CASE REPORT. The spectrum of cutaneous polyarteritis nodosa. A case report of two contrasting cases and review of the literature

Ian Liang[1], Mariya Hamid[1], Deshan Sebaratnam[2], and Nick Manolios[1]

[1]Westmead Hospital
[2]University of New South Wales

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Abstract

Cutaneous polyarteritis nodosa is a rare neutrophilic vasculitis. We present two cases that reflect the gamut of this disorder including one case whose delayed diagnosis led to permanent nerve deficit and scarring.

Ian Liang[1,4], Mariya Hamid [1], Deshan Sebaratnam [2,4], Nicholas Manolios[1,4]

Affiliations.

Ian Liang, BMed. Resident medical officer, [1]Department of Rheumatology, Westmead Hospital, Sydney. NSW. Australia 2145;[4]Clinical Associate Lecturer, Faculty of Medicine and Health, The University of Sydney, Australia. 2006 Mariya Hamid. BSc (Biomed), MBBS, MMed (Clin Epi). Rheumatology registrar, [1]Department of Rheumatology, Westmead Hospital, Sydney. NSW. Australia 2145 Deshan Sebaratnam. FACD FRCP. [2]Department of Dermatology, Liverpool Hospital, Sydney, NSW, Australia 2170,[3]Faculty of Medicine, University of New South Wales, Sydney, Australia 2052 Nicholas Manolios, MBBS (Hons) PhD MD FRACP FRCPA.[1]Department of Rheumatology, Westmead Hospital;[4]Professor of Rheumatology, Faculty of Medicine and Health, The University of Sydney, Australia. 2006

Corresponding author:

Dr Ian Liang Dept of Rheumatology, Westmead. Sydney. NSW Westmead Hospital, Cnr Hawkesbury Road and Darcy Rd, Westmead NSW 2145 Tel: +61 0406 780 068 Email.*ian.liang@health.nsw.gov.au*ORCID ID. 0000-0002-5142-8707**Running title:** Cutaneous Polyarteritis Nodosa**Funding.** Nil

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AbstractIntroduction: Rheumatologists are well versed with the clinical syndrome of polyarteritis nodosa (PAN) involving medium sized muscular arteries of the kidneys and other internal organs. However, they may not be so well acquainted with a rarer similar disorder known as cutaneous polyarteritis nodosa (cPAN). This latter condition is rare and involves neutrophilic vasculitis of medium-sized arteries in the reticular dermis and subcutaneous tissue only. It is distinct from systemic polyarteritis nodosa (sPAN)

because of the lack of internal organ involvement. Uncertainty exists whether the two conditions are different entities or on the same scale of vasculitis. Milder forms of cutaneous polyarteritis nodosa resolve with nonsteroidal anti-inflammatory medications, whereas more severe refractory cases, often require corticosteroids and immunosuppressives.**Case presentation:** We present two cases of cutaneous polyarteritis nodosa that reflect the gamut of this disorder. In our first case which followed a benign clinical course, a 34-year-old Filipino female presents with bilateral tender red nodules that resolved following initiation of prednisone and methotrexate. In our second case which featured a significant delay in diagnosis, a 55-year-old man with a five-month history of right lower limb ulcers with associated right common peroneal neuropathy was commenced on prednisone and methotrexate but was left with scarring and permanent peripheral nerve deficit.**Conclusions**: The two cases highlight the condition, informs the reader and expands the reported experience of cutaneous polyarteritis nodosa which is a rare condition encountered in clinical practice. Abbreviations. cPAN, cutaneous polyarteritis nodosa; sPAN, systemic polyarteritis nodosa. Key words. Polyarteritis nodosa, cutaneous polyarteritis nodosa, vasculitis, medium vessel vasculitis, case report

INTRODUCTION

cPAN is a rare form of vasculitis that involves the small-medium sized arteries, has a more benign course, and a more favourable prognosis compared to systemic PAN [1]. Due to the rarity of this condition, the current evidence-based management for this condition has only been limited to case reports and case series with no randomized controlled trials to inform the best approach to management. These two cases highlight the spectrum of cPAN as well as one approach to its management.

CASE PRESENTATION

Case 1. A 34-year-old Filipino female presented with a three month history of multiple bilateral tender red nodules over the distal lower limbs [Fig 1]. She felt well with no constitutional symptoms, no prior history of preceding infection, tuberculosis exposure, or animal contact. She had migrated from the Philippines five years ago. She had no smoking, alcohol or intravenous drug use. Prior to this episode, she had no significant medical issues, and was not on any medications or herbal supplements. On examination, she had tender erythematous subcutaneous nodules on her lower limbs with angular purpura [Fig 1]. There were bilateral ankle effusions, and no other synovitis elsewhere. The abdomen was soft and non-tender. Urinalysis, full blood count, biochemistry and creatinine kinase levels were normal. Erythrocyte sedimentation rate (ESR) was 44 mm/hr (N $<$ 20 mm/hr), and C-reactive protein (CRP) 10 mg/dL (N $<$ 4 mg/dL). Antinuclear antibody, extractable nuclear antigen, cryoglobulin, cryofibrinogen, rheumatoid factor, anticardiolipin antibody, β-2 glycoprotein antibody, lupus anticoagulant, antineutrophil cytoplasmic antibodies, hepatitis B, hepatitis C, HIV, measles, mumps, and rubella were negative. The interferon gamma release assay was negative. Incisional biopsy demonstrated fibrinoid necrosis of an arteriole with a marked perivascular infiltrate composed of lymphocytes, neutrophils, histiocytes and eosinophils, extending to the subcutis. Histiocytes were inconspicuous and PUTT and ABPAS staining demonstrates no pathogens. [Fig 2]. Whole body PET-CT and CT abdominal angiogram showed no systemic vessel involvement, or end organ ischemia. Prednisone 40mg daily was commenced with normalisation of ESR, CRP, and complete resolution of subcutaneous nodules after two weeks. Prednisone was reduced and methotrexate commenced as a steroid-sparing agent.*Case 2.* A55-year old man was referred with a five month history of right lower limb ulcer associated with sensory changes in the lower limb. There were no constitutional symptoms or other symptoms to suggest systemic disease. Examination demonstrated a stellate ulcer with retiform purpura [Fig 3] and sensory deficit along the sural nerve. Physical examination was otherwise unremarkable. An incisional biopsy demonstrated a prominent lymphohistiocytic infiltrate of small to medium sized vessels in the deep dermis and subcutis. A moderate lymphohistiocytic infiltrate was noted within vessel walls with endarteritis obliterans, degenerate vessel walls and fibrin thrombi with karyorrhexis in affected lumens. His investigations showed normal urinalysis, blood

count, urea, and electrolytes with no features of systemic involvement on imaging. Nerve conduction studies demonstrated isolated right common peroneal neuropathy with no evidence of a generalised neuropathy or mononeuritis multiplex. The patient was commenced on a tapering regime of prednisone 60mg daily, methotrexate 15mg weekly and colchicine 0.5 mg tds with resolution of the ulcer over a period of months. The sensory deficit remained fixed. Follow-up one year later showed no recurrence of symptoms or signs of vasculitis.

DISCUSSION

cPAN can affect all ages with the average age of diagnosis being 40-50 years old with a greater predominance in women [2]. The estimated prevalence is 31 cases in 1 million, and it is estimated that it accounts for 4% of all cases of polyarteritis nodosa [3]. In contrast to PAN, cPAN is limited to the skin and associated muscles and joints surrounding the affected area [2]. Clinical signs include tender subcutaneous nodules typically affecting the lower limbs, which may progress to ulceration in 50% of the cases [1]. Other dermatological features include livedo reticularis, livedo racemosa and purpura [1]. Late- stage features are necrosis, neuropathy, myositis and neuritis [1]. cPAN can be distinguished from sPAN by its lack of systemic involvement, hypertension, bullae, livedo reticularis gangrene of extremities, leucocytosis and eosinophilia [2]. Unlike PAN, it is not fatal if left untreated but follows a benign course that may either become chronic or relapsing and remitting over several years [1]. Multiple associations with cPAN include group A beta haemolytic streptococcus infections, hepatitis B and C, inflammatory bowel disease, CMV, parvovirus B19, tuberculosis, malaria, and drugs such as minocycline, sulphonamides and IV amphetamines [1, 2]. An incisional biopsy to deep fat for histopathology is mandatory to establish the diagnosis, as well as tissue biopsy for microbial culture depending on the clinical context. Differential diagnoses for other forms of small to medium vessel vasculitis include lymphocytic thrombophilic arteritis, panniculitis, venous thrombosis and atypical infection. Further investigations should include; cryoglobulins, ANA, ANCA, RF and complement levels to exclude secondary causes [1-2, 4]; and; imaging to exclude systemic organ involvement. There is no consensus on initial treatment, dosage, length of treatment, or specific drug combination [5, 6]. Current studies have noted that mild cPAN can be adequately treated with NSAIDs, colchicine, topical corticosteroids, and low dose corticosteroids [1, 4, 6]. The presence of ulceration in the initial episode predicts an increased risk of relapse and is associated with a worse prognosis [7]. In such patients, case series have demonstrated up to 1mg/kg/day of prednisone was associated with a significant reduction of pain, disappearance of subcutaneous nodules and significant improvement of cutaneous ulcers [1, 8]. For patients who were refractory to prednisone, the addition of IV cyclophosphamide, azathioprine and IVIG have been shown to induce remission [5-6, 9]. Studies have also advised for aggressive treatment for patients who had constitutional symptoms, severe course of disease or high acute phase reactants [5, 6]. Studies have found that a flare of cPAN usually follows attempts to wean prednisone [8]. Steroid sparing agents include colchicine, hydroxychloroquine, methotrexate, sulphapyridine, pentoxifylline and dapsone [1, 4-5]. Patients with cPAN should be followed up twice yearly and have regular surveillance to exclude possible progress to systemic PAN [1]. The likelihood of cPAN progressing to sPAN is rare. In a large case series examining 79 patients with cPAN there was no progression to systemic PAN in a follow-up period of up to 30 years [8]. However, a case series noted that patients have developed sPAN up to 19 years after the initial diagnosis [10].

LEARNING POINTS/TAKE HOME MESSAGES

We hope readers can appreciate that cPAN is a distinct entity different to sPAN, with a more benign clinical course. The risk of progression from cPAN to sPAN remains unclear, albeit slow. Prompt recognition of this rare condition is required to prevent permanent neurological deficit and scarring. In terms of management, cPAN is steroid responsive and steroid sparing agents are effective to prevent relapse.

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5. **Consent for publication** – The patients featured within this case report have provided written consent to grant to any third party, in advance and in perpetuity, the right to use, reproduce or disseminate the article in its entirety or in part, in any format or medium.
6. **Availability of data and material** – The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary material.
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FIGURE LEGEND.Figure 1. Erythematous subcutaneous nodules and angular purpura on the posterior lower legs*Figure 2.* Histopathological section of lower limb subcutaneous nodule. The findings demonstrated a mixture of lymphocytes, neutrophils, histiocytes and scatted eosinophils surrounding the small arteries and extending into the fibrous septa and peri-septal lobules of the subcutaneous tissue. The internal elastic lamina of the arteriole was preserved. There were no granulomas, and further stains indicated no mycobacterial or fungal elements. These findings were consistent with PAN.*Figure 3.* Stellate ulcer with retiform purpura. The incisional biopsy demonstrates a prominent lymphohistiocytic infiltrate of small to medium sized vessels in the deep dermis and subcutis. A moderate lymphohistiocytic infiltrate was noted within vessel walls with endarteritis obliterans, degenerate vessel walls and fibrin thrombi with karyorrhexis in the affected lumen. FIGURES Figure 1.

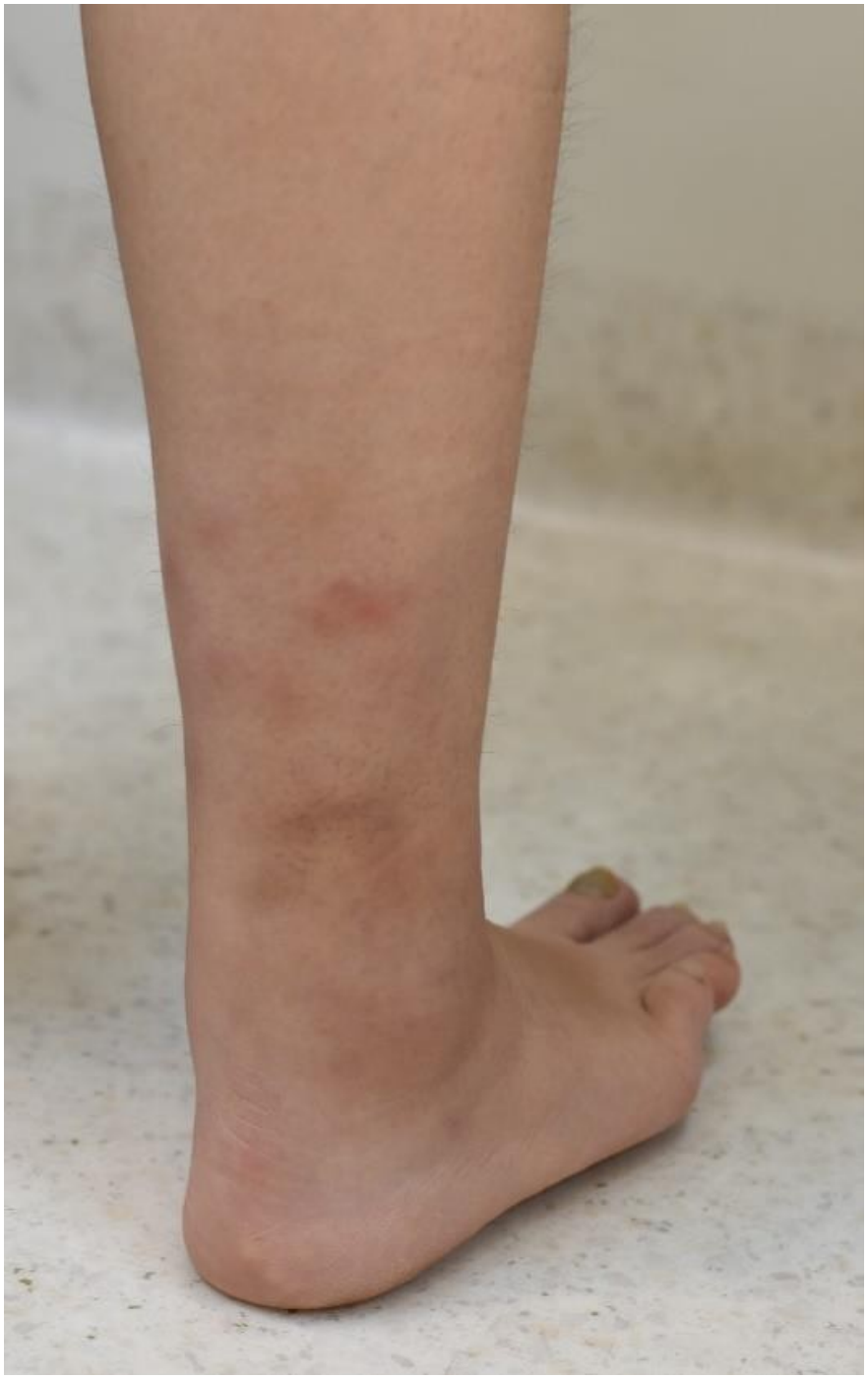

Figure 2.

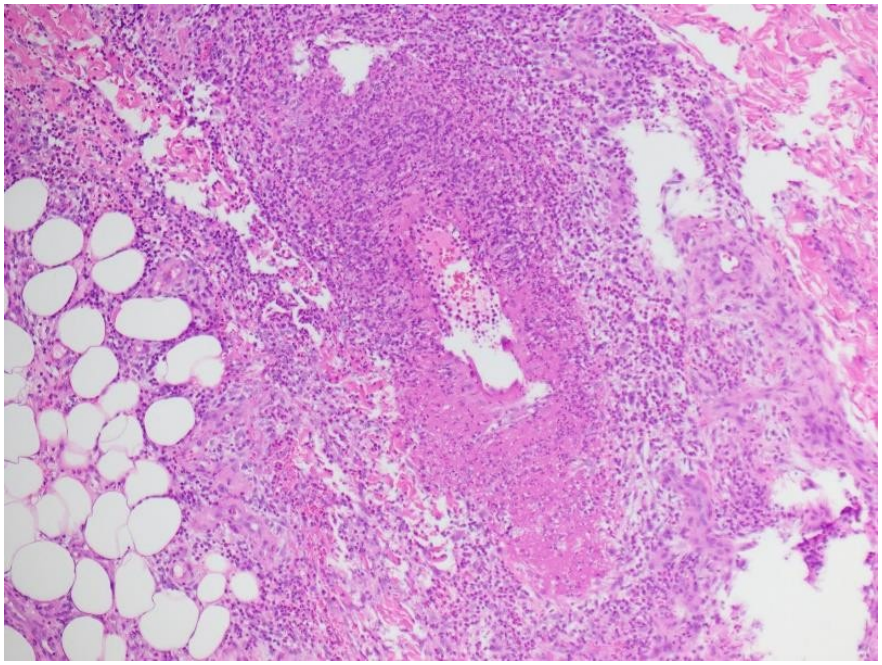

Figure 3.