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Three Masquerading Manifestations But the Same Childhood Vasculitis

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Abstract Henoch-Schönlein purpura (HSP) is a common childhood vasculitis. Despite its first description in the 1800s, aetiology remains unclear. Initial intestinal symptomatology may be severe and mislead the underlying vasculitic process. HSP may have delayed development of rash which makes the diagnosis challenging. We describe two cases of HSP with prominent initial abdominal symptomatology, and one case with refusal to walk to illustrate the protean features. In the first case, the gastrointestinal symptoms subsided rapidly with the onset of florid dermatological manifestations, whereas the second case presented as acute gastrointestinal emergency. The third case had more severe limb pain and relatively mild abdominal symptoms. A high index of suspicion with prompt diagnosis is pivotal to avoid unnecessary treatment such as antibiotics, corticosteroid or surgery for this systemic disease with cutaneous manifestations. We address clinical questions on the usage of empirical antibiotics and corticosteroids by performing literature search. Unlike other vasculitis, literature review suggests that a definite bacterial agent is usually not associated with HSP and corticosteroid is only indicated with severe renal involvement.

Key words Antibiotics; Corticosteroid; Henoch-Schönlein purpura; Immunoglobulin A; Infection

Introduction

Henoch-Schönlein purpura (HSP) is a immunoglobulin (Ig) A-mediated systemic small-vessel vasculitis with a predilection for the skin, gastrointestinal tract, joints, and kidneys.[1-3] HSP affects about 20/100,000 children each year and 75% of cases occur in children between 2 and 11 years with a peak at 4 to 7 years.[1-3] The condition is twice as prevalent in boys as in girls. HSP is generally self-limiting, and treatment is aimed at relieving symptoms and preventing complications. The diagnosis of HSP with the typical rash associated with HSP is usually straight forward but can be challenging, particularly when the initial symptomatology is gastrointestinal. A high index of suspicion with prompt diagnosis is pivotal to avoid unnecessary treatment such as antibiotics or surgery for this systemic disease with cutaneous manifestations. We report three cases and performed a literature review on the role of antibiotics and corticosteroid in managing HSP.

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Cases

Case 1

An 8-year-old boy developed intermittent colicky abdominal pain and repeated vomiting. The following day he developed a purpuric, palpable, excoriative, itchy and

nontender rash over the lower limbs. He had one episode of diarrhoea but no history of per-rectal bleeding or urinary symptom. There was a travel history to Southern China during the previous week. The younger sister and parents had similar symptoms suggestive of gastroenteritis. Abdominal computed tomography scan done on the day of admission to exclude appendicitis showed mesenteric adenitis. The following laboratory studies were performed: erythrocyte sedimentation rate 15 (0-10 mm/hour); clotting profile (normal), C3 (normal), and ANA (negative). The patient was empirically treated with intravenous amoxicillin/clavulanic acid. He remained afebrile and was discharged 6 days later. The family then attended our hospital for further opinion. The rash had spread to the arms and the ear helices (Figure 1) but the mucous membranes, heels, palms and joints were spared. Blood pressure was normal. His haematologic, hepatic and renal functions and urinalysis were normal. There were no bacteria or viruses isolated from the leg ulcers. Skin biopsy of the rash was consistent with the diagnosis of HSP (Figure 2). Histopathology section showing focal subcorneal pustules and basketweave cornified layers with smudging of interface. There is superficial perivascular mixed inflammatory infiltrate with focal extravasated red cells, apparent nuclear dusts and focal fibrinoid necrosis of vessel walls. Immunofluorescein study shows vascular stain of IgA, C3 and fibrin. The skin lesions gradually resolved.

Case 2

A 4-year-old girl initially presented with periorbital puffiness and a nonpruritic, palpable rash over the extensor surface of both arms. She developed persistent, severe lower abdominal pain the next day, which was associated with vomiting and scanty blood streaked stool. She was diagnosed to have intussusception with a subsequent emergency resection of a portion of the bowel in Shenzhen, China. In the days following the operation, the rash began to spread to the lower limbs and down to the dorsum of the feet. This was associated with painful swelling of the ankles and smoky urine. She also had another episode of vomiting, which prompted the mother to bring the patient to our hospital in Hong Kong. On examination, the patient was afebrile and the vital signs were stable. There was an extensive purpuric, non-blanchable, palpable rash over the right cheek, buttocks, lower back, and the extensor surface of the arms and legs, with non-pitting oedema of the ankles and wrists, and periorbital puffiness around the right eye. The abdomen was soft and nontender, with a surgical wound from the intussusception operation. Blood pressure was normal. Complete blood cell count, renal function tests and liver function tests were normal. Urinalysis revealed no haematuria or proteinuria. Skin biopsy was not necessary for diagnosis. HSP was clinically diagnosed and the patient gradually improved.

Case 3

A 4-year-old girl presented with acute-onset severe leg pain and refusal to walk. The mother reported mild fever, diarrhoea and cough, and noted feet swelling and multiple bruises over her calves. The girl had been seen by a general practitioner and treated conservatively. Examination revealed oedema of the feet and painful palpable purpuric rash over the calves, left anterior thigh and buttocks (Figure 3). A diagnosis of HSP was made. Investigations showed normal complete blood cell counts, renal and liver function, C-reactive protein, C3, C4, ASO titre, immunoglobulins, coagulation profiles, and urinalysis. Skin biopsy was not necessary for diagnosis. She was discharged home but returned 3 days later with poor appetite, abdominal distension, vomiting and loose stools. Faecal occult blood, blood culture, nasopharyngeal aspirate for common respiratory viruses, IgG and IgM to parvovirus B19 by immunofluorescent test were negative. She got better in the next two days and was discharged home.

Discussion

Gastrointestinal symptoms can manifest early in the clinical course and may delay the diagnosis of this vasculitis as in our first two cases. Abdominal pain, the most common symptom, is typically severe and colicky. Nausea, vomiting, and melena are common. Intestinal obstruction and intussusception may occur as an abdominal emergency and require surgical intervention as in our second case. It has been shown that contrast enemas are safe to perform in patients with HSP with suspected intussusception, and this procedure may obviate surgical treatment.[4] In our second case, conservative therapy may be feasible for HSP patients with small bowel intussusception as long as emergency operating facilities are available, and an experienced paediatric surgical team is able to follow up the patient.[5] Furthermore, factor XIII activity has been reported to correlate with the severity of abdominal symptoms.[6] Measuring factor XIII activity helps to identify those patients with severe gastrointestinal manifestation who may benefit from substitution therapy.[7]

Assessment of antineutrophil cytoplasmic antibodies

(ANCA) may be useful in diagnosing vasculitic diseases in atypical cases of HSP. ANCA are associated with certain forms of systemic vasculitis, and have been reported previously to be of the IgG and IgM isotype.[8] Nevertheless, adult HSP is closely associated with circulating IgA ANCA, which may be directed against a different autoantigen than that recognised by IgG ANCA.[8] In a paediatric study, IgA ANCA in cytoplasmic pattern was detected in a significantly higher percentage of HSP patients (82.3%) in the acute phase compared to those in the disease controls (38%) (p=0.004). IgA ANCA was negative in 88% of the patients in the resolution phase (p=0.001 for acute vs resolution phases). The authors conclude that IgA ANCA may be useful to confirm the diagnosis of HSP in children.[9] However, no relationship was found between disease severity of HSP and IgA ANCA.

There was no overt renal manifestation in the three cases. Persistent renal disease is an important long-term complication of HSP.[2] Approximately 34% of children with HSP develop kidney disease either in the form of isolated

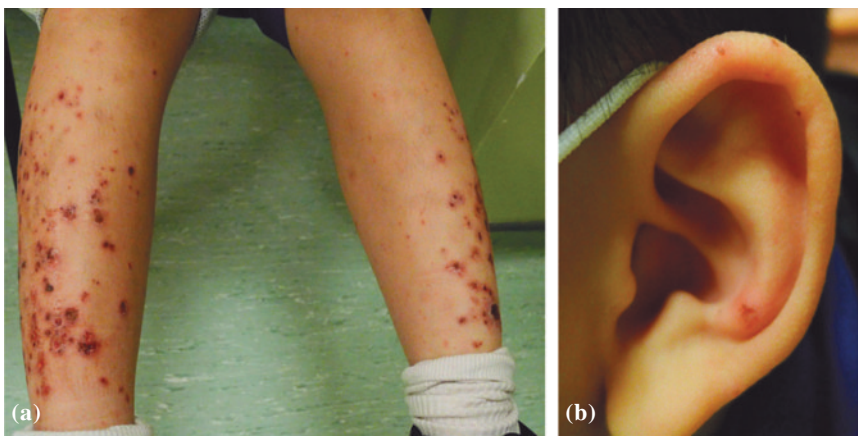

Figure 1 (a) Extensive ecoriative purpuric lesions of HSP involving both legs; and (b) HSP rash involving the ear.

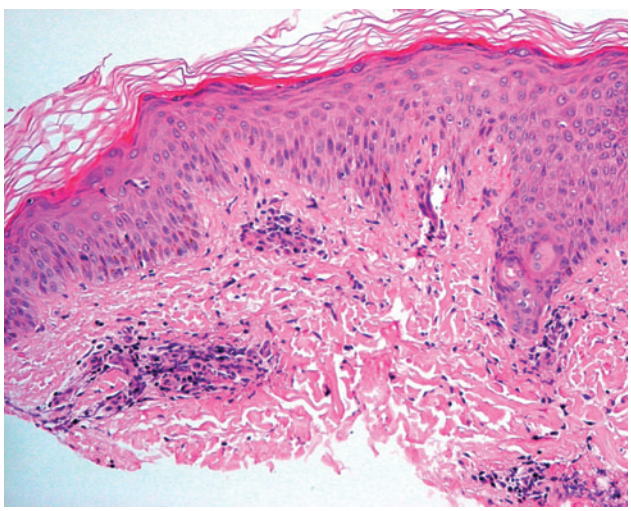

Figure 2 Histopathology section showing superficial perivascular mixed inflammatory infiltrate with focal extravasated red cells, apparent nuclear dusts and focal fibrinoid necrosis of vessel walls. Immunofluorescein study shows vascular stain of IgA, C3 and fibrin. The picture is consistent with HSP.

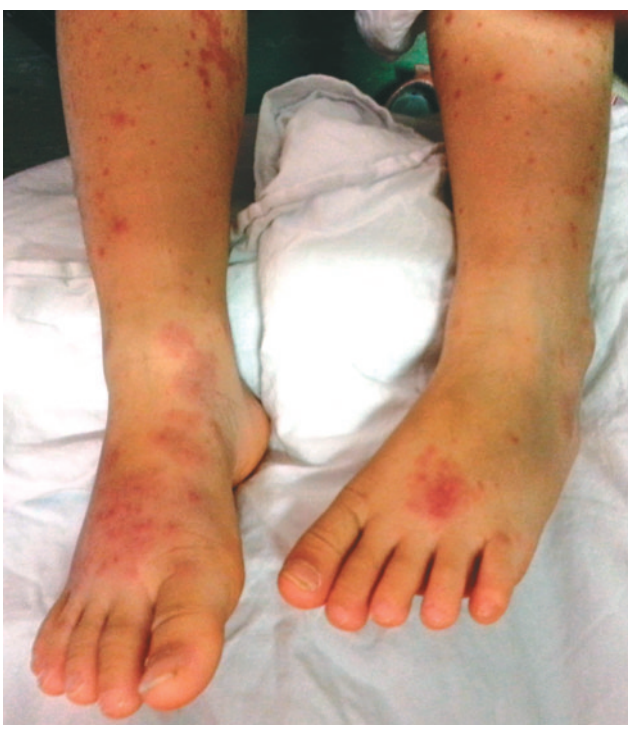

Figure 3 Girl with HSP on lower limbs who refused to walk.

haematuria or proteinuria, or acute nephritic or nephrotic syndrome. Of those who have isolated haematuria or proteinuria, 1.6% goes on to develop long-term renal impairment, while this number rises to 19.5% in those who develop nephrotic or nephritic syndrome during the acute phase of the disease.[4] Therefore renal function and urinalysis should be monitored regularly at follow-ups. Nephropathy is more severe in children older than 8 years.

Corticosteroids and antiplatelet drugs have been used to prevent long-term renal complications. However, recent Cochrane Review showed neither prednisolone nor antiplatelet drugs were useful in preventing persistent renal involvement.[10] PubMed (a service of the U.S. National Library of Medicine) was searched for the terms "Henoch-Schönlein" and "corticosteroid", with limits activated (Humans, published in the last 10 years). As of January 2013, 199 publications were reviewed, but only few publications were relevant. It appears that prednisolone was effective in preventing persistent renal disease at 6 months in those patients who had kidney disease at presentation.[11] The routine use of prednisolone or antiplatelet drugs is not recommended, as the quality of evidence was considered low. In general, use of prednisolone for HSP is recommended only for severe cases with renal pathology of crescentric lesions or heavy proteinuria in the nephrotic range.[2]

Fish-oil therapy has proven to be promising in halting the progression of IgA nephropathy. Five children with biopsy-proven HSP with repeated episodes of haematuria and proteinuria were treated with fish oil (1 g orally twice daily) and some efficacy was demonstrated.[12] The authors proposed that randomised prospective trials are needed to confirm this observation

Edstrom et al report on treatment experience of severe Henoch-Schönlein and immunoglobulin A nephritis. In three of the five patients an angiotensin-converting enzyme inhibitor (ACEI) was added for hypertension. The mean duration of follow up after starting fish-oil therapy was 49.2 weeks. The protein excretion rate prior to starting fish oil was 1041 mg/day and on the last follow-up visit the rate had decreased to 104 mg/day ($p<0.05$). The average blood pressure (BP) prior to therapy was 135/82. On the last follow-up visit the average BP off ACEI had decreased to 100/54 ($p<0.05$). After a year of follow up serum creatinine and glomerular filtration rates have remained stable at 51.2 micromol/L and 128 mL/min/1.73 m^2, respectively. The authors conclude that treatment with corticosteroids, cyclophosphamide and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker was effective in increasing glomerular filtration rate, reducing proteinuria and decreasing the disease activity index.[13]

Our cases were managed conservatively without the use of systemic corticostroid. The purpuric rash of HSP classically involves the extensor surface of the limbs. It is pressure and gravity-dependent.[14] The rash is typically palpable and does not blanch. Palpable purpura is present in almost 100% of patients with HSP and is the presenting sign in 50%.[15] Haemorrhagic vesicles-bullous HSP may rarely occur.[15] Junior et al reported three female patients (1.3%) with haemorrhagic vesicles and bullous lesions associated with palpable purpura and concluded that this manifestation may represent a more severe and prolonged disease course with scars or may precede typical skin lesions.[16] Subcutaneous nodules are rarely observed.[17] In the third case, it is the painful nature of the rash which makes the diagnosis rather atypical. It is seldom described if the cutaneous lesions in HSP are painful or not. Characteristic histological finding of HSP is neutrophil infiltration in and around dermal vessels (leucocytoclastic vasculitis).[18] Pain is a subjective perception of an unpleasant sensation which originates in a specific region of the body. Nociceptors are abundant in the dermis and dermal purpuric vasculitis could manifest as pain. Along similar consideration, vasculitis involvement elsewhere such as in the viscera manifests as abdominal pain.

PubMed was searched for the terms "Henoch-Schönlein" and "infection", with limits activated (Humans, published in the last 10 years). As of January 2013, 193 publications were reviewed. Approximately 60 to 75% of patients with HSP have a history of preceding upper respiratory tract infection.[17] A wide variety of infectious agents have been reported as potential triggers of HSP. Group A beta-haemolytic streptococcus (GAS) is found in 20-50% of patients with acute HSP.[2] In addition to GAS, others have reported a significant association of antecedent *Bartonella henselae* infection with HSP.[19] Parvovirus B19 had also been proposed in the aetiology of HSP although a recent study demonstrated that only one of 29 HSP patients had evidence of parvovirus B19 infection.[20] Other HSP-associated pathogens include *Staphylococcus aureus*, *Helicobacter pylori*, *Haemophilus parainfluenza*, *Mycoplasma pneumoniae*, *Yersinia*, *Campylobacter*, Coxsackie virus, adenovirus, Epstein-Barr virus, varicella-zoster virus, hepatitis A virus, and hepatitis B virus.[2,21,22] Nevertheless, HSP is generally a non-infectious vasculitis and there is little evidence to suggest empirical antibiotic usage in the absence of pathogen isolation.[1,2,23-28] Antibiotic

was only used in our first case but no apparent microbials were involved in these cases.

Although the notion that HSP should be considered when a child presents with acute abdominal symptoms and a purpuric rash is well accepted in clinical practice, the timely diagnosis of the various masquerading manifestations of this childhood vasculitis remains challenging. It is hoped that this report helps to alert readers to the protean manifestations of HSP. A high index of suspicion with prompt diagnosis is pivotal to avoid unnecessary treatment such as antibiotics or surgery for this systemic disease with cutaneous manifestations.

Declaration of Interest

None

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