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【 CASE REPORT 】

Polyarteritis Nodosa with Marked Eosinophilia, Associated with Severe Gastrointestinal Tract Involvement and Recurrent Venous Thrombosis

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Abstract:
A 45-year-old man was admitted with acute abdominal pain and eosinophilia. Abdominal computed tomography revealed thickness of the ascending and transverse colon with decreased contrast enhancement and a small amount of ascites. In an emergency operation, the necrotic colon was resected. Histopathology showed subserous medium-sized arteritis with abundant eosinophil infiltrates and thrombosis in the portal vein branches. He was diagnosed with polyarteritis nodosa (PAN), and immunosuppressive therapy improved his condition. Two years later, the disease recurred with ischemic cutaneous lesions and marked eosinophilia. Our experience suggests that marked eosinophilia in PAN may imply severe organ involvement, including gastrointestinal necrosis, as well as the association of venous thrombosis.

Key words: polyarteritis nodosa, hypereosinophilic syndrome, medium-sized vasculitis, colon, eosinophilia, acute surgical abdomen

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Introduction

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis of the medium or small arteries that frequently involves the skin, peripheral nerves, musculoskeletal structure, and gastrointestinal tract (1, 2). The gastrointestinal involvement in PAN includes acute cholecystitis, gallbladder infarction, and bowel infarctions or perforation (1). Histologically, neutrophil infiltrates are usually seen in the vessel wall, while eosinophilic inflammation may be found less commonly (3).

Hypereosinophilic syndrome (HES) is a rare leukoproliferative disorder characterized by unexplained prolonged eosinophilia (>1,500/μL, usually for more than 6 months) with organ damage induced by tissue eosinophilia (4). Multiple organs are often involved, including the cutaneous, respiratory, cardiovascular, and gastrointestinal systems (4). In addition, this disorder can cause serious venous thrombosis in the cutaneous, cardiac, cerebral, portal, and deep vein systems (5-11).

We herein report a case of PAN, that presented with necrosis of the colon, associated with recurrent venous thrombosis and marked eosinophilia, as observed in HES.

Case Report

A previously healthy 45-year-old man was admitted to our hospital for acute abdominal pain. The patient had had vomiting and diarrhea eight days before admission as well as abdominal pain for four days. His medical history included hay fever and pruritic rash for 20 years, which tended to worsen in winter. He denied a history of asthma or sinusitis. The patient was not taking any medicine. He

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had smoked 10 cigarettes daily for 20 years and did not drink alcohol regularly.

On a physical examination, his body temperature was 38.5℃, blood pressure was 139/77 mmHg, and pulse rate was 79 beats per minute. He was alert, and his oxygen saturation was 96% on room air temperature. There was slight muscular guarding on the abdomen and severe tenderness on the right flank region, with rebound tenderness. Laboratory data revealed the following: white blood cell count, 13,100/μL (eosinophils, 22%, 2,282/μL); platelet count, 97,000/μL; sodium level, 131.3 mEq/L; potassium level, 4.3 mEq/L; chloride level, 92.2 mEq/L, lactate dehydrogenase level, 284 U/L; and C-reactive protein level, 19.1 mg/dL. The levels of transaminase and renal function test results were within the normal range. The levels of the international normalized ratio of prothrombin time and fibrinogen and fibrinogen degradation products were all elevated at 1.24 seconds, 589 mg/dL, and 19.1 μg/mL, respectively. Antinuclear antibodies, antineutrophil cytoplasmic antibodies (ANCA), and antiphospholipid antibodies were not detected in the sera.

Contrast-enhanced computed tomography (CT) of the abdomen revealed thickness of the ascending and the transverse colon with decreased enhancement, small amount of ascites, and increased attenuation of mesenteric fat and paraaortic lesions (Fig. 1). In addition, thrombosis in the superior mesenteric vein was suspected. An emergency operation was performed as colonic necrosis and diffuse peritonitis were suspected, and a necrotic colon of 15-cm length at the hepatic flexure (Fig. 2A) was observed, with occlusive thrombophlebitis in the right branch of the middle colonic vein and the right subcolonic veins (Fig. 2B). Resection of the necrotic colon with construction of artificial anus was performed. Grossly, there was ulceration and hemorrhaging in the resected colon, with inflammatory changes extending to the subserosa. A histological examination revealed medium-sized arteritis with significant infiltration of eosinophils and neutrophils in the subserosa (Fig. 3A) as well as damaged elastic fibers of the arterial walls on elastic van Gieson staining (Fig. 3B). A screening test for parasites in the serum and stool was negative, and FIP1-like-1-platelet-derived growth factor receptor (FIP1 L1-PDGFR) was also negative. A bone marrow examination performed one month after therapy revealed hypocellular marrow without myeloblasts, and the result of T cell receptor (TCR) rearrangement was negative. We therefore established a diagnosis of gastrointestinal involvement of PAN associated with reactive eosinophilia, as the case met the definition of PAN (12).

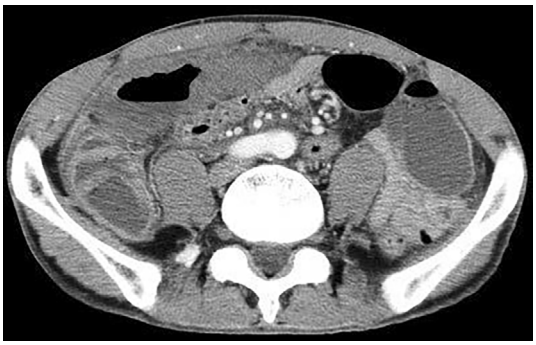

Figure 1. Contrast-enhanced CT revealed thickness of the ascending and transverse colon with decreased enhancement, suggesting necrotic lesions of the colon.

One week after surgery, his rashes worsened, and multiple erythematous papulae appeared on the trunk and extremities with further elevation of eosinophils (10,080/μL), but a skin biopsy revealed mild perivascular inflammation. Induction therapy with high-dose glucocorticoids and intravenous cyclophosphamide, targeting gastrointestinal PAN, improved his condition (Fig. 4). Although we were unable to deny the possibility of a cutaneous allergic reaction to the various drugs used in the perioperative period, the cutaneous lesions also disappeared within a few weeks. In addition, anticoagulation therapy with heparin followed by apixaban was also

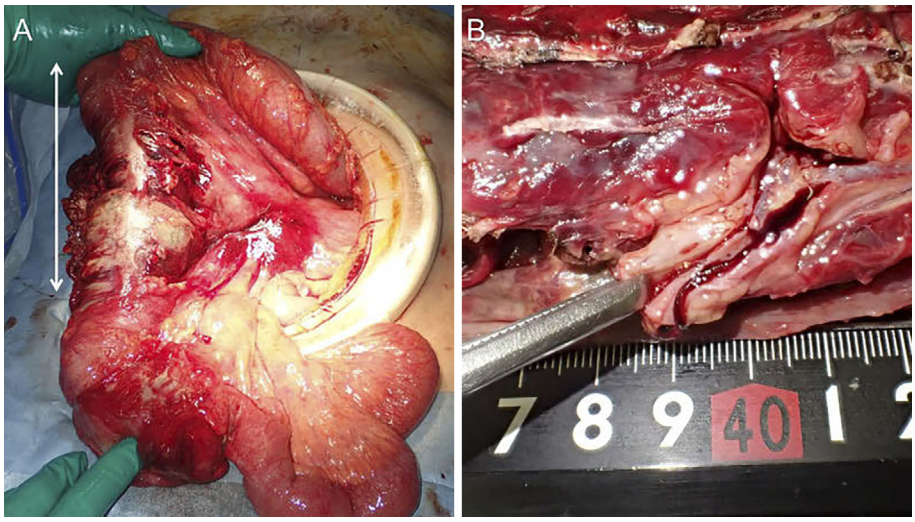

Figure 2. On emergency operation, the necrotic colon 15 cm in length at the hepatic flexure, shown with white arrow, was recognized (A), with thrombosis in the branches of the portal veins (B).

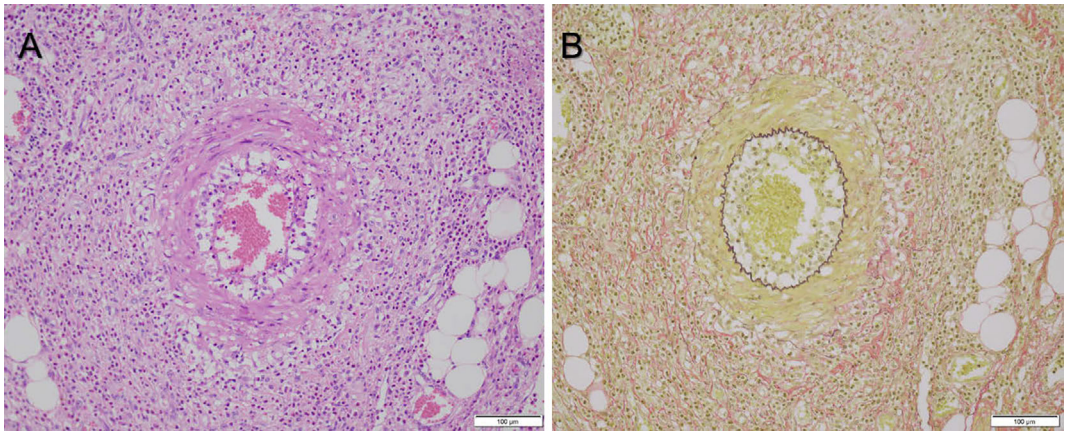

Figure 3. **Pathological findings of the lesions revealed significant infiltrates of eosinophils and neutrophils in subserous medium-sized arteries (A), with damaged elastic fibers noted on elastic van Gieson staining (B).**

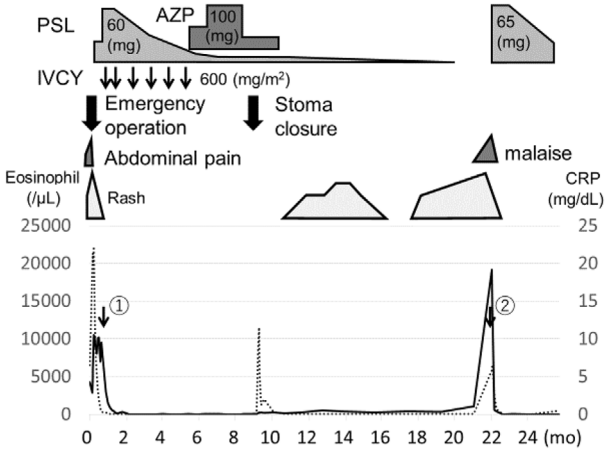

Figure 4. **The clinical course and eosinophil counts. The eosinophil counts and CRP levels are indicated with solid and dotted lines, respectively. "①" and "②" indicate the first and second examinations of the bone marrow, respectively. PSL: prednisolone, IVCY: intravenous cyclophosphamide, AZP: azathioprine**

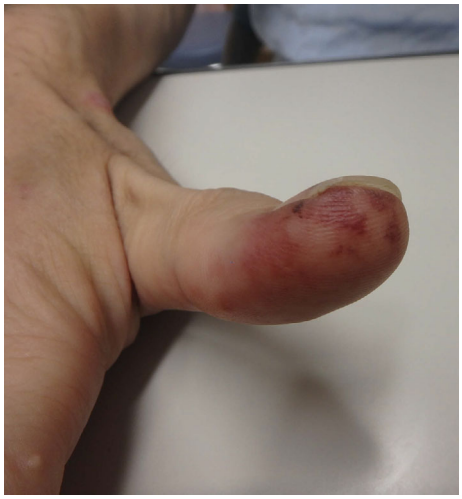

Figure 5. **Purpura with tenderness at the right thumb at recurrence.**

started for venous thrombosis and continued for three months. He was discharged two months after surgery. Azathioprine was used as maintenance therapy, but this agent was subsequently discontinued due to nausea (Fig. 4).

Nine months after the operation, the patient remained well while taking 5 mg of prednisolone daily and underwent stoma closure. He stopped all medications 20 months after the initial presentation. Twelve weeks after stopping glucocorticoids, he was again admitted for malaise and cutaneous lesions, with marked eosinophilia (eosinophils, 19,159/μL). He had swelling of the right cheek and multiple erythematous macules on the extremities and truncus. Furthermore, purpura with tenderness at the right thumb was noted (Fig. 5), which was considered compatible with ischemic lesions due to PAN, although a skin biopsy was not performed. Contrast-enhanced CT revealed deep vein thrombosis in the left renal vein. A biopsy and examination of the bone marrow, performed the day after readmission under no glucocorticoid therapy, showed hypocellular marrow with a nucleated cell count of 43,000/μL but proliferation of eosinophilic series [myelocyte 1.0%, metamyelocyte 20.8%, stab cell 4%, and segmented leukocyte 43.8% (normal range, 1-5% for each)]. Therapy with glucocorticoids and edoxaban was started, which again improved his symptoms.

Discussion

Our case initially presented with colon necrosis due to medium-sized vasculitis with significant eosinophil infiltrates, which was associated with recurrent venous thrombosis and marked eosinophilia. The case had neither signs of myeloproliferative disorders (myeloblasts in the bone marrow, TCR rearrangement, FIP1 L1-PDGFR gene) nor any causes of reactive eosinophilia (drugs, parasitic infection), thus suggesting a possible diagnosis of idiopathic HES. However, we ultimately considered his hypereosinophilic

state to be a secondary reaction to PAN and its organ involvement, considering the relationship between the eosinophil counts and the vasculitic phases (Fig. 4). Our case did not have any signs suggesting small-vessel vasculitis, such as ANCA-associated vasculitis, cryoglobulinemic vasculitis, or IgA vasculitis, and met only two (eosinophilia and extravascular eosinophils) of the criteria for EGPA (13). Eosinophil-rich medium-sized vasculitis has also been reported in juvenile temporal arteritis, which is characterized by localized eosinophilic arteritis with sparse giant cells of the temporal arteries in the young. This disease concept seems pathologically similar to our case, particularly with regard to the arterial size involved and abundant eosinophil infiltrates, although our case did not have any cranial symptoms or signs suggesting this disorder (14).

A retrospective cohort study of 54 PAN cases encountered between 1986-2000 showed that 8 (15%) had bowel infarction or perforation (4 large bowel, and 4 small bowel), suggesting gastrointestinal tract involvement of PAN as a rare but potentially fatal complication (9). Recently, gastrointestinal involvement was also recognized as the one and only poor prognostic factor in PAN (15). Another study of systemic necrotizing vasculitis with surgical abdomen found that eosinophilia was reported in 0 of 12 PAN cases, in marked contrast to its observation in all 4 cases of EGPA (10). To our knowledge, marked eosinophilia in gastrointestinal PAN, as seen in our case, has not been reported, and only one case of HES with necrotizing vasculitis in the skin and the small intestine, resulting in bowel perforation, has been reported (2).

The recurrent deep vein thrombosis in our case was likely associated with a hypereosinophilic state. A previous review suggested that up to 25% of HES patients develop thromboembolic complications and that 5-10% of patients die from them (5). Venous thrombosis can even be the initial manifestation of HES (6-8, 16, 17). Fujita et al. reported two cases of HES with life-threatening thrombotic complications. The common histological characteristics among the cases were thrombosis with marked eosinophilia and eosinophil degranulation. An immunohistological analysis in one case revealed the expression of eosinophilic cationic protein (ECP) (16), suggesting that some cationic proteins in the eosinophil granules may cause tissue and endothelial cell damage through cytotoxic effects (18). Furthermore, thrombus formation may be enhanced by the effects of ECP on the coagulation-fibrinolysis system (19, 20).

In conclusion, we experienced the unique case of a patient with medium-sized vasculitis who had abundant eosinophil infiltrates in the colon and recurrent venous thrombosis that was ultimately accurately diagnosed to be gastrointestinal tract involvement of PAN. Our experience suggests that marked eosinophilia in PAN may imply severe organ involvement, including gastrointestinal necrosis, as well as the association of venous thrombosis.

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

Hiroshi Oiwa and Kohei Taniguchi contributed equally to this work.

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