Cutaneous Polyarteritis Nodosa as a Sequela of Rheumatic Fever in a 7-Year-Old Filipino Male: A Case Report*

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ABSTRACT

Introduction. Childhood Polyarteritis Nodosa (PAN) is a rare, systemic necrotizing vasculitis of the small to medium-sized vessels with an uncertain global distribution. The primary etiology is unknown. However, PAN is commonly associated with preceding Group A streptococcus infection in children. The most common cutaneous manifestations of PAN include tender subcutaneous nodules, livedo reticularis, digital ischemia and ulceration. To date, no reports have documented cutaneous PAN as a sequela of rheumatic fever.

Case Report. This is a report of a 7-year-old Filipino male who presented with multiple, well-defined erythematous to hyperpigmented, firm, tender nodules, with some areas of lace or net-like macules and patches, some resolved leaving hyperpigmentation measuring 1x1 cm to 2x2 cm on the lower back, bilateral upper and lower extremities accompanied by fever, malaise, arthralgia and myalgia with a previous history of rheumatic fever. A 6mm skin punch biopsy revealed findings consistent with PAN. The patient was managed with prednisone. Due to the limited response to treatment, he was eventually given mycophenolate mofetil.

Conclusion. Childhood polyarteritis nodosa (PAN) is a rare form of necrotizing inflammation of the medium-sized blood vessels primarily linked to Group A streptococcal infection in children, with no known reported cases associated with rheumatic fever. However, in this case, we were able to observe that PAN could present as a probable rare sequela of rheumatic fever. This warrants close follow-up among such patients.

Keywords: *polyarteritis nodosa, rheumatic fever, vasculitis*

INTRODUCTION

The exact etiology of PAN is unknown.[9,21] However, immune complex-mediated pathogenesis has been suggested based on the presence of IgM and C3 on affected arterial walls.[3] Preceding streptococcal pharyngitis, viral infection, exposure to vaccines and medications are known to trigger PAN.[21] The most frequently reported infectious cause in adult and pediatric populations is Group A streptococcus, confirmed by elevated levels of anti-streptolysin (ASO) and positive culture in 86% of cases.[2] Hepatitis B, commonly known to cause PAN in adults, is now rarely associated with childhood PAN with the advent of good vaccination practices.[21] Patients with PAN often present with tender, erythematous subcutaneous nodules, livedo reticularis or racemose, and ulceration.[4,5] The clinical features of PAN can vary depending on the blood vessels and organs affected. PAN has two subtypes (1) Classic or Systemic PAN, and (2) Cutaneous PAN. Commonly associated symptoms include fever, malaise, abdominal pain, myalgia, and arthropathies. Involvement of the heart, kidneys, and testes may manifest as hypertension, hematuria, proteinuria, and, in some cases, testicular pain.[3] As of this writing, the authors have not encountered any literature identifying cutaneous PAN in the pediatric population as a sequela of rheumatic fever.

CASE REPORT

This is a report of a 7-year-old Filipino male from Metro Manila who was admitted due to patches and nodules. History started eight weeks prior to consult, patient presented with pain and swelling of the left knee and leg. At that time, the patient had no fever, sore throat, difficulty in ambulation or cutaneous lesions. Six weeks prior to consult, there was reported progression of the swelling, now involving the left ankle and foot and

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accompanied by a febrile episode. Consult was done with a private physician where the patient was given an unrecalled diagnosis and pain medication but with no noted improvement hence he was advised admission under the Pediatric service. Admitting impression at that time was rheumatic fever with arthritis. Diagnostic tests done revealed leukocytosis with predominance of neutrophils on CBC, elevated ASO titer at 400 IU/mL, and elevated ESR at 84 mm/Hr. An echocardiography done revealed mild tricuspid and pulmonic regurgitation with a normal ejection fraction at 60%. The patient was then started on Penicillin G 475,000 TIV every 6 hours and Paracetamol 190 mg TIV every 4 hours as needed for fever, with noted improvement and was subsequently discharged with Aspirin 80mg/tab 3 tablets every 6 hours for 5 days (50 mg/kg/dose) and Paracetamol 250mg/5mL 10mL every 8 hours to complete 7 days as his take home medications and was advised to follow up at the outpatient department. The patient was apparently well until eight days prior to consult, when undocumented fever developed without other associated symptoms. No lesions were noted at this time. Paracetamol syrup as needed for fever was given which provided temporary lysis of fever. No other medications were taken nor applied. No consultation was done. Four days prior to consult, still with persistence of fever, patient's mother noted appearance of multiple erythematous macules, patches and nodules on the medial aspect of the left foot associated with arthralgia of the bilateral knees, with no noted pruritus, stinging sensation nor tenderness. No medications were taken nor applied and still no consultation done. In the interim, there was an increase in the number of lesions, now also seen on the bilateral upper extremities, knees, shins, medial aspect of the right foot and lower back, still with arthralgia, febrile episodes and swelling of the feet now also accompanied by malaise and myalgia. Persistence of symptoms prompted consult at the emergency room and subsequent admission by the pediatric service as a case of Arthritis secondary to cutaneous vasculitis. He was then referred to Pediatric Rheumatology service for the arthritis and Dermatology service for skin biopsy. Past medical history was unremarkable with no prior history of blood transfusion, needle stick injury nor any history of Hepatitis B nor C infection. Pertinent physical examination revealed multiple, well-defined erythematous to hyperpigmented, firm, tender nodules with some areas of lace or net-like macules and patches, some resolved leaving hyperpigmentation measuring 1x1 cm to 2x2 cm on the bilateral upper and lower extremities and lower back (Figures 1A-O) accompanied by swelling of the 2nd, 3rd, 4th digits of the right hand and non-pitting edema of bilateral hands and feet. There were no noted oral lesions nor blanching on diascopy. The rest of the organ systems were unremarkable.

Diagnostic tests done to rule out systemic involvement and other potential causes revealed leukocytosis on CBC and elevated levels of ESR and CRP while blood culture, kidney and liver function tests, urinalysis, Chest X-ray and electrocardiogram were all normal. However, due to the patient's limited financial resources, work-up for Hepatitis B and C were not done. A 6 mm punch biopsy was taken from a slightly erythematous to hyperpigmented nodule over the left leg (Figures 2A-B).

Patient was then started on Prednisone 5mg/tab, 1 tablet twice daily, Mupirocin 2% ointment to biopsy site twice a day for 7 days, Naproxen 275 mg tab, 1/2 tab twice daily for the pain, Paracetamol as needed for fever and Piperacillin-Tazobactam 1750 mg/IV every 8 hours. Daily wound care, use of mild soap and application of emollients were advised. On the subsequent hospital days, there was noted improvement as evidenced by resolution of erythema on most lesions, decrease in size of nodules leaving behind hyperpigmented macules and patches with no new lesions noted (Figures 3A-D), no recurrence of febrile episodes nor pain. Wound on biopsy site was well-coaptated with no noted discharge. Removal of suture from the biopsy site was also done during this admission.

Skin punch biopsy revealed findings consistent with Polyarteritis Nodosa. Microscopic finding showed on scanning view, a septal panniculitis with large vessel vasculitis and small vessel vasculitis at the dermal-fat junction (Figure 4). On closer view, the blood vessel is medium sized artery with fibrin deposition and neutrophils in its thick walls and surrounded by a marked inflammatory infiltrate, dense mixed cell infiltrates composed of neutrophils, eosinophils and histiocytes with no thrombus. The lobules of fat are partially involved and thinly infiltrated by neutrophils (Figure 5). Other sections showed small blood vessels occluded by thrombus and surrounded by neutrophils, located in the deep reticular dermis; nuclear dust not prominent. The overlying epidermis is unremarkable. There was a sparse to moderate, superficial and deep, perivascular infiltrate of lymphocytes and eosinophils in the dermis.

The patient was subsequently discharged as a case of Cutaneous Polyarteritis Nodosa with the following take home medications: Paracetamol syrup 250 mg/5mL syrup 4 mL every 4 hours as needed for fever; Naproxen 275 mg/tab 1/2 tablet twice daily as needed for pain; Prednisone 5mg/tab, 1 tablet twice daily; mild soap and

emollients. Upon follow up with the Pediatric service, there was noted resolution of previous skin lesions. However, still with appearances of new livedo reticularis lesions in the interim over the lower extremities. No new subjective complaints were noted. Prednisone 5mg/tab, 1 tablet twice daily was continued and patient was started on Mycophenolate mofetil 500 mg/tab, 1 tablet twice daily due to the limited response to prednisone and was advised monthly follow up.

CASE DISCUSSION

Childhood Polyarteritis Nodosa, a rare, systemic disease similar to rheumatic fever, is caused by Group A streptococcus.[19,21] It presents as vasculitis of the small to medium-sized blood vessels affecting multiple organ systems.[19,21] It has two subtypes: (1) Classic or Systemic PAN and (2) Cutaneous PAN, which accounts for >30% of childhood PAN.[7] Both subtypes present with cutaneous lesions and constitutional symptoms. However, the classic subtype has multi-organ involvement with more severe presentations in contrast to the cutaneous subtype, which has minimal organ involvement, mostly limited to the skin, musculoskeletal, or peripheral nerves.[8] Clinical presentation largely depends on the involved blood vessels and organs affected.[3] In this case, cutaneous PAN was considered because aside from cutaneous lesions and constitutional symptoms presented by the patient, there was only limited organ involvement, mainly the musculoskeletal system, in contrast to classic PAN, where there is multi-organ involvement.

ETIOPATHOGENESIS

The exact etiopathogenesis of PAN is not fully known.[9] However, the presence of IgM and C3 deposits on affected vessels suggests an immune complex-mediated mechanism.[21] Various triggers such as streptococcal infection, viral illnesses, and exposure to vaccines and medications are known to predispose to developing PAN.[21] Group A streptococcus, as evidenced by elevated anti-streptolysin O (ASO) and positive throat culture, is the most commonly reported infectious cause associated in the pathogenesis of PAN in both adults and children.[3,8,21] Pathologically, these predisposing factors act as antigenic triggers which contribute to the immune-complex formation and deposition on the vessel wall. leading to development of segmental and transmural inflammation and subsequent fibrinoid necrosis which are prone to aneurysm.[10,21] PAN has also been linked to Parvovirus B19 infection, autoimmune diseases such as rheumatoid arthritis, hairy cell leukemia and loss-of-function mutations in the CECR1 gene or deficiency of adenosine deaminase 2 (ADA2) linked to the adenosine inflammatory-response pathway responsible in regulating inflammation.[5,8,11]

Since there has been no previous report of PAN induced by rheumatic fever, and this is the first case encountered as of this writing, the probable cause, in this case, was an initial infection with Group A streptococcus as evidenced by the elevated ASO titer resulted in a complex immune response leading to rheumatic fever and subsequently to PAN. This begins with molecular mimicry where Group A streptococcus antigen, such as M protein, resembles the host's protein. This resemblance leads to immunological cross-reactivity between host and bacterial antigens during infection.[22] The cross-reactive antigens on Group A streptococcus mimic the host molecules and induce an autoimmune response against the host tissue during the infection.[22] This eventually leads to the development of Group A streptococcus sequelae, such as rheumatic fever.[22] Over time, this autoimmune dysregulation will activate the complement cascade, forming immune complexes and deposits on blood vessel walls.[21] These immune complexes cause inflammation and damage, as observed in PAN.[21]

EPIDEMIOLOGY

The mean age at diagnosis of childhood PAN is 9 years old with no gender predilection.[3] Although there is insufficient data available worldwide for both childhood PAN and rheumatic fever induced PAN, individuals of Asian descents are found to be more likely affected by vasculitis.[1,2]

HISTOPATHOLOGY

The histopathologic finding of PAN usually shows necrotizing medium vessel vasculitis with mixed cellular infiltrates.[1] The fibrinoid necrosis of the vessel wall frequently observed in PAN, is likewise microscopically observed in rheumatic fever. [3,12]

HISTORY AND PHYSICAL EXAMINATION

Rheumatic Fever commonly presents with fever (>90% of patients) and arthritis (>75% of patients) which involves the large joints particularly the elbows, knees and ankles.[18] Other clinical manifestations of rheumatic fever include carditis (>50% of patients) presenting as tachycardia and cardiac murmurs, sydenham chorea (30% of patients).[18] Rarely, rheumatic fever can have cutaneous manifestations (<1% of patients) such as erythema marginatum and subcutaneous nodules characterized by firm, mobile and painless nodules typically located on the

extensors and is often associated with presence of carditis.[3,4]

The most common cutaneous findings of PAN are dusky red to purple firm, painful subcutaneous nodules that may vary from 0.5 to 1 cm, livedo reticularis or racemosa on the trunk, upper extremities and lower extremities particularly on the knees, anterior legs and dorsum of the feet as well as digital ischemia and ulceration.[4,13] Reports in the literature indicate that cutaneous lesions accompanied by arthralgia or myalgia are more common in children with PAN.[14,15] Constitutional symptoms are often present in children such as fever, malaise, weight loss and arthralgia.[13] In contrast, gastrointestinal, renal and neurologic involvement are more often encountered in adults with PAN.[16] Additional clinical presentations are largely dependent on the blood vessels and organs involved such as abdominal pain in patients where mesenteric artery inflammation is present; hypertension, myocardial infarction, hematuria and proteinuria in renovascular arteries involvement.[3,8]

In this case, the patient initially presented with fever, arthritis and arthralgia, consistent with the clinical diagnosis of rheumatic fever. Seven weeks later, multiple erythematous, firm, painful subcutaneous nodules developed, accompanied by constitutional symptoms of fever, malaise, arthralgia and myalgia. These clinical manifestations were consistent with cutaneous PAN.

EVALUATION

The diagnosis of cutaneous polyarteritis nodosa in the pediatric age group is mainly clinical and is confirmed by biopsy of fresh, well-developed cutaneous lesion preferably taken within 24 to 48 hours to determine the size of blood vessel involved.[3,5,7,8] Based on the established diagnostic criteria for childhood PAN brought about by the collaborative efforts by European League Against Rheumatism (EULAR), Pediatric Rheumatology International Trials Organization (PRINTO) and Pediatric Rheumatology European Society (PRES), it is required to fulfill 1 of the 2 major criteria, either evidence of necrotizing vasculitis of small or medium sized vessels on biopsy or aneurysms, stenosis or occlusion on angiography plus 2 out of 5 of the following minor criteria, namely:[5]

1. Presence of skin involvement (livedo reticularis, tender subcutaneous nodules, superficial or deep infarctions)
2. Myalgia, muscle tenderness
3. Hypertension
4. Peripheral neuropathy (sensory neuropathy or motor mononeuritis multiplex) and
5. Kidney involvement (proteinuria, hematuria or RBC cast or GFR <50% of normal value for age).[5]

Currently, there is no specific laboratory test to diagnose cutaneous PAN in the pediatric group. However, these routine laboratory, serologic and imaging studies such as CBC, liver and kidney function tests, hepatitis profile, ASO titer, chest X-ray, and angiography are requested to aid in determining the extent of disease and organ involvement and to exclude other possible causes.[9] Anemia, leukocytosis with elevation of acute phase reactants such as ESR and CRP are frequently encountered.[13]

TREATMENT AND MANAGEMENT

Glucocorticoids remain the gold standard of therapy for polyarteritis nodosa using oral prednisone (1 to 2mg/kg/day) and intravenous pulse therapy at 30 mg/kg/day.[3] Mild PAN may be managed with steroid monotherapy.[3] Alkylating agents such as cyclophosphamide aid as adjunctive therapy. For systemic or refractory cases, azathioprine, mycophenolate mofetil, plasma exchange and tumor necrosis factor alpha inhibitor have been found to be successful.[3] Patients with infection-associated PAN should receive treatment based on the etiologic agent.[13]

CLINICAL COURSE AND PROGNOSIS

Most cases of PAN with limited cutaneous involvement have a relatively benign course.[20] Previous studies have reported better prognosis for children than adults presenting with cutaneous PAN with mortality rate of 1 to 4% in children versus 14.5 to 24.6% in adults.[14,15] The extent of extracutaneous organ involvement is a major factor in determining the prognosis of polyarteritis nodosa.[17] Individuals who have limited organ involvement have a better prognosis than those with widespread organ involvement.[17] It is important to highlight early diagnosis as untreated classic PAN can be fatal secondary to cardiovascular or renal failure.[17]

In patients with a history of rheumatic fever and are diagnosed with PAN, it is crucial not only to monitor the disease progression and relapse of PAN, but also to remain vigilant for potential recurrence of rheumatic fever which is observed in over 65% of patients.[19] This substantially increases the risk of developing rheumatic heart disease, particularly in those who initially presented with symptoms of carditis.[19] Close monitoring and good compliance to medications are essential to prevent disease progression.

SUMMARY/CONCLUSION

This is a case of a case of a 7-year-old Filipino male with a known history of rheumatic fever as revealed by elevated ASO titer which presented subsequently with subcutaneous nodules on the lower back, bilateral upper and lower extremities accompanied by fever, arthralgia, myalgia and malaise. These clinical manifestations were consistent with the diagnosis of cutaneous PAN which was later confirmed by 6mm punch biopsy. The patient was then managed with prednisone. He was subsequently started on mycophenolate mofetil due to his limited response to initial treatment.

The likelihood and diagnosis of Polyarteritis Nodosa should be considered in children presenting with fever, tender subcutaneous nodules, arthralgia, and livedo reticularis, along with a history of rheumatic fever, although uncommon. Most cutaneous PAN have a benign course and is manageable with corticosteroids and steroid-sparing agents to maintain remission of the disease.

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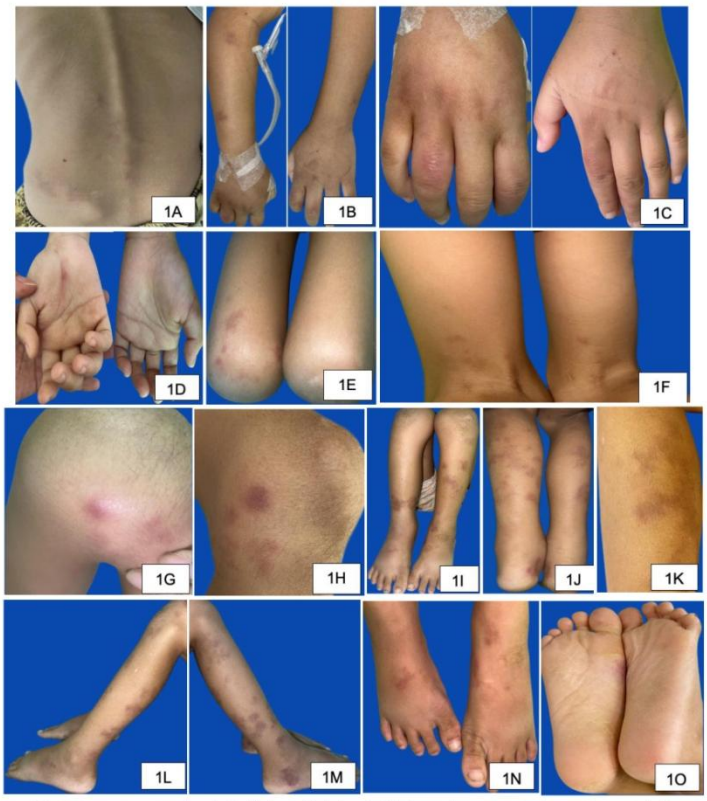
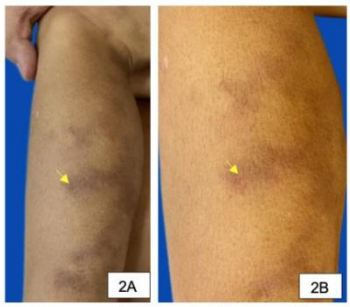
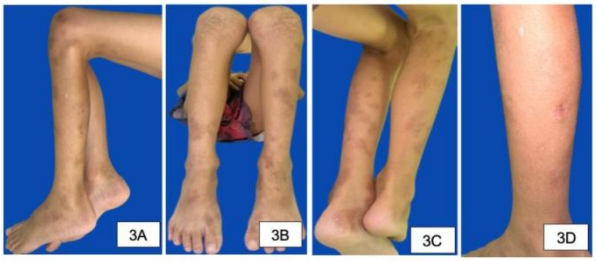


Figures 1A-O. Images upon referral. Multiple, well-defined slightly erythematous to hyperpigmented, firm, tender nodules with some areas of lace or net-like macules and patches, some resolved leaving hyperpigmentation.



Figures 2A-B. A 6 mm punch biopsy taken from a nodule on the left leg.



Figures 3A-D. Images on subsequent hospital days. There was noted improvement as evidenced by resolution of erythema on most lesions, decrease in size of nodules leaving behind hyperpigmented macules and patches.

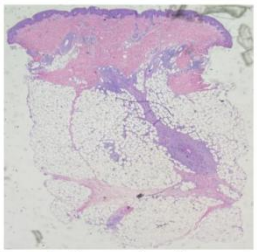


Figure 4. On scanning view, a septal panniculitis with large and small vessel vasculitis at the dermal-fat junction.

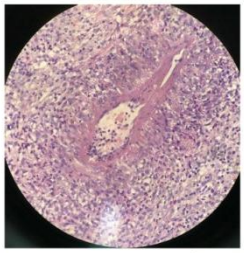


Figure 5. A medium-sized artery with fibrin deposition and neutrophils in its thick walls surrounded by a dense mixed cell inflammatory infiltrates composed of neutrophils, eosinophils and histiocytes. No thrombus formation noted. The lobules of fat are slightly involved and thinly infiltrated by neutrophils.