CASE REPORT

Gangrenous digital infarcts in a severe case of cutaneous polyarteritis nodosa

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Accepted 24 May 2017

SUMMARY

Cutaneous polyarteritis nodosa (CPAN) is a rare diagnosis which is distinct from polyarteritis nodosa (PAN). PAN is a medium-vessel vasculitis which can affect multiple organs and classically produces microaneurysms in the vasculature. CPAN is limited to the skin mainly affecting small vessels. There is an absence of microaneurysms in CPAN and it does not affect internal organs. However, the histopathological findings on the skin are similar to PAN. CPAN rarely progresses to PAN but relapses more often. We will illustrate a challenging case of a patient with CPAN who developed gangrenous infarcts despite initial immunosuppressive treatment with high-dose steroids and azathioprine. His treatment had to be escalated to intravenous cyclophosphamide which induced disease remission.

BACKGROUND

Cutaneous polyarteritis nodosa (CPAN) is not well understood due to the rarity of the disease. The pathogenesis of the disease remains unknown but there are some postulated theories. It very rarely progresses to polyarteritis nodosa (PAN), the reasons for which also remain unknown. CPAN is mainly localised to the skin but can have some extra-cutaneous manifestations which will be discussed later. It follows a much more benign course compared with PAN; however, it is more likely to relapse. The ACR diagnostic criteria¹ for PAN cannot be used to make a diagnosis of CPAN. However, histological criteria for arteritis exist in the Chapel-Hill nomenclature² based on the size and distribution of vessel involvement. Differentiation between PAN and CPAN can be made by determining the size of vessel involvement. Currently no validated diagnostic criteria exist for CPAN and treatment remains anecdotal. A severity index has been proposed by Chen³ in 1989 which can be used as a basis for dividing patients into treatment groups (in discussion section). We describe a patient with severe CPAN requiring escalating immunosuppressive therapy. This case also raises several questions of vital importance (in the Discussion section) for the management.

CASE PRESENTATION

A 62-year-old man of Pakistani origin presented to his general practitioner (GP) complaining of a rash on his legs along with swelling of the ankles. He was also complaining of systemic symptoms: fever, night sweats and malaise. At the same time,

he had noticed blue discolouration of the pulp of his fingers bilaterally. He was initially suspected to have cellulitis and had courses of flucloxacillin and doxycycline in the community. However, due to non-resolution of his symptoms, he was referred to a hospital where he was assessed by the rheumatology team. His medical history included hypertension for which he was on bendroflumethiazide and impaired glucose tolerance.

Assessment in the hospital revealed a purpuric rash on his legs (figure 1) along with oedema of the ankles. He was also noticed to have infarcts bilaterally on the pulp of his fingers (figure 1). He was afebrile, with pulse of 84/min regular and a blood pressure of 115/72. Cardiovascular examination did not reveal any stigmata of endocarditis with normal heart sounds. He had clear vesicular breath sounds and abdominal examination was unremarkable with no signs of organomegaly or lymphadenopathy. There was no neurological deficit. Urinalysis showed no signs of haematuria or proteinuria.

INVESTIGATIONS

Various laboratory tests were ordered along with a skin biopsy. His investigation results are as follows.

Figure 1 Top: Purpuric rash on the legs; bottom left: right hand digital infarcts; bottom right: left hand digital infarcts (all pictures taken before any treatment).

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To cite: Mahmood-Rao H, Ding T, Gandhi N. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-220300

Figure 2 The artery at the junction of the dermis and cutis is shown at magnification $\times 200$. Fibrinoid necrosis of the artery wall is clearly visible (arrow) and there is thrombus within the lumen (*).

Haemoglobin 136 g/dL, white cell count $10.54 \times 10^9/L$, Na⁺/K⁺ 139/4.7 mmol/L, urea 5.9 mmol/L, creatinine 101 μ mol/L, C-reactive protein 107 and erythrocyte sedimentation rate of 64. A transthoracic echocardiogram did not reveal any signs of infective endocarditis. Immunology screen revealed that his anti-nuclear antibody (ANA) was weakly positive 1:160 speckled. Extractable nuclear antigens (ENA) negative, rheumatoid factor (RF) negative, anti-neutrophil cytoplasmic antibody (ANCA) negative, proteinase 3 1 U/mL, myeloperoxidase 4 (MPO) 1.6 U/mL, double-stranded DNA 7 IU/mL, no cryoglobulins, c3 1428 mg/L and c4 237 mg/L. His hepatitis B surface antigen and core antibody were negative. Hepatitis C antibody and HIV antigen were negative.

Figure 3 CT angio reconstruction of the abdomen showing normal abdominal and pelvic vasculature.

Figure 4 Magnetic resonance angiogram (MRA) of the lower limbs showing normal vasculature.

The punch biopsy of skin showed essentially normal epidermis. Increased vascularity of the dermis was noted with foci of red cell extravasation together with a scattering of siderophages and a light infiltrate of neutrophils in the interstitium. A more prominent perivascular inflammatory cell infiltrate composed of lymphocytes and plasma cells with only minimal neutrophils was seen extending from the superficial dermis through into the superficial subcutis. Within the superficial dermis, an occasional capillary featuring fibrin thrombi was noted; however, fibrinoid necrosis of the capillary walls was not convincingly demonstrated and leukocytoclasia was not a feature. Within the deep dermis, at the junction of the subcutis, a single small artery was present which showed a combination of both fibrinoid necrosis (figure 2) of its wall and an intraluminal thrombus. The presence of this vessel with appropriate background changes raised the possibility of PAN on histology.

CT angiogram of the abdomen (figure 3) showed no aneurysm or microaneurysm of the abdominal and pelvic vasculature. Magnetic resonance angiogram (MRA) of the lower limbs (figure 4) demonstrated normal vasculature as well. Arterial duplex ultrasound study of the upper limbs revealed patent

Figure 5 Above left: worsening left index finger digital infarcts; above right: worsening right hand digital infarcts; below: left toe digital infarcts (pictures taken after treatment with steroids and azathioprine).

vessels with normal triphasic velocity. With the absence of microaneurysms, a diagnosis of CPAN was confirmed.

TREATMENT

The patient was started on oral prednisolone 60 mg/day along with low-dose aspirin and vasodilators (losartan, nifedipine). In view of the extent of digital ischaemia, an iloprost infusion for 5 days was administered. Bone protection with calcium and vitamin D₃ was started along with weekly alendronic acid. His inflammatory markers very quickly normalised with oral steroids. He was then discharged from hospital.

His initial review in the clinic after 2 weeks showed no new digital infarcts with some clinical improvement. The prednisolone dose was reduced to 50 mg/day. Azathioprine was added for long-term immunosuppression. However, a review 1 month later in the clinic revealed worsening infarcts on the fingers which had progressed to gangrene and new digital infarcts on the left foot toes (figure 5). At this point, he was readmitted to the hospital for further iloprost infusion. Due to the development of gangrenous infarcts, it was decided to start the patient on intravenous cyclophosphamide (CYC) following the CYCLOPS regime with three daily pulses of 1 g methylprednisolone. He was given pneumocystis jirovecii prophylaxis with co-trimoxazole 960 mg three times a week. He was also given treatment with mesna 400 mg pre and post each infusion of CYC to prevent urological side effects.

After eight pulses of CYC, his condition has improved significantly. His prednisolone dose is now 15 mg daily. His infarcts on the right hand have disappeared with significant improvement in the toe infarcts. Unfortunately, the left index finger tip infarct failed to reverse and is beginning to autoamputate. The patient is now back at work and independent. He requires two further cycles of CYC before treatment completion and we are reducing his steroids by 1 mg every month. After the completion of CYC

treatment, we plan to restart him on azathioprine to maintain long-term disease remission.

DISCUSSION

CPAN was first described by Lindberg in 1931⁵ as cases of necrotising vasculitis which were limited to the skin. CPAN is a disease limited to the skin with similar histopathological findings as PAN with the absence of microaneurysms in the vasculature. It is now considered to be a separate entity from PAN with a favourable prognosis compared with PAN.⁶ It has more relapses and rarely progresses to PAN.⁴

The aetiology of CPAN is unknown. However, it has been associated with hepatitis B and C infections.⁷ Streptococcal infections have also been implicated. A study in Japan indicated that it affects women more than men with onset being at age typically >40 and the peak number of cases being between 50 and 59 years of age.⁸

The pathophysiology of CPAN is not understood well. One hypothesis suggests the involvement of immune complexes via type three hypersensitivity reactions.⁸

CPAN presents with a variety of skin lesions such as pupura, livedo reticularis, subcutaneous nodules, ulcers and gangrene. These may be associated with systemic symptoms such as fever, night sweats or weight loss. It may be associated with extra-cutaneous manifestations such as myositis or peripheral neuropathy.

CPAN only affects small arteries in the subcutaneous tissue. Arkin⁹ first described the histopathological changes seen in PAN in 1930. The same changes are seen in CPAN affecting only the dermal vessels. The evolution of changes has been described in four stages. These changes have been confirmed in a recent Japanese study.¹⁰ The first stage shows endothelial loss and fibrin thrombi along with infiltration with neutrophils without any obvious internal elastic lamina disruption and medial fibrinoid necrosis. The second stage has mixed cellular infiltrates showing

fibrinoid necrosis with fibrinoid leakage extending through the disrupted sites of the internal elastic lamina to the media. The third stage shows intimal fibroblastic proliferation and perivascular neovascularisation with predominant infiltrates of histiocytes and lymphocytes. The final stage has minimal cellular inflammation with occlusive intimal thickening. All changes can coexist in the same patient. These changes are highly specific to dermal vessels and if no vessel is captured on a skin biopsy, a re-biopsy is highly desirable.

Chen⁹ conducted a long-term observational study of 20 patients in which he retrospectively proposed dividing patients into three groups depending on the severity of their symptoms. The first group consisted of patients with mild cutaneous disease. The second group comprised patients with significant cutaneous disease and systemic symptoms. Patients in the third group had persistent cutaneous symptoms with positivity of either RF or ANA. All patients from the third group progressed to developing PAN. As per this index, the patient of this case study fits into group 2. Chen's severity index is useful to identify patients with severe disease requiring higher level of immunosuppression. However, we note that only prednisolone was used for immunosuppression in this study with no usage of steroid sparing agents.

There is currently no evidence base for treatment of CPAN. No randomised controlled trials have been conducted. Only anecdotal evidence is available. Non-steroidal anti-inflammatory drugs (NSAIDs) are used in mild cases with some benefit. Some cases require administration of systemic corticosteroids.¹¹ Intractable cases require immunosuppression with CYC, azathioprine or methotrexate.¹² There is no anecdotal information available on treatment for relapses of CPAN. Further studies are needed to compare various immunosuppressants to reduce long-term usage of steroids and its associated side effects. Treatments to improve peripheral circulation are advised. These can include

vasodilators, antiplatelet therapy and anticoagulation where appropriate.⁸

The overall prognosis of CPAN is favourable although progression to PAN is described as occurring rarely. CPAN is more likely to relapse than PAN. Due to these factors, regular long-term rheumatology follow-up is advised.¹³

This case raises four important questions for optimal management of CPAN. (1) Is long-term immunosuppression required to maintain remission? (2) Which immunosuppressive agent is optimal? (3) The length of time for its administration? (4) Which agent should we use for relapses? Current evidence does not answer these questions. This highlights the importance of further research into CPAN; however, due to the rarity of the disease, it remains a challenge.

Contributors Conception and design; drafting of manuscript: HM-R. Approval of the version of the manuscript to be published: TD. Histopathology description and arteritis image: NG.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- ▶ Cutaneous polyarteritis nodosa (CPAN) is a distinct entity from polyarteritis nodosa (PAN) mainly localised to the skin, which rarely progresses to PAN.
- ▶ Diagnosis is achieved by confirmation on histopathology and absence of microaneurysms.
- ▶ There are no guidelines available for treatment.
- ▶ Severe immunosuppression may be required to induce disease remission in some cases.
- ▶ More research into CPAN is required.

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