New disease

Isolated lower limb medium-vessel vasculitis: a new entity?

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Summary

A 47-year-old female was referred with bilateral ischaemic lesions affecting her toes with associated gangrene. Systemic examination was normal and her medical history was unremarkable. Close examination of the hands revealed splinter haemorrhages. Her feet were dusky in colour and the toes were dark and weeping, each becoming gangrenous, with erythema around the metatarsal phalangeal joint. Dorsalis pedis and posterior tibial pulses were intact with strong Doppler signals. Investigations for surgical pathology and malignancy were all negative as were routine blood tests and tests for autoimmune and viral markers. Vasculitis was diagnosed when her toes showed improvement with steroids, however, attempts to reduce the steroid dose were unsuccessful and azathioprine was introduced. Despite immunosuppression and immunomodulators, her toes deteriorated and were amputated. Histology revealed findings consistent with a medium-vessel vasculitis which antineutrophil cytoplasmic antibody was negative. A similar vasculitis has not been formally reported in the literature.

BACKGROUND

This case of vasculitis had presented to rheumatology with negative autoimmune markers. In particular, it is noted that antineutrophil cytoplasmic antibody (ANCA) was negative. In addition to this, we note that the vasculitis had affected only the lower limb digits. This unique presentation of a vasculitis has the potential to cause a delay in diagnosis and therefore a delay in treatment. Given that delays in treatment can lead to irreversible damage of the organ or limbs affected,¹ our case highlights the importance of considering vasculitides even when autoimmune investigations are negative. Furthermore, to the best of our knowledge, isolated lower limb ANCA-negative medium-vessel vasculitides are rarely reported in literature. Finally, the case highlights the difficulties faced when differentiating between and diagnosing vasculitides.

CASE PRESENTATION

A 47-year-old Caucasian female presented with bilateral ischaemic lesions affecting all of her toes with associated gangrene. Her history started in December 2008 when she attended her general practitioner (GP) having noticed her toes becoming pale blue and experiencing paresthesia, she had no history of exposure to cold. In March 2009, her toes had not improved and had become increasingly painful and dusky, her GP arranged admission to hospital.

Aside from hypothyroidism from the age of 20 and pernicious anaemia, her medical history was unremarkable. Her surgical history included a gastric bypass in 2004 (secondary to obesity) and a laparoscopic cholecystectomy in 2007, recently her weight had been stable. There was no significant family history. Social history revealed minimal alcohol intake and she was a non-smoker. Medication history revealed continuous use of the combined oral contraceptive pill (COCP) since she experienced menorrhagia aged 17 years. Systemic examination, including blood pressure and funduscopy, was

normal. Close examination of the hands revealed splinter haemorrhages. Her feet were dusky in colour and the toes were dark and weeping, each becoming gangrenous with erythema around the metatarsal phalangeal joint (figure 1). Dorsalis pedis and posterior tibial pulses were intact with strong Doppler signals.

Investigations for surgical pathology and malignancy were all negative (table 1) as were investigations for autoimmune and viral markers (table 2)

DIFFERENTIAL DIAGNOSIS

- ▶ Isolated vasculitis
- ▶ Thromboangitis obliterans (Buerger's disease)
- ▶ Polyarteritis nodosa (PAN).

TREATMENT

She was asked to stop taking the COCP and was commenced on prednisolone 30 mg, her toes showed some improvement with the prednisolone and vasculitis was diagnosed. Attempts to reduce the steroid dose were unsuccessful and azathioprine was introduced. In January 2010, she was readmitted to hospital as her toes were worsening and becoming increasingly painful (figure 2). A course of iloprost was given followed by a dose of cyclophosphamide.

OUTCOME AND FOLLOW-UP

Her toes showed mild improvement, however in February 2010, her toes worsened and became infected. Vascular surgeons amputated seven toes and samples were sent to histology. Histology revealed appearances consistent with a medium-vessel vasculitis, no micro aneurysms were noted and there was no inflammation of the small vessels. Unfortunately, cryoglobulins and cryofibrinogen were not looked for during histological examination. Postamputation healing is complete and symptoms have not re-occurred.

Figure 1 (A,B) Initial presentation of dusky, gangrenous feet.

DISCUSSION

The vasculitides are defined as a group of multisystem diseases characterised by blood vessel inflammation,² secondary to leucocyte infiltration of the vessel wall and reactive damage.³

The classification of vasculitides is a debated area,⁴ however, typically they are classified according to vessel size and definitive diagnosis is always histological via tissue sampling/biopsy.⁴ Accurate diagnosis of the vasculitides guides appropriate treatment, where the vasculitis cannot be classified and no diagnosis exists experience and clinical judgement are key.¹

Our case highlights the difficulty in making an accurate diagnosis of digital ischaemia even with detailed

investigations, as there are many differential diagnoses including Buerger's disease,⁵ PAN⁶ and cryoglobulinaemia.

Buerger's disease is a possible differential diagnosis. Although men are most commonly affected, there are isolated case reports of affected females⁵; however, the positive response to steroids does not support this diagnosis, nor does the negative smoking status or normal angiography. While PAN cannot be formally excluded, there was an absence of symptoms to meet the classification criteria⁷ and no microaneurysms on histology, making this diagnosis less likely. Mesenteric and renal angiograms can often aid in the confirmation or exclusion of PAN.⁸ The absence of exposure to cold enabled exclusion of cryoglobulinaemia as a differential, although we are aware of the limitation

Figure 2 (A,B) Deterioration of feet despite treatment.

Table 1 Investigations for surgical pathology and malignancy

Investigation	Result
Routine blood tests	Hb: 13.8 g/dl (11.5–16.5) WCC: 9.2×10^9 (4–10) Kidney and liver functions normal (except for a γ -GT of 214) Ferritin: 359
Inflammatory markers	CRP: 40.2 ESR: 47
Tumour markers	CEA: 4.0 (normal) CA 12-5: 14.4 (normal) CA 19-9 (normal)
USS venography	Normal with no occlusions
Arterial angiography	Normal
USS Doppler leg arteries	Normal
USS abdomen	Liver and aorta normal
CT abdomen and pelvis	Normal
Echocardiography	Normal
Urine Dip	Traces of protein, blood and glucose
Serum cholesterol	Fasting: 4.91 (HDL: 2.10, LDL: 2.45)

γ -GT, γ -glutamyltransferase; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; Hb, haemoglobin; LDL, low-density lipoprotein; USS, ultrasound scanning; WCC, white cell count.

that cryoglobulins were not tested for during histology. Furthermore, there has been no recurrence of symptoms since the amputation and the feet have healed well. Finally the presence of splinter haemorrhages means a diagnosis of a systemic disease cannot be excluded as early ANCA-associated vasculitides can be ANCA negative.⁹

Early treatment of vasculitis minimises disease associated damage,¹ the most common treatments involve steroids and cytotoxic medications. During treatment, careful monitoring for disease remission and drug-induced toxicity are fundamental and guide treatment.¹⁰ For the classified vasculitides the limited information available

Table 2 Results of autoimmune and viral markers

Investigations	Result
Autoimmune	Antithrombin III-81 (normal)
Protein C	77% (normal)
Free protein S	84% (normal)
Lupus AC	0.96 (negative)
RF	6.7
Cryoglobulins	Negative
ANCA	Negative
Ab to nuclei	Negative
Reticulin R1	Negative
Smooth muscle Ab	Negative
Mitochondria (M2 and non-M2) Ab	Negative
Liver, kidney, microsomal Ab	Negative
Ribosomal Ab	Negative
Anticardiolipin Ab	Negative
Cold agglutinin titre	Negative
Fibrinogen	8.4 (high) 1.5–4.5
Cryofibrinogen	Negative
IgG	4.67 (low)
IgM	1.16 (normal)
IgA	1.24 (normal)
Serum electrophoresis	Normal
Viral markers-Hep B Sag	Negative
Hep C Ab	Not detected
HIV	Negative
Parvovirus	Negative

Ab, antibody; ANCA, antineutrophil cytoplasmic antibody; Hep, hepatitis; Ig, immunoglobulin; RF, rheumatoid factor.

suggests that the treated outcomes are superior to untreated outcomes.¹⁰

To the best of our knowledge, an isolated lower limb ANCA-negative medium-vessel vasculitis has not been reported in the literature and may represent an unclassified vasculitis or new disease entity.

Learning points

- ▶ The diverse presentation of vasculitides and the multitude of differential diagnoses means vasculitides are often hard to precisely diagnose and diagnosis can potentially be missed and should always be considered.
- ▶ Delays in the treatment of vasculitides can result in permanent, often irreversible damage.
- ▶ Digital ischaemia/gangrene can occur due to small vessel vasculitis without the presence of ANCA or other immunological markers.

Acknowledgements Pathology Laboratory and staff at the University Hospitals of Morecambe Bay NHS Foundation Trust.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Gore D, Bukhari M. Isolated lower limb medium-vessel vasculitis: a new entity?. *BMJ Case Reports* 2011;**10**:1136/bcr.02.2011.3872, date of publication

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