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【 CASE REPORT 】

An Atypical Case of Non-asthmatic Eosinophilic Granulomatosis with Polyangiitis Finally Diagnosed by Tissue Biopsy

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Abstract:
A 78-year-old woman with fever of unknown origin that had persisted for 3 months, systemic edema, and cervical lymphadenopathy was admitted to our hospital. Skin purpura and jaw claudication were subsequently observed. Histopathological examinations of the lymph nodes, skin, and temporal artery revealed findings characteristic of eosinophilic granulomatosis with polyangiitis (EGPA). However, she had no past medical history of asthma with modest eosinophilia. Although EGPA is a systemic vasculitis characterized by asthma and eosinophilia, various limited forms have been described. This was therefore considered to be an atypical form of non-asthmatic EGPA complicating with temporal arteritis (TA) diagnosed by tissue biopsy.

Key words: eosinophilic granulomatosis with polyangiitis, Churg-Strauss syndrome, temporal arteritis

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is a rare systemic vasculitis of unknown etiology that is typically characterized by bronchial asthma, significant eosinophilia, and necrotizing vasculitis (1). EGPA has three progressive phases: a prodromal allergic phase, such as bronchial asthma and rhinosinusitis; an eosinophilic phase; and a vasculitis phase. The American College of Rheumatology published the following six clinical criteria for the diagnosis of EGPA: asthma, eosinophilia >10% in a differential white blood cell count, mononeuropathy or polyneuropathy, transient pulmonary opacities on chest X-ray, paranasal sinus abnormality, and a biopsy specimen containing a blood vessel showing eosinophil infiltration in the extravascular areas (2). The presence of four or more of these six clinical criteria yields a sensitivity of 85% and a specificity of 99.7% for EGPA. EGPA may occur at any age, except during infancy, and shows a similar female-to-male ratio. In the Chapel Hill Conference definition, revised in 2012 (CHCC 2012), EGPA is mainly regarded as necrotizing vasculitis preexisting asthma and eosinophilia affecting the small blood vessels (3). However, several atypical cases of EGPA that did not precede asthma and eosinophilia have been reported. Among these, cases lacking typical clinical findings and that were diagnosed using only pathological images of the disordered tissue were considered to represent a "limited-form of EGPA" (4). We herein report a very rare case of the limited form of EGPA complicated with temporal arteritis (TA), which was diagnosed by a tissue biopsy.

Case Report

A 78-year-old woman was admitted to our hospital with a 3-month history of fever, systemic edema, and swollen cervical masses. She had no medical history of bronchial

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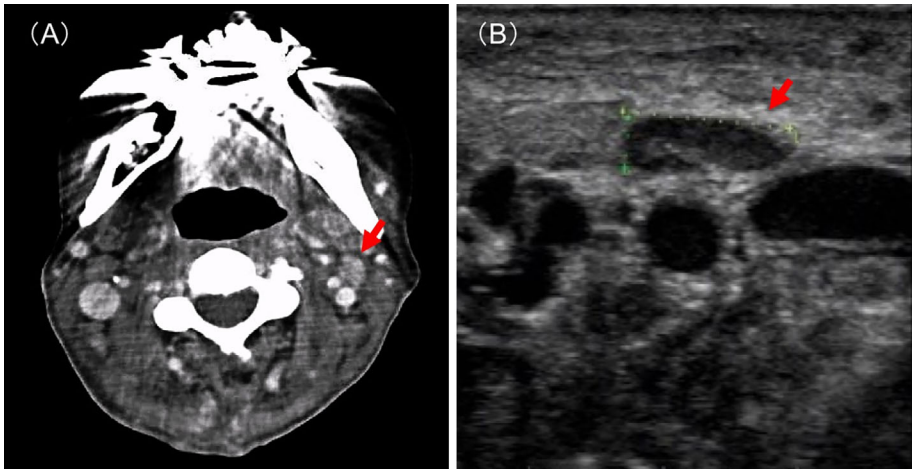

Figure 1. The CT (A) and US (B) findings. (A) Lymph node staining with contrast agent was recognized in the left neck. (B) US revealed a low-echoic area of lymphadenopathy that measured approximately 5×15 mm in diameter.

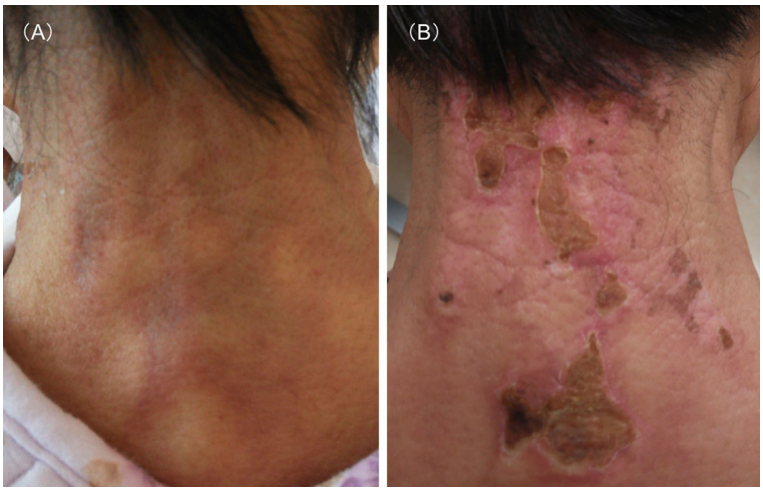

Figure 2. (A) Purpura on the back of the neck. (B) Two weeks after treatment.

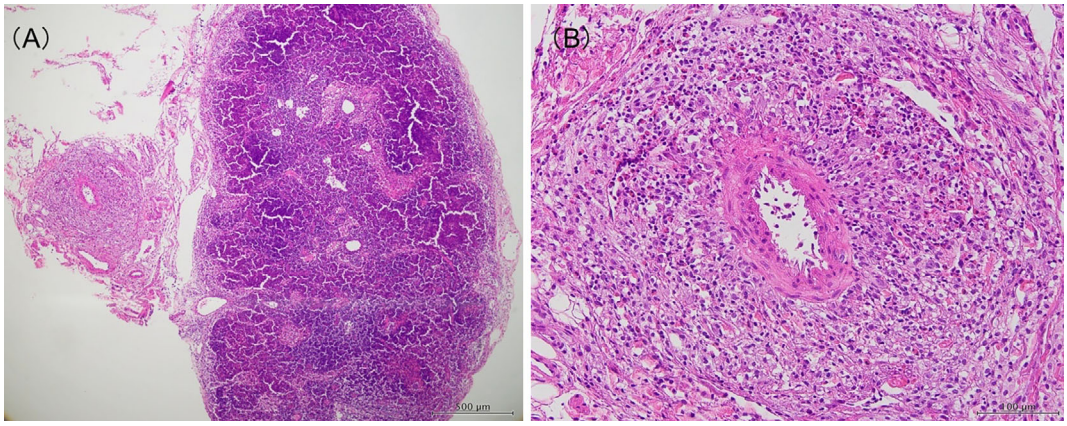

Figure 3. (A) Lymph node and surrounding blood vessel, (B) Small vessels around the lymph node show vasculitis associated with fibrinoid degeneration and the formation of granulomas with prominent eosinophil infiltration. Hematoxylin and Eosin staining; (A) magnification ×40, (B) magnification ×200.

asthma or any other allergic disorders. She had never smoked and was not an alcohol abuser. She had no family history of connective tissue disease. A physical examination revealed the following: pulse rate, 90 beats/min; blood pressure, 130/68 mmHg (normal); fever, 37.3℃; and respiratory rate, 18 breaths/min. The findings of a respiratory examination were normal with no rales or rhonchi. Cervical lymphadenopathy and systemic edema were evident. The results of a neurological examination were normal. A laboratory examination revealed the following findings: white blood cell count, 12,650/μL; hemoglobin, 10.0 g/dL; platelet count, 386×10^3/μL; C-reactive protein, 15.79 mg/dL; erythrocyte sedimentation rate, 102 mm in the first hour; IgE, 131 IU/dL; and IgG4, 53 mg/dL. The differential counts on the peripheral smear were as follows: neutrophils, 76.5%, lymphocytes, 9.0%; monocytes, 9.0%; and eosinophils, 5.5%. The results of liver and renal function tests were within the normal limits. Neither anti-nuclear antibodies nor antineutrophil cytoplasmic antibodies (ANCA) were detected. Ultrasonography revealed a swollen lymph node of approximately 5×15 mm in diameter on the left side of the neck. Whole-body contrast computed tomography demonstrated no other lymph node swelling except a cervical mass (Fig. 1). Two sets of blood culture tests were negative. To determine the causal etiology of the symptoms, we performed a cervical lymph node biopsy. After admission, she also complained of pain at the back of the neck and jaw claudication. Thereafter, new purpura appeared at the pain site (Fig. 2). Thus, skin and temporal artery biopsies were also performed. Histological examinations of the lymph node revealed vasculitis associated with fibrinoid degeneration and the formation of granulomas with prominent eosinophil infiltration in the small vessels around the lymph node (Fig. 3) and characteristic findings of EGPA. Tissue biopsies of the skin and left superficial temporal artery also showed the infiltration of inflammatory cells with eosinophils and narrowing of the vascular lumen (Fig. 4, 5). Although the clinical manifestations, such as the absence of asthma and neuropathy, did not completely meet the diagnostic criteria of EGPA, we diagnosed the patient with atypical EGPA based on the pathological findings, which were characteristic of EGPA, with the exclusion of granulomatosis with polyangiitis (GPA) and polyarteritis nodosa (PAN). Accordingly, we started treatment with prednisolone (PSL; 20 mg/day), and the symptoms and laboratory data promptly improved (Fig. 6). We gradually reduced the PSL dose to 5 mg/day as a maintenance dose over a 5-month period and have not observed recurrence for more than 2 years.

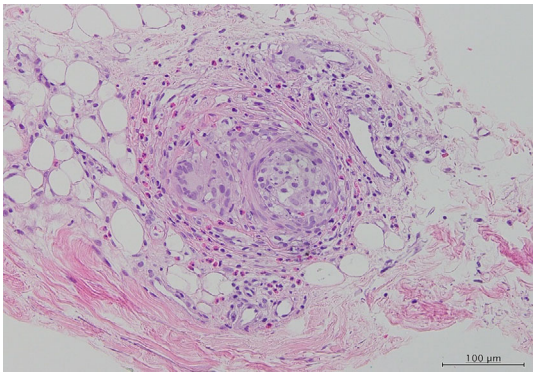

Figure 4. Skin from the back of the neck biopsy showing the narrowing of the lumen of the artery due to granuloma with eosinophil infiltration. Hematoxylin and Eosin staining; magnification ×400.

Discussion

EGPA is clinically diagnosed based on the ACR 1990 criteria for the classification of Churg-Strauss syndrome, which includes asthma, eosinophilia, mono- or poly-neuropathy, pulmonary infiltrates, paranasal sinusitis, and extravascular eosinophils on biopsy. In this case, the patient had sustained fever, cervical lymphadenopathy, and new-onset jaw claudication and purpura of the neck. While these symptoms are not listed in the diagnostic criteria for EGPA, the histologi-

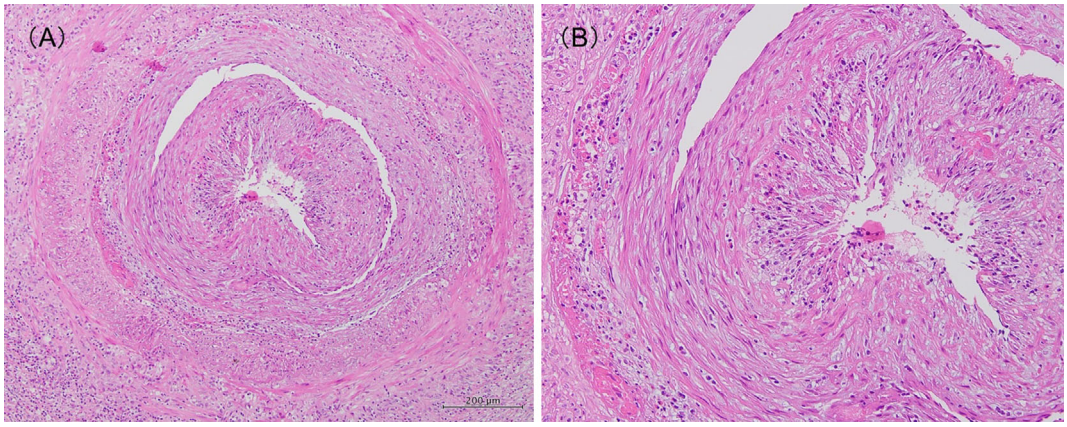

Figure 5. Cross-sections of the left temporal artery showing eosinophil infiltration, marked thickening of the wall, and narrowing of the lumen. Hematoxylin and Eosin staining; (A) magnification ×40, (B) magnification ×100.

cal findings of all the biopsy specimens from the sites of lymphadenopathy and purpura, and the temporal artery demonstrated distinctive characteristics of EGPA; thus, we diagnosed this case as atypical EGPA. Several similar cases lacking the hallmark features of EGPA, that were only diagnosed by tissue biopsy have been previously reported as a limited form of EGPA (Table 1) (5-14). With the exception of severe cases, EGPA usually improves with steroid treatment alone, as was observed in this case. However, it remains unclear whether these variant forms of EGPA represent clinicopathological entities that are distinct from typical EGPA.

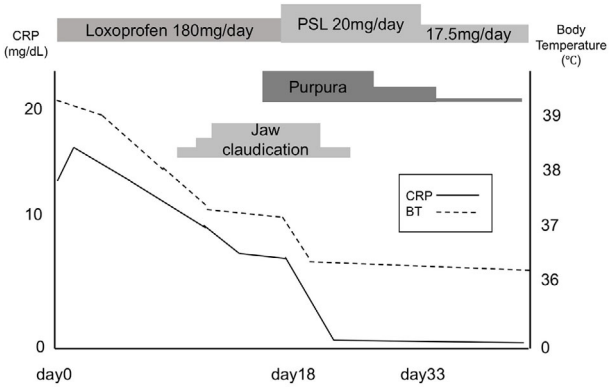

Figure 6. **The clinical course after admission.**

In this case, the exclusion of GPA and PAN was of importance since these diseases present similar clinical and pathological features and often require combination therapy of PSL with an immunosuppressant. GPA was excluded because there were no lesions in the upper respiratory tract, lungs, or kidneys, along with the absence of proteinase 3 ANCA. In addition, the pathological eosinophilic infiltration of GPA into the vessel wall is milder in comparison to EGPA (15). PAN was also unlikely because this case presented distinct histological findings of extravascular granulomas formation and eosinophilic infiltration in the blood vessels (16).

This case is also unique due to the vasculitic involvement of the temporal arteries (TA). There are only 9 descriptions in the literature of TA as a manifestation of EGPA. This includes 4 cases of a giant cell variety (giant cell arteritis: GCA) and 5 cases of other histologic patterns (Table 2) (6, 17-24). Among these, only the case of Bollinger, et al. involved non-asthmatic EGPA; however, a pathological

Table 1. **Summary of the clinical manifestations in the reported cases of non-asthmatic EGPA in the literature.**

References	Age/ sex	Eosinophilia	Neuropathy	Pulmonary infiltrates	Paranasal sinusitis	Other symptoms	ANCA
5	58/M	+	+	−	−	Rapid progress renal failure	MPO-ANCA
6	27/M	+	−	−	−	Temporal arteritis, purpura	-
7	35/F	−	+	+	+	Digital gangrene	MPO-ANCA
8	53/M	+	−	−	+	Mass in the neck	-
9	61/M	+	+	−	−	Skin purpura	MPO-ANCA
10	32/M	+	+	−	+	Rash lower limbs, polyarthralgia	MPO-ANCA
11	67/F	+	−	−	−	Renal eosinophil infiltration	MPO-ANCA
12	21/M	−	−	+	−		-
13	52/M	+	−	−	−	Vasculitis of the transverse colon and gallbladder	-
14	38/M	+	+	+	−	Erythematous maculopapular eruptions	-
This report	78/F	±	−	−	−	Temporal arteritis, lymphadenopathy, systemic edema	-

EGPA: Eosinophilic granulomatosis with polyangiitis, ANCA: antineutrophil cytoplasmic antibodies, MPO: myeloperoxidase

Table 2. **EGPA Cases Complicated with Temporal Arteritis in the Literature.**

References	Age/sex	Asthma	Eosinophilia	Neuropathy	Pathological findings of temporal artery		
					Eosinophil infiltrate	Giant cell	Necrotic lesion
17	59/F	+	+	+	+	+	+
18	49/F	+	+	+	+	−	+
19	23/M	−	+	−	±	+	+
20	25/M	+	+	+	+	+	+
21	41/M	+	+	−	+	−	−
22	48/M	+	+	−	+	−	−
23	74/M	+	+	−	+	−	−
24	77/F	+	+	+	−	+	−
6	27/M	−	+	−	+	−	−
This report	78/F	−	±	−	+	−	−

examination revealed giant cell TA (19). Thus, this appears to be the first case report of the limited form of EGPA complicated with non-giant cell TA. Juvenile temporal arteritis with eosinophilia (JTAE), which principally occurs in young individuals, also causes TA with non-giant cell and eosinophil infiltration (25). However, this disease is characterized by a lack of systemic symptoms. The clinical features of cervical lymphadenopathy, eosinophilia, and eosinophilic infiltration in the lesion are often observed in Kimura Disease (26). In contrast, our case involved elderly-onset systemic vasculitis with no elevation of serum IgE and a histological examination revealed no marked infiltration of eosinophils and no lymphoid follicular structure with a germinal center, which is a characteristic of Kimura disease.

In summary, EGPA is a systemic vasculitis that precedes asthma and which causes various vasculitis symptoms; however, atypical cases exist. We should bear in mind that there are some atypical cases of EGPA that do not always meet the diagnostic criteria and rigorously ensure tissue biopsies if the diagnosis is considered to be difficult.

The authors state that they have no Conflict of Interest (COI).

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