CASE REPORT

Orchitis: An unusual presentation of polyarteritis nodosa

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ABSTRACT

Polyarteritis nodosa (PAN), a systemic necrotizing vasculitis with multiorgan development, is generally restricted to the medium-sized muscular arteries. The varied initial clinical presentations of PAN can lead to a delayed diagnosis. We present the case of a middle-aged male patient who presented with an acute onset right-sided testicular pain as the initial clinical symptom with ischemic changes on ultrasonogram, thereby requiring orchiectomy. This was reported to be a case of tubercular epididymo-orchitis. On review, the biopsy revealed features of necrotizing arteritis as seen in PAN with fibrinoid necrosis and giant cells, thus highlighting the fact that vasculitis due to PAN may have a localized presentation at the time of diagnosis. PAN should be distinguished from other causes of epididymo-orchitis and other vasculitis lesions, the most common being tubercular etiology in the Asian population.

KEY WORDS: Epididymo-orchitis, polyarteritis nodosa, vasculitis

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INTRODUCTION

Polyarteritis nodosa (PAN) was first described in 1866 by Kussmaul and Maier.[1] It is a rare multisystem necrotizing inflammatory vasculitis typically affecting medium-sized muscular arteries and occasionally small muscular arteries.[2] The classification of vasculitis depends on size and type of vessel involved, presence of immune complexes, association with known autoimmune disease and systemic or localized distribution. PAN and Kawasaki disease are two vasculitis syndromes which affect muscular arteries in the absence of small vessel involvement. In PAN, the involvement of renal and visceral arteries is characteristic. Skin, joints, muscles, nerves, and gastrointestinal tract are commonly involved with sparing of lungs.[3,4] PAN, as currently defined, is not associated with antineutrophilic cytoplasmic antibodies (ANCA). The spectrum of PAN has been narrowed substantially owing to the identification of other forms of vasculitis that were previously considered PAN, as distinct entities. The diagnosis of PAN should be confirmed by biopsy whenever possible.

We present the case of a middle-aged male patient who presented with an acute onset right-sided testicular pain requiring orchiectomy, and the biopsy was reported as tubercular epididymo-orchitis. On review, it revealed features of necrotizing arteritis, characterized by fibrinoid necrosis of the walls of small and medium-sized testicular arteries along with the presence of several giant cells. Hence the possibility of PAN was considered. However, vasculitis indistinguishable from PAN may be observed in infection (bacterial, viral), connective tissue disorders such as lupus erythematosus and rheumatoid arteritis, Wegener's granulomatosis (WG), Churg-Strauss syndrome (CSS), and microscopic polyangiitis (MPA).[5] It is thus important to exclude infectious diseases which mimic vasculitis since most vasculitis require aggressive therapy with glucocorticoids and cytotoxic agents.

CASE REPORT

A 41-year-old male presented with acute onset pain in his right testis requiring emergency admission in the surgery ward. Color Doppler revealed absent flow in his right testis. He was diagnosed to have right-sided testicular torsion and underwent an urgent right-sided orchiectomy with left-sided orchidopexy. The biopsy was reported as tubercular epididymo-orchitis, and the patient was started on antitubercular drugs. A Mantoux test was done which came out to be negative. Chest X-ray was normal.

On review, the slides showed evidence of necrotizing vasculitis along with necrosis and inflammation mainly centered around the vessels. There was prominent transmural inflammation of

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large- and medium-sized muscular arteries. The inflammation consisted of polymorphs along with mononuclear cells and several giant cells. Some of the veins showed thrombophlebitis. Necrotizing vasculitis and fibrinoid necrosis were noted within the vascular lumina resulting in thrombosis of lumen. The testicular parenchyma was remarkable. Stains for acid-fast bacilli were negative [Figure 1]. The overall features were considered to be those of necrotizing vasculitis and the possibility of PAN was considered strongly. He was referred to the Department of Rheumatology for further work up. On history taking, he complained of polyarthralgia for the past 3 months, along with anorexia and weight loss of about 8 kg. He also had a few hyperpigmented, nodular, mildly painful rash over the medial aspects of both his soles and over palms as well. Clinical examination was unrewarding. Routine investigations revealed: Hemoglobin-11.2 g, total count-6000/cumm, platelets-2.5 lakhs/cumm; creatinine-0.8 mg/dl, liver function tests and electrolytes were normal. Viral markers, hepatitis B virus surface antigen, anti-hepatitis C virus and HIV I and II were negative. Renal angiogram was normal. Anti-nuclear antibodies (Hep-2), both c-ANCA and p-ANCA along with ELISA-based myeloperoxidase and PR3 estimation were normal.

He was started on steroids along with methotrexate as a second immunosuppressive, following which his constitutional features improved and he did not have any further complication.

DISCUSSION

PAN is a multisystemic necrotizing vasculitis affecting the medium-sized muscular arteries mostly with a predilection for the gut and kidney.[1,6] The population prevalence estimates for PAN range from 2 to 33 per million. In the recent times, the classification of MPA as a distinct disease has significantly has reduced the true incidence of PAN. PAN appears to affect middle-aged or older adults with a peak incidence in the sixth decade of life and a male predominance of 1.5:1.[2]

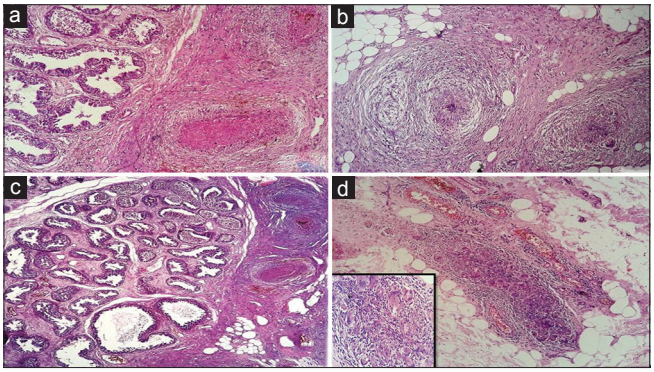

Figure 1: (a) Scan power view showing angiocentric granulomatous vasculitis, with fibrinoid necrosis (H and E, ×40), (b) Scan power view showing similar vasculitis in other foci (H and E, ×40), (c) Scan power view showing areas of normal testis and areas of vasculitis (H and E, ×40), (d) Low power view showing fibrinoid necrosis and granuloma along with a few foreign body giant cells (H and E, ×100). Inset showing high power view of the same

The pathogenetic mechanisms in PAN are poorly understood. Capillaries, veins, and venules are not involved. The thickening of inflamed vessel wall and intimal proliferation cause luminal narrowing predisposing to thrombosis and ischemia.[4] It is accompanied by advential inflammation, pseudoaneurysm formation, and thrombosis with organization and scarring. The primary differential diagnosis is non-vasculitic necrosis secondary to infarction or infection.

There are no laboratory abnormalities specific for PAN. Histologic confirmation of vasculitis in medium-sized arteries from the symptomatic organ is desirable. If biopsies are negative or cannot be obtained, visceral angiography must be done which may reveal multiple micro-aneurysms supporting the diagnosis of PAN.[7]

Testicular vasculitis is uncommon, and PAN should be included in the differential diagnosis of acute onset testicular pain, swelling, and even palpable nodules. The testes are frequently involved in PAN, but only 2%–18% of patients are symptomatic.[2,6] Testicular disease is also one of the criteria for PAN as per the American College of Rheumatology (ACR). Testicular involvement in PAN may occur in isolation without concomitant systemic disease. It may also be the only presenting feature of systemic PAN making it more difficult to diagnose.[3] Imaging studies may not distinguish vasculitis from neoplasia, and definitive diagnosis requires examination of histologic material. The most common differentials of granulomatous vasculitis lesions were infection, WG, CSS, PAN, and MPA. In all of these diseases, granuloma formation may occur either with minimal vascular wall damage or may be associated with fibrinoid degeneration of vessel wall.[5,7]

In the presence of granulomatous vasculitis, causes such as WG and CSS have to be excluded. WG is a c-ANCA associated small vessel necrotizing granulomatous vasculitis mostly affecting the upper and lower respiratory tract and is usually associated with rapidly progressing glomerulonephritis. PAN, on the other hand, is an ANCA negative necrotizing vasculitis of medium-sized vessels. Although granulomatous vasculitis is not the hallmark of PAN, granulomas associated with PAN has been reported in some rare cases.[5,8] PAN can in virtually involve all organ with the exception of the lung. CSS is another small vessel p-ANCA-associated vasculitis characterized by hypereosinophilia and extravascular granuloma in patients with asthma and allergic rhinitis. Histologically, in CSS, the extravascular necrotizing granuloma is associated with eosinophilic infiltrates contrasting with the polymorphous infiltrate of neutrophils, plasma cells, and histiocytes observed in WG.[5] Systemic small vessel vasculitis MPA may be difficult to be distinguished from PAN. Glomerulonephritis, ANCA positivity, and absence of arteriographic findings favor MPA over classic PAN. Often sarcoidosis complicated by systemic vasculitis may not only mimic systemic granulomatous angiitis such as CSS but also PAN or MPA.[9] Table 1 compares the clinicopathological differences between WG, CSS, MPA, and PAN.

The classification of vasculitis is challenging owing to the heterogeneous nature of the lesion.[10] The 2012 revision of Chapel

Table 1: Clinicopathological comparison of the features of microscopic polyangiitis, Wegener's Granulomatosis, Churg-Strauss syndrome, and polyarteritis nodosa

Clinicopathological features	*MPA*	*WG*	*CSS*	*PAN*
Vessel size	Small to medium	Small to medium	Small	Medium
Vessel type	Capillaries, venules and arterioles, sometimes arteries and veins	Capillaries, venules and arterioles, sometimes arteries and veins	Capillaries, venules and arterioles, sometimes arteries and veins	Muscular arteries, spares veins
Granulomatous inflammation	-	+	+	+/-
Other organs involved				
Lungs	Yes	Yes	Yes	No
Kidney	Yes	Yes	Less common	No
ANCA positive	p-ANCA (75%)	c-ANCA (80%)	p-ANCA (78%)	No
Hepatitis B association	No	No	No	Yes (<10% of cases)
Microaneurysm	+/-	+/-	-	++
Likelihood of disease recurrence (%)	33	>50	25	<10

MPA: Microscopic polyangiitis, WG: Wegener's granulomatosis, CSS: Churg-Strauss syndrome, PAN: Polyarteritis nodosa, ANCA: Antineutrophilic cytoplasmic antibodies, +: Present. -: Absent, ±: Maybe present, ++: Always present

Hill Consensus Conference (CHCC) nomenclature for vasculitis retained the primary reliance on the size of the affected vessels but added several important categories, subcategories like the role of ANCA in the etiopathogenesis of vasculitis.[10] An important limitation in this current concept of vasculitis classification is that it is mainly pathology based and is of very little diagnostic value at bedside.[11]

The European medical agency (EMA) algorithm for classification of vasculitis uses a combination of the ACR (1990) classification criteria and the CHCC 1994 definitions for MPA, granulomatosis with polyangiitis, CSS, and PAN.[10] The purpose of the EMA algorithm also referred to as "Watts' criteria," was to harmonize the classification of PAN- and ANCA-associated vasculitis.[12] It was primarily done for epidemiologic studies but is now applicable to other research areas.

However, the EMA algorithm does not represent an original classification system *per se* because it was built using various elements of the CHCC nomenclature and ACR criteria.[10,11] The major advantage of this system is that it provides a hierarchy of classifying the four major types of vasculitides. It provides a detailed definition for the entry criteria like clinical, laboratory, histological, or imaging characteristics besides including a subgroup of undifferentiated vasculitis. The algorithm also ensures that it is used for cases only with some evidence of vasculitis.[12] The main strength of the algorithm is its ability to classify the diseases within the subcategory of ANCA-associated vasculitis.

Isolated necrotizing vasculitis of the testis, as found in our case, may mimic a testicular neoplasm, testicular torsion or infection.[13,14] Thus, histopathologic study is perhaps the only reliable diagnostic modality of testicular PAN. Histologically, the outline of the artery is destroyed and replaced by a layer of fibrin. Fibrinoid necrosis which is homogenous and eosinophilic in appearance is typical and a defining feature of PAN as opposed to the detail-less caseous necrosis of tuberculosis. There is marked periadventitial inflammation accompanied by characteristic segmental transmural inflammation of the muscular arteries. The cellular infiltrate contains polymorphonuclear leukocytes and mononuclear cells. Leukocytoclastic may be noted. Well-formed granuloma with epithelioid cells and Langhan's giant cells with lymphocytic cuffing as seen in tuberculosis is not encountered in PAN. Vasculocentric inflammation and arteritis are distinctly unusual in other causes of granulomatous orchitis such as tuberculosis.[15] It is thus important to distinguish PAN from tubercular epididymo-orchitis in the Asian population.

Testicular vasculitis need not be a manifestation of systemic PAN alone but may occur as an isolated, incidental finding. It is important to distinguish cases of isolated testicular vasculitis from PAN, as the latter diagnosis has poor prognosis and needs aggressive therapy.[16,17] The presence of recent testicular infarcts may be a poor prognostic sign. In view of the rarity of the disease and the potentially severe adverse effects of the treatment, the diagnosis of PAN should be confirmed by biopsy whenever possible.

CONCLUSION

Here, a rare case of unilateral testicular PAN has been described, the diagnosis of which was based on the histopathological study. Testicular pain may be the first presenting symptom of vasculitis, and such cases require careful clinical work up. Early treatment with steroids and immunosuppressive agents may impact disease course if the diagnosis of PAN could be established.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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