Investigating patients with a vasculitic rash

Each month we present authoritative advice on the investigation of a common clinical problem, specially written for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

DAVID HEYWORTH-SMITH
MB BS(Hons), FRACP, FRCPA

JOHN QUIN
MB BS(Hons), BSc(Hons), PhD, FRACP, FRCPA

Dr Heyworth-Smith is an Immunologist, Queensland Health Pathology Services, Princess Alexandra Hospital, Brisbane, Qld; Dr Quin is Director of Immunology, South Western Sydney Area Health Service, Liverpool Hospital, Liverpool, NSW.

Series Editor
CHRISTOPHER S. POKORNY
MB BS, FRACP

Dr Pokorny is Honorary Secretary, Board of Continuing Education, Royal Australasian College of Physicians, and a Gastroenterologist in private practice, Sydney, NSW.

Vasculitis is inflammation of the wall of blood vessels. It may be only cutaneous or may present with cutaneous involvement – usually a rash, although other cutaneous presentations include panniculitis (inflamed subcutaneous fat) and ulceration. A vasculitic rash may herald a serious underlying condition requiring specific therapy, including immunosuppressive therapy in some cases.

Palpable purpura is the typical appearance of a vasculitic rash. This implies extravasation of blood from damaged dermal vessels. The lesions are palpable because of both extravasated blood and local vascular inflammation and oedema. Ultimately, tissue damage in vasculitis results from obstruction of the affected vessel and ischaemia of the subtended tissues. 'Bystander' tissue damage may occur if there is a particularly florid inflammatory cell infiltrate. Both ischaemia and local tissue destruction may lead to painful ulceration.

Classification of vasculitis

The existence of multiple names and descriptions complicate the classification of vasculitis. The Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis provided a scheme based on vessel size affected (Table 1).[1] This is helpful in clinical diagnosis because the site and calibre of vessels affected is suggestive of the aetiology. However there may be considerable overlap of vessel size affected.

'Hypersensitivity vasculitis' and 'hypersensitivity angiitis' are frequently used synonyms for small vessel vasculitis. Small vessel vasculitis is the underlying pathology in many skin rashes, but medium sized vessel vasculitis may also affect the skin (for example, panniculitis and ulceration can occur in polyarteritis nodosa).

Diagnosis of the vasculitic rash

For most vasculitides, there is no single diagnostic test; diagnosis is therefore based upon the collation of clinical and laboratory information. To start with, evidence of systemic involvement must be sought to establish that the condition is vasculitis. Numerous conditions mimic true vasculitis and should be considered in the differential diagnosis. Prominent differential diagnoses to consider are listed in Table 2.

History

Chronology and associated features such as fevers and arthritis should be sought. A detailed

IN SUMMARY

- **Most vasculitic rashes are caused by small vessel vasculitis.**
- **Many cases are related to a new medication – e.g. beta-lactam antibiotics, sulfonamides, allopurinol, phenytoin.**
- **Infectious causes of a vasculitis must be excluded.**
- **Urinalysis should always be obtained; if normal, concomitant renal vasculitis is unlikely.**
- **Histological confirmation by skin biopsy is desirable.**

Table 1. Types of vasculitis and some typical laboratory findings

Small vessels (arterioles, capillaries, venules)

Henoch–Schonlein purpura
- – elevated serum IgA, proteinuria, haematuria, laboratory evidence of recent streptococcal infection

Cryoglobulinaemic vasculitis
- – cryoglobulins, low complement

Hypocomplementaemic urticarial vasculitis
- – low complement

Cutaneous leucocytoclastic vasculitis

Microscopic polyangiitis*
- – positive ANCA

Wegener's granulomatosis*
- – positive ANCA

Churg–Strauss disease*
- – positive ANCA, eosinophilia

Systemic lupus erythematosus†
- – homogenous antinuclear antibody, anti-double stranded DNA antibody, low complement

Rheumatoid arthritis†
- – rheumatoid factor, antikeratin (antifilaggrin or anti-CCP) antibodies

Drug-induced vasculitis

Medium vessels (visceral arteries)

Polyarteritis nodosa

Kawasaki disease

Large vessels (aorta and its primary branches)

Giant cell arteritis

Takayasu's artertis‡

* Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.
† Vasculitis associated with connective tissue diseases.
‡ Takayasu's arteritis does not directly involve the skin.
CCP = cyclic citrullinated peptide.

medication and drug history is required. Many vasculitic rashes follow commencement of a new medication. Antibiotics, particularly beta-lactam antibiotics and sulfonamides, are frequently implicated. Phenytoin, granulocyte colony stimulating factor and allopurinol are reported causes of vasculitis. Hydralazine and propylthiouracil may induce antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

A history of a preceding infection may suggest Henoch–Schönlein purpura. Constitutional symptoms such as arthritis, fevers, weight loss and night sweats may point to a systemic vasculitis such as microscopic polyangiitis or a connective tissue disease such as systemic lupus erythematosus (SLE). Presence of persistent sinus pain or bloody nasal discharge suggests Wegener's granulomatosis.

Past medical history is important. Known chronic hepatitis C virus infection raises the possibility of cryoglobulinaemic vasculitis. Approximately 30% of cases of polyarteritis nodosa are associated with chronic hepatitis B infection. Inflammatory bowel disease can cause a cutaneous leucocytoclastic vasculitis.

Table 2. Differential diagnosis of vasculitis

Primary immune disorders
Vasculitis
Catastrophic antiphospholipid antibody syndrome

Infective disorders
Infective endocarditis
Rickettsial diseases
Neisserial infection
Meningococcal disease
Disseminated gonococcal infection
Ecthyma gangrenosum (*Pseudomonas* septicaemia)
Secondary syphilis

Coagulopathy or vascular fragility
Autoimmune thrombocytopenia purpura
Thrombotic thrombocytopenia purpura
'Senile' ecchymoses
Prolonged corticosteroid therapy
Disseminated intravascular coagulation

Atheroembolism or cholesterol embolism

Atrophie blanche (livedo racemosa)

Kaposi's sarcoma

Physical examination

Physical examination may reveal palpable purpura or ulceration, or other features of vasculitis including livedo reticularis, urticaria and panniculitis. In addition to purpura, physical signs of immune complex vasculitis include nail fold infarcts and nail bed splinter haemorrhages.

Laboratory investigations

Evidence of systemic vasculitis should be sought. Systemic involvement mandates more vigorous intervention if organ damage is demonstrable. Urinalysis is most important and should be obtained in every case. If urinalysis is normal, concomitant renal vasculitis is unlikely. Other noncutaneous manifestations of small vessel vasculitis include mononeuritis multiplex, serositis, pneumonitis, gastrointestinal disturbance and ocular involvement. Cardiac murmurs must be assiduously sought because infective endocarditis induces high levels of immune complexes and may cause a vasculitic rash.

Cholesterol embolism (atheroembolism) can produce similar appearances to vasculitis, especially in the lower limbs. Concomitant renal impairment may further confuse the issue. The principal clue to this entity is evidence of atheromatous disease, such as peripheral vascular disease. Histological examination of lesions due to cholesterol emboli is diagnostic, with characteristic cholesterol deposits.

Case: a young woman with a rash

Presentation

A 19-year-old woman presented with a rash on her legs and buttocks three weeks after having a sore throat. The rash was prominent on the posterior aspect of her thighs and gluteal regions (Figure A). Other symptoms were fatigue, fevers, arthalgias in her interphalangeal and knee joints, and colicky abdominal pains. She was previously in good health and was on no regular medications. Neither antibiotics nor other medications were reported.

She was afebrile. Her pulse was 79 and blood pressure 130/75 mmHg. Examination of the rash demonstrated palpable purpura. Her joints were tender, but no synovitis or effusions were present. Cardiorespiratory, abdominal and neurological examinations were normal. A urinalysis demonstrated 2+ blood and 1+ protein.

Laboratory investigation showed a mild leucocytosis of 12 x 10^9/L. The erythrocyte sedimentation rate (ESR) was elevated: 45 mm/h (normal, <30 mm/h). Serum urea and creatinine levels were normal, as were liver function tests. Measurement of serum IgA was elevated at 5 g/L. A pharyngeal swab cultured *Streptococcus* species.

A skin biopsy (Figure B) confirmed cutaneous vasculitis with thrombosis and fibrinoid necrosis of small blood vessels, with an inflammatory cell infiltrate around the vessels (leucocytoclastic vasculitis). Direct immunofluorescence of the biopsy specimen showed deposition of fibrinogen, complement proteins and immunoglobulins (especially IgA) in the walls of involved blood vessels.

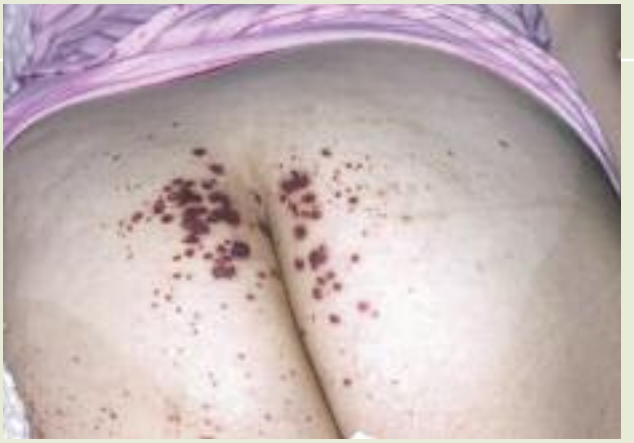

Figure A. Vasculitic rash on the patient's buttocks.

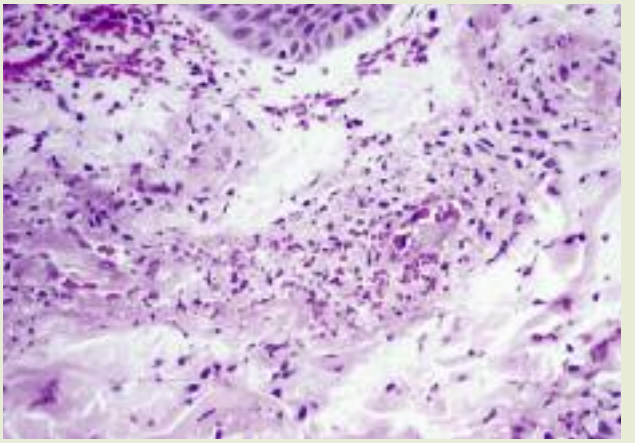

Figure B. Skin biopsy showing leucocytoclastic vasculitis.

Discussion

The pertinent findings are:

- onset after a streptococcal infection
- arthralgias
- abdominal pains
- haematuria and proteinuria
- biopsy proven leucocytoclastic vasculitis.

These are features of Henoch–Schonlein purpura, which is a small vessel vasculitis most common in children under 10 years old. It is often preceded by a viral or streptococcal upper respiratory tract illness, and may recur after subsequent infections.

The pathogenesis is presumed to involve immune complex deposition in the walls of small blood vessels, complement activation and inflammation. Mild renal involvement with proteinuria and haematuria occurs in 85% of individuals, but clinical nephritic syndrome is rare. Gastrointestinal manifestations are frequent: colicky pain, diarrhoea, and rarely melaena.

The illness is often self-limited in children. In more severe cases and in older patients, corticosteroid therapy may be required. Generally the prognosis for full recovery is good, but progression to renal failure is reported.

Laboratory investigations are listed in Table 3. The full blood examination is usually nonspecific, but it excludes thrombocytopenia and microangiopathic changes, which are a hallmark of thrombotic thrombocytopenia purpura. Eosinophilia suggests an eosinophilic vasculitis such as Churg–Strauss disease. A coagulation profile, including activated partial thromboplastin time, prothrombin time and fibrinogen, is helpful if a coagulation disorder is suspected.

Raised creatinine suggests renal involvement. The inflammatory markers C-reactive protein and erythrocyte sedimentation rate may be normal or elevated in vasculitis but are nonspecific. If elevated, these markers can be useful in monitoring

progress and response to therapy.

Rheumatoid factor may be elevated in many inflammatory and infective conditions, but high levels are supportive of rheumatoid disease in the setting of concomitant synovitis. Cryoglobulinaemia and Sjögren's syndrome are usually rheumatoid factor positive.

Complement levels may be depressed in immune-complex-mediated vasculitis with complement activation and consumption. Antinuclear (ANA), extractable nuclear (ENA) and anti-double stranded DNA antibodies may be positive in SLE and other connective tissue diseases. Cryoglobulin measurement should be considered in the setting of chronic hepatitis C infection, if complement levels are reduced or when symptoms are worsened by cold exposure.

ANCA testing is mandatory, but a negative ANCA result does not exclude vasculitis. The ANCA-positive vasculitides are Wegener's granulomatosis, Churg–Strauss disease and microscopic polyangiitis. Wegener's granulomatosis is most often associated with C-ANCA and PR3-ANCA, and microscopic polyangiitis and Churg–Strauss disease are associated with P-ANCA and MPO-ANCA. However, both microscopic polyangiitis and Churg–Strauss disease may be ANCA negative. ANCA-negative Wegener's granulomatosis is rare. Polyarteritis nodosa is usually ANCA negative, but 10 to 15% of cases are ANCA positive and these cases have a mixture of features of polyarteritis nodosa and microscopic polyangiitis.

A positive ANCA is not pathognomonic of vasculitis. Positive ANCA results

Table 3. Laboratory investigations in suspected vasculitis

Urinalysis
Full blood examination
Biochemical profile
Rheumatoid factor
Antinuclear antibodies (ANA)
Anti-double stranded DNA antibodies
Antibodies to extractable nuclear antigens (ENA)
C3 and C4 complement
ANCA (C-ANCA, P-ANCA, PR3-ANCA and MPO-ANCA)
Serum protein electrophoresis
Cryoglobulins
Antistreptolysin O titre (ASOT)
Hepatitis B and hepatitis C serology

ANCA = antineutrophil cytoplasmic antibody.
C = classical/cytoplasmic.
P = perinuclear.
PR3 = antiproteinase 3.
MPO = antimyeloperoxidase.

(particularly atypical ANCA patterns) occur in many inflammatory conditions, including systemic infections (especially infective endocarditis), inflammatory bowel disease, cystic fibrosis, autoimmune hepatitis and other nonvasculitic autoimmune disorders.

Histology

Histological confirmation of the diagnosis is desirable. A skin biopsy can be performed conveniently at the bedside or in the clinic. Biopsy of the edge of a new lesion is preferable. Usually two to three lesions are biopsied and one specimen is sent for an immunofluorescence study. Specimens for immunofluorescence may be frozen in liquid nitrogen. Otherwise it is best to arrange with the local pathologist for suitable collection media for fresh specimens.

Punch biopsies are convenient to perform for both doctor and patient; however, crush artefact may occur if the specimen is carelessly gripped with forceps. Also punch biopsies are limited when deeper subcutaneous tissue is the site of the vasculitis (for example, in panniculitis, when an excision biopsy may be better).

Provision of history details and clinical differential diagnosis is helpful to the pathologist. In difficult cases, discussion of the findings with the pathologist is often useful.

Conclusion

Investigation of a suspected vasculitic rash should be directed by accurate historical and clinical findings. Many cases in community practice are from a drug reaction, and removal of the offending agent usually allows resolution. In-depth discussion of individual vasculitides is beyond the scope of this article, and we direct readers to the further reading list for review articles. MT

Reference

1. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides: proposal of an international consensus conference. Arthritis Rheum 1994; 37: 187-192.

Further reading

1. Savige J, Gillis D, Benson E, et al. International Consensus Statement on Testing and Reporting of Antineutrophil Cytoplasmic Antibodies (ANCA). Am J Clin Pathol 1999; 111: 507-513.
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