

Chronic Testicular Pain: A Unique Presentation of Isolated Testicular Polyarteritis Nodosa (PAN) with Hepatitis B Infection: A Case Report and a Review of the Literature

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Abstract

Polyarteritis Nodosa (PAN) is a vasculitis of unknown origin that affects the medium and small arteries of our organ system. Isolated Polyarteritis Nodosa is a rare condition that may be due to modulation of local immune reaction by exposure to certain local triggering agent without any systemic immune reaction. Symptomatic PAN confined to the testis in hepatitis B infection is extremely rare and not reported frequently. We report a case of isolated testicular PAN in hepatitis B infection with chronic unilateral testicular pain and successfully treated by interferon α , systemic steroid and cyclophosphamide for 7 month.

Keywords: Polyarteritis nodosa; Testicular vasculitis; Hepatitis-B infection

Background

Polyarteritis nodosa (PAN) is systemic necrotizing vasculitis of small and medium sized muscular arteries that can affect skin, joint, heart, kidney, gastrointestinal tract, and nervous system including both central and peripheral (Table1) [1]. Lung is the only organ that is usually spared in PAN, as opposed to other ANCA associated vasculitis [2].

The incidence reported for PAN is 0.7/100,000 per year, PAN affects males more than females in the 4th and 6th decade of life. Etiology in most cases is unknown; however there is evidence of an association with an immune pathogenic factor as a triggering event. Most of the patients develop constitutional symptoms (i.e., malaise, fever and weight loss) in early stage; hence diagnosis is frequently delayed and often complicated. PAN may vary from focal to multisystem and from mild to extensive disease in severity. If systemic PAN left untreated, it carries significant morbidity and mortality, but prolonged therapy with steroid and cyclophosphamide showed increase 5-year survival rate from 10-82% [3,4].

PAN is often a multi-organ vasculitis, but isolated symptomatic form of PAN without systemic involvement is very rare. There are many reports on incidental findings of isolated PAN seen in organ removed during autopsies or surgically removed due to unexplained clinical features or misdiagnosis [5-8]. However the diagnosis of isolated PAN of the testes with HBV infection is very rare and not reported frequently. We present the case of a 35-year-old African American male with past medical history significant for hepatitis B infection, who presented to the emergency department with chronic unilateral testicular pain. The final diagnosis of isolated testicular vasculitis was established following histopathological report on testicular biopsy in a disease limited to the right testes.

Case Report

A 35-year-old African American male with past medical history of hepatitis B virus infection presented to the emergency department with right sided testicular pain. Over the past several months he had a history of recurrent emergency department visits for right testicular pain and was treated for various medical conditions ranging from groin strain and epididymo-orchitis to testicular torsion. Past medical and surgical history was unremarkable. No known drug allergies, no recent travel and no history of drug use, alcohol abuse or smoking history. Patient

Manifestation	Description	Frequency (%)
General symptoms	Fever, malaise, weight loss, arthralgias, myalgias	90
Neurologic	Mononeuritis multiplex, peripheral neuropathy	75
Cutaneous	Nodules, purpura, Livedo	60
Renal	Increased creatinine, hypertension, hematuria, proteinuria	50
Gastrointestinal	Abdominal pain, rectal bleeding	40
Orchitis	Testicular pain, swelling	20
Other		<10
Ophthalmologic	Retinal vasculitis/exudates, conjunctivitis, keratitis, uveitis	8
Vascular manifestations	Claudication, ischemia, necrosis	6
Cardiac	Cardiomyopathy, pericarditis	5
Central nervous system	Stroke, confusion	5
Respiratory	Lung infiltrates, pleural effusions	3

Table 1: Clinical manifestations of PAN.

was on HBV infection treatment and multivitamin supplement. He was married, with one child and no history of sexually transmitted disease. On his last visit to the ER; the patient also complained of constitutional features of low grade fever along with weight loss. He then subsequently admitted for further workup. On examination, patient was tachycardiac with heart rate of 107/min regular, blood pressure 132/84, temperature 37.2 and respiratory rate of 18/min with no localized or generalized lymphadenopathy. Genital exam revealed symmetrical testis, no swelling, and redness seen. Cremasteric reflex and temperature were

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also normal on palpation, but right testis was tender to touch with no change in pain intensity on raising right testis. Testis was isolated with no mass and no inguinal lymphadenopathy detected on physical examination.

Investigations were done included complete blood profile which showed white blood cell count of 4.9 K/L (82% neutrophils), hemoglobin of 11.7 g/dl and platelets were 141K/L. Urine analysis showed +1 protein, 5-10 white blood cells, and no red cells per high power field. Blood chemistries were normal with creatinine of 0.9 mg/dl; however erythrocyte sedimentation rate and C-reactive protein were significantly elevated 45 mm/hr. and 10.5 mg/dl respectively. Further testing of these abnormal tests were added to find out the cause, which included HIV, RPR, Gonococcal/Chlamydia, Coccidioides, Epstein Barr Virus and Parvovirus, all came out negative. We got the clue from initial work up as ESR and CRP were abnormally elevated. We thought it may be some chronic illness or autoimmune. So we sent some autoimmune work up. The autoimmune work up included was anti-neutrophil cytoplasmic antibodies, C3 and C4 complement, liver function test, antinuclear antibody and cryoglobulin. All were unremarkable. The testicular ultrasound also did not show any thing. Eventually we reached at a decision to do biopsy of right testicle as this diagnosis was becoming dilemma for us. So we did biopsy from superior, middle and inferior poles of right testis. The biopsy from superior and inferior pole was unremarkable but result from middle pole showed medium sized necrotizing vasculitis with white blood cells infiltration consistent with Polyarteritis Nodosa (Figure 1). Hence, diagnoses of isolated PAN of the right middle pole of testis.

Treatment

Patient was treated with interferon alpha (10 million international units subcutaneously 3 times a week for 16 weeks. We added prednisolone 1 mg/kg for 7 months and then subsequently started tapered prednisolone, along with cyclophosphamide 600 mg/meter² every 2 weeks for 3 dosages than every 4 week till 7 months.

Outcome and follow-up

After discharge of patient we continued to follow our patient for 1 month and then every 3 month till 7 months with complete blood profile and serum and urine chemistries at each visit. We also perform liver function panel after 6 months. Patient overall responded well to our treatment as all his blood work and serum and urine chemistries turned out in normal range. However patient refused for further follow-ups including HBV infection viral markers.

Discussion

Most of the vasculitides affecting the testis are secondary to PAN.

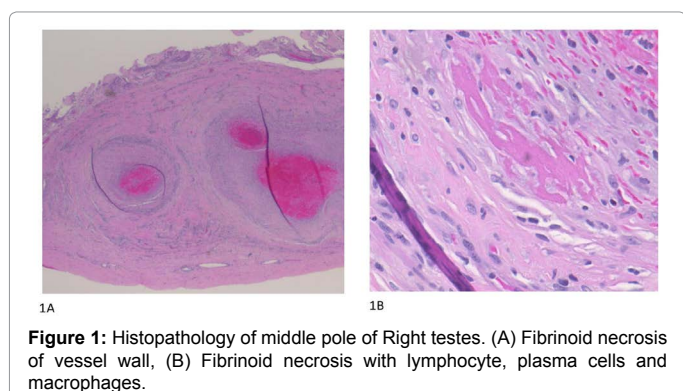


Figure 1: Histopathology of middle pole of Right testes. (A) Fibrinoid necrosis of vessel wall. (B) Fibrinoid necrosis with lymphocyte, plasma cells and macrophages.

Commonest Causes of testicular pain	Torsion of the spermatic cord (testicular torsion)
	Epididymitis and epididymo-orchitis
	Testicular abscess
	Torsion of the testicular appendices
	Trauma of the testis with formation of a hematoma, rupture or posttraumatic torsion
	Testicular tumors
	Viral orchitis
	Post vasectomy pain
	Idiopathic orchialgia (possibly psychogenic or posttraumatic)
	Ureteral colic
	Prostatitis
	Sexual arousal related orchialgia
	Incarcerated inguinal hernia
	Local testicular disorders
Rare causes of testicular pain	Lyme disease
	Polyarteritis Nodosa
	Testicular leukemia
	Drug related (mazindol)
	Cremasteric spasm
	Genitofemoral neuritis
Referred pain	Ilioinguinal neuritis
	Gluteal nodular fibrositis
	Iliac artery aneurysm
	Acute appendicitis

Table 2: Differential diagnosis of acute unilateral testicular/scrotal pain.

Other less frequent causes are Wegener's granulomatosis, giant cell arteritis, Henoch-Schönlein purpura, and hypersensitivity polyangiitis [9]. Testicular involvement is seen in 18% of systemic PAN, but on autopsy the involvement of testis was as high as 86% [10]. Testicular involvement is usually seen as a part of systemic PAN, in which patients has symptoms from other organ (abdominal pain, neuritis, and nephropathy) in addition to testicular symptoms. In those instances diagnosis can be made on clinical grounds but testicular biopsy may be required for histological confirmation. However the challenge begins when PAN presents primarily with testicular involvement. Isolated organ involvement by PAN is well known at sites such as testis, epididymis, appendix, uterus, gallbladder and breast [5,11-13]. The case reported in literature where isolated testicular PAN is described, it is interesting to note that some of these patients subsequently have evidence of systemic involvement; on the other hand, others didn't show any sign of systemic involvement and remained asymptomatic after long term follow-up [10,14-17]. PAN is by definition a systemic disease, it is unsure whether similar cases that present locally with no systemic involvement are highlighted as isolated PAN or as isolated testicular vasculitis with features resembles PAN.

We described here the patient visited to emergency with recurrent attacks of testicular pain. Each time he presents with testicular pain was treated for medical conditions ranging from groin strain and epididymo-orchitis to testicular torsion, but this time he was presented with testicular pain along with weight loss and fever. In the present case, a thorough history and clinical examination along with biochemical analyses enabled us to exclude all the common causes of acute unilateral testicular pain (Table 2). As the recurrent attacks of testicular pain was the chief complaint in patient, which raises our concern to suspect PAN as an interpretation of the systemic features of the patient and history of hepatitis B virus infection. Our suspicion further strengthens when CRP and ESR were elevated, which was confirmed by histopathological finding of right testicular biopsy. This surprised us when a patient

American College of Rheumatology Criteria for the Classification of PAN	
Criterion (#3 Are Necessary)	Definition
Weight loss >4 kg	Loss of >4 kg of body weight since the illness began, not caused by dieting or other factors
Livedo reticularis	Mottled reticular pattern over the skin in portions of the extremities or torso
Testicular pain or tenderness	Pain or tenderness of the testicles not caused by infection, trauma, or other causes
Myalgias, weakness, or leg tenderness	Diffuse myalgias (excluding shoulder and hip girdle), weakness of muscles, or tenderness of leg muscles
Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy
Diastolic BP >90 mm Hg	Development of hypertension with the diastolic BP >90 mm Hg
Increased blood urea nitrogen (BUN) or creatinine level	Increase of BUN >40 mg/dL or creatinine level >1.5 mg/dL, not caused by dehydration or obstruction
HBV	Presence of hepatitis B surface antigen or antibody in serum
Arteriographic abnormality	Arteriogram showing aneurysms or occlusions of the visceral arteries, not caused by arteriosclerosis, fibromuscular dysplasia, or other noninflammatory causes
Biopsy of small or medium-sized artery containing polymorphonuclear neutrophils	Histologic changes showing the presence of granulocytes or granulocytes and mononuclear leukocytes in the artery wall

Table 3: 1990 American college of rheumatology criteria for the classification of polyarteritis nodosa.

presented with right testicular pain which later on diagnosed as isolated testicular PAN on histopathology without affecting other organs. As the Isolated testicular PAN is a rare phenomenon and is not usually considered as a differential diagnosis on patients presenting with unilateral testicular pain.

The diagnostic criteria for PAN came in to being in 1990 by American College of Rheumatology in order to differentiate PAN from other forms of vasculitis. A committee of ACR physicians selected 10 disease features of PAN; in order for PAN to be diagnosed, at least 3 of the 10 ACR criteria should be present when radiographic or pathological diagnosis of vasculitis is made (Table 3). According to this criteria out of 90 patients only 28.9% had testicular pain or tenderness and similarly out of 510 patients only 2.6% had vasculitis other than PAN [18]. Later on, another study conducted in Korea, mentioned around similar percentage of patients diagnosed with PAN had testicular pain and tenderness [19].

Most of the time PAN is an idiopathic disease, however HBV, HCV, HIV, Parvovirus B19 infection has shown an association in the pathogenesis of PAN [20,21]. It is evident that there is a subset of patients who experience systemic vasculitis as a consequence of chronic hepatitis B associated immune complex disease [1,22]. Although PAN is very rare complication of HBV infection seen in about 1-5% of patients having HBV infection, 23 HBV infections seems to affect about 30% of patient population with PAN [22,23] and the exact pathogenesis behind HBV associated PAN is still unknown. Therefore it is very important to test patients with all of these organisms which play a role in pathogenesis of PAN [24,25]. It's difficult to establish a diagnosis, as there are no specific laboratory abnormalities for PAN. Although acute phase reactants such as ESR and C-reactive protein are increased, along with chronic anemia which is mostly present but they

are non-specific markers as they may be present in other inflammatory or chronic diseases. Histopathological studies of small to medium size blood vessel are mainstays of diagnosis of PAN [26].

Clinically it is very difficult to distinguish viral associated PAN from classic PAN, but there are certain differences in viral associated PAN entities. Certain clinical disorders are more common in viral associated PAN comparison to classic PAN, like gastrointestinal disorders, testicular disorders, severe arterial hypertension and renal infarction and also more common in patients who are younger than 40 years [20,27]. If isolated PAN progresses to systemic disease it carries a risk of increased morbidity; however, due to the rarity of this disease the rate of progression is not well understood.

The emerging concern is the treatment of patients having isolated PAN with or without systemic clinical manifestations. Whether medical treatment alone will be helpful or surgical alone or surgery followed by medical treatment with immunosuppressive drugs will be helpful. Most recent studies shows that, even if the vasculitis affected organ is being surgically removed and if there is no other systemic clinical manifestation indicating other organ involvement, still immunosuppressive treatment is required due to systemic nature of disease [28]. On the other hand few other studies stated that if the vasculitis affected organ has been surgically removed and there is no systemic clinical features indicating other organ involvement then there is no more need of immunosuppressive therapy [17,29]. However, there are recent studies supporting the use of immunosuppressive drugs based on five factor score calculated as prognostic factor [30,31]. One of these studies mentioned that it depends on the prognostic factor which based on serum creatinine, proteinuria, cardiomyopathy, CNS involvement and gastrointestinal involvement [30]. In 2011 this score was revised and includes only 4 factors, where the original score include central nervous system involvement, proteinuria but not age and absence of ENT manifestations [31]. This score is used to predict prognosis as well as guide treatment strategies. Every prognostic factor carries one score. If the FFS (Five factor score) is zero, steroids alone can be used. If the FFS is above zero, then cyclophosphamide should be used along with systemic steroids [32,33]. The goal of the therapy is to obtain HBV seroconversion (HBV e antigen to antibody), because as soon as seroconversion is obtained patients shows complete remission without any relapse. This has been observed in half of HBV-PAN patients been treated with antiviral therapy [20]. There is no consensus regarding the use of cyclophosphamide in patients having isolated PAN along with HBV infection [22]. Since we know that chronic HBV infection leads to liver cirrhosis and carcinoma, so use of antiretroviral regime is recommended for long term use. The suggested most effective and modified approach to treat isolated PAN in patient with HBV infection is with antiretroviral therapy along with systemic steroids and immunosuppressive drugs like cyclophosphamide. Therefore our preferred regime to treat patients having PAN with HBV infection is antiviral therapy with systemic steroids and cyclophosphamide.

Limitation of our case report is that we were not able to determine hepatitis B seroconversion (HBV e antigen to antibody) as the patient refused blood work and was lost to follow-up after 7 month.

In conclusion, testicular pain and systemic symptom development are worth to think something beyond the local disease. PAN should be one of our differential diagnoses in patient present with isolated testicular pain and tenderness with some constitutional systemic features especially in Hepatitis B virus infection. A thorough history and physical examination is necessary, superadded with biochemical analysis in patient present with acute or chronic testicular pain. FFS

should be used as a prognostic score in order to start appropriate treatment with systemic corticosteroid alone or in combination with cyclophosphamide. Work up should be done to exclude the systemic disease. Clinical follow-up is also very important to assess the effects and side effects of medication and development of PAN in other body organ system.

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