Clin Kidney J (2012) 5: 600–602
doi: 10.1093/ckj/sfs128
Advance Access publication 6 November 2012

CKJ

Teaching Point
(Section Editor: F.P. Schena)

Lymphoma presenting as Henoch–Schönlein purpura

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Keywords: Henoch–Schönlein purpura; lymphoma; malignancy; vasculitis

Introduction

Henoch–Schönlein purpura (HSP) is a systemic vasculitis affecting the small blood vessels of the skin, the gastrointestinal tract and the kidneys. HSP typically affects children and is self-limiting. Less commonly it presents in adults. Several triggers for HSP have been recognized, including infections, medications and malignancy. This report describes a patient presenting with HSP who was found to have an underlying malignancy and highlights that in adults presenting with HSP a careful search for an underlying cause should be undertaken.

Case report

A 57-year-old man was referred from the Internal Medicine service at another hospital with presumed HSP. He presented with a 2-week history of fever, lethargy and night sweats, and 5 days of a widespread purpuric rash on the upper and lower extremities and new renal impairment, and a skin biopsy had shown a leukocytoclastic vasculitis. Apart from a history of malaria 20 years ago, for which he received prompt treatment, he was fit and healthy. A physical examination revealed an ill, febrile patient with palpable purpuric eruptions on all extremities (Figure 1). He was noted to have cervical lymphadenopathy and splenomegaly. His blood profile showed anaemia and thrombocytopaenia (haemoglobin 99 g/L, platelet count 113×10^9/L, white cell count 10.5×10^9/L, neutrophils 8.0×10^9/L, monocytes 1.0×10^9/L, lymphocytes 0.8×10^9/L). He had renal impairment and an abnormal urinalysis (creatinine 119 μmol/L, urine red cells 50 per high powered field, urine protein creatinine ratio 198 g/mol). He was noted to have elevated serum immmunoglobulins with a moderate polyclonal immune response (IgG 16.6 g/L, IgA 4.3 g/L, IgM 4.3 g/L). Rheumatoid factor, antinuclear antibodies, anti-neutrophil cytoplasmic antibody (ANCA) screen, antistreptolysin-O titers, hepatitis serology and cryoglobulins were all negative or within the normal limits. Tests for infection including malaria and tuberculosis were negative. Tests for immune-mediated haemolysis were positive (haptoglobins <0.4 g/L, lactate dehydrogenase 585 U/L, positive direct antiglobulin test).

He was commenced on high-dose oral prednisone (100 mg daily) for haemolytic anaemia. A bone marrow biopsy was non-diagnostic. The renal biopsy light microscopy showed mesangial hypercellularity in all three glomeruli, with one glomerulus showing a segmental proliferative lesion (Figure 2). There was no scarring or interstitial inflammation. Immunofluorescene microscopy showed strong mesangial positivity for IgA, positivity for IgM and C3, and was negative for IgG and C1q. A computed tomography (CT) scan of the body demonstrated splenomegaly and cervical, thoracic and abdomino-pelvic lymphadenopathy (Figure 3). These findings prompted a right axillary node biopsy which showed typical features of angioimmunoblastic T-cell lymphoma (replacement of the nodes normal architecture with T cells, staining positive for CD3, CD4, CD10 and BCL6, with numerous high endothelial venules and follicular dendritic cells).

The patient was commenced on cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone chemotherapy. After the first cycle, the rash, arthralgia and fevers resolved. Following six cycles, his renal function improved (creatinine 78 μmol/L, urine red cells 25 per high powered field, urine protein creatinine ratio 18 g/mol), as had his blood count (Hb 116 g/L, platelet 151×10^9/L, white cell count 5.6×10^9/L, neutrophils 3.51×10^9/L, monocytes 0.82×10^9/L, lymphocytes 1.29×10^9/L, haptoglobins 1.06 g/L). A CT body demonstrated normalization of the splenic size and no lymphodenopathy. He is now awaiting an autologous bone marrow transplant.

Discussion

HSP is a systemic vasculitis characterized by deposition of Immunoglobulin A (IgA) immune complexes in tissues. It is characterized by the clinical tetrad of palpable purpura, arthralgia ± arthritis, abdominal pain and renal disease. It is the most commonly seen vasculitis in childhood, the

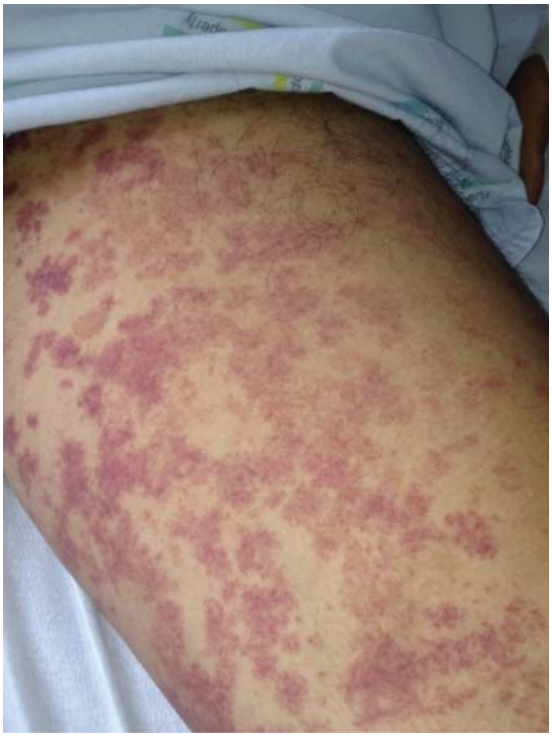

Fig. 1. Palpable purpura on the proximal lower extremity.

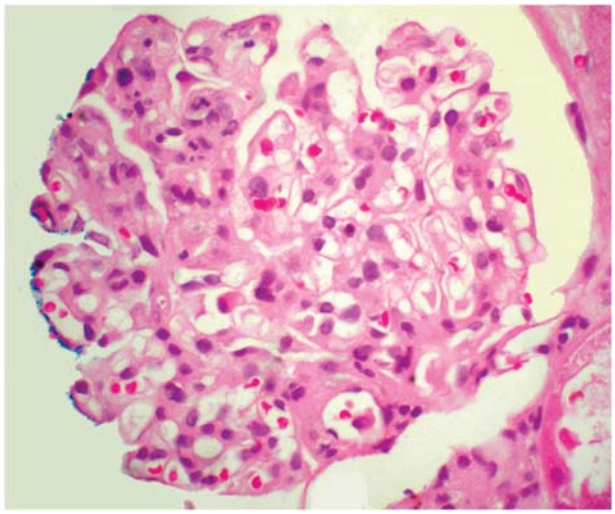

Fig. 2. The glomerulus shows diffuse mesangial hypercellularity, and a segmental proliferative lesion with neutrophils (upper left).

majority of cases being reported in children and in this group the condition is typically self-limiting [1].

HSP is less common in adults and often does not present with the classic tetrad. If clinical features are present and IgA can be demonstrated on tissue biopsy, this establishes the diagnosis and allows a distinction to be made from other systemic vasculitidies. A biopsy of the purpura typically demonstrates leucocytoclastic vasculitis, with inflammation most prominent in the post-capillary venules. As immunofluorescence in skin biopsy is often inconsistent [2], histology from other tissue is often

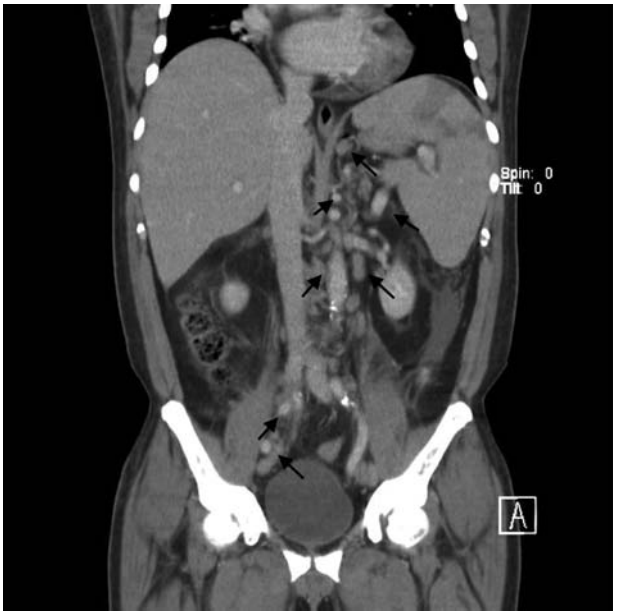

Fig. 3. CT of the abdomen: the coronal view shows an axial splenic length of 16.5 cm and abdomino-pelvic lymphadenopathy (black arrows).

sought. The renal biopsy changes may be mild with mesangial expansion or severe with a necrotizing cresentic glomerulonephritis with dominant expression of IgA; the changes are indistinguishable from those seen in IgA nephropathy.

The clinical diagnosis of HSP was made by the Internal Medicine service based on the presentation with palpable purpura, acute renal impairment and leucocytoclastic vasculitis on skin biopsy. As the patient had renal disease he was referred for further evaluation. However, when the patient was reviewed, there were a number of atypical features noted. Typically, there is neither coagulopathy, nor thrombocytopaenia, as was seen with our patient. The clinical features of lymphadenopathy and splenomegaly were also out of keeping with idiopathic HSP. This led to further evaluation demonstrating autoimmune haemolysis and lymphoma.

The aetiology of HSP is unknown; however, there are often precipitating triggers, such as an infective illness, a reaction to drugs or malignancy. Given the patient's history of malaria and the finding of splenomegaly, we undertook a careful search for infective causes including a thick and thin film for malaria, and other infectious serology, all of which were all negative. Bacterial infections [3], viral infections [4], vaccinations [5] and parasites such as *Plasmodium falciparum* [6] have been described as potential triggers. A number of drugs have also been described as precipitating HSP [7]; however, our patient was not on any medications.

Malignancy has been reported as a potential trigger in patients with systemic vasculitis [8, 9], and specifically in adult-onset HSP [10–12] with a relative risk of 5.25 for malignancy found when compared with age-matched controls without HSP [13]. Myeloproliferative and lymphoproliferative malignancies are reported to be three to five times more common than solid malignancies when considering all types of vasculitis [9]. However, the prevalence of haematological malignancy is comparatively rare in adult-onset HSP, when compared with solid

malignancies and is associated with a poor prognosis [11]. Malignancy may be diagnosed either concurrently or after the diagnosis of HSP [9]. Importantly, when HSP occurs after a diagnosis of malignancy is known, it may signal that metastasis, or progression of the primary lesion have occurred [10, 11].

The pathogenetic mechanisms that lead malignancy to present as HSP or any vasculitis remain poorly understood [7]. It is believed that vasculitis behaves like a paraneoplastic syndrome and several mechanisms have been proposed, and these include (i) molecular mimicry between tumour neoantigens and endothelial cells, (ii) decreased immune complex clearance, (iii) increased antibody production, (iv) dysregulated antibody class switching from IgM to IgA, (v) reduced sialylation of the IgA hinge region and (vi) increased inflammatory cytokine release during neoplastic processes [14].

The renal prognosis for children presenting with HSP is generally favourable with 5–20% developing chronic kidney disease (CKD) [15, 16]. In adults, CKD is reported to occur in 35–69% although these represent a selected cohort of patients who underwent renal biopsy [17–20]. Little prospective randomized controlled trial evidence exists to guide therapy in patients with HSP although observational data exist [21]. Agents that have been used include, but are not limited to, pulse methylprednisolone, oral prednisione, cyclosporine, cyclophosphamide, azathioprine, mizorobine, plasma exchange, urokinase alone or in a combination [21]. In the case presented here, a diagnosis of angioimmunoblastic T-cell lymphoma was concurrently discovered in the absence of any other identifiable trigger of HSP resulting in a prompt initiation of chemotherapy and improvement of renal function.

In conclusion, we present a patient who presented with HSP but had atypical features, and who was found to have an underlying lymphoma.

Teaching points

(i) HSP classically presents with purpura, arthalgia, abdominal pain and renal impairment. In adults, there may be fewer clinical features and a tissue biopsy demonstrating that tissue deposition of IgA is required to confirm the diagnosis.
(ii) Renal disease is more common in adults and the renal prognosis for adults is worse.
(iii) A number of potential triggers have been identified in patients with HSP including infection, medications and malignancy. In adults presenting with HSP, a careful evaluation should be undertaken to determine a trigger, especially if atypical features are present. In patients for whom there is a known history of malignancy, the development of HSP should result in re-evaluation for a new metastatic lesion.

Acknowledgements. The authors would like to thank Dr Janeen Milner, General Practitioner, Auckland, New Zealand for reviewing and commenting on the manuscript. Consent has been obtained from the patient for discussion of his case.

Conflict of interest statement. None declared.

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Received for publication: 24.5.12; Accepted in revised form: 16.8.12