The Turkish Journal of Pediatrics 2023; 65: 868-873
https://doi.org/10.24953/turkjped.2022.935

Case Report

A rare complication of IgA vasculitis: renal and intestinal ischemia successfully treated with plasmapheresis

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ABSTRACT

Background. IgA vasculitis (IgAV) is a multisystemic small vessel vasculitis and is the most common vasculitis in childhood. The characteristic findings of IgAV are palpable purpuric rash, abdominal pain, arthralgia or arthritis, and hematuria. Ischemic complications are very rare in IgAV. Thrombotic complications can be observed after a COVID-19 infection. Also in the presence of familial Mediterranean fever, IgAV may have an atypical or more severe course.

Case. We present a case of IgAV complicated with renal infarction and intestinal ischemia. There was no recent or distant history of COVID-19 in the patient or family members, but the patient's COVID-19 antibody was positive. In addition, *MEFV* gene analysis of the patient showed homozygous M694V mutation. The patient did not respond to enoxaparin, pulse methylprednisolone, intravenous immunoglobulin (IVIG), iloprost, and cyclophosphamide treatments. She was successfully treated with six sessions of plasmapheresis.

Conclusions. Plasmapheresis seems to be an effective treatment option in IgAV-related ischemic findings that do not respond to intensive immunosuppressive therapy.

Key words: IgA vasculitis, mesenteric ischemia, plasmapheresis, renal infarction, familial Mediterranean fever.

IgA vasculitis (IgAV), formerly called Henoch-Schönlein purpura or HSP, is a multisystemic small vessel vasculitis and it is the most common vasculitis in children.[1] It is considered an IgA-mediated autoimmune disease. The characteristic findings of IgAV, including palpable purpuric rash, abdominal pain, arthralgia or arthritis, and hematuria, are not always present at the same time.[2] Ischemic complications are very rare and renal infarction has been previously reported in only two pediatric cases.[1] Although mesenteric vasculitis is rare in IgAV patients, it is the most urgent complication of IgAV due to the risk of bowel necrosis and massive gastrointestinal hemorrhage.[2]

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Received 2nd November 2022, revised 5th February 2023, 27th May 2023, accepted 14th July 2023.

SARS-CoV-2, causes a respiratory infection with symptoms ranging from a mild upper respiratory tract infection-like illness to severe pneumonia. It has also been reported to show extrapulmonary findings such as thrombotic, cardiac, and dermatological complications.[3]

Herein, we present a case diagnosed with IgAV complicated with renal infarction and intestinal ischemia. She did not have acute COVID-19 infection but was found to be positive for COVID-19 antibodies. Also, *MEFV* gene analysis showed homozygous M694V mutation.

Case Report

A 14-year-old female patient was referred to our center from an external hospital with complaints of purpuric rash on her lower extremities and abdominal pain for 3 days.

In the external center, severe abdominal pain had persisted despite steroid treatment (30 mg/day) and bilateral renal infarction was detected in abdominal computed tomography.

The patient's past medical history was unremarkable. In the family history, the father reported using colchicine because of familial Mediterranean fever (FMF) but the patient did not describe any previous history of recurrent abdominal pain or fever attacks. Physical examination revealed a rash typical of IgAV on her legs, severe abdominal pain and widespread tenderness in the abdomen. Other system examinations were normal with normal vital signs. The patient's pain visual analog scale (VAS) score was evaluated as 10 (Fig. 1). Complete blood count and biochemical tests were normal. Acute phase reactants were elevated (C-reactive protein 226 mg/L, erythrocyte sedimentation rate 83 mm/h). Proteinuria was detected with dipstick in urine analysis and the protein level in the 24-hour urine was 7.8 mg/m²/h, indicating mild proteinuria. Antinuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA), anti-neutrophilic cytoplasmic antibody (ANCA) tests, and antiphospholipid antibody tests were all negative. While complement-3 (C3), and C4 levels were normal, von Willebrand factor (vWF) antigen was found to be high at 305% (normal value <100%). Adenosine deaminase 2 (ADA2) enzyme activity level was normal. Renal color Doppler ultrasonography and transthoracic echocardiography were normal. Abdominal computed tomography angiography and abdominal magnetic resonance angiography revealed infarcts in all parenchymal and corticomedullary areas of the kidneys, especially in the lower poles, and ischemia in the intestinal wall of the ileal segments and mesentery without any aneurysm or stenosis (Figs. 2 and 3). There was no recent or distant history of COVID-19 in the patient or family members, but the patient's COVID-19 antibody was positive (COVID-19 IgG 12.8 U/mL).

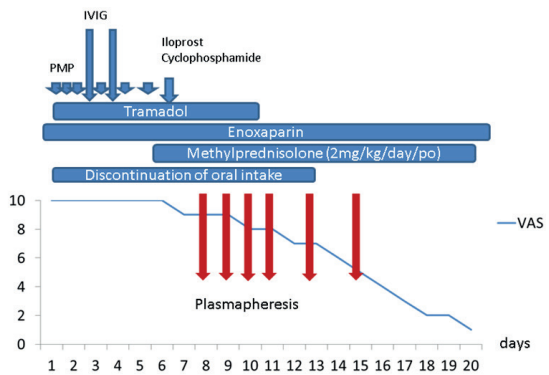

Fig. 1. Treatments used and pain visual analog scale (VAS) of the patient.

IVIG: intravenous immunoglobulin, PMP: intravenous pulse methylprednisolone

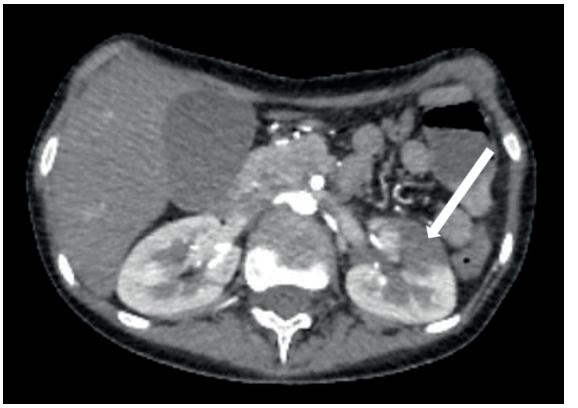

Fig. 2. Computed tomography angiography showing significant renal infarction in the upper pole of left kidney.

The patient was diagnosed as IgAV with renal and mesenteric vasculitis. Oral intake of the patient was discontinued. Intravenous hydration and antibiotics were started. Enoxaparin and pulse methylprednisolone treatment (30 mg/kg/day) was started. In the follow-up, six doses of pulse methylprednisolone (30 mg/kg/dose) were administered and steroid treatment was continued at a dose of 2 mg/kg/day. In the follow-up, abdominal pain did not improve. Total parenteral nutrition was started. Intravenous immunoglobulin (IVIG) (1 g/kg/day, 2 days) and iloprost treatments were given. Since abdominal pain continued

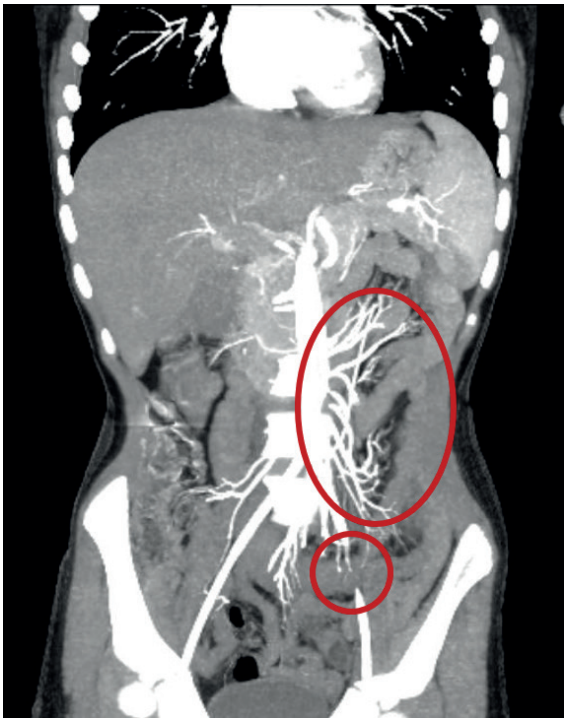

Fig. 3. Computed tomography angiography showing increased mesenteric vascularization at the level of the ileal loops in the left lower quadrant (upper ellipse) and contrast filling defect in the left iliac artery (lower circle).

a single dose of cyclophosphamide infusion was administered. Despite all these treatments, severe abdominal pain and need for narcotic analgesics continued. No significant regression was observed in VAS. Acute phase responses remained elevated and findings consistent with vascular involvement detected in magnetic resonance imaging continued in the control abdominal ultrasonography. For this reason plasmapheresis treatment (with fresh-frozen plasma replacement) was started and applied six times. On the 10th day of her hospitalization, after the 4th plasmapheresis, her abdominal pain started to regress and her pain VAS score gradually decreased. The patient tolerated oral feeding. Acute phase reactants became normal.

The patient was discharged with oral methylprednisolone (30 mg/day) and mycophenolate mofetil (500 mg/day). No mutation was detected in the *ADA2* gene, but *MEFV* gene analysis showed homozygous M694V mutation and colchicine treatment was started. Corticosteroids were discontinued on the 2nd month and she has been followed under remission with mycophenolate mofetil and colchicine treatments for five months.

Informed consent was received from the legal guardians of the child for publication.

Discussion

IgA vasculitis is the most common vasculitis in children. It is described by non-thrombocytopenic palpable purpura, arthritis or arthralgia, and gastrointestinal and renal findings. It is a systemic disease in which antigen-antibody (IgA) complexes enable the alternative complement pathway, resulting in inflammation and small vessel vasculitis.[4,5] Gastrointestinal involvement may be in the form of abdominal cramp-like pain, vomiting, hematemesis, hematochezia, melena, ischemic bowel, and rarely massive gastrointestinal bleeding and bowel obstruction.[2] Renal manifestations range from microscopic hematuria and mild proteinuria to nephrotic and nephritic syndrome and renal failure.[6,7]

Ischemic complications are very rare in IgAV. Talwalkar et al.[8] described renal infarction secondary to IgAV in a 12-year-old girl in 1984. Similarly, in 2014 Gracchi et al.[1] detected renal infarct in a 5-year-old male patient with IgAV. To the best of our knowledge, our case is the third case in the literature. Although mesenteric vasculitis, arterial and venous thrombosis due to IgAV are also very rare, they are associated with high mortality and are the most life-threatening complications.[2,9] In 2003, Wang et al.[2] described mesenteric vasculitis and intestinal ischemia in a 15-year-old male patient with IgAV. They reported that after pulse methylprednisolone treatment, the ischemic bowel symptoms and signs were improved without surgical operation. In 2020, Dhaliwal et al.[9] described a 15-year-old girl who presented with IgAV rash and developed diffuse

alveolar hemorrhage, intestinal ischemia, and venous thrombosis. The patient was treated successfully with pulse methylprednisolone, intravenous immunoglobulin, and intravenous cyclophosphamide.

The presence of increased factor VIII, homocysteine, lipoprotein A, vWF, and antiphospholipid antibodies are associated with prothrombotic events in IgAV. Together with the inflammatory event in IgAV, these factors increase the risk of thrombosis.[9] In 2011, Tayer-Shifman et al.[10] reported that systemic inflammation may increase procoagulant factors, decrease natural anticoagulants and fibrinolytic activity in untreated FMF patients, and therefore, more thrombotic events are expected in untreated FMF patients compared to healthy individuals, and colchicine may play a role in reducing inflammation and thus hypercoagulopathy. Our patient did not have any previous signs and symptoms compatible with FMF but *MEFV* gene analysis showed homozygous M694V mutation. We think that FMF may have contributed to the clinic presentation of our patient, because she had quite an atypical and severe disease course, complicated by thrombosis. It is also known that polyarteritis nodosa (PAN) is more commonly observed in children with FMF.[11] The absence of hypertension and aneurysm or stenosis in the angiography studies allowed us to exclude the diagnosis of PAN in our case. ADA2 deficiency is also a genetic disease characterized by thrombotic findings similar to PAN.[12] In this respect, enzyme and gene analysis were sent from the patient for differential diagnosis.

While COVID-19 is an important cause of hypercoagulopathy among adult patients, little information is available about thrombotic complications in children with COVID-19 to date.[13] In a cohort study published by Aguilera-Alonso et al.[13] in 2021, only 4 of 537 children diagnosed with COVID-19 developed thrombotic complications. Of these patients, 368 were hospitalized, 58 were followed up in the pediatric intensive care unit, and 47 cases were diagnosed with multisystemic inflammatory syndrome (MIS-C). Renal infarction in adults has been reported as a result of coagulopathy associated with COVID-19.[14,15] The youngest patient in the literature was a 37-year-old patient with no pre-existing comorbidities or risk factors who had bilateral renal infarction with COVID-19 pneumonia.[15] COVID-19 may cause intestinal ischemia via certain mechanisms. These are direct viral invasion of intestinal and vascular epithelium via angiotensin-converting enzyme 2 (ACE 2) receptors, systemic extend of pulmonary coagulopathy, complement-mediated vasculopathy, and platelet activation via spike protein binding to the ACE 2 receptor. However, the rarity of intestinal ischemia in the presence of COVID-19 limits our knowledge on this subject.[16] A case of COVID-19-associated neutrophilic arterial vasculitis has been reported in the literature, similar to thrombotic complications in PAN.[17] Thirteen cases of COVID-19-related acute mesenteric ischemia have been reported, including a 9-year-old girl.[18]

In 2019, Liu et al.[19] investigated the efficacy of a combination of methylprednisolone, cyclophosphamide, and plasmapheresis therapy versus pulse methylprednisolone and cyclophosphamide therapy in 60 children with IgAV nephritis. They reported that in the treatment of severe IgAV nephritis in children, plasmapheresis can further alleviate kidney damage, improve clinical outcome, and not increase the incidence of adverse reactions. In 2008, Acar et al.[20] treated a 13-year-old girl with severe gastrointestinal bleeding secondary to IgAV with plasmapheresis because she did not respond to pulse methylprednisolone and cyclophosphamide therapy. No gastrointestinal bleeding was observed after four sessions of plasmapheresis. They stated that plasmapheresis treatment can be an effective treatment in patients with IgAV who present with severe symptoms, including severe gastrointestinal symptoms. In 2006, Wortmann et al.[21] reported that they successfully treated a case with refractory intestinal vasculitis secondary to IgAV with plasmapheresis.

Our case with IgAV-related bilateral renal infarction and intestinal ischemia similarly did not respond to pulse methylprednisolone, IVIG and cyclophosphamide treatments, and was successfully treated with six doses of plasmapheresis.

Although very rare, the course of IgAV can be complicated by thrombotic and ischemic manifestations. Thrombotic complications can be observed after COVID-19 infection. In the presence of FMF, IgAV may be atypical and more severe, and thrombotic complications may occur. We think that the COVID-19 infection and FMF in our case triggered the common renal and mesenteric thrombosis associated with IgAV. Plasmapheresis seems to be an effective treatment option in IgAV-related ischemic findings that do not respond to intensive immunosuppressive therapy.

Ethical approval

Informed consent was received from the legal guardians of the child for the publication of the case report.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: BS, ŞT; data collection: ŞT, MG; analysis and interpretation of results: BS, MÇ, SK, ŞT, HES; draft manuscript preparation: ŞT, BS. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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