

Cutaneous Polyarteritis Nodosa: A Case Report and Literature Review

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Abstract

Cutaneous polyarteritis nodosa (CPN) is an uncommon form of vasculitis. It exists as a separate entity, though bearing similar name with polyarteritis nodosa (PAN) which is an aggressive systemic vasculitis with multi-organ involvement. CPN runs a chronic but benign course. Its aetiology is unknown and it usually presents with painful nodules on the legs with mild constitutional symptoms, and extracutaneous features of arthralgias, arthritis, neuropathy and myopathy. No mortality has been reported thus far. It is therefore important to distinguish CPN apart from PAN. Symptomatic treatment with judicious use of systemic steroids and anti-inflammatory agents will suffice in most cases.

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Key words: Exacerbations, Initial evaluation, Histological proof, Long-term follow up, Remissions

Introduction

Cutaneous polyarteritis nodosa (CPN) is an uncommon form of vasculitis of the small-and medium-sized arteries in the reticular dermis and subcutaneous tissue. It remains limited and runs a chronic, benign course. This condition may encompass extracutaneous features such as arthralgias, arthritis, neuropathy and myopathy. In contrast, polyarteritis nodosa (PAN) is a form of nodular vasculitis that most frequently involves the medium-sized muscular arteries of the kidneys, liver, heart, and gastrointestinal tract. It is however important to distinguish them apart as the clinical course and management of these conditions differ from each other.

We report our first patient with CPN and discuss its features and the differences between CPN and PAN.

Case Report

A 51-year-old Chinese man presented with an erythematous erysipeloid-like plaque of 6 weeks' duration on the left foot dorsum. He had received a few courses of oral antibiotics prior to his visit but to no avail. He was otherwise well with no other medical history of note. The initial diagnosis was that of an atypical mycobacterial infection. A skin biopsy was done and the patient was started on cotrimoxazole empirically. However he developed a drug reaction on the fifth day of medication. Cotrimoxazole was discontinued and prednisolone at 30 mg daily was started, and he recovered uneventfully a week later.

Histology of the skin biopsy showed superficial and

deep chronic mixed inflammatory infiltrate around the blood vessels and adnexal structures. However, the biopsy specimen was not deep enough to include the subcutaneous tissue due to the proximity of the underlying tendon. Histological impression was that of chronic inflammation. Special stains for fungi and mycobacteria, the direct immunofluorescence test, fungal culture and mycobacterial culture were all negative. X-ray of the foot was unremarkable. Prednisolone was gradually tapered off over 2 months and the left foot appeared much better. He did not return for follow up.

One year later, he presented with spontaneous onset of vasculitic plaques and nodules over the right shin of 1 month's duration (Fig. 1), with a few smaller lesions on both thighs. He had no other notable symptoms and the history was unrevealing. The rest of the examination revealed a healthy man with a normal blood pressure. A second skin biopsy taken from a right calf nodule showed fibrinoid necrosis of the medium-sized artery (Fig. 2) with surrounding neutrophilic infiltrate in the subcutis, and similar changes were seen in the smaller vessels. The histological diagnosis was consistent with polyarteritis nodosa. Direct immunofluorescence (DIF) showed fibrinogen deposits on the walls of the blood vessels throughout the dermis and subcutis. Other investigations including the liver function test, serum creatine kinase and aldolase, urine microscopy, anti-nuclear antibodies, anti-neutrophil cytoplasmic antigen (ANCA), HBsAg, anti-HBc IgM, chest X-ray and ECG were either normal or negative.

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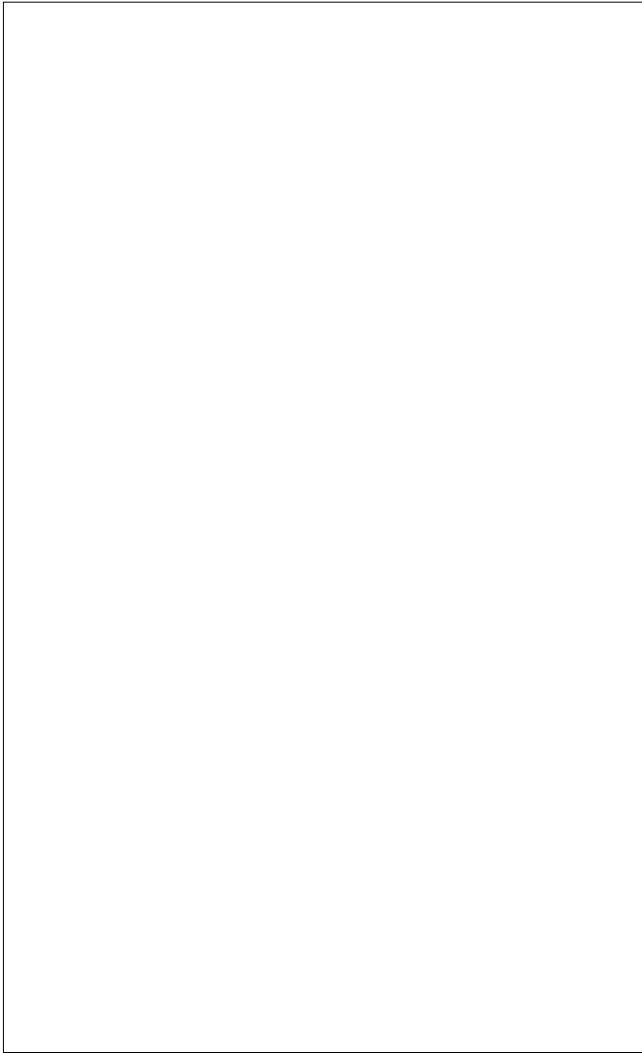


Fig. 1 Painful plaques and modules on the right shin.

The patient was started on prednisolone 10 mg bid to which he was not fully compliant. A few small active lesions were still seen during his last visit. He was however happy with his current status and was not keen for a higher dose of prednisolone.

Discussion

Periarteritis nodosa, or now known as PAN, was originally described by Kussmaul and Maier in 1866.¹ However the concept of limited PAN was only described much later in 1931,² and since then it has been debated as to whether CPN indeed exists as a distinct entity.

In CPN, the site of involvement is primarily the legs with over 95% of the lesions located in this region.³ Lesions located elsewhere include the arms in 50% of patients, trunks in 33%, head and neck in 33% and buttocks in 20%. The most frequent manifestation is that of a painful subcutaneous nodule, which can be easily mistaken for erythema nodosum or panniculitis. Sometimes it can present as multiple small nodules (less than

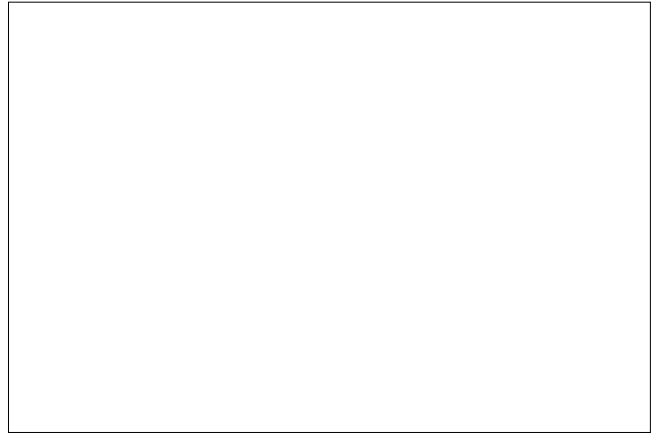


Fig. 2. Arterial fibrinoid necrosis seen under H & E stain (x100).

1 cm), numbering as many as 100.⁴ These are often located in the dependent areas or pressure points. Ulcers develop in less than 50% of patients, and may persist for days to many months.⁵ Livedo pattern can be seen after a flare of new nodules formation² as it radiates out from the new lesion in a “starburst” formation. Gangrene, urticaria, bullae formation and acral oedema are cutaneous signs seen occasionally. Common generalised symptoms include malaise, fever, myalgias and sore throat. Myalgia, which clinically manifested as muscle aches, tenderness and stiffness, is frequently observed⁶ over the calves. Muscle biopsy in such cases may reveal microscopic lesions of polyarteritis nodosa. Arthralgia is found in 10% of CPN.⁶ Adjacent joints near the skin lesions as well as distant joints may be involved. In most instances, despite the intensity of arthralgias, roentgenographic changes were always minimal or absent. CPN has therefore been misdiagnosed as seronegative rheumatoid arthritis. Nondestructive arthritis has been reported in a few patients, although synovial biopsies have not shown evidence of synovial arteritis.^{7,8} Neurological problems, particularly mononeuritis multiplex, are often indistinguishable clinically from those of PAN. Symptoms include numbness, mild paraesthesia, or rarely painful neuritis. Sensory disturbances, pain, weakness, and absent reflexes were reported in all 15 patients seen in one series.⁹

In 1972 Borrie⁹ reviewed 102 cases of PAN and he concluded that 10% of these were actually CPN. None of these patients died of the disease and the tendency was for the condition to fade away. For other authors, CPN is essentially PAN with cutaneous symptoms, whether or not other organs are involved.¹⁰ The third view is that CPN is only a stage in the evolution of the systemic disease.¹¹ But the majority of authors believe that CPN is a distinct entity with localised cutaneous vascular disease and runs a chronic, benign course with exacerbations and remissions that

TABLE I: DIFFERENCES BETWEEN PAN AND CPN

	PAN	CPN
Blood pressure	Frequently elevated	Normal
Sex (M:F)	2:1	1:1
Leukocytosis	Frequent, at times severe	Normal to moderate increase
Eosinophilia	Frequent	None
Proteinuria	Frequent	None
Visceral involvement	Frequent	None
Neuromuscular changes	Diffuse	Localized to areas of skin lesions
Prognosis	Frequently fatal in the first 2 years without treatment	Chronic, relapsing, benign disease

PAN: polyarteritis nodosa; CPN: cutaneous polyarteritis nodosa

never seriously compromise the health of the patient. Table I summarises the clinical differences between CPN and PAN.⁶ The age of onset in this series is variable, ranging from 5 to 68 years of age. There is no association of degree of severity with age of onset and there is no sex predilection.

A histological specimen showing panarteritis is the only definitive proof of periarteritis nodosa. A deep wedge biopsy is preferred to a punch biopsy. Generally a single artery is maximally involved with inflammatory panarteritis, while the surrounding vessels show some non-specific perivascular inflammatory changes. In severe cases there is complete destruction of the vessel wall with replacement of the wall by an eosinophilic fibrinoid material. Leukocytoclastic vasculitis may be seen. One of the most striking features is the localisation of the inflammation to the immediate vicinity of the affected vessel and the absence of infarction in the neighbouring tissue.⁹ There is no correlation between severity of the microscopic changes and that of the severity of disease.

A study of 10 cases of CPN by DIF revealed 9 positive findings.¹² Deposition of IgM was found on the vessel walls in 6 cases, and C3 in 4 cases, and 2 cases with both C3 and IgM. DIF findings are not sufficiently specific to differentiate between CPN and PAN.

The aetiology of CPN remains unknown, but presumably has an immune-complex mediated pathogenesis, as shown by IgM and C3 deposits in the biopsy specimens. Streptococcal infection is believed to cause this immune-complex mediated disease.¹³ Most reported patients^{14,15} had an upper respiratory tract infection with pharyngitis, an elevated anti-streptolysin O test (ASOT), or a positive throat culture for streptococci, or concomitant rheumatic fever or post-streptococcal glomerulonephritis. Four paediatric patients ranging in age from 2 to 14 years with CPN had evidence of antecedent strepto-

coccal infection,¹⁶ and it was suggested that all children with CPN should be investigated for it. However other authors found no such association with streptococcal infection.^{17,18} Four out of 9 patients in one study had serologic evidence of hepatitis B infection¹⁹ and the authors suggested that CPN is therefore a cutaneous variant of PAN which has known association with hepatitis B infection. Crohn's disease and ulcerative colitis have also been associated with CPN.^{20,21} Other systemic disorders associated with CPN include superior and inferior vena cava thromboses and hepatitis C infection.²²

Laboratory tests are generally not helpful either in the diagnosis or monitoring of the disease. Slight abnormalities may be seen as in a raised ESR, moderate leukocytosis and mild anaemia.⁶ Serologic tests for syphilis, rheumatoid factor, and ANA are usually negative. ASOT may be of value in CPN of childhood.¹⁶ ANCA has been reported as a sensitive marker for Wegener's granulomatosis, microscopic angiitis (MPA) and some cases of classic PAN.^{23,24} But ANCA serologic reactions in CPN have not been previously reported.

No patient has died from CPN *per se*, and the tendency has been for the condition to slowly fade away.⁹ It runs a benign chronic course lasting from months to years even though the acute symptoms may take 2 to 8 weeks to resolve. The myositis and neuritis symptoms are the first to disappear within a matter of months. In contrast, skin nodules take years to clear with gradual decrease in frequency and severity. Remission may occur spontaneously or after steroid therapy and recurrences are common.^{5,25} But none of the 23 patients in one series developed classic PAN despite the occasional cutaneous flares during long-term observations.⁶ However Chen²⁶ reported 2 out of 20 CPN patients who progressed to the systemic form after 18 years of follow-up. Even though CPN and PAN are evidently different, there is seemingly a remote possibility that the former may progress to the latter. Therefore the patient may need to be followed up, perhaps less frequently if he is in remission.

CPN does not require the intensive treatment to bring about remissions that is necessary for classic PAN. Overzealous treatment should therefore be avoided to minimise unnecessary side-effects. Corticosteroids remain the mainstay of treatment for CPN. The aim is to control the acute exacerbation and pain-relief, rather than to suppress all manifestation of the disease. Usually a dose of 20 mg of prednisolone daily or less is needed to achieve this.⁹ Treatment can be discontinued as the condition becomes less severe. Disease flare can be controlled with intermittent systemic steroids.²⁷ Other non-steroidal drugs used are summarised in Table II. Non-steroidal anti-inflammatory drugs (NSAIDs)^{6,26} may be helpful when used alone or together with systemic steroids. Pain-relief is an added advantage beside the

TABLE II: NON-STEROIDAL DRUGS USED IN THE TREATMENT OF CPN

Drug	Comment
NSAIDs—acetyl salicylic acid, indomethacin	When steroid is contraindicated Added advantage of pain-relief
Methotrexate (low-dose)	May be helpful in recalcitrant cases Limited by its toxicity
Penicillin	In children with evidence of streptococcal throat infection
Miscellaneous—sulfapyridine, nicotinic acid, stanazolol, cyclophosphamide, heparin, pentoxifylline	Case reports and anecdotal reports only

NSAIDs: non-steroidal anti-inflammatory drugs;

CPN: cutaneous polyarteritis nodosa

anti-inflammatory property of NSAIDs, and acetyl salicylic acid^{15,28} and indomethacin³ are commonly used. NSAIDs are useful first-line drugs for patients with steroid contraindications. Low-dose methotrexate (MTX) has been used anecdotally in the treatment of PAN and other vasculitides since the 1970s^{29,30}. Three patients with recalcitrant CPN were reported to respond favourably to low-dose weekly MTX,³¹ with dose ranging from 5 to 25 mg given for a duration of 6 to 12 months. However this cannot be recommended as a first-line treatment because of its known toxicity. Penicillin may be useful in cases with streptococcal infection, especially in children. Penicillin prophylaxis has been advocated in such patients,³² but others have noted recurrences despite this.¹⁴ But patients who suffer from frequent flare of the disease as a result of repeated streptococcal infections should be considered for penicillin prophylaxis.⁶ Other agents mentioned in the literature include the use of sulfapyridine,⁶ nicotinic acid,³ stanazolol³³ and cyclophosphamide.²⁰ There were other anecdotal reports with subcutaneous heparin²⁷ and pentoxifylline.¹⁸

Conclusion

It is not easy to determine in the initial stages whether CPN exists as a distinct cutaneous disease or as part of a multi-organ systemic disease. Therefore all patients with apparent cutaneous lesions should be evaluated for systemic involvement, using the 1990 American College of Rheumatology (ACR) criteria for PAN as a guide, as this would affect prognosis and treatment. Search for some of the common and treatable aetiological agents forms a crucial part of the initial work-up. Aggressive treatment is not required in most cases of CPN, and symptomatic treatment with prednisolone or NSAIDs will suffice. However all patients should ideally be on long-term follow up as there is still a remote chance of it progressing to the systemic form.

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