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Classic polyarteritis nodosa presenting initially as a case of cutaneous polyarteritis nodosa: A case report

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ABSTRACT

Classic polyarteritis nodosa (PAN) is an uncommon form of aggressive systemic vasculitis involving small-to-medium sized arteries usually of renal vasculature and other visceral organs but characteristically sparing the lung vasculature. Cutaneous PAN (c-PAN) is still a rare type of small-to-medium vessel vasculitis with involvement of skin without any systemic or visceral involvement. However, extracutaneous features such as arthritis, arthralgia, myopathy, and myositis can co-exist with the cutaneous features. c-PAN can be confirmed histopathologically by the presence of polymorphonuclear leukocytes around the medium-sized vessels with evidence of fibrinoid necrosis and luminal thrombi at the bifurcations. While c-PAN has a benign but chronic course and can be managed with low doses of short-course oral steroids or anti-inflammatory drugs, systemic involvement has an aggressive course and needs adequate and prompt immunosuppression with high dose oral steroids, cyclophosphamide, rituximab, or other immunosuppressive. We present a case of a 33-year-old male who landed in our OPD with features of c-PAN and on further investigative workup was found to have a renal infarct.

Key words: Cutaneous polyarteritis nodosa; Classic polyarteritis nodosa; Perinuclear anti-neutrophil cytoplasmic antibodies, cytoplasmic anti-neutrophil cytoplasmic antibodies, FFS

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INTRODUCTION

Polyarteritis nodosa (PAN) first described by Kussmaul and Maier in 1866 is an uncommon systemic vasculitis of medium vessel arteries involving system organs such as kidney, heart, gastrointestinal tract, and central nervous system (CNS).[1]

For PAN to be diagnosed, at least three of the ten American College of Rheumatology criteria should be present which include weight loss of 4 kg or more, livedo reticularis, testicular pain/tenderness, myalgia or leg weakness/tenderness, mononeuropathy or polyneuropathy, diastolic blood pressure >90 mmHg, elevated blood urea nitrogen or creatinine level unrelated to dehydration or obstruction, presence of hepatitis B surface antigen or antibody in serum, arteriogram demonstrating aneurysms or occlusions of the visceral arteries, and presence of polymorphonuclear neutrophils in a biopsy specimen from a small- or medium-sized artery.[2]

Cutaneous symptoms are observed in 25–60% of classic PAN. On the other hand, cutaneous PAN (c-PAN) is designated for the cutaneous limited of PAN which has a benign prognosis. However, there has been still ongoing debate about whether c-PAN is an independent entity or merely an early phase in the spectrum and can progress to classic PAN with systemic involvement. For a diagnosis of c-PAN, there have to be cutaneous manifestations such as subcutaneous nodules, livedo, purpura, and ulcers along with histopathological findings of fibrinoid necrotizing vasculitis of small- and medium-sized arteries with the absence of all exclusion manifestations. The exclusion criteria include fever

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>38°C for >2 weeks, hypertension, rapidly progressing renal failure or renal infarction, cerebral hemorrhage or cerebral infarction, myocardial infarction or ischemic heart disease or pericarditis or heart failure, pleuritis, intestinal hemorrhage or intestinal infarction, peripheral neuropathy out of the affected skin lesion, arthralgia (arthritis) or myalgia (myositis) out of the skin lesion, and abnormal arteriography (multiple microaneurysm, stenosis, and obliteration).[3]

The challenge lies in differentiating between the two as the clinical course and management differs between classic PAN and c-PAN.

We report our first patient who presented with features of c-PAN and how we worked our way up in assessing the systemic involvement to find it out to be a classic PAN.

CASE PRESENTATION

A 33-year-old male presented to our center with pain over bilateral lower limbs associated with multiple superficial to deep tender ulcers of varying sizes with eaten away appearance along with multiple palpable tender subcutaneous nodules over the calves almost symmetrically arranged for a period of 1½ months. The ulcers were in varying stages of healing with most of them exhibiting bright reddish granulation tissues that bled on the slightest manipulation whereas some of them had healed completely leaving blackish-to-brownish hyper pigmentation and atrophic scarring at places. Lesions involved region below knee to feet bilaterally. However, they were more predominant around the ankle region with a livedoid appearance bilaterally as shown in Figure 1. He reported occasional episodes of fever after the onset of lesions. The calf muscles were tender to touch. His blood pressure was 120/80 mmHg. He had taken a few oral medications over the counter irregularly but to no avail.

With this history and clinical findings, differentials of cutaneous PAN, erythema induratum of Bazin, and pyoderma gangrenosum were considered and investigations were worked up in the line. Total and differential blood count, urine routine microscopy, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), pathergy test, Mantoux test, chest X-ray, liver function test, renal function test (RFT), serology, serum antinuclear antibody (ANA), p-ANCA stands for Perinuclear anti-neutrophil cytoplasmic antibodies c-ANCA stands for Antineutrophil Cytoplasmic Autoanibody, Cytoplasmic, pus for culture and sensitivity, and an excisional biopsy specimen of a subcutaneous nodule from the left calf for histopathological examination were sent and the patient was admitted under oral and topical antibiotics and analgesics for wound care and further investigative workup.

The investigation reports revealed raised ESR (62 mm/h), raised CRP (79.80), and trace albumin in urine routine microscopy. The histopathological findings of the specimen revealed diffuse dense infiltrates of neutrophils followed by eosinophils and lympho-histiocytes. The small-sized vessels showed infiltration by polymorphs with degeneration of arterial walls with fibrinous deposition. Some vessels showed occlusion of the lumen with thrombosis. There were also focal areas in the dermis with dense neutrophilic aggregates within fibrinoid material as shown in Figures 2 and 3. c-ANCA, p-ANCA, and serology came out to be negative. Rest all reports likewise were within normal limits. All these findings were in favor of c-PAN. Since cutaneous manifestations occur in 25–60% of classic PAN, 24-h urine protein was sent to assess renal involvement, and computed tomography (CT) aorta angiography was advised to see for the involvement of vasculature in the brain, heart, gastrointestinal tract, and kidneys. Till the reports were due, the patient was started

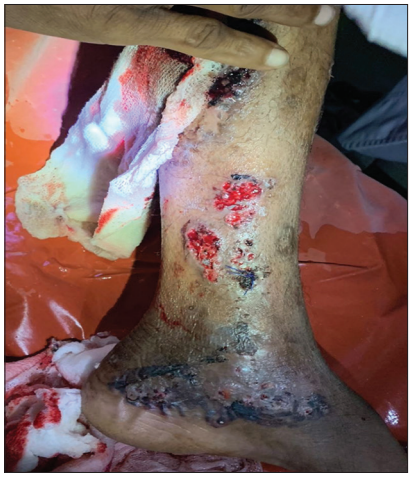

Figure 1: Ulcers with punched-out appearance with livedoid changes around the left medial malleolar region

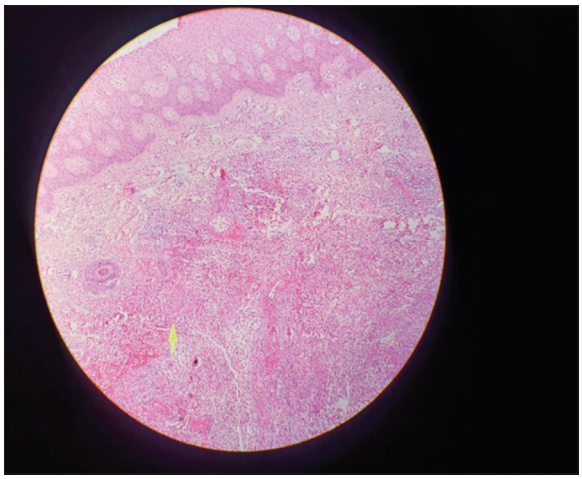

Figure 2: Low power magnification (×10) showing inflammatory cells around small-sized blood vessels and a few focal areas of fibrinous deposits in the dermis

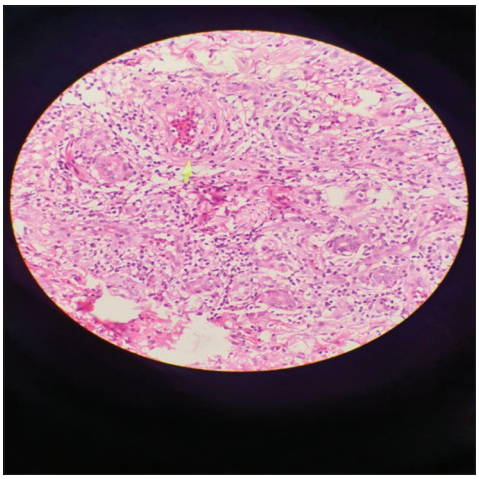

Figure 3: High power magnification (×100) showing deposits of polymorphs around the small vessel wall

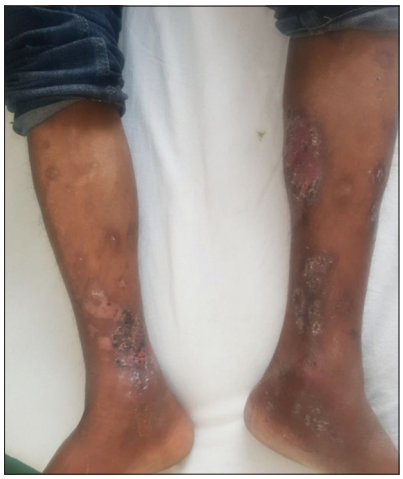

Figure 4: Healed lesions with atrophic scarring, hyperpigmentation, and few dried crusted plaques on day 30

on low-dose oral steroids (0.5 mg/kg/day) keeping c-PAN as a working provisional diagnosis.

Investigations revealed protein loss with 24 h urine protein 0.97 g/24 h with CT aorta angiography revealing multiple wedge-shaped infarcts seen as non-enhancing hypo dense areas within the left kidney, largest measuring 26×22 mm in the upper pole (cortex and medulla) without any contrast extravasation. Although there was no nodular dilation of the right renal artery up to bifurcation, intralobular and arcuate arteries could not be delineated well.

The diagnosis was revised then as a classic PAN and prompt immunosuppression was attempted by escalating the dose of oral steroid to 1 mg/kg/day after a nephrology consultation, the patient was counseled about the disease and was discharged with regular follow-up advice after every 15 days for close monitoring.

Outcome and follow-up

Fifteen days later, we received a very happy patient with most of his lesions in the healed state. His blood pressure was noted to be 120/80 mmHg with no new symptoms. The patient was kept on the same dose for another 2 weeks and was asked to follow-up after 15 days. Fifteen days later, all of his lesions were healed with post-inflammatory hyperpigmentation and atrophic scarring in places which is shown in Figure 4. No new complaints suggesting GI, CNS, or cardiac involvements were present. The renal function was reassessed clinically with blood pressure assessment, urine routine microscopy to look for microalbuminuria and RFT was done, all of which were within normal limits. His weight initially was 51 kg which increased to 53 kg over a month. Nephrology consultation was done and the dose of oral steroid was now tapered to 0.75 mg/kg/day for the next 4 weeks with the plan to taper off the drug completely over the next 4 months. Five-factor scoring was used to calculate the prognostic risk which came out to be zero for our patient. He was counseled about the value of follow-up as the overall 5 and 8-year survival rates for FFS=0 were 93 and 86%, respectively.

DISCUSSION

PAN is a rare form of systemic vasculitis usually affecting small-to-medium-sized vessels causing significant morbidity and mortality. It usually presents with constitutional symptoms with angiographic evidence of aneurysms or segmental stenosis of arteries of renal and mesenteric vasculature. Unlike some other forms of vasculitides, PAN is not associated with anti-nuclear and anti-nuclear cytoplasmic antibodies (ANCA). Systemic PAN usually presents with constitutional symptoms, new-onset hypertension, elevated ESR, and absent autoimmune antibodies such as ANA, ANCA, and rheumatoid factor.[4,5]

C-PAN, on the other hand, only involves skin that results from a complex interaction of auto-inflammatory and autoimmune factors and immunodeficiency. Infections by *Streptococcus*, hepatitis B, HIV, and parvovirus B 19 are known to trigger it. In addition to skin problems, patients with cutaneous PAN may also have generalized symptoms such as malaise, fever, sore throat, joint pain, and muscle aches. Neurological symptoms may also be present and include numbness, tingling, sensory disturbances, weakness, and absent reflexes.[6] Our patient had initially presented with multiple ulcers, tender nodules, occasional febrile episodes, and muscle pain localized to the lesion sites with no other systemic symptoms to point toward the systemic PAN.

A common finding in a patient with classic PAN with renal involvement is hypertension which is postulated to

be secondary to activation of renal-angiotensin system due to renal ischemia.[7] Our patient, however, had no hypertension despite the renal involvement as suggested by initial proteinuria and aorta angiography finding of a renal infarct later on. Our study, therefore, emphasizes on the fact that the absence of common findings such as hypertension should not necessarily rule out systemic involvement in a case of a c-PAN and a liberal investigative workup is to be done to not miss the internal organ involvement.

The presence of three of the ten criteria, including leg pain, arteriographic abnormality as seen as renal infarcts suggested by multiple wedge-shaped hypo dense areas around the vasculature in the upper lobe of the left kidney and histopathological finding of polymorphs around small-sized vessel walls helped us label the case as classic PAN. It is not in the scope of our study to discuss all the differentials but, no investigation reports supported the alternative diagnoses that were considered such as erythema induratum of Bazin or pyoderma gangrenosum.

Glucocorticoids and cyclophosphamide are the cornerstone of classic PAN therapy, the main determinants for treating a patient being the distribution of involvement of internal organs and disease progression. Current approaches consider treating mild forms with corticosteroids alone. Prednisone or prednisolone is used at the dose of 1 mg/kg/day with subsequent tapering when remission is achieved.[8,9] In the presence of persistent critical organ involvement, cyclophosphamide is used in addition to steroids.[8]

In our case, steroid monotherapy was given and during the follow-up, the renal status was assessed with urine routine microscopy and RFT which came out to normal on the 15th day and the 30th day of high dose steroid (1 mg/kg/day). We believe the normal blood pressure and the improving microalbuminuria responding well shortly to steroids could be due to rich collaterals compensating for the infracted region in the kidneys.

CONCLUSION

Although it is not in the scope of our study as dermatologists to address classic PAN, we report this case to reinforce the subtle fact that amid the ongoing ambiguity about classic PAN and c-PAN being different entities or simply two poles of the same entity in a spectrum; it is always wise to be liberal with the investigations to look for systemic involvement as the management of these two differs.

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