast-enhanced computed tomography of abdomen and left testicle. The thickened wall of the jejunum (dotted circle) partially displays a contrast-filling defect (**a**). The testicle partially displays high-density areas (white arrows) (**b**)

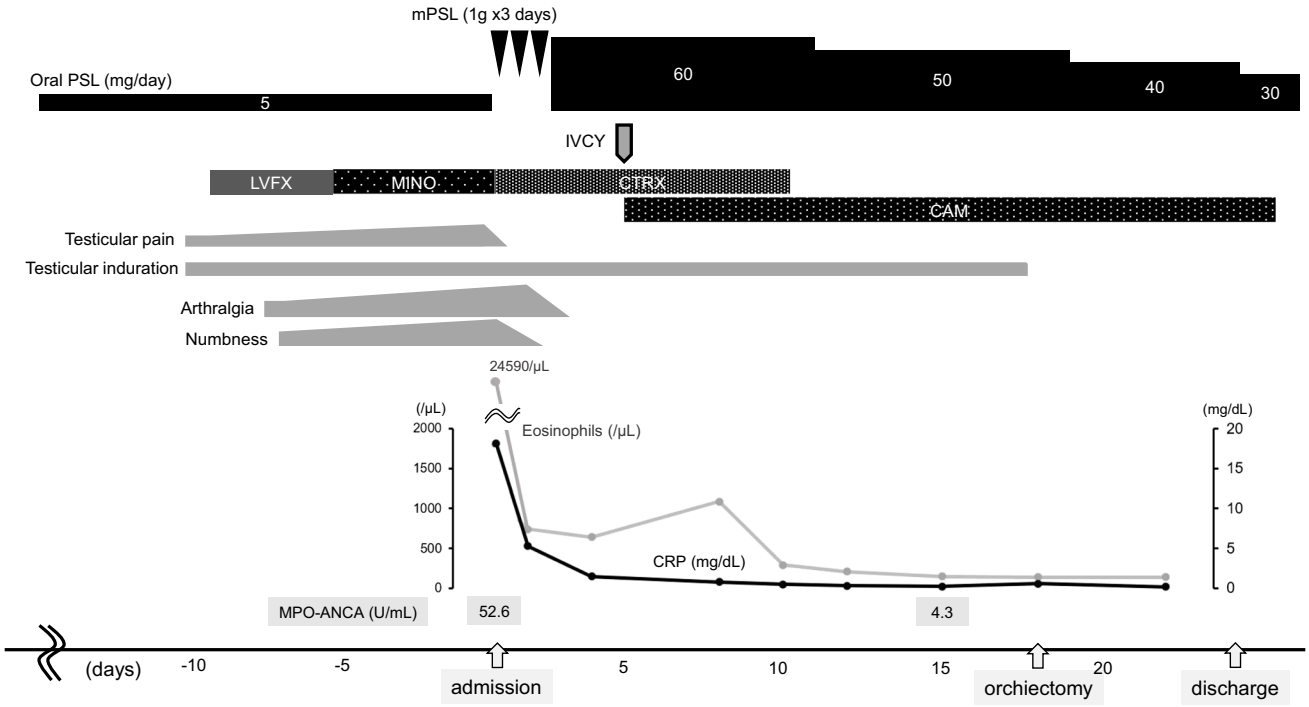

Fig. 2 Clinical course. PSL, prednisolone; mPSL, intravenous infusion of methylprednisolone; IVCY, intravenous infusion of cyclophosphamide; LVFX, levofloxacin; MINO, minocycline; CTRX, ceftriaxone sodium; CAM, clarithromycin; CRP, C-reactive protein; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody

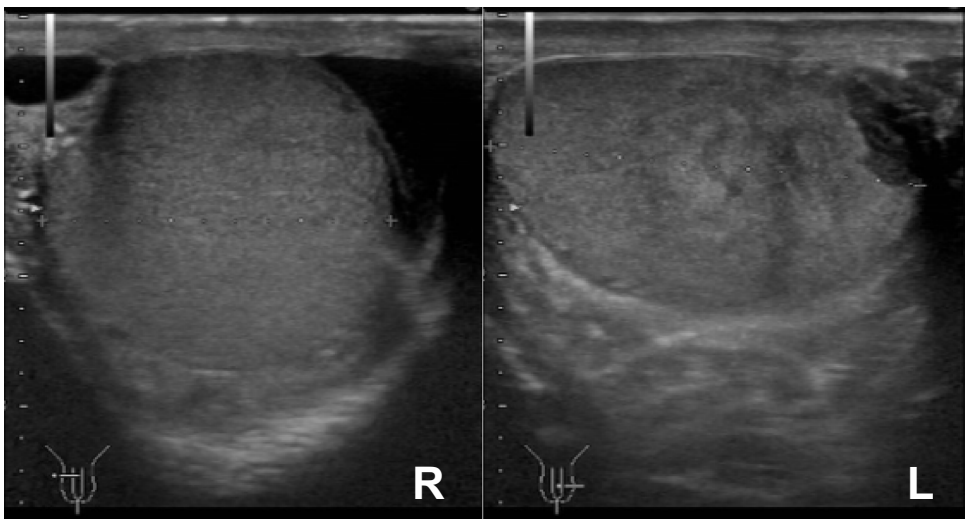

Fig. 3 Ultrasonography of the testicles. The intact testicle on the right (R) and the affected testicle displaying multiple focal hypoechoic areas on the left (L)

Strategy for reviewing

We reviewed previously published English-language articles on cases of testicular vasculitis in EGPA through PubMed/MEDLINE and Web of Science researches. We used keywords including "eosinophilic granulomatosis with polyangiitis," "Churg-Strauss syndrome,"

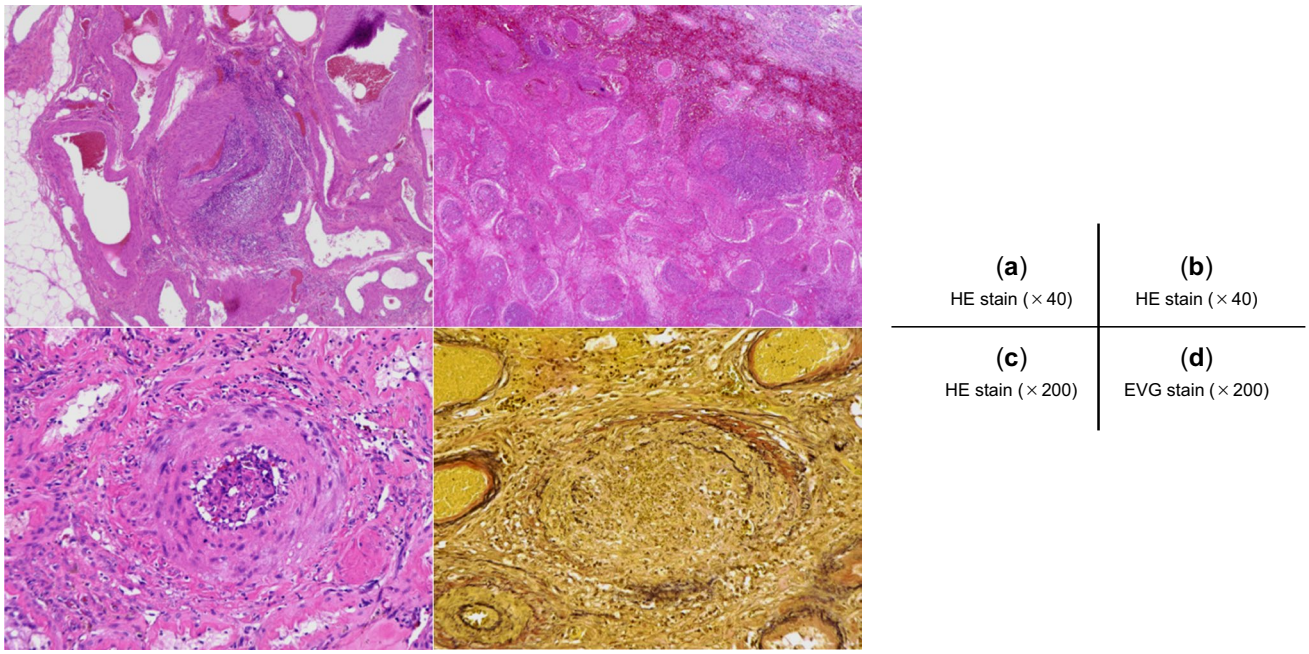

Fig. 4 Histology of extirpated testicle. Extreme infiltration of lymphoid cells around the arteries (**a**), interstitial hemorrhage, and tubular necrosis (**b**). Fibrinoid necrosis (**c**) and ruptured intimal elastic lamina (**d**) of the small-sized artery. HE, hematoxylin–eosin; EVG, Elastica van Gieson

"testicular," "testicle," "testis," "testes," "vasculitis," "arteritis," "orchitis," and "epididymitis."

Results of the literature review

Three cases of TV associated with EGPA have been reported in the English-language literature [5–7]. We summarized the clinical findings of four patients, including three reviewed cases and our case (Table 1). In the three reviewed cases, all patients developed TV unilaterally while complicating neither bronchial asthma nor other allergic disorders. One patient had a history of EGPA; however, this patient had no other symptoms related to EGPA at the onset of TV [5]. One of the two patients who developed TV as the first clinical episode of EGPA had fever 2 weeks before the development of other organ involvement, including sensory polyneuropathy and thoracic myelitis, with a negative result for MPO-ANCA [6]. Another patient who realized his right testicular symptom 1 month before the diagnosis of EGPA developed pulmonary lesions, urinary abnormalities, and sensorimotor polyneuropathy related to the disease, as well as positive MPO-ANCA test result [7]. Surgical resection was ultimately performed on the affected testicle in all patients, and histological examination demonstrated fibrinoid necrotizing vasculitis with no granulomatous lesions. Eosinophil infiltration was found in two patients, while focal infarction and hemorrhage were observed in one patient. Immunosuppressive therapies, including PSL monotherapy or PSL with IVCY, were administered to two patients. In contrast, no immunosuppressant was administered to another patient solely presenting with TV, resulting in remission of EGPA.

Discussion

Herein, we present a case of TV as an early and principal clinical sign of EGPA. The testicle is one of the most easily affected organs because it has abundant blood flow from three arterial supplies, including the cremasteric, testicular, and deferential arteries [8]. Systemic vasculitis impairs the testicle and its surrounding tissues, and TV has been identified in cases of localized or isolated vasculitis [9, 10]. In primary systemic vasculitis, polyarthritis nodosa (PAN) is the most prevalent causal disease involving TV [10, 11] and has been described as a focal type of PAN in some case reports [12–15]. Moreover, testicular pain and tenderness have been used as clinical items in the 1990 American College of Rheumatology (ACR) classification criteria for PAN [4]. Symptomatic TV was found in 2−18% of patients with PAN, whereas TV was more frequently identified as a subclinical result in autopsy analyses [9, 16]. Some cases of TV have also been reported in GPA [17–20], and TV has been observed in 12−36% of GPA patients with genitourinary involvement [21]. To the best of our knowledge, only three cases of TV have been reported in an English-language article, while other types of systemic vasculitis causing TV, such as MPA [10], unclassifiable ANCA-associated

Table 1 Clinical characteristics of testicular vasculitis related to eosinophilic granulomatosis with polyangiitis in our and reviewed cases

	Previous reports			This case
	DaJusta et al. [5]	Fukui et al. [6]	Li et al. [7]	
Age, years	21	70	57	47
EGPA diagnosis*	Previous	Later	Later	Later
BA history	ND	None	None	8 years
Affected testicle				
Symptoms (side)	Pain, scrotum enlargement, extreme tenderness (right)	Pain, swelling (right)	Discomfort, pain, swelling (right)	Pain, diffuse induration, tenderness (left)
Imaging studies	US: partially hypoechoic area; CT: unremarkable finding	CT: swollen right scrotum	ND	US: multiple focal hypoechoic areas with increased blood flow; CT: partial high-density areas
Histology	Fibrinoid necrosis of the vascular wall with focal infarction, interstitial hemorrhage, and necrotic seminiferous tubules	Eosinophilic vasculitis and fibrinoid necrosis in small-sized arteries with a vascular wall rupture in the spermatic cord	Fibrinoid necrosis of the vascular wall with eosinophils infiltration in interstitial tissue	Fibrinoid necrosis and partial rupture of the vascular wall, interstitial hemorrhage, and necrotic changes of seminiferous tubules
Surgical procedure	Inguinal orchiectomy	Inguinal orchiectomy	Orchiectomy	Inguinal orchiectomy
Findings at admission				
Other involvement**	None	Paranasal sinusitis, papules, sensory polyneuropathy, myelitis	Pulmonary infiltration, proteinuria and hematuria, sensorimotor polyneuropathy	Myalgia, arthritis, paranasal sinusitis, pulmonary infiltration, abdominal pain (jejunum involvement), sensory polyneuropathy
Eosinophilia	Slightly	Extremely	Extremely	Extremely
ANCA	ND	Negative	MPO-ANCA positive	MPO-ANCA positive
Immunosuppressive therapy	None	PSL	PSL, IVCY	mPSL, PSL, IVCY
Outcome	Improved	Improved	Improved	Improved

EGPA eosinophilic granulomatosis with polyangiitis, *BA* bronchial asthma, *ND* not described, *US* ultrasonography, *CT* computed tomography, *ANCA* antineutrophil cytoplasmic antibody, *MPO* myeloperoxidase, *PSL* oral prednisolone, *IVCY* intravenous infusion of cyclophosphamide, *mPSL* intravenous infusion of methylprednisolone

*Since the onset of testicular vasculitis (TV)

**Except for TV symptoms

vasculitis [22], giant cell arteritis [23], and IgA vasculitis [24, 25], have been presented as rare cases. Minocycline has also been found to induce TV along with positivity for ANA and ANCA [26]. The common histopathological features of TV related to PAN, GPA, MPA, and EGPA are fibrinoid necrotizing vasculitis with infarction and/or hemorrhage [5–7, 10, 12–15, 18–20], whereas the formation of granulomatous lesions has only been demonstrated in TV related to GPA [18–20]. The dominant infiltration of eosinophils around vascular lesions was observed in two cases of TV related to EGPA [6, 7], allowing differentiation between TV in EGPA and other types of vasculitis. Meanwhile, our case had no obvious finding of eosinophil infiltration, suggesting that prior immunosuppressive therapy might have led to the scavenging of invasive eosinophils despite irreversible testicular damage.

The initial clinical episode in this patient was a unilateral testicular manifestation, which eventually led to the pathological evidence of EGPA. When we focused on overall testicular involvement in primary systemic vasculitis, more than 10% of patients were found to initially have testicular symptoms alone prior to other typical organ involvement, while TV was simultaneously observed at the diagnosis of the disease in more than 40% of patients [10], suggesting that TV can be a crucial manifestation as an early sign in the development of systemic vasculitis. Even in the isolated type of TV, approximately 80% of patients have genital symptoms without constitutional symptoms such as fever and fatigue [10]. In fact, our patient and two of the reviewed cases initially demonstrated unilateral testicular pain prior to developing other involvements [6, 7]. Another patient had TV as the focus of EGPA relapse [5]. Bilateral testicular pain was reported as one of the initial symptoms in a pediatric case of EGPA, but testicular biopsy was not performed [27]. Another case of epididymo-orchitis, which was treated before developing a clinical episode suggestive of EGPA, also presented without any pathological information on the testicle [28]. Nevertheless, clinical episodes of bronchial asthma and/or other allergic disorders were not present or uncertain in the reviewed cases [5–7]. Bronchial asthma has been highlighted as a pivotal clinical sign not only in the 1990 ACR criteria [4] but also in the newly suggested 2022 ACR/European Alliance of Association for Rheumatology classification criteria [3], in which clinical items of obstructive airway disease are alternatively used. When patients have a distinct episode of obstructive airway disease, it may be helpful for predicting the development of EGPA. However, no episodes of bronchial asthma were observed in the reviewed cases, with the exception of our patient. Given the possibility of TV developing as the localized sign of vasculitis while being absent of bronchial asthma, it may be suggested that testicular manifestation can be an early and sole clinical finding in the development of EGPA.

In our review of three cases [5–7] and this case, surgical resection of the affected testicle was ultimately required. Some cases of TV have also been pathologically diagnosed through orchiectomy, even in other types of vasculitis [12–15, 18–20, 22, 23]. Among these cases, some patients with an isolated type of TV who underwent surgical resection of the testicle had no subsequent immunosuppressant to maintain remission. The other patients were administered immunosuppressive drugs for constitutional and visceral involvement associated with causal vasculitis. When testicular involvement had to be focused on to determine the diagnosis of vasculitis, most reported cases ultimately required an orchiectomy. Clinically discriminating between infections, neoplasms, torsion, and autoimmune diseases, including vasculitis, in cases of testicular involvement, is necessary. However, there are limitations in definitively determining the different diagnoses merely through imaging studies [11, 22, 29–31], suggesting that pathological examination should be performed not only in suspected cases of testicular vasculitis but also in those of testicular neoplasm. In our patient and some previous cases, testicular cancer was suspected. Moreover, orchiectomy had to be performed because a biopsy might have led to spreading of the malignant tissue to adjacent organs.

In conclusion, we present a case of TV in EGPA and review three published English-language articles. According to our findings, TV could emerge as the first EGPA episode. Meanwhile, orchiectomy was eventually performed in most reported cases of TV, not only in patients with EGPA but also in those with other types of vasculitis because it was impossible to deny the differential diagnosis of testicular neoplasm. It may be necessary to establish an advanced diagnostic strategy for early diagnosis of the TV while avoiding surgery.

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Author contribution All the authors participated in the treatment of this patient and developed an argument for this case. T-I and Y-Shi reviewed the literature and prepared the draft of this manuscript. Y-Shi contributed to revision of the manuscript. All authors have revised and approved the final manuscript.

Declarations

Consent to participate Informed consent and permission for publication were obtained from the patient in this case.

Disclosures None.

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