Amlodipine-induced cutaneous vasculitis: An unusual manifestation of a common medication

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CASE

A woman, aged 36 years, presented to the local hospital with sudden-onset tender and pruritic palpable purpura over her bilateral lower legs, associated with symmetrical swelling of the dorsal hands and feet with overlying pinpoint petechiae (Figure 1). She denied symptoms of other system involvement or systemic features such as fevers, night sweats or weight loss. Three days prior to her presentation, she was commenced on 10 mg amlodipine daily by her general practitioner for early onset hypertension. The patient otherwise had no other medical history or was she was not taking regular medications, but she had suffered a recent right wrist fracture after a fall following which she used paracetamol for pain management as required. There were no other provoking events such as infection or recreational drug use. There was no relevant family history.

Excluding the described cutaneous rash and swelling, the remainder of the physical examination was unremarkable, including an absence of synovitis, nailfold capillary changes and mucosal changes.

QUESTION 1

What are the differential diagnoses for palpable purpura over the lower limbs?

QUESTION 2

What is the significance of palpable purpura over non-palpable purpura?

ANSWER 1

Possible differential diagnoses for palpable purpura over the lower limbs are summarised in Table 1.

ANSWER 2

Palpable purpura, when the purpura can be felt on examination, is an important clinical clue. In vasculitis, the inflammation of blood vessel walls allows the leakage of both haemorrhage and inflammatory infiltrate.[1]

Palpable purpura can distinguish a diagnosis of vasculitis from conditions that present as non-palpable purpura such as coagulopathies, platelet disorders and meningococcaemia.

CASE CONTINUED

Haematological and biochemical markers, inflammatory markers and autoimmune serology were normal (Table 2). The patient refused a skin biopsy.

Amlodipine was ceased and the patient was commenced on 20 mg oral prednisolone tapered by 5 mg every week until 0 mg. The patient demonstrated complete resolution of purpura and oedema of hands and feet following prednisolone weaning, thereby suggesting drug-induced vasculitis as the most likely diagnosis, with the culprit medication being amlodipine.

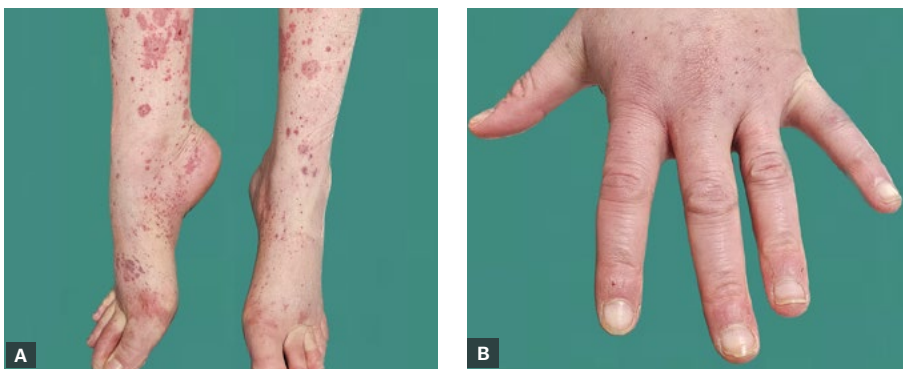

Figure 1. (A) Sudden-onset tender and pruritic palpable purpura over the patient's bilateral lower legs, 3 days following commencement of amlodipine. **(B)** Pinpoint petechiae and soft tissue swelling over the dorsal aspect of the left hand.

Table 1. Differential diagnoses, characteristics and reason for exclusion in the case study patient with palpable purpura of the lower limbs

Differential diagnosis	Characteristics	Reason for exclusion in the case study
IgA vasculitis (Henoch–Schonlein purpura)[9]	• Childhood predominant (ages 4–7 years) • Associated with arthralgias, abdominal pain, haematuria or proteinuria • Preceding infection – usually upper respiratory tract infections • IgA deposition in dermal vessels on biopsy	• Older age • Absence of systemic features, or preceding infection
ANCA-associated vasculitides; GPA, eGPA, MPA[9]	• Multi-organ systemic manifestations including pulmonary cavities and infiltrates with haemoptysis, interstitial lung disease, mucosal ulcerations, conjunctivitis, episcleritis, uveitis, neuritis, pericarditis, carditis, haematuria and glomerulonephritis. Specific organ involvement dependent on type. Underlying past history including asthma (eGPA). Dermal granulomas (eGPA and GPA) or eosinophil-rich histology (eGPA) on biopsy • Positive ANCA; cANCA or PR3 for GPA, pANCA or MPO for eGPA and MPA	• Negative ANCA • Absence of systemic features or relevant past history
Cryoglobulinemia[9]	• Various types (types 1, 2, 3). Cutaneous palpable purpura, livedo reticularis, ulcerations. Arthralgias, weakness, neurological involvement, Raynaud phenomenon. Less commonly haematuria, proteinuria, glomerulonephritis, renal failure • Underlying systemic diseases including lymphoproliferative disorders, hepatitis C, autoimmune diseases • Positive cryoglobulins, rheumatoid factor, decreased complement – specifically complement 4	• Completely negative rheumatological screen, absence of systemic features
Immune-mediated thrombocytopenic purpura[9]	• Petechaie and purpura • Thrombocytopenia	• Absence of thrombocytopenia
Recurrent macular vasculitis[9]	• Relapsing, short-lasting macules and purpura. Induction by exertion • Evidence of hypergammaglobulinaemia • Perivascular immunoglobulin deposits on biopsy	• Lack of macular morphology. Not triggered by exercise • No hypergammaglobulinaemia
Infection-induced vasculitis[9]	• Multiple infectious pathogens including *Streptococcus pyogenes*, hepatitis B and C, HIV, and COVID-19 among others • Symptoms are variable and pathogen-specific but can include fever, lymphadenopathy and positive microbiology cultures or serology	• Lack of infective symptoms or signs • Negative viral serology
Idiopathic or primary cutaneous small vessel vasculitis[10]	• Mild, without evidence of extracutaneous manifestations or drug or infective triggers. Usually singly episodic but can recur in up to 10% of cases • Gradual resolution usually within 3–4 weeks after onset albeit with risk of residual hyperpigmentation	• Diagnosis of exclusion
Drug-induced vasculitis[11]	• Preceding drug trigger including beta-lactam antibiotics, TNF-alpha agents, allopurinol, sulfasalazine, anti-thyroid medications/propylthiouracil, hydralazine, phenytoin, thiazide diuretics, anticoagulants and NSAIDs, among others • Can include systemic manifestations but are usually milder • Variable duration between drug commencement and symptoms	• Favoured diagnosis in this case

ANCA, anti-neutrophil cytoplasmic antibody; cANCA, cytoplasmic anti-neutrophil cytoplasmic antibody; eGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; IgA, immunoglobulin A; MPA, microscopic polyangiitis; MPO, myeloperoxidase; NSAIDs, non-steroidal anti-inflammatory drugs; pANCA, perinuclear anti-neutrophil cytoplasmic antibody; PR3, proteinase 3; TNF-alpha, tumour necrosis factor-alpha.

CASE CONTINUED

Drug-induced vasculitis induced by paracetamol can also be considered; however, the patient has tolerated paracetamol in the past without reaction, and the time frame of rash development and resolution following amlodipine commencement and cessation is much more compelling.

QUESTION 3

What tools can be used to determine the likelihood of whether an adverse drug reaction is caused by a medication or caused by other factors?

QUESTION 4

If this patient were to undergo a biopsy, what could be the expected histological features?

Table 2. Haematological and biochemical markers, inflammatory markers and autoimmune serology for this case study patient, supporting the absence of a systemic cause for the patient's rash

Investigations	Patient results (normal laboratory range)
Full blood examination	• Haemoglobin 117 g/L (115–165) • White-cell count 10.5×10^9 /L (4.0–11.0) • Eosinophils 0.3×10^9/L (0.0–0.5) • Platelets 372×10^9/L (150–450)
Biochemistry (Serum)	• Sodium 138 mmol/L (135–145) • Potassium 3.7 mmol/L (3.5–5.2) • Urea 4.2 mmol/L (2.3–7.6) • Creatinine 52 μmol/L (40–90)
Liver function tests	• Bilirubin 10 μmol/L (0–20) • ALT 40 U/L (0–30) • AST 49 U/L (0–30) • ALP 125 U/L (30–100) • GGT 57 U/L (0–30)
Inflammatory markers	• ESR 10 mm/h (<20) • CRP <1/L (0–10)
Coagulation profile	• aPTT 29 seconds (24–34) • INR 1.1 (<1.3) • Fibrinogen 3.6 g/L (1.5–4.0)
Urine	• Normal urine microscopy, no growth, no haematuria • Protein/creatinine ratio: 9 mg/mmol (0–30)
Autoimmune panel	• ANA, ENA, RF, Anti-CCP – negative • Antiphospholipid antibodies – negative • ANCA PR3 and MPO – negative • C3 C4 – normal
Viral serology	Negative screening for HIV, hepatitis A, B and C

ALT, alanine aminotransferase; ALP, alkaline phosphatase; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; aPTT, activated partial thromboplastin time; AST, aspartate transferase; C3, Complement 3; C4, Complement 4; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; ENA, extractable nuclear antigen; ESR, erythrocyte sedimentation rate; GGT, gamma glutaryl transferase; INR, international normalised ratio; MPO, myeloperoxidase; PR3, proteinase 3; RF, rheumatoid factor.

QUESTION 5

What cutaneous adverse reactions have been observed in the setting of amlodipine?

ANSWER 3

Assessment of the likelihood an adverse event is caused by a medication is usually based on clinical judgement; however, the Naranjo algorithm has been devised to systematically assess for a causal relationship between a drug and a clinical event.[2] The algorithm and our patient's scoring is listed in Table 3. The reaction is considered definite for a score of nine or higher, probable if 5–8, possible if 1–4, and doubtful if zero or less.

Notably, the initial intended application of the Naranjo algorithm was for the analysis of drug-related events for research publications and for reports to drug-monitoring centres rather than routine clinical practice, as demonstrated by some of the questions (eg a drug rechallenge is not always performed in clinical practice).

ANSWER 4

Generally, biopsies, usually a 3-mm punch, should be taken under 48 hours after the development of the target vasculitic lesion, and from the most tender, reddish or purpuric lesion to optimise diagnostic yield.[3] Samples should be sent for histopathology (in formalin) and direct immunofluorescence (in saline-soaked gauze).

Histopathology is usually reflective of leukocytoclastic vasculitis and can include vascular fibrin deposition, nuclear debris and perivascular inflammatory cell infiltration; a range from neutrophilic infiltration, particularly within the first 24 hours, to lymphocytes and macrophages, often after 24 hours, can be visualised.[3] Older lesions demonstrate scant nuclear debris, fibrin deposition, erythrocyte extravasation and mononuclear infiltration.[3] The presence of tissue eosinophilia is a useful indicator of drug-induced vasculitis, but its presence is not mandatory for diagnosis.[3]

Direct immunofluorescence can identify key differential diagnoses including immune complex-mediated vasculitis such as immunoglobulin A (IgA) vasculitis and hence should also be taken.

Table 3. The Naranjo algorithm, and this case study's scores[2]

Question	Yes	No	Do not know	Patient's score
Are there previous conclusive reports on this reaction?	+1	0	0	+1
Did the adverse event appear after the suspected drug was administered?	+2	–1	0	+2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
Did the adverse reaction reappear when the drug was re-administered?	+2	–1	0	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	–1	+2	0	+2
Did the reaction reappear when a placebo was given?	–1	+1	0	0
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
Patient's total score:				7 (probable)

+, add to total score; –, subtract from total score; 0, zero points; 1, one point; 2, two points.

ANSWER 5

Calcium channel blockers are used as first-line treatment in the management of essential hypertension. Cutaneous adverse reactions to amlodipine are rare; epidemiological studies identified a rate of 48 cutaneous adverse drug reactions per 1 million calcium channel blocker prescriptions, with a female-to-male predominance of 3 : 1.[4] Well-described manifestations include peripheral oedema, maculopapular eruptions and flushing.[4] Fixed drug eruptions, lichenoid and eczematous eruptions, granuloma annulare, drug-induced hyperpigmentation, erythema multiforme and Stevens–Johnson's syndrome/toxic epidermal necrolysis are less common but have been described in the literature.[4,5]

Vasculitis has been reported following amlodipine use.[5–8] A search using the Food and Drug Administration Adverse Events Reporting System (FAERS) database has identified 124 cases of cutaneous vasculitis in the setting of amlodipine from 1998 to the present date, out of 92,258 total cases of adverse events. Cutaneous vasculitis can present as palpable purpura, petechiae, ecchymoses, urticaria, haemorrhagic bullae or superficial ulceration. Vasculitis from amlodipine can include leukocytoclastic (small vessel) vasculitis, exercise-induced vasculitis and pigmented purpuric dermatoses; histopathology is generally required to differentiate the conditions.[5–8] Pedal oedema can accompany the vasculitis; however, cases have also been reported of isolated purpura.[5] Amlodipine-induced purpura is theorised to occur because of relaxation of the precapillary sphincter and subsequent increase in capillary hydrostatic pressure, an extension of its intended pharmacological action; and supported by the lack of associated autoimmune markers.[5] Most cases demonstrate rapid and marked clinical improvement following cessation of amlodipine with or without treatment with systemic corticosteroids.[6,7]

Conclusion

This case study patient demonstrated a strong temporal association between commencement of amlodipine and development of the cutaneous vasculitis presenting as purpura and oedema of the hands and feet, which promptly resolved on cessation of the offending drug. Despite the lack of histopathology, an adverse drug reaction is probable, as per the Naranjo algorithm (score of 7). In contrast to other published cases, this case study patient developed a cutaneous reaction swiftly after drug commencement.[5,7]

In conclusion, a thorough history of recent medication changes is important in the assessment of cutaneous vasculitis.

Key points

- A broad range of differential diagnoses exists to investigate palpable purpura of the lower limbs, including both limited-cutaneous and systemic vasculitis.
- Palpable purpura is an important clue that can distinguish a diagnosis of vasculitis from conditions that present as non-palpable purpura such as coagulopathies, platelet disorders and meningococcaemia.
- Drug-induced cutaneous vasculitis is most common secondary to other medications such as antibiotics; however, other medications can cause it too, including common medications such as amlodipine.
- A thorough history of recent medications, including timelines, is important in the assessment of cutaneous vasculitis.

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