A Ruptured Jejunal Arterial Aneurysm in a Young Woman Undergoing Chronic Hemodialysis Due to Myeloperoxidase-antineutrophil Cytoplasmic Antibody-associated Vasculitis

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Abstract:
A 21-year-old woman was admitted to our hospital because of massive intestinal bleeding. She started hemodialysis due to myeloperoxidase antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) at 18 years of age. Her ANCA titers remained stable; however, her C-reactive protein increased on 5 mg/day prednisolone before admission. Computed tomography angiography revealed a ruptured jejunal arterial aneurysm. Transcatheter arterial embolization, blood transfusion and the reinforcement of steroid therapy resolved her symptoms of AAV. Our case of a young patient with AAV and medium-sized arterial vasculitis is rare and emphasizes that the ANCA titer does not always rise, especially in patients with nonrenal vasculitis flare-ups.

Key words: aneurysm, antineutrophil cytoplasmic antibody-associated vasculitis, dialysis, flare-up, gastrointestinal bleeding, hematochezia

We herein report a young patient with massive intestinal bleeding caused by a ruptured jejunal arterial aneurysm, probably due to a flare-up of MPO-ANCA-positive MPA. Until the episode occurred, she had stably undergone chronic hemodialysis due to MPO-ANCA-associated glomerulonephritis, and her MPO-ANCA titer did not rise. Our case of a young patient with MPO-ANCA-positive MPA and medium-sized arterial vasculitis is rare. ANCA titers do not always rise in nonrenal vasculitis flare-ups, and a high index of suspicion for AAV is critical for a prompt diagnosis and management of vasculitis flare-ups.

Case Report
A 21-year-old Japanese woman on chronic hemodialysis (HD) visited our emergency room with complaints of nausea, abdominal pain, massive hematochezia, and dizziness.
A MPO-ANCA level of 7.2 U/mL, were within the normal range. Because of her anuria, she required HD. Computed tomography showed multiple nodules in a random pattern and patchy ground-glass opacities in her lungs (Fig. 1A, B) and bilateral slightly atrophic kidneys. She did not experience hemoptysis, but hemosiderin-laden macrophages were found in the bronchoalveolar lavage fluid, thus indicating alveolar hemorrhaging. A kidney biopsy revealed that most of the glomeruli showed global sclerosis, probably due to advanced crescent formation, and some glomeruli showed fibrous crescents with segmental sclerosis and collapse of glomerular capillaries (Fig. 2). Tubular atrophy, destruction of the tubules and severe inflammatory cell infiltration in interstitial tissue were found in the large areas of the cortex (Fig. 2). The interlobular arteries and arterioles did not show necrotizing angiitis. Immunofluorescence revealed peripheral lobular depositions of C3 and IgM in the sclerosing glomerulus, and electron microscopy showed discrete electron-dense deposits in the sclerotic lesions, suggesting that the depositions were nonspecific. These findings indicated the advanced phase of pauci-immune crescentic glomerulonephritis.

Polyarteritis nodosa (PAN) is defined as necrotizing arteritis of the medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and not associated with ANCA (1). Distinguishing PAN from MPA is sometimes difficult, as the clinical manifestations of both are similar and the existence of MPO-ANCA does not always rule out a diagnosis of PAN. However, our patient showed glomerulonephritis and possible pulmonary capillaritis as typical MPA manifestations. Therefore, she was diagnosed with MPA and MPO-ANCA-associated glomerulonephritis and was treated with steroid pulse therapy (500 mg methylprednisolone, daily boluses given for 3 days) and then 40 mg/day oral prednisolone. The clinical course after introduction of corticosteroid therapy is shown in Fig. 3. She underwent chronic HD with tapering off prednisolone in 1 year without any active findings of MPA. One month after steroid withdrawal MPO-ANCA titer increased.

She was diagnosed with ANCA-associated vasculitis at 18 years of age (2 years and 10 months prior to this presentation). She was referred to our hospital because of headache, dizziness, nausea, edema, reduced urine volume, severe anemia and renal failure. Physical examination on admission revealed, a body temperature of 36.0°C, blood pressure of 141/83 mmHg, heart rate of 91/min and oxygen saturation of 98% (room air). Her body weight was 48.65 kg with pitting edema in her legs. Her conjunctiva was anemic and her breath sounds showed bibasilar crackles. She did not have tinnitus and not associated with ANCAs (1). Distinguishing PAN from MPA is sometimes difficult, as the clinical manifestations of both are similar and the existence of MPO-ANCA does not always rule out a diagnosis of PAN. However, our patient showed glomerulonephritis and possible pulmonary capillaritis as typical MPA manifestations. Therefore, she was diagnosed with MPA and MPO-ANCA-associated glomerulonephritis and was treated with steroid pulse therapy (500 mg methylprednisolone, daily boluses given for 3 days) and then 40 mg/day oral prednisolone. The clinical course after introduction of corticosteroid therapy is shown in Fig. 3. She underwent chronic HD with tapering off prednisolone in 1 year without any active findings of MPA. One month after steroid withdrawal MPO-ANCA titer increased.

Figure 1. Computed tomography of the chest. A and B: Multiple nodules in a random pattern and patchy ground-glass opacities are found in her lungs.

Figure 2. Light microscopic findings of a kidney biopsy. Most of the glomeruli show global sclerosis and some glomeruli show fibrous crescents with segmental sclerosis and collapse of glomerular capillaries. Tubular atrophy, destruction of tubules and inflammatory cell infiltration in the interstitial areas are found. Periodic acid-Schiff staining. Original magnification ×200.
The incidence of gastrointestinal (GI) involvement in older reports was 5-11% in patients with GPA (8, 9) and 30-56% in patients with MPA (10, 11). However, the incidence of GI involvement in patients with AAV has been reported to be 6.5% or 7% in relatively large co-

![Graph](image)
horts (12, 13). The number of GI manifestations has been reported, and the most common GI symptoms are abdominal pain and rectal bleeding, occurring in 79% and 50% of patients, respectively (13). GI involvement in AAV may be caused by both small vessel vasculitis and rare medium-sized arterial vasculitis. Small vessel vasculitis can cause hemorrhagic ulcers or rarely ulcers with perforations. The occlusion or rupture of inflamed medium-sized arterial vasculitis with or without aneurysms may produce tissue ischemia or GI/intraperitoneal bleeding (14). As a result of tissue ischemia, ulceration, necrosis or perforation of the GI tract occurs (1, 15). Kirkland et al. reported 4 patients with GI bleeding among 7 MPA patients with medium vessel involvement in his hospital over a 9-year period (16). However, the ANCA data were not available. To the best of our knowledge, a total of 11 patients with AAV (3 cases of GPA (17-19) and 8 cases of MPA (13, 20-26)) presenting GI bleeding or intraabdominal bleeding due to medium-sized arteries vasculitis, which was confirmed by imaging, laparoscopy or histology of resected tissues, were reported in the literature after the first international Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis in 1994 (27) (Table). The medium-sized arteries involved were the left gastric artery in 4 cases, the superior mesenteric artery and its branches in 4 cases and the inferior mesenteric artery in 2 cases. The mean age was 65.2 years. Most patients showed some constitutional symptoms before GI involvement. The incidence rates of abdominal pain and GI bleeding were 27% and 36%, respectively. In total, 63% of patients showed intraabdominal bleeding. All 3 patients with abdominal pain showed intraabdominal bleeding. A total of 63% of patients were proven to have arterial aneurysms. There were no patients who showed GI involvement after long-term chronic dialysis, as in our case. A surgical resection of the GI tract was performed in 4 cases. TAE with a coil was performed in 3 cases, and TAE with an un-

Figure 4. Computed tomography angiography in the arterial phase. A: Multiple microaneurysms at the mesenteric arterial branches (arrows) and active bleeding with contrast medium extravasation in the jejunum (asterisk) are found. B: No apparent microaneurysms at the mesenteric arterial branches are observed. Arrow shows high-density spot, indicating that n-butyl 2-cyanoacrylate (NBCA) and a lipiodol mixture is packed in the 2nd jejunal branch of the superior mesenteric artery.

Figure 5. Digital subtraction angiography. A: Multiple microaneurysms at the mesenteric arterial branches (arrows) and contrast agent extravasation into the jejunum (asterisk). B: The jejunal artery aneurysm rapture (arrow) and contrast agent extravasation into the jejunum (asterisks). C: Active bleeding with contrast medium extravasation is not observed after transcatheter arterial embolization of the 2nd jejunal branch of the superior mesenteric artery.
Table 1. Gastrointestinal Arterial Bleeding Due to Medium-sized Arterial Vasculitis in Antineutrophil Cytoplasmic Antibody-associated Vasculitis.

| Case No. | References | Reported year | Age / Sex | Phenotype/Serotype | Constitutional symptom | Organ involved | GI symptom | Intra-abdominal bleeding |
|----------|------------|---------------|-----------|--------------------|------------------------|---------------|------------|--------------------------|
| 1        | 17         | 1995          | 56/M      | GPA/C-ANCA         | Yes                    | L, K          | Abdominal distention    | Yes                      |
| 2        | 20         | 1998          | 54/M      | MPA/anti-MPO       | No                     | L, K          | Initial and 2nd: massive hematochezia | No                      |
| 3        | 21         | 2001          | 74/M      | MPA/anti-MPO       | Yes (dialysis required) | L, K (dialysis required) | Massive melena | No                      |
| 4        | 18         | 2004          | 78/F      | aGPA/anti-MPO      | Yes                    | Liver, Spleen, Kidney, Gallbladder, Pancreas, Ovaries, Uterus, Adrenal Glands, Mesentery, Sternum | No | Yes                      |
| 5        | 22         | 2004          | 69/M      | MPA/anti-MPO       | Yes                    | K             | Severe generalized abdominal pain | Yes                      |
| 6        | 19         | 2004          | 58/F      | aGPA/anti-PR3      | Yes                    | Skin, K       | Initial: Bloody bowel movements | Initial: No 2nd: Yes |
| 7        | 23         | 2009          | 70/F      | MPA/anti-MPO       | Yes                    | K, heart, pancreas, adrenal gland, bladder | No | Yes                      |
| 8        | 24         | 2011          | 74/M      | MPA/anti-MPO       | Yes                    | K (dialysis required) | Initial: melena, 2nd: hematochezia | No |
| 9        | 25         | 2013          | 56/M      | MPA/anti-MPO       | Yes                    | L, K (dialysis required) | No | Yes                      |
| 10       | 26         | 2017          | 74/M      | MPA/anti-MPO       | Yes                    | K             | Abdominal pain          | Yes                      |
| 11       | 13         | 2018          | 55/M      | MPA/anti-MPO       | ND                     | Skin, Joint, Eye, EN, L, K, Prostate | Abdominal pain | Yes                      |
| Our case | 21/F       | 2018          | 74/M      | MPA/anti-MPO       | No                     | K (on dialysis), L | Abdominal pain, massive melena | No |

GI: gastrointestinal, GPA: granulomatous polyangiitis, aGPA: atypical granulomatous polyangiitis, MPA: microscopic polyangiitis, C-ANCA: cytoplasmic antineutrophil cytoplasmic antibody (ANCA), anti-MPO: anti-myeloperoxidase ANCA, anti-PR3: anti-protease 3 ANCA, ND: not described, L: lung, K: kidney, EN: ear, nose and throat, SMA: superior mesenteric artery, IMA: inferior mesenteric artery, BT: blood transfusion, TAE: transcatheter arterial embolization, CYC: cyclophosphamide, PE: plasma exchange, IVIgG: intravenous immunoglobulin, NBCA: n-butyl 2-cyanoacrylate

Continued

| Case No. | Medium-sized artery involved | Angiography | Laparotomy | Treatment after GI involvement | Autopsy | Outcome |
|----------|------------------------------|-------------|------------|--------------------------------|---------|---------|
| 1        | Left gastric artery (a)      | Bleeding from a branch of ileal a. | Cardiopulmonary resuscitation | Ruptured a. with aneurysm | Died (hemorrhagic shock) | Alive |
| 2        | Branch of ileal a.           | Bleeding from a branch of ileal a. | Initial: TAE, BT, steroid 2nd: ileotomy | No | Died (pulmonary hemorrhage) | Died (hemorrhagic shock) |
| 3        | Branch of ileal a.           | Bleeding from a branch of ileal a. | TAE (coil), steroid, CYC | No | Died (hemorrhagic shock) | Died (hemorrhagic shock) |
| 4        | Gastric subserosa            | 2nd: bleeding from gastropiploic vessels 3rd: leaking aneurysm in the splenic a. | Initial and 2nd: ligation of artery, BT, steroid, CYC 3rd: pancreatectomy, splenectomy, infliximab | No | Died (hemorrhagic shock) | Died (hemorrhagic shock) |
| 5        | Initial: gastroduodenal a.   | Initial: bleeding vessels in the supracolic compartment, abnormal, enlarged mesenteric circulation 2nd: bleeding form gastropiploic vessels | Ruptured aneurysm in the gastric subserosa | No | Died (catheter-related sepsis, respiratory tract infection) | Died (hemorrhagic shock) |
| 6        | Initial: Middle colic a.     | Initial: rupture of multiple superior mesenteric aneurysms | Initial: small bowel removal, splenectomy, appendectomy, steroid, PE, CYC, BT 2nd: colectomy, blood transfusion, PE | No | Died (hemorrhagic shock) | Died (hemorrhagic shock) |
| 7        | Left gastric a.              | Steroid | Ruptured left gastric a. | Ruptured left gastric a. | Died (hemorrhagic shock) | Died (hemorrhagic shock) |
| 8        | Branch of the left gastric a.| Steroid | Rupture of branch of the left gastric pseudoaneurysm | Died (hemorrhagic shock) | Died (hemorrhagic shock) | Died (hemorrhagic shock) |
| 9        | Initial: a branch of IMA     | Initial: bleeding from a branch of IMA 2nd: bleeding from a branch of IMA | Initial: TAE (steel coil), steroid 2nd: TAE (steel coil), BT, steroid, CYC, PE, IVIgG | No | Died (hemorrhagic shock) | Alive |
| 10       | Left gastric a.              | Ruptured left gastric a. | Steroid, CYC, gastrectomy | No | Died (hemorrhagic shock) | Alive |
| 11       | IMA                          | Microaneurysms in IMA | Steroid, BT, TAE (NBCA) | No | Died (hemorrhagic shock) | Alive |
| Our case | Branch of jejunal a.         | Bleeding from aneurysms in a branch of jejunal a. | Steroid, BT, TAE (NBCA) | No | Died (hemorrhagic shock) | Alive |
known material was performed in 1 case; these procedures successfully stopped the arterial bleeding. Eight patients died and, as for the breakdown of causes of death, 1 death was caused by hemorrhagic shock due to GI bleeding, 5 were caused by hemorrhagic shock due to intraperitoneal bleeding, 1 was caused by pulmonary hemorrhaging and 1 was caused by sepsis. The diagnosis and treatment of GI middle-sized arterial vasculitis with bleeding may be difficult and relies mostly on imaging. Our patient received TAE with NBCA. TAE with NBCA, which enables the occlusion of collateral vessels connected to the bleeding focus, should be considered a safe, efficient method for the treatment of GI bleeding (28).

Experimental and clinical data have provided evidence that ANCs are not only biomarkers of AAV but they also play an important role in its pathogenesis (29). However, ANCs may not be the only factor for disease activation because increases in ANCs are not often followed by relapse (30-32). On the other hand, serial measurements of PR 3- and MPO-ANCA titers in patients with AAV during remission can help predict relapses, and preemptive increases in immunosuppression treatment following fourfold titer rises reduce the risk of relapse (4). Moreover, adjustments to immunosuppression therapy based on smaller titer changes appear to result in favorable outcomes (4). Recently, it was reported that an increase in ANCs is strongly related to a relapse in patients with renal involvement, whereas an increase in ANCs is only weakly associated with a relapse in patients with nonrenal disease (6). More recently, this was confirmed in Japanese hemodialysis patients with ANCA-associated glomerulonephritis (33). Although the pathogenesis is not known, the ANCA titer did not rise at the time of the MPO-AAV flare-up in our dialysis patient. Throughout her clinical course though within the low titer, MPO-ANCA titer was normalized by high dose corticosteroids, and the CRP level seemed to be reduced by the increased dose of corticosteroids, suggesting that the elevation of CRP titer associated with a low MPO-ANCA titer might reflect the AAV activity in our patient.

Several investigators found that the relapse rates are lower if steroid treatment is continued long term (34-36). In a cohort in Japan, a prednisolone dose of ≤2.5 mg/day at 24 months after the initiation of remission induction therapy was associated with later relapse (37). Moreover, the use of steroid therapy for longer than 6 months is reported to be associated with a significantly increased risk of infection but not a significant reduction in the risk of relapse (38). On the other hand, it has been reported that the relapse rate was significantly lower after initiating chronic dialysis than before initiating chronic dialysis (33, 39-41). Considering the older age of patients with AAV receiving chronic dialysis in Japan, Miyabe et al. recommended that the early tapering of steroids should be considered to avoid death rather than focusing only on relapse (33). These recommendations might not be adaptable to our young dialysis patient taking 5 mg/day prednisolone at the time of relapse 34 months after the initiation of remission induction therapy. However, given the side effect that are associated with lengthy and high-dose use of corticosteroids, there is a need for other effective and safe therapies. Although there is still not enough evidence in patients undergoing HD, we need to consider treatments with a combination of low-dose corticosteroids and either azathioprine, rituximab, methotrexate or mycophenolate mofetil based on the JCS 2017 Guidelines on Management of Vasculitis Syndrome recommendation for remission-maintenance of MPA in our patient (42).

In summary, it is difficult to predict a flare-up of AAV. When dialysis patients with AAV show elevated CRP levels without a significant rise in ANCs, we need to rule out dialysis complications, and a high index of suspicion for AAV is critical for the prompt diagnosis and timely management of vasculitis flare-ups. When patients show sudden GI symptoms with bleeding, imaging of medium-sized arteries and TAE should therefore be considered.

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

References

1. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 65: 1-11, 2013.
2. Kamesh L, Harper L, Savage CO. ANCA-positive vasculitis. J Am Soc Nephrol 13: 1953-1960, 2002.
3. Wilde B, van Paassen P, Wützke O, Tervaert JW. New pathophysiological insights and treatment of ANCA-associated vasculitis. Kidney Int 79: 599-612, 2011.
4. Han WK, Choi HK, Roth RM, McCluskey RT, Niles JL. Serial ANCA titers: useful tool for prevention of relapses in ANCA-associated vasculitis. Kidney Int 63: 1079-1085, 2003.
5. Yamaguchi M, Ando M, Kato S, et al. Increase of Antimyeloperoxidase Antineutrophil Cytoplasmic Antibody (ANCA) in Patients with Renal ANCA-associated Vasculitis: Association with Risk to Relapse. J Rheumatol 42: 1853-1860, 2015.
6. Kemna MJ, Damoiseaux J, Austen J, et al. ANCA as a predictor of relapse: useful in patients with renal involvement but not in patients with nonrenal disease. J Am Soc Nephrol 26: 537-542, 2015.
7. Calatroni M, Oliva E, Gianfreda D, et al. ANCA-associated vasculitis in childhood: recent advances. Ital J Pediatr 43: 46, 2017.
8. Hasworth SJ, Pusey CD. Severe intestinal involvement in Wegener’s granulomatosis. Gut 25: 1296-1300, 1984.
9. Srinivasan U, Coughlan RJ. Small intestinal perforation complicating Wegener’s granulomatosis. Rheumatology (Oxford) 38: 289-290, 1999.
10. Gayraud M, Guillemin L, le Toumelin P, et al.; French Vasculitis Study Group. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. Arthritis Rheum 44: 666-675, 2001.
11. Lhote F, Cohen P, Guillemin L. Polyarteritis nodosa, microscopic polyangiitis and Churg-Strauss syndrome. Lupus 7: 238-258, 1998.
12. Mahr A, Katsahian S, Varet H, et al.; French Vasculitis Study Group (FVSG) and the European Vasculitis Society (EUVAS). Revisiting the classification of clinical phenotypes of anti-neutrophil cytoplasmic antibody-associated vasculitis: a cluster analysis. Ann Rheum Dis 72: 1003-1010, 2013.
