CASE REPORT

Parvovirus leading to thrombotic microangiopathy in a healthy adult

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SUMMARY

A healthy 47-year-old man initially presented with symptoms of body rash, myalgias, dark urine, nausea and vomiting. Acute kidney injury, and positive urine analysis for blood and protein warranted a kidney biopsy, which revealed micro thrombi in kidney vasculature, suggestive of thrombotic microangiopathy. Serology revealed positive parvovirus B19 IgM antibodies and biopsy tests revealed a viral genome on PCR. Despite plasma exchanges and treatment with rituximab, renal function continued to deteriorate to end-stage renal disease.

BACKGROUND

This is the first case report, to the best of our knowledge, of parvovirus B19 infection in an immunocompetent adult who presented with acute kidney injury (AKI) as a result of thrombotic microangiopathy (TMA), did not recover on conventional treatment and soon progressed to end-stage renal disease.

CASE PRESENTATION

We report the case of a 47-year-old Caucasian man in good health, who presented to his family physician, with symptoms of sinusitis. X-rays of the paranasal sinuses revealed mucosal thickening and air–fluid levels in both maxillary antrums. The patient was treated with amoxicillin 500 mg three times a day for 7 days.

A week later, he felt generally unwell, had nosebleeds and myalgias, and went to his general practitioner, who prescribed ibuprofen and acetaminophen/methocarbamol for pain. A day later, the patient noticed widespread rash on his legs and hands. His rash worsened and he later developed pain and swelling over his hands and feet. As his condition failed to improve, he was prescribed 60 mg of prednisone. There was marginal improvement in his symptoms, but a day later he started to notice dark-coloured urine, followed by frank blood-stained urine. He reported a sore back, nausea, vomiting and exhaustion. His medical history was significant for Raynaud-like symptoms but negative for photosensitivity, dry mouth, dry eyes, oral ulcers and arthritis.

On the basis of the presence of preceding history of sinusitis, AKI, presence of overt haematuria, rash and arthropathy, the patient underwent a renal biopsy. The specimen showed significant injury and presence of micro-thrombi in the vasculature, consistent with TMA. On electron microscopy, there were no immune complex deposits. Later, serological investigation showed positive IgM for parvovirus and the renal biopsy revealed viral genome by PCR. Based on the temporal association between clinical symptoms, AKI, seroconversion, onset of TMA and isolation of viral genome from the renal biopsy, we diagnosed the patient as having TMA secondary to parvovirus B19.

INVESTIGATIONS

On the day of admission, the patient's haemoglobin was 150 g/L; platelets $200\,000\times10^9$ and lactate dehydrogenase (LDH) 150 U/L. Two days later, his haemoglobin fell to 120 g/L, later dropping further to 72 g/L—requiring 3 units of packed red cells—his platelet count at that time was $21\,000\times10^9$. Serum creatinine was 438 µmol/L (normal 60–120 µmol/L) and urea 15.9 mmol/L (normal 4–7 mmol/L). His urine analysis was positive for blood and protein. Microscopy showed more than 40 red cells per high power field, but no red cell casts. His initial laboratory results showed C3: 1.04, C4: 0.10 (normal), normal myeloperoxidase (MPO) and proteinase 3 (PR3) antineutrophil cytoplasmic antibody levels, and he tested negative for hepatitis B, hepatitis C, HIV, antinuclear antibody and anti-glomerular basement membrane (GBM) antibodies. Lupus anticoagulant, anticardiolipin antibodies and cold agglutinins were negative as shown in table 1. International normalised ratio was 1, liver enzymes were normal, mono test was negative and serum immunoglobulins were within the normal range. For his low platelets, a blood smear was performed on three different occasions and revealed no evidence of schistocytes or intravascular haemolysis. Based on our clinical suspicion of vasculitis, a biopsy of the kidney was organised, relevant serological investigations were sent and intravenous solumedrol administered.

DIFFERENTIAL DIAGNOSIS

TMA is a histological picture that is also seen in scleroderma and malignant hypertension. There were no clinical features to suggest scleroderma in this patient, his blood pressures were lower than 160 mm Hg systolic and there were no neurological manifestations throughout his stay, making malignant hypertension unlikely.

Antiphospholipid syndrome was considered based on the history of arterial thrombi, but his lupus anticoagulant and anticardiolipin antibodies were negative.

Presence of blood and protein in urine along with AKI reflects glomerular damage and vasculitis; MPO and PR3 levels were normal as was

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Table 1 Serological investigations, coagulation tests and genetic mutations affecting the alternate complement pathway and autoantibodies

ESR	79
ANA	Negative
ANCA	(MPO-11, PR3-3)
Anti-GBM	Negative
Cryoglobulins	Negative
PT	Normal
APPT	43
Lupus anticoagulant	Negative
Russell's viper venom test	Negative
Mono test	Negative
C3	0.87
C4	0.10
Surface regulation for alternate pathway	Normal
Factor H autoantibody	Negative
Soluble MAC level	Normal
C3 nephritic factor	Negative
Pathogenic variants in the gene for complement factor H	None

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ESR, erythrocyte sedimentation rate; GBM, glomerular basement membrane; MPO, myeloperoxidase; PR3, proteinase 3.

anti-GBM levels, which made Goodpastures syndrome unlikely. A few days later, the patient's serology came back IgM positive for parvovirus. The histologist later reviewed the biopsy and demonstrated the presence of the viral genome by PCR in the kidney biopsy.

TREATMENT

Owing to the patient's rash, non-specific symptoms, AKI and history of sinusitis with bloody sinus discharge, vasculitis was suspected; we gave him 0.5 g of methylprednisolone ×3 days. On receipt of the kidney biopsy report, he received 23 sessions of plasma exchange. His platelets rose briefly with the plasma exchanges but his creatinine failed to improve and he had to be initiated on extracorporeal blood purification. In the absence of recovery, we initiated treatment with intravenous rituximab, two doses of 1 g, 14 days apart. We closely followed his creatinine, platelets and LDH, but despite having an improving urine output, the patient's renal status failed to recover.

OUTCOME AND FOLLOW-UP

In the absence of renal recovery, we performed a follow-up biopsy, which showed extensive glomerulosclerosis in 24/31 glomeruli, an increase in mesangial matrix, no evidence of acute TMA, marked tubular atrophy, and interstitial fibrosis and moderate arterial hyalinosis. Based on the extent of the damage, further treatment was considered to have a low probability of success. Unfortunately, the patient was given the recommendation to begin renal replacement therapy and referred for a transplant assessment.

DISCUSSION

Parvovirus B19 is a small, non-enveloped, single-stranded DNA virus that was discovered in 1975,[1] and first linked with human disease in 1981.[2] This common, worldwide virus primarily infects children and immunocompromised individuals.[3] There are several well-established outcomes of parvovirus B19 infection in immunocompetent individuals, they include erythaema infectiosum, transient aplastic crisis and hydrops fetalis/intrauterine death in pregnancy. In most cases, the parvovirus B19 causes only mild, if any, symptoms and is typically eradicated by the individual's natural immune response.[4] However, in immunocompromised individuals, parvovirus B19 can cause more severe clinical manifestations.[5]

Parvovirus typically enters erythroid progenitors in the bone marrow by binding to glycosphingolipid globoside (Gb4), also known as the blood group P antigen. However, the P antigen receptor has been found in renal tissue, but its cellular localisation is unclear. Thus, the mechanism of entry of the virus in glomerular cells is incompletely understood. The virus, however, has been implicated in expanding the spectrum of clinical disorders involving the kidney including proliferative glomerulonephritis,[4 6] collapsing glomerulopathy,[4 7] focal segmental glomerulosclerosis, renal transplant dysfunction, acute allograft rejection and TMA in a renal transplant recipient.[4 8]

Parvovirus B19 DNA has been detected by nucleic acid amplification in a variety of tissues for extended periods, indicating that presence in tissues does not signify active infection and association does not necessarily mean causation.[4] Our patient had TMA; human parvovirus has been proposed to cause TMA by direct infection of the glomerular endothelial cells as the mechanism of renal injury. The P antigen has been demonstrated on endothelial cells and parvovirus B19 DNA has been localised to these cells in cases of B19 vasculitis. Thus, infection could lead to endothelial cell dysfunction or cell death, leading to capillary thrombosis and glomerular death.[8] TMA has been reported, but only in post renal transplant recipients, and never in an immunocompetent individual.

Parvovirus infection in an immunocompetent adult can be associated with deficiencies of the alternate complement pathway or with C3 nephritic factor. A thorough analysis of the genetic mutations of the alternate complement pathway was made and no abnormalities were identified.

Learning points

Parvovirus B19-induced thrombotic microangiopathy (TMA) should be part of the differential diagnosis in immunocompetent patients with typical rash, arthralgias and non-specific symptoms, with acute kidney injury, thrombocytopenia and presence of haemolysis. Clinical suspicion followed by early initiation of intravenous immunoglobulin is likely to lead to a clinical recovery.[8]

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Competing interests None declared.

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