

Case Report

Polyarteritis Nodosa Presenting as Hypertensive Crisis

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Abstract:

Hypertensive crisis is a deadly complication that should be avoided at all costs, let alone when it is associated with a rare disease, such as Polyarteritis Nodosa (PAN). We present a case of an adult female who initially came to Bangladesh Medical College Hospital (BMCH) with a prolonged high-grade fever responding to antipyretics. Upon follow up, the patient went into a hypertensive crisis, which led to the admission to Coronary Care Unit (CCU). The hypertension was difficult to control until the culprit was revealed. Polyarteritis Nodosa was then diagnosed by angiography, which showed tight stenosis of the left renal artery. Prompt treatment was initiated, and the patient's blood pressure normalized. Our case highlights the importance of detecting such diseases, since it may be easily missed as it usually presents with nonspecific symptoms. Newly detected Hypertension in patients of any age should not be taken lightly and should be investigated promptly. We hope our case report sheds enough light on this issue for other clinicians and researchers to identify and prevent later on.

Keywords: Polyarteritis Nodosa(PAN), hypertensive crisis.

Introduction:

Polyarteritis Nodosa (PAN) is a multi-system necrotizing inflammatory vasculitis of the medium-sized arteries with clinical manifestations resulting from ischemia and infarction of affected tissues and organs including the skin, muscles, joints, heart, nervous system, lungs, gastrointestinal tracts and kidney. Pathogenesis of PAN is currently unknown, but there have been links to the hepatitis B virus (HBV) which is believed to arise due to secondary immune complexes¹. There are also instances of genetic mutations, loss-of-function mutations in CECR1 (also known as ADA2), has been described in multiple sources of literature²⁻⁴. According to vessel size involvement, PAN can be separated into two subtypes: microscopic polyangitis (MPA), which affects small-sized vessels, and classic PAN (c-PAN), which affects medium-sized vessels⁵. MPA is characterized by the presence of perinuclear anti neutrophil cytoplasmic antibodies (ANCA)

specific for myelo-peroxidase (in more than 80%), while c-PAN belongs to ANCA-negative primary vasculitis. Classic PAN should be differentiated from the cutaneous form due to the presence of visceral involvement. It is a disease which carries with it the risk of death, while cutaneous PAN follows a benign, chronic course, characterized by recurrent episodes limited to the skin, muscles and joints. Renal and gastrointestinal involvement has the greatest impact on c-PAN outcome⁶⁻⁸. Arterial hypertension is a common manifestation of c-PAN⁸ but rarely is it malignant^{9,10}. Here, we present a case report in which an adult lady was found to have PAN complicated by a hypertensive crisis.

Case presentation:

A 26 years old lady with no significant medical history, presented with an intermittent fever that started one month earlier, measured 39 degrees Celsius and was responding to antipyretics given at home. There was no diurnal variation. The fever was associated with a runny nose, a dry cough and night sweats. The patient also complained of mild post-prandial generalized abdominal pain, for which she did not require any analgesia. There was no vomiting or any change in bowel habit. Three days prior to the first peak of fever, the patient had a painful swelling in the left ankle and knee, which led the patient limping. The systemic review was otherwise unremarkable. Past history is unremarkable also. The patient has no risk factors for acquiring an infectious disease. She initially sought medical attention at a nearby local private hospital, where she received three types of antibiotics (IV flucloxacillin, IV ceftriaxone, and oral azithromycin), with no improvement.

Upon presentation to BMCH, the patient's blood pressure was 115/64 mmHg, the heart rate was 138 beats per minute, respiratory rate was 32 breaths per minute, and she was afebrile at 36.4 degrees Celsius. Examination showed a dehydrated patient with cracked lips and no lymphadenopathy. There was bilateral lower limb pitting

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edema up to the tibia with no skin changes or discoloration.

Initial investigations revealed that the patient had anemia (hemoglobin of 8.9 g/dl), leukocytosis (18.5×10^9 cells per liter), high erythrocyte sedimentation rate (ESR) of 80 mm/Hr and high C-reactive protein (CRP) of 55 mg/l. Liver function tests and renal parameters were within normal limits. No electrolyte abnormalities were seen. Infectious workup (including tuberculosis, Epstein-Barr virus, cytomegalovirus, mycoplasma, H5N1, human immunodeficiency virus, hepatitis, Brucella) was negative. Chest X ray was normal. Renal sonogram showed bilaterally symmetrical kidneys of 11.3 cm in size, with mild renal parenchymal disease. Immunology testing was done: anti-neutrophil cytoplasmic antibodies (ANCA) and antinuclear antibody (ANA) anti-double-stranded DNA & Complements (C3, C4) were within normal limits. Immunoglobulins (Ig M, Ig A and Ig E) were all normal except for a high Ig G (16.2 μ g/ml). Bone marrow aspirate revealed no evidence of leukemia, granuloma, or infiltration. The left foot X-ray was normal. Skeletal survey showed no lytic bone lesions. MRI of the left ankle showed a mild reactive inflammatory process. CT scan of the abdomen revealed both kidneys were normal in shape and size with mild renal parenchymal disease. The patient was then discharged on conservative management with the plan to be seen in six weeks' time for reassessment and further evaluation.

Six weeks later, the patient got readmitted. Her condition was stable. She was afebrile (36.6 degrees Celsius), had no joint pain, but he had bilateral lower limb edema. Blood pressure upon this admission was 135/75 mmHg. Repeated CT scan of abdomen showed a decrease in the kidney size, post-contrast enhancement, a minimal decrease in perfusion of the left kidney, a hypodense lesion in the lower pole in addition to past findings. This was interpreted as an underlying infiltration, vasculitis, and possible granulomatous disease. Doppler ultrasound showed poor left kidney blood flow. CT angiography showed left renal artery occlusion 2.3 cm from its origin (Fig 1), tight stenosis of the short segment is seen at the origin of the left iliac artery, left anterior tibial artery occlusion with retrograde filling at its origin. Echocardiography was normal.



Fig1: CT angiography showing complete occlusion of the left renal artery

On the 2nd day of admission, her blood pressure was found to be 195/120 mmHg associated with headache, dizziness, visual disturbance and vomiting. Ophthalmologic examination showed retinal hemorrhages, cotton wool spots, and papilledema. Otherwise, physical examination was unremarkable. Patient has shifted to Coronary Care Unit (CCU), and her blood pressure was controlled initially on cilnidipine (10mg), prazosin (2mg) and Clonidine (90mcg). Routine laboratory work up was within normal limits with a serum creatinine of 2.7mg/dl, and a 24-h creatinine clearance of 22.93 mL/min. Electrocardiogram showed left ventricular hypertrophy. Even though the patient was kept on the three aforementioned antihypertensive, she had relapses of hypertension. She started to develop a gradually increasing pedal edema, manifesting as ascites, sacral edema, with upper and lower limb edema. She also gained a total of three kilograms in her weight and developed proteinuria (+4 on urinalysis), hypoalbuminemia (18 g/dL), and hyponatremia (124 mg). Her antihypertensive medications were increased to the maximum dose and she was started on labetalol infusion. She was given three doses of intravenous albumin (0.5 g) along with furosemide. Her blood pressure was reduced to 120/71 mmHg. Repeated urinalysis showed +1 sugar, +3 protein, granular cast, with a negative culture.

She was given pulse therapy consisting of methylprednisolone 30 mg per kg per day for five days, cyclophosphamide 250 mg, methotrexate 7.5 mg weekly along with folic acid 5 mg orally. The patient was kept on oral prednisolone 2 mg per kg per day as maintenance. She underwent left renal balloon angioplasty with successful recanalization of the left renal artery. At this point, her edema greatly improved, blood pressure was in the range of 120/70 mmHg. The left renal doppler was performed, showed a significant improvement of the blood flow in the left renal artery.

Discussion:

Polyarteritis Nodosa (PAN) is a rare necrotizing primary vasculitis that causes systemic inflammation and targets small to medium-sized vessels¹¹. It is a rare disease with an incidence ranging between 4.6 cases per million in England to 77 cases per million in an area hyper endemic for hepatitis B virus infection¹². It affects both sexes and has been diagnosed in people of all racial groups. The etiology and pathogenesis of PAN is unknown. Hepatitis B is known to be associated with PAN, but probably due to vaccination, it currently accounts for less than 10% of all cases of PAN in the developed world.¹³ In contrast to microscopic polyangitis, PAN is not associated with ANCA and does not affect the glomeruli¹⁴.

PAN is generally an acute multisystem disease with a relatively short prodromal period. Constitutional symptoms like fever, malaise, and weight loss are seen in 70% of cases¹⁷. Pain due to peripheral neuropathy is frequent and an early symptom with an incidence rate of 70%. Musculoskeletal manifestations include myalgia (30% to

73%), arthralgia (50%) and asymmetric polyarthritis (20%). Cutaneous involvement is seen in around 50% of patients. Gastrointestinal tract involvement is one of the most severe manifestations, most commonly presenting with abdominal pain (34%). Psychiatric disturbances, mainly severe depression may be seen in 8% of patients. Renal involvement is estimated to occur from 25% to as high as 70% of patients¹⁷. It frequently leads to variable degrees of renal insufficiency and hypertension. Renal ischemia-induced activation of the renin angiotensin system is thought to be responsible for the hypertension. For unknown reasons PAN spares the lungs.

Diagnosis may be difficult due to rarity of the disease, variety of clinical manifestations and resemblance to other inflammatory diseases. The diagnosis of PAN is usually confirmed by tissue biopsy of a clinically affected organ. On the other hand, in the case of renal involvement, affected arteries may not be seen due to sampling error and renal angiography may become more diagnostic, with a specificity of approximately 95%¹⁵. The typical angiographic findings consist of multiple renal aneurysms in medium and small-sized arteries.

No single pattern of laboratory findings can be established to diagnose PAN. Initial laboratory markers may show elevated acute phase reactants (ESR and CRP), normocytic normochromic anemia, and may include an abnormal renal profile and liver profile if there is an associated hepatitis infection. Urinalysis may show proteinuria. Hepatitis markers should be done to exclude secondary causes of PAN. Immunological labs should be negative for ANCA and ANA, the presence of both of which should steer the diagnosis away from PAN. Complement levels in PAN would be elevated in the case of a hepatitis infection¹⁶. Our patient's laboratory findings are consistent with the literature description of PAN labs, however, there was no hepatitis infection that could be identified.

As mentioned above, the diagnosis of PAN can be confirmed by a biopsy. Angiography can be used as an alternative to a biopsy. In our case, the diagnosis was suspected after the patient developed hypertensive crisis. CT angiography was performed, and the typical finding of a complete occlusion of the left renal artery was found².

The American College of Rheumatology (ACR) has established criteria that would help researchers and clinicians identify and suspect Polyarteritis Nodosa. This criteria's main purpose is to differentiate and classify cases as PAN versus other types of vasculitis. Thus, it is mainly used for research purposes rather than clinical diagnosis. A minimum score of 3/10 is required to classify a case as PAN (Table 1). When the ACR criteria are applied to our patient, the score is 3/10, since she developed hypertension, had abnormal renal function tests, and angiography showed an occluded left renal artery.¹⁵

Table 1: American College of Rheumatology criteria for diagnosis of PAN

Criteria	Whether present in our patient
Unexplained weight loss > 4 kg	No
Arteriographic abnormalities	Yes
Livedo reticularis	No
Testicular pain or tenderness	No
Myalgias, weakness, or leg tenderness	No
Mononeuropathy or polyneuropathy	No
Diastolic BP > 90 mmHg	Yes
Hepatitis B virus	No
Elevated BUN or Creatinine	Yes
Biopsy of a small or medium sized artery containing PMN	Not performed

Hypertensive emergency is defined as having an acute elevation in systolic or diastolic blood pressure that is associated with end-organ damage, such as heart, kidneys, and the central nervous system. Hypertensive urgency shares the same definition, though it occurs without end-organ damage and may simply manifest with a headache and/or vomiting^{17,19}.

It is not unusual for PAN to present with elevated blood pressure, as O'Connell MT et al. has mentioned.¹⁸ They reported three cases of PAN which presented initially with a hypertensive crisis, some of which were associated with encephalopathy¹⁷. In contrast, our patient initially presented with a one-month history of fever, and subsequently developed a hypertensive crisis. The patient's high blood pressure was very difficult to control before establishing the diagnosis of PAN and commencing its management. Once adequate management of PAN was initiated, the patient's blood pressure stabilized and her condition improved significantly. The mechanism in which PAN leads to high blood pressure is believed to be mostly related to renal involvement. As the renal arteries get involved, the blood flow to the kidneys decreases with an end result of elevated blood pressure¹.

In a previous study⁹, the clinical characteristics of 165 patients with PAN were reviewed. Seven patients who developed malignant hypertension during the first year of evolution of PAN were identified. Unlike our case, renal insufficiency, digestive signs, orchitis, and positive serology for hepatitis B were present in the majority of those patients.

Ribi C et al. have indicated that PAN's mainstay treatment is corticosteroids. In their study, steroids were able to maintain remission in half of their population. In those who were resistant to corticosteroids, which represented 40% of their population, azathioprine or pulse cyclophosphamide was able to achieve remission in those patients²⁰. Rituximab may be used on top of the aforementioned drugs in refractory cases, a

study done by Seri Y et al. has shown.²¹ In our patient, initial steroid therapy was unable to induce remission, thus cyclophosphamide was given, after which our patient's blood pressure was easier to control. Renal angioplasty was indicated to relieve the stenosis in the renal artery.

Untreated PAN has a 5-year survival rate of <10%⁵. Treatment is based on a high dose steroid regimen combined with monthly intravenous pulse cyclophosphamide, which has achieved a 5-year survival rate of 82% in some studies⁵.

Conclusion:

Polyarteritis Nodosa is a rare but deadly disease that needs prompt diagnosis. Fortunately, enough research has been able to help physicians identify these cases and prevent serious complications from occurring. We have reported a case in which PAN was seen in a pediatric patient, complicated by a hypertensive crisis unresponsive to conventional therapy, and finally being reduced back down after identifying the underlying culprit.

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