Novel Pediatric Granulomatosis with Polyangiitis With a Marked Bloody Pericardial Effusion and Bloody Stool: A Case Report

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Case report

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Abstract

Background

Granulomatosis with polyangiitis (GPA) is a syndrome of refractory vasculitis in the upper respiratory tract, lungs, kidneys, and systemic small and medium-sized arteries; adults and children have similar courses. A pediatric GPA case with a preceding bloody pericardial effusion, which caused cardiac tamponade, and bloody stool has not been reported.

Case presentation:

A 14-year-old boy was referred for the evaluation of prolonged fever. He had chest pain and bloody stools, and diagnostic imaging showed a pericardial effusion. Immediately after admission, his systolic blood pressure decreased (85/70 mmHg), and pericardiocentesis was performed, with aspiration of approximately 500 mL of bloody pericardial fluid. Because pericardiocentesis increased the blood pressure (115/65 mmHg), the cause of the blood pressure decrease was diagnosed as cardiac tamponade. Because the pericardial fluid cytology was negative for malignant disease, as were chest MRI and gallium scintigraphy, colonoscopy was performed and showed multiple irregular-shaped aphthae from the right transverse colon to the cecum on the contralateral side of the mesenteric attachments, and a biopsy of the aphthous region showed necrotizing granulomatous inflammation. The patient also had an elevated serine proteinase 3-anti-neutrophil cytoplasmic antibody (PR3-ANCA) level (141 IU/mL) on serological examination. Head MRI showed thickening of nasal and sinus mucosa and a cystic mass in the left sphenoid sinus. Therefore, GPA was diagnosed based on these findings, and treatment with oral prednisolone (PSL) and azathioprine was started. After the treatment, the bloody stool disappeared, and there was no recurrence of pericardial effusion even after completing PSL tapering, and the PR3-ANCA level was maintained in the normal range.

Conclusions

Although pericarditis is a common cardiac complication of GPA, there have been no previous reports of cardiac tamponade due to pericarditis. This is the first case of a pediatric patient with cardiac and gastrointestinal complications preceding the main symptoms, including upper and lower respiratory tract and renal symptoms, although cases of GPA with bloody stools are extremely rare. In conclusion, the sequencing of measuring ANCA levels appears important assuming the vasculitic syndrome as one of differential diseases causing persistent fever and bloody stool including such as the inflammatory bowel disease.

Background

Granulomatosis with polyangiitis (GPA) is one of the vasculitis syndromes that used to be called Wegener's granulomatosis and was reclassified as GPA at the 2012 Chapel Hill Consensus Conference (CHCC 2012). The three main symptoms of GPA are 1) necrotizing granulomatous inflammation involving the upper and lower respiratory tracts, 2) necrotizing glomerulonephritis, and 3) systemic necrotizing granulomatous vasculitis affecting predominantly small to medium vessels, in which anti-neutrophil cytoplasmic antibody (ANCA) is involved [1]. Although the clinical course of pediatric GPA is similar to that in adults [2], adult cases with gastrointestinal complications such as inflammatory bowel disease [3, 4] and cardiac diseases [5, 6] have been reported.

A pediatric GPA case in which bloody stool and diarrhea as gastrointestinal symptoms and epicarditis as a cardiac complication preceded the main symptoms is presented. In this case, cardiac tamponade was caused by a pericardial effusion derived from epicarditis, but no similar cases were found in adults. In addition, there were also no previous reports of pediatric GPA cases with gastrointestinal involvement preceding the main symptoms.

Case Presentation

A 14-year-old boy with no specific past or family history was referred to our institute in order to identify the origin of fever. He presented with bloody stool for several days two months before admission, but the bloody stool disappeared spontaneously. Furthermore, he suffered from remittent fever of around 39°C and malaise followed by diarrhea and appetite loss three weeks before admission. Thus, he consulted a referral doctor and was referred to our institute. However, he had chest pain during the outpatient follow-up one week before admission, and a pericardial effusion was observed on transthoracic echocardiography and thoracoabdominal contrast-enhanced CT. Because the pericardial effusion continued to increase, he was admitted to our institute for detailed examination and treatment of the underlying disease.

At the time of admission, his height and weight were 170 cm (+ 0.7 standard deviation (SD)) and 47.2 kg (-0.8 SD), respectively, and no obvious weight loss was found, because his weight two months earlier was 48.0 kg. Body temperature, blood pressure, heart rate, respiratory rate, and oxygen saturation on room air were 37.1°C, 116/61 mmHg, 110 beats/minute, 14 breaths/minute, and 97%, respectively. On physical examination, he had a mild pale complexion and eyelid conjunctiva, diminished heart sounds, anterior chest pain relieved by bending forward, and mild tenderness in the lower mid-abdomen. Laboratory examinations on admission showed a white blood cell count of 7200/μL (neutrophils 68.5%, lymphocytes 23.5%, and eosinophils 2.0%), C-reactive protein of 2.4 mg/dL, erythrocyte sedimentation rate at one hour of 93 mm, hemoglobin of 8.3 g/dL, ferritin of 31 ng/mL, total protein of 7.4 g/dL, albumin of 3.3 g/dL, IgG of 1901 mg/dL, brain natriuretic peptide of 27.5 pg/mL, serine proteinase 3-anti-neutrophil cytoplasmic antibody (PR3-ANCA) of 141 IU/mL, and fecal human hemoglobin level of 105 ng/mL. No remarkable abnormalities were found on urinalysis and electrocardiography. On chest X-ray, the cardiothoracic ratio increased from 41.0–55.0% in the week before admission (Fig. 1a). Transthoracic echocardiography showed an echo-free space of about 30 mm from the apex to the pericardium on the

left ventricular axial view, indicating a pericardial effusion (Fig. 1b). In addition, anomalous motion of the ventricular septum was also confirmed, and the diameter of the inferior vena cava was 22 mm, with no respiratory variability. However, on the second day of admission, pericardiocentesis was performed because of his sudden systolic blood pressure decrease to 85/70 mmHg; approximately 500 mL of bloody pericardial fluid were aspirated by puncture (Fig. 1c), and his blood pressure increased to 115/65 mmHg. Therefore, it was diagnosed that the decreased blood pressure was due to cardiac tamponade. The fine needle aspiration fluid was an exudative pericardial fluid, and no malignant cells were confirmed by cytodiagnosis. In addition, no heart tumor was identified on chest contrast-enhanced MRI, but contrast delay along the pericardium was observed, which was consistent with the finding of pericarditis (Fig. 1d), and gallium scintigraphy also showed no abnormal accumulation systemically. After pericardiocentesis, bloody stool persisted, though the inflammatory response tended to decrease. Therefore, esophagogastroduodenoscopy (EGD) and colonoscopy (CS) were performed, but EGD showed no macroscopic or histological abnormalities. However, CS showed multiple irregular-shaped aphthae on the contralateral side of the mesenteric attachments from the right transverse colon to the cecum (Fig. 2a), but no abnormal findings were observed on small intestinal capsule endoscopy. Mucosal biopsy at the ascending colon and cecum showed nonspecific inflammatory cell infiltration into the submucosa and some granulomatous findings with prominent neutrophilic infiltration adjacent to blood vessels (Fig. 2b). Head MRI showed nasal and sinus mucosal thickening and a cystic mass in the left sphenoid sinus, but no obvious abnormalities were found on renal biopsy. No abnormal variants relating monogenic inflammatory bowel diseases could be detected on the findings of whole-exome sequencing. GPA was diagnosed according to the American College of Rheumatology or the 2012 Revised International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis [1] and the Endorsed Consensus Criteria for the Classification of Childhood Vasculitides of the European League Against Rheumatism (EULAR)/Paediatric Rheumatology European Society (PRES) [7], the EULAR/Paediatric Rheumatology International Trials Organisation (PRINTO)/PRES proposed validated classification criteria [8] and the algorithm of the European Medicines Agency (EMEA) [9]. After the diagnosis, treatment with intravenous prednisolone (PSL) (40 mg/day) and azathioprine (AZA) (100 mg/day) was performed on the 21st day of hospitalization, and negative fecal occult blood was confirmed on the 29th day. The patient was discharged on the 36th day, and PR3-ANCA converted to negative during outpatient treatment. However, the PR3-ANCA level increased again, the fecal occult blood test became positive, and the appearance of urine micro occult blood and protein were confirmed with the end of PSL tapering. Therefore, oral PSL was resumed, and methotrexate (MTX) (12 mg/week) was added. Currently, he has no apparent clinical symptoms, and PR3-ANCA has remained around 3.0 IU/mL with the combination therapy of AZA and MTX.

Discussion And Conclusions

GPA is classified as a subcategory of small vasculitis, anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) in the CHCC 2012. AAV also includes microscopic polyangiitis (MPA) and eosinophilic polyangiitis with polyangiitis (EGPA) [1].

In GPA, PR3-ANCA is frequently elevated, and it was reported that the sensitivity and specificity of PR3-ANCA for GPA were 65–67% and 86–89%, respectively [10], but the mechanism by which ANCA is involved in GPA has been unclear. In previous reports, neutrophil extracellular traps (NETs), which are chromatin fibers released by PR3-ANCA and neutrophil activation by inflammatory cytokines, vascular endothelial cell damage due to abnormal cytokine production, and neutrophil cell death were involved in the pathogenesis of GPA. Therefore, it was suggested that the titer of PR3-ANCA was an indicator of vasculitis [11, 12]. The main symptoms of GPA were upper and lower airway tract and renal symptoms with frequencies of almost 70%, 78%, and 65%, respectively, and increased PR3-ANCA titers and detection of histological granulomatous inflammation were seen in 63% and 54% of GPA patients, respectively [8]. In typical GPA cases, the main symptoms are often observed in the order of upper airway, pulmonary, and renal symptom, whereas the present case was atypical, since no main symptoms were observed with cardiac and gastrointestinal symptoms preceding, despite sinus lesions confirmed on head MRI. However, EULAR/PRINTO/PRES childhood GPA/Wegener's granulomatosis includes the following 6 findings: 1) histopathological granulomatous inflammation; 2) upper respiratory tract lesions; 3) laryngeal, tracheal, and bronchial lesions; 4) pulmonary lesions on chest X-ray and CT; 5) positive MPO/PR3-ANCA, and 6) renal lesions. Of these, histopathological granulomatous inflammation, upper airway lesions, and positive PR3-ANCA were observed in the present case. Therefore, this case was diagnosed as childhood GPA with sensitivity of 93.3% and specificity of 99.2% [8]. There were few past reports of GPA in which the initial symptoms were derived from cardiac and gastrointestinal complications, as in the present case. In particular, no GPA cases of cardiac tamponade due to epicarditis have been reported previously, but only an adult EGPA case with cardiac tamponade was reported [13]. On the other hand, we identified 21 GPA cases resulting in bloody stool, most commonly in middle-aged males with bleeding sources in the small and large intestine, and most appeared synchronously or were delayed with respect to airway and renal symptoms. In these cases, gastrointestinal symptoms preceded in only three adult cases, and the source of bleeding in all cases was the colon. In addition, two of three cases rapidly developed renal dysfunction and alveolar hemorrhage later [14–16]. An additional table file shows this in more detail [see Additional file 1].

The treatment plan for the patient in the present case was made according to the disease severity determined using the EULAR recommendation [17]. First, because the patient presented with cardiac tamponade caused by epicarditis and a pericardial effusion, PSL was used for the severe form of GPA, and remission was confirmed within 2 weeks with CRP turning negative, the PR3-ANCA titer decreasing, and disappearance of bloody stool. Therefore, cyclophosphamide was not used as the remission induction drug, but AZA was used as the remission maintenance drug. However, after PSL was stopped, bloody stool and an increased PR3-ANCA titer appeared, resulting in relapse; therefore, combination therapy with MTX was also required. According to a cohort study of Japanese AAV performed by the Japan Research Committee of the Ministry of Health, Labour, and Welfare for Intractable Vasculitis, in Japanese GPA, the remission rate at six months after starting treatment was 87%, the relapse rate at 18 months after starting treatment was 15%, and the mortality rate at 24 months after starting treatment

was 6% [18]. In addition, because GPA progresses rapidly, aggressive immunosuppressive therapy was selected even for this case.

In conclusion, the present case was the first pediatric GPA case with cardiac and gastrointestinal complications preceding major symptoms, as well as a rare case of cardiac tamponade due to epicarditis, which was not reported in past GPA cases. Based on the experience of this case, the sequencing of measuring ANCA levels appears important assuming the vasculitic syndrome as one of differential diseases causing persistent fever and bloody stool including such as the inflammatory bowel disease and other chronic gastrointestinal diseases.

List Of Abbreviations

AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis; AZA: azathioprine; CHCC 2012: 2012 Chapel Hill Consensus Conference; CS: colonoscopy; EGD: esophagogastroduodenoscopy; EGPA: eosinophilic granulomatosis with polyangiitis; EMEA: European Medicines Agency; EULAR: European League Against Rheumatism; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; MTX: methotrexate; NETs: neutrophil extracellular traps; PRES: Paediatric Rheumatology European Society; PRINTO: Paediatric Rheumatology International Trials Organisation: PR3-ANCA: serine proteinase 3-anti-neutrophil cytoplasmic antibody; PSL: prednisolone; SD: standard deviation

Declarations

Ethics approval and consent to participate

This case report was approved by the institutional ethics committee for the Faculty of Medicine, Juntendo University, Japan.

Consent for publication

Written informed consent was obtained from the parents of the patient for publication of this case report and any accompanying images.

Availability of data and materials

The datasets used in this report are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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The authors had no funding sources for this study.

Authors' contributions

All authors were involved in the care of this patient. KM, NM, and JK wrote the initial draft of the manuscript. FH wrote the part about cardiovascular complications. JK, EY, KK, MK, IN, TK, KR, SM, ME, HK, IT, KT, and ST critically approved and revised the overall content of the manuscript. All authors read and approved the final manuscript. KM and KJ contributed equally to this work and should be considered as co-first authors.

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Figures

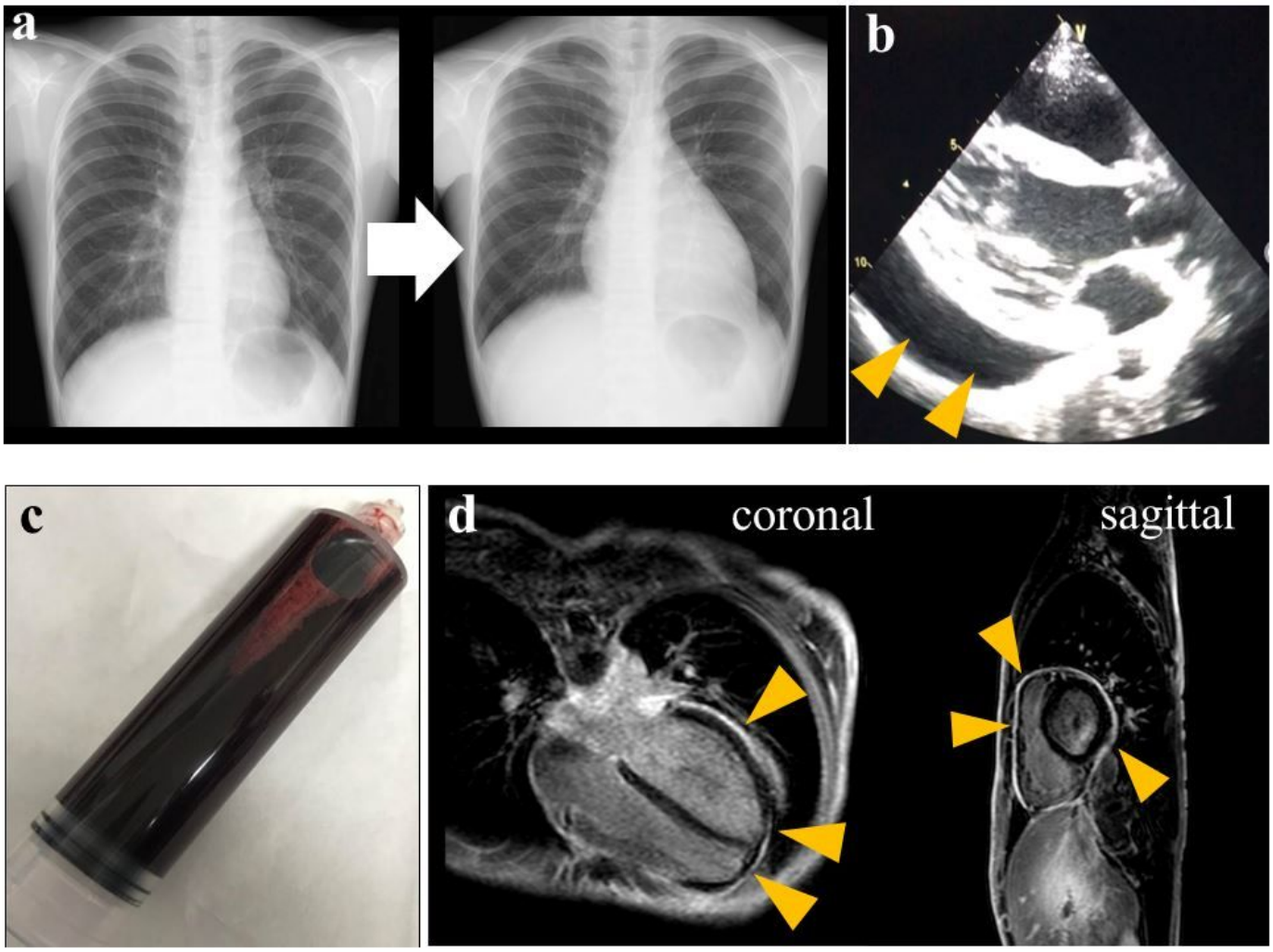

Figure 1

Findings of cardiovascular complications: a Cardiothoracic ratio of chest X-ray changes 41.9 % to 55.0 % in a week. b Echocardiography shows a pericardial effusion (arrowhead). c Aspirated content by pericardiocentesis shows the bloody pericardial effusion. d Cardiac MRI shows contrast-enhanced delay consistent with the pericardium (arrowhead), suggestive of pericarditis.

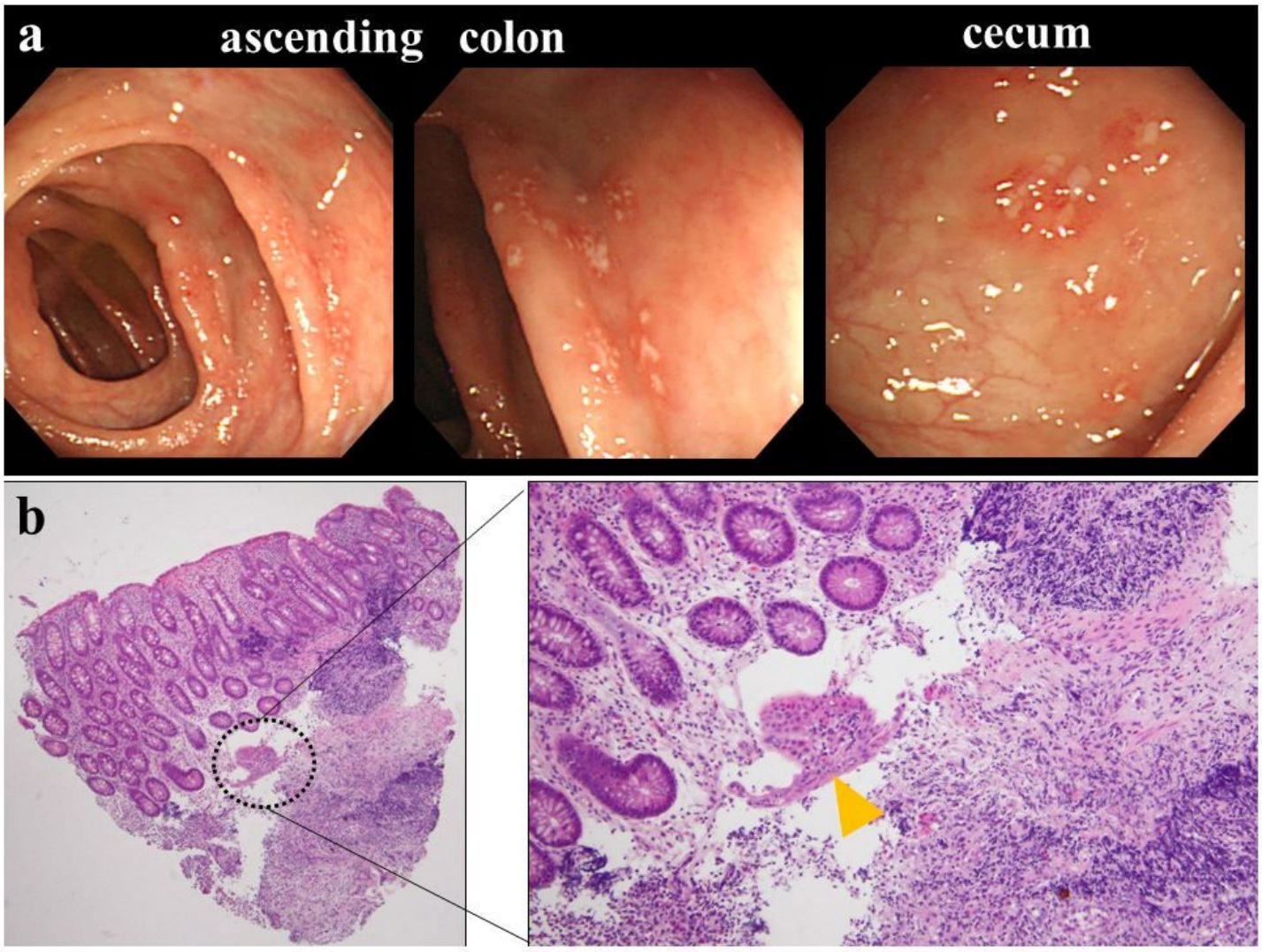

Figure 2

Findings of colonoscopy and histopathological findings of the colonic biopsy a Colonoscopy shows multiple irregular-shaped aphthae on the opposite side of the mesenteric attachment site from the cecum to the right transverse colon. b Colonic biopsy shows nonspecific infiltration to the colonic submucosa, and some granulomatous findings with prominent neutrophil infiltration adjacent to blood vessels (arrowhead).

Supplementary Files

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