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Acute renal insufficiency and pancreatitis in a child with atypical Henoch–Schönlein purpura: efficacy of a single dose of cyclophosphamide

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Abstract

A 9-year-old boy with petechiae on the legs and abdominal pain was unsuccessfully treated with steroids. He was admitted to our hospital for the onset of fever, ecchymosis, and arthralgia. Skin lesions suggested vasculitis, but they were not typical of Henoch–Schönlein purpura. He showed ecchymosis of the scrotal bursa, diffusion of petechiae to the trunk and arms, vomiting, severe abdominal pain, oliguria with hyponatremia, hypoalbuminemia, low C3 levels, high levels of creatinine, blood urea nitrogen, and tubular enzymes, proteinuria, and glycosuria. The urinary sediment showed macrohaematuria, and hyaline and cellular casts. Ultrasound showed polyserositis. He was treated with intravenous furosemide, albumin, and methylprednisolone. He underwent colonoscopy and gastroscopy because of development of acute pancreatitis and severe anaemia. Typical lesions of Henoch–Schönlein purpura were observed in the small intestine and colon mucosa. He received three high doses of methylprednisolone, followed by intravenous cyclophosphamide. A dramatic and persistent response was observed after these doses. A single high dose of cyclophosphamide is appropriate in Henoch–Schönlein purpura with acute renal failure and severe pancreatitis that are non-responsive to high-dose steroids.

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Introduction

Henoch–Schönlein purpura (HSP) is the most frequent vasculitis in paediatric patients. HSP is a clinical condition characterized by palpable purpura, joint swelling and arthralgia, and abdominal pain with possible intestinal bleeding. In more severe cases, these patients show acute abdomen.

A total of 30% to 50% of patients with HSP present with glomerulonephritis with a frequently benign outcome. However, a low incidence of acute renal failure (ARF) or nephrotic syndrome has been reported.[1] Renal involvement can be reversible, but it requires corticosteroid treatment, and in some cases, immunosuppressive treatment for possible evolution in chronic renal failure.[1] The severity of histological involvement documental by renal biopsy and the severity of initial clinical presentation are correlated with renal outcome. However, recognized protocols for ARF in HSP are not available and a different therapeutic approach needs to be used.[2]

Acute pancreatitis is a rare, dramatically evolutive, life-treating manifestation of HSP and it can be associated with a fulminant course. Acute pancreatitis is associated with ARF. In patients with HSP, abdominal pain is a possible symptom of haemorrhagic effusion and oedema of the small bowel wall, secondary to vasculitis. However, persistent abdominal pain needs to be fully investigated by serum pancreatic amylase[3–4] and lipase levels, and by abdominal magnetic resonance imaging. In these cases, corticosteroid treatment is associated with parenteral feeding. To the best of our knowledge, we report the first case of paediatric HSP with ARF and pancreatitis. The patient was successfully treated with a single dose of cyclophosphamide.

Methods

A 9-year-old boy with autism and a gluten-free diet, which was prescribed for gluten sensitivity, showed petechiae on the legs and persistent abdominal pain. He was unsuccessfully treated with oral steroids. For persistence of these manifestations, which were associated with fever, ecchymosis, arthralgia of the feet and knees, he was admitted to our hospital. Skin lesions indicated vasculitis, with a small ecchymosis, without purpuric palpable lesions that are commonly observed in HSP. Furthermore, diffusion of petechiae to the trunk was not typical of HSP.

In the following days, he showed ecchymosis of the scrotal bursa, diffusion of petechiae to the trunk and arms, vomiting, and severe abdominal pain with oliguria. Haematological assays showed the following: hyponatremia (126 mEq/L), hypoalbuminemia (2.8 mg/dL), a low C3 level (68.4 mg/dL; normal levels: 90–180 mg/dL), and a high creatinine level (1.98 mg/dL) and blood urea nitrogen level (69 mg/dL). A low percentage of blood coagulation factor XIII was found (70.80%; normal: 75.20%–154.80%).

Urinalysis showed mild proteinuria (0.27 g/L) and glycosuria (16 mg/dL), with increased tubular enzyme activity (urinary alkaline phosphatase, gamma-glutamyl transferase, N-acetyl-B-D-glycosaminidase).

The urinary sediment showed a carpet of red blood cells, with 10 to 20 white blood cells/field, and hyaline and cellular casts. Abdominal ultrasound showed intraperitoneal and intrapleural effusion. A microbial stool culture was negative.

Therefore, the patient was treated with intravenous (i.v.) furosemide, albumin, and methylprednisolone (2 mg/kg/day). Five days after steroid treatment, diuresis was started with progressive normalization of diuresis and creatinine levels, and a reduction in peripheral oedema, skin purpura, and arthritis.

For the high levels of pancreatic amylase (235 U/L; normal levels: 13–53 U/L) and lipase (556 IU/L; normal levels: 13–60 U/L), he stopped enteral feeding and received parenteral nutrition. He had a greatly and persistently increased D-dimer level (33.7 mg/L; normal levels: 0.0–0.5 mg/L) and reduced fibrinogen level (84 mg/dL), with normal values of transaminases and gamma-glutamyl transpeptidase. A progressive reduction in the haemoglobin level (6.9 g/dL) required red blood cell transfusion. Abdominal computed tomography showed pancreatic oedema with ascites.

To exclude atypical Kawasaki disease, and for the suspicion of Rickettsia infection with haemorrhagic skin lesions[5] or cholestatic hepatitis secondary to Epstein–Barr virus (EBV) or cytomegalovirus infection,[6] he underwent the following: specific serology for EBV, cytomegalovirus, and Rickettsia; and electrocardiographic and echocardiographic studies at the start of symptoms and during follow-up. The electrocardiographic and echocardiographic studies did not show pericarditis or coronary involvement. Specific serology for EBV, CMV, and Rickettsia showed normal results.

To exclude post-streptococcal nephropathy, a throat swab culture was performed and was negative. Anti-streptolysin O titre and anti-DNAse B were negative. Autoimmune tests (lupus anticoagulant, anti-cardiolipin, anti-phospholipids, anti-beta2 microglobulin antibodies, antinuclear antibodies, extractable nuclear antigen, anti-double-stranded DNA, anti-Saccharomyces cerevisiae antibodies, anti-neutrophil cytoplasmic antibodies, α-smooth muscle actin isoform, anti-thyroperoxydase, and anti-thyroglobulin) were negative.

Therefore, the patient underwent colonoscopy and gastroscopy. Diffuse purpura was observed in the small intestine and colon mucosa, with relief of the typical purpuric mucosal lesions of HSP, characterized by "coin-like" elevated lesions. Celiac disease was excluded and gluten sensitivity was confirmed.

Informed consent for publication was obtained from the parents of the child. Ethical committee approval was waived because retrospective analysis of a case was not required.

Results

After obtaining written informed consent, the patient received methylprednisolone pulse therapy with three consecutive doses at 30 mg/kg/day, followed by intravenous cyclophosphamide at 750 mg/m^2. This treatment is not supported by an international treatment protocol and single-dose cyclophosphamide in this condition is still under investigation. He showed rapid resolution of clinical and biochemical parameters (Table 1). Amylase, lipase, and albumin levels progressively normalized. Therefore, he gradually started enteral feeding 6 days after cyclophosphamide infusion. Serositis showed progressive and complete resolution.

For a favourable outcome, we decided to continue treatment with azathioprine (50 mg/day). Complete resolution of the clinical manifestations was observed.

Table 1. Outcome of biochemical parameters of the patient.

	Hb (g/dL)	C3	BUN	Creatinine (mg/dL)	Proteinuria (g/L)	Haematuria (/μL)	Pancreatic amylase (UI/L)	Lipase (IU/L)
At admittance	10	68	68	1.98	0.27	81	46	49
After steroids (2 mg/kg/day)	6.9	92	17	0.6	Negative	Negative	235	556
After steroids (30 mg/kg/day) plus cyclophosphamide (750 mg/m^2)	9	100	11	0.6	Negative	Negative	53	49
At follow-up		102		0.6	Negative	Negative	50	28

Hb: haemoglobin; C3: complement 3; BUN: blood urea nitrogen.

Discussion

The clinical presentation of the patient was complex and difficult to control. The diagnosis of HSP was confirmed by the coexistence of skin lesions (distributed in the buttocks and legs), ARF, abdominal pain, and pancreatitis. Autoimmune antibodies were negative, which excluded an autoimmune disease, such as systemic erythematous lupus. A diagnosis of haemolitic uremic syndrome was not supported by the absence of schistocytes at the urinary sediment and in peripheral blood, a normal platelet count, normal levels of lactate dehydrogenase, bilirubin, and transaminases, and the absence of diarrhoea. Furthermore, the diagnosis of haemolitic uremic syndrome could not explain the skin lesions and pancreatitis.

Cyclophosphamide is useful in paediatric HSP with severe complications such as renal disease, including rapidly progressive glomerulonephritis, nephrotic syndrome, and renal insufficiency. Some studies have suggested the efficacy of immunosuppressive drugs in association with steroid protocols, including methylprednisolone pulses in severe cases of HSP nephritis.[7] Several studies have suggested that galactose-deficient IgA1 is associated with anti-glycan antibodies, which contribute to formation of circulating immune complexes and mesangial deposition with secondary renal injury in HSP.[7] Complement activation plays a role in the pathogenesis of HSP. Complement activation may start the inflammatory cascade and enhance glomerular injury.[8] Therefore, immunosuppressive drugs, such as cyclophosphamide, can be effective for treating severe cases of HSP, as demonstrated in HSP nephritis.

Pancreato-biliary involvement is unusual in HSP, and it is not described in association with ARF. This complication deserves consideration, especially in patients with severe abdominal pain.[9,10] To the best of our knowledge, this is the first case of paediatric HSP presenting with ARF and acute pancreatitis, which was successfully treated with a single dose of cyclophosphamide. A recent review of all cases of HSP-related pancreatitis showed a higher incidence in males and highlighted the importance of timely treatment with steroids to obtain a good outcome.[11] Pancreatitis was diagnosed early in our patient and promptly treated with high-dose steroids. However, the clinical presentation was severe and steroid-resistant, which required immunosuppressive treatment.

A previous study reported a series of six children with HSP who developed severe gastrointestinal bleeding and were resistant

to methylprednisolone at 2 mg/kg/day or a pulse (10–30 mg/kg) i.v.[11] All of the patients responded to a single dose of cyclophosphamide (500 mg/m^2) i.v. and none of them developed new flares of gastrointestinal bleeding. No patients required surgical intervention. This previous study suggested that a single high dose of cyclophosphamide is beneficial in HSP with severe gastrointestinal involvement that is non-responsive to steroids. However, this treatment had not been attempted in HSP-related pancreatitis. Our patient showed a prompt, favourable response to a single dose of cyclophosphamide, with resolution of clinical, radiological, and biochemical data. The following treatment with azathioprine, which was based on previous cases of complicated HSP reported in the literature,[12] was followed by complete resolution of the clinical manifestations.

A single high dose of cyclophosphamide may be suitable in HSP with ARF and severe pancreatic involvement, in which ARF, pancreatitis, and systemic vasculitis are non-responsive to high-dose steroids. In complicated cases, we propose that patients should receive azathioprine after cyclophosphamide until resolution of the vasculitis occurs and organ injury is restored.

Limitations

The limitations of this report are as follows. This is a single case report, so a future study with a larger number of patients is required to confirm our findings. Furthermore, our patient had two severe complications of HSP: acute pancreatitis and ARF. Further studies need to analyse the clinical course and the response to different protocols of treatment in patients with isolated acute pancreatitis associated with HSP.

Authors' contributions

Maria Cristina Maggio followed up the patient, treated the child in the stages of his illness, and wrote the paper. Silvio Maringhini evaluated renal involvement and followed the clinical course of the patient. Saveria Sabrina Ragusa revised the references and prepared the bibliographic support for choosing treatment. Giovanni Corsello revised the paper.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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