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Case Report

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Minocycline-Induced Polyarteritis Nodosa Presenting With Testicular Pain: A Case Report and Selected Review of the Literature

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Abstract

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis that affects small and medium-sized arteries, leading to aneurysm formation and ischemia in different organs of the body. Although not common, testicular manifestations have been documented. We discuss a case of 18-year-old male with minocycline-induced systemic PAN who presented with unilateral testicular pain. The definitive diagnosis was made after testicular biopsy demonstrating focally necrotizing vasculitis affecting small and medium vessels. Following the diagnosis he was discharged on prednisone, and was started on rituximab by his rheumatologist. He is clinically much improved during his surveillance follow-up visits with his rheumatologist and urologist. Minocycline-induced polyarteritis nodosa can present with constitutional symptoms and testicular pain among patients using the acne treatment. Prompt diagnosis is essential to ensure proper treatment and prevention of complications. Optimal management of these patients requires close collaboration amongst urologists and rheumatologists for accurate tissue diagnosis and close surveillance.

Keywords: Minocycline; Polyarteritis nodosa; Testis; Vasculitis

Introduction

Testicular pain is a non-specific finding which may be mechanical, infectious, oncologic, or rheumatologic in its etiologies. Polyarteritis nodosa (PAN) is a critical rheumatologic condition that can present with genitourinary manifestations. This condition has a slight male predominance, and its prevalence is estimated to be 31 cases/million [1]. Its peak incidence occurs in the fourth to sixth decade of life. Our patient, 18 years old, is certainly younger than many of the reported cases. Urologic symptoms may appear as the earliest manifestation of the systemic disease. Previous reports have shown that patients diagnosed with PAN have testicular pain with increased vascularity seen on scrotal US. Moreover, hematuria is also seen in 15% of patients, and orchitis/epididymitis is seen in 2-18% of patients with PAN [2]. Here we present an 18-year-old male with acute on chronic testicular pain. The case presentation is followed by a selected review of the literature on this topic.

Case Report

An 18-year-old male with 9-month history of intermittent chronic left testicular pain and swelling associated with weight loss, arthralgias, and myalgias, presented with an acute onset of left testicular pain of 1-week duration. On initial presentation to his rheumatologist, he had been taking minocycline 100mg twice daily for 2 years for acne. The medication was discontinued by his rheumatologist and changed to azithromycin for management of his acne. He tested positive for ANA (1:160) and anti-histone antibody (2.7 units) at that time, and was started on prednisone 60mg daily by his rheumatologist, which was tapered down over the course of 6 months to 5 mg every other day. Initial specific ANCA testing was negative for anti-MPO and anti-PR3. One week prior to admission, he presented to the emergency department with testicular pain and swelling, and was discharged with an increase in his prednisone dose to 20 mg once daily. One day prior to admission, the testicular pain intensified with a new onset of left lower quadrant abdominal pain. Associated symptoms included dysuria, hesitancy, and gross hematuria.

On exam, the left testicle was mildly tender to palpation without any masses. The left epididymis was firm and focally tender, and there was a palpable left varicocele. The right testicle was non-tender without any masses. His labs were remarkable for hemoglobin of 10.1 g/L, hematuria on urinalysis with 44 red blood cells per high power field (RBCs/HPF), elevated

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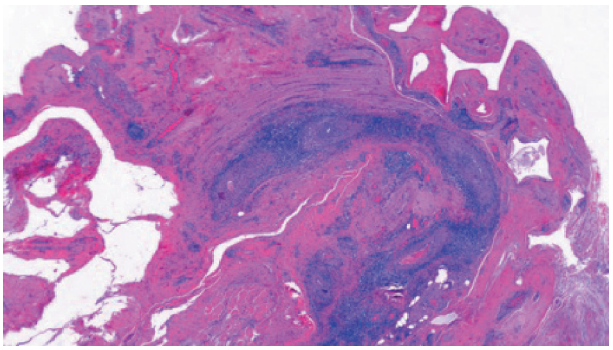

Figure 1. Left paratesticular tissue with perivascular infiltrates containing of lymphocytes and plasma cells (H&E, 20 × original magnification).

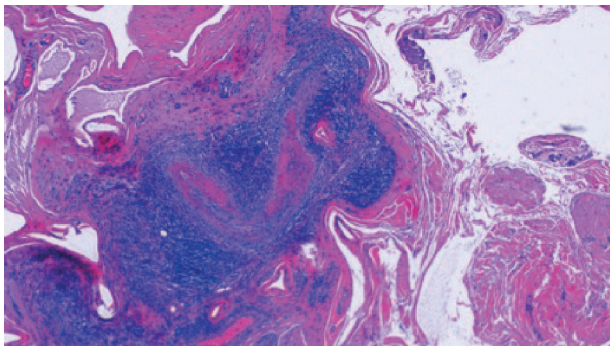

Figure 2. Left paratesticular tissue with focal necrotizing vasculitis of small and medium sized vessels and perivascular infiltrates containing of lymphocytes and plasma cells (H&E, 40 × original magnification).

erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), positive ANA (> 1:1280) and positive ANCA (MPO positive 2.3). Scrotal ultrasound demonstrated heterogeneous appearing testes with increased vascularity in bilateral testes and epididymis, and a possible left varicocele.

On admission he was continued on the same dose of oral prednisone until biopsy results were obtained for definitive diagnosis. His abdominal pain and hematuria had completely resolved, and testicular pain was improving each day. Given the testicular symptoms, the patient underwent bilateral testicular and paratesticular tissue biopsy to rule out systemic vasculitis. The bilateral paratesticular biopsies demonstrated focally necrotizing vasculitis affecting small and medium vessels with fibrinoid necrosis (Fig. 1, 2). Staining for IgG and IgG4 revealed rare scattered IgG4 positive plasma cells among a population of IgG positive cells. Immunofluorescence was otherwise negative for an immune complex mediated vasculitis as the complement and fibrinogen staining related to focal, active areas of inflammation involved by fibrinoid necrosis. Testicular tissue was negative for inflammation, infarction, or parenchymal vasculitis.

Additional workup for suspected vasculitis included a MRA of the chest and abdomen, with attention to the renal arteries. Our patient showed aortic root dilation on MRA of the chest with the absence of renal aneurysm or infarct on MRA of the abdomen. Although this was not a new finding, it is important to continue to monitor with his cardiologist. After biopsy results were back, the patient's dose of prednisone was increased to 60 mg daily to reduce inflammation and he resumed follow-up with rheumatology as an outpatient. He was advised to avoid minocycline for treatment of acne in the future. On his follow-up visit with his rheumatologist 1 month after discharge, he was given a 2 g infusion of rituximab and prednisone was tapered down to 15 mg daily. The plan is to continue rituximab infusions every 4 - 6 months for a total of three to four cycles in addition to the prednisone. Two months following discharge, he is asymptomatic and has not had any recurrence of his testicular pain, abdominal pain, or hematuria.

Discussion

The differential diagnosis of acute testicular pain commonly includes testicular torsion, appendicular torsion, orchitis, epididymitis, or tumor. Many clinicians often neglect to consider testicular pain as a presenting symptom of vasculitis. To our best knowledge, our patient is the youngest of all the patients who had testicular pain as an initial manifestation of systemic PAN (Table 1, [3-18]). In addition to testicular pain, our patient displayed diffuse myalgias, unexplained weight loss meeting the diagnosing criteria for PAN [19].

Typically, pathogenesis of PAN is idiopathic, although hepatits B, hepatitis C, and HIV are associated with the vasculitis [2]. In addition, there are documented cases of minocycline-induced PAN [3]. It is hypothesized that myeloperoxidase enzyme oxidizes minocycline into reactive metabolites, which can trigger the induction of pANCA and lead to an autoimmune response [3]. In consistency with this finding, our patient had a history of minocycline use for acne treatment, and also demonstrated MPO-ANCA positivity on laboratory testing. It should be noted that patients with systemic PAN are typically negative for ANCA, and its positivity in the setting of necrotizing vasculitis should strongly suggest the presence of another form of vasculitis, including microscopic polyangiitis [2].

While our patient's symptoms were highly suggestive of vasculitic etiology, histopathologic finding is the most definitive diagnosis of PAN. Active lesions of the affected arteries in the PAN typically demonstrate areas of fibrinoid necrosis and neutrophilic infiltration, as seen in the biopsy slide of our patient [2]. This differs from granulomatosis with polyangiitis, formerly known as Wegener granulomatosis, which demonstrates necrotizing granulomatous inflammation of small and medium-size vessels in addition to PR3-ANCA positivity. Another consideration in the differential of testicular pain among systemic vasculitis is Henoch-Schonlein purpura (HSP). However, HSP is associated with the presence of immune complexes containing IgA along with its cutaneous manifestation of palpable purpura. Given the high index of suspicion for vasculitis in the absence of palpable testicular mass, orchiectomy was avoided as testicular biopsy was sufficient to establish the diagnosis.

Management options for testicular pain in the setting of PAN are not clearly established. While there are reports of testicular PAN treated with orchiectomy alone without any recurrence of disease after 1 to 3 years of follow-up [11, 13, 15, 16,

Table 1. A Selected Review of the Literature on Testicular Polyarteritis Nodosa [3-18]

Study, date	Patient age/ final Dx	CC	Labs and ultrasound	Pathology	Tx	Sx after tx	Significance
Lenert, 2013 [3]	21/minocycline-induced systemic PAN	Left testicular pain + systemic sx	Labs: elevated ESR, CRP, (+) p-ANCA, (+) ANA; U/S: wedge-shaped lesion	Medium-size testicular artery with mononuclear cell infiltration and area of testicular necrosis	Removal of minocycline, short course of prednisone and hydroxychloroquine	Asymp- and disease free at 2 years	Systemic vasculitis associated with chronic minocycline use
Gervaise, 2014 [4]	28/systemic PAN	Right testicular pain	Labs: mildly elevated CRP; U/S: no Doppler flow in right testis with numerous hypoechogenic areas and some areas of normal parenchyma	Gross: heterogeneous in appearance with alternating areas of ischemia without necrosis and healthy parenchyma c/w acute vasculitis	IV prednisolone and cyclophosphamide	Asymp-	Diagnosis of testicular vasculitis on CT angio: thrombosis of distal testicular artery, no confirmed biopsy
Bing, 2012 [5]	46/systemic PAN	Left flank pain with gross hematuria after running	Labs: elevated ESR and CRP, anemia, (-) ANA, (-) ANCA; renal U/S: left-sided, upper pole, pelvi-calyceal distension and peri-nephric edema	N/A	Glucocorticoid, cyclophosphamide, methotrexate	Asym- and disease free at 2 years	Diagnosis based on presence of aneurysms on left renal angiogram
Toepfer, 2011 [6]	55/systemic PAN	Left testicular pain, with recurrence on the right 3 weeks after initial evaluation, recurrent systemic ischemic events	Labs: all (-); U/S: decreased blood flow	Testicular specimens: interstial hemorrhage and focal atrophy; Abdominal wall skin bx: thrombotic vasculopathy with leukocytoclastic vasculitis	Bilateral orchiectomy, methylprednisone + cyclophosphamide	Recurrence of ischemic events at 3 weeks and 5 weeks; asymp- after systemic tx at 6 months	Asynchronous testicular necrosis as initial sign of systemic PAN
Ahmad, 2010 [7]	65/systemic PAN	Left testicular pain and swelling, developed frank painless hematuria during workup	Labs: (+) ANCA, elevated ESR; U/S: mycotic aneurysmal lesions of the testicle	N/A	Glucocorticoid	"Cinically well"	Left renal hematoma on CT scan, small aneurysms found in both kidneys on angiography
Meeuwissen, 2008 [8]	72, 61, 28/ systemic PAN	Testicular pain preceeding systemic symptoms (1), concurrent systemic sx and testicular pain (2)	Labs: elevated ESR, CRP, (-) ANCA, (-) ANA, anemia; U/S: heterogenic, enlarged testis	Gross: edematous, blue colored testis with multiple necrotic areas; Microscopic: segmental destruction of vessel wall of small and medium-sized arteries by mononuclear inflammatory infiltrate; fibrinoid necrosis and thrombi	Orchiectomy, methylprednisolone taper (after onset of systemic symptoms)	Asymp- and disease free at 16 months - 80 months	Testicular involvement as prominent sign of PAN
Kolar, 2007 [9]	29/systemic PAN	Right scrotal pain + systemic sx	Labs: elevated ESR, CRP, (-) ANCA; U/S: enlarged and swollen right epididymis with reduced blood flow; reduced testicular artery flow	N/A	Glucocorticoids + cyclophosphamide	N/A	Improved testicular artery flow after systemic treatment without need for orchiectomy

Table 1. A Selected Review of the Literature on Testicular Polyarteritis Nodosa [3-18] - *(continued)*

Study, date	Patient age/ final Dx	CC	Labs and ultrasound	Pathology	Tx	Sx after tx	Significance
Susanto, 2003 [10]	74/systemic PAN	Left testicular pain + systemic sx	Labs: elevated ESR, CRP, anemia, leukocytosis, microscopic hematuria; (-) ANCA; U/S: small right testicular cyst and mild enlargement of left testicle with normal epididymis	Skin/muscle bx: vasculitis of medium vessels with mixed cellular infiltrate in intramuscular arterioles and their branches	Oral prednisone (1 mg/kg/day) and cyclophosphamide (2 mg/kg/day) × 6 months	Asymp- at 1 year	Febrile episode of epididymo-orchitis as initial manifestation of PAN
Eilber, 2001 [11]	43/systemic PAN	Hematuria, left testicular mass, systemic sx	Labs: elevated ESR, (+) ANA; U/S: suspicious heterogeneous intratesticular lesion	Inflammatory infiltrate and thrombosis in vessel lumina, necrosis of intimal layer	Orchiectomy only	Asymp-	PAN presenting with hematuria and testicular lesion
Brimo, 2011 [12]	35 (avg) 23-53 (range)/isolated testicular PAN (12), systemic PAN (2)	Testicular pain (86%), mass (7%)	Labs: all negative except 2 with elevated CRP and ESR, (-) ANCA; 1 with (+) ANA; U/S: hypoechoic mass suspicious for cancer	Transmural necrotizing inflammation of small to medium-sized ateries with fibrinoid necrosis and acute inflammation	Orchiectomy, systemic treatment: predisone, or prednisone + cytoxan (in half of isolated cases and all of systemic cases)	N/A	Case report of testicular vasculitis, 14 confirmed to be PAN, half of isolated cases still received systemic treatment
Fraenkel-Rubin, 2002 [13]	26/iIsolated testicular PAN	Left testicular pain	Labs: negative ESR, CRP, ANA, ANCA, CBC; U/S: diffuse damage consistent with interstitial process	Fibrinoid necrosis of medium and small sized arteries with acute transmural inflammation with lymphoplasmacytic and eosinophilic infiltrates	Orchiectomy only	Asymp- and disease free at 2.5 years	Use of Birmingham Vasculitis Activity Score (BVAS) in determining need for systemic treatment for isolated PAN
Pastor-Navarro, 2007 [14]	26/isolated testicular PAN	Painful bilateral testicular swelling	Labs: all (-); U/S: multiple non-vascularized, heterogeneous, hypoechoic focal lesions; small reactive hydrocele	Areas of intraparenchymal hemorrhage, fibrinoid necrosis, pleomorphic infiltration	Right orchiectomy, glucocorticoid	Asymp- at 1 year	Concurrent bilateral testicular involvement
Tanuma, 2003 [15]	40/isolated testicular PAN	Left testicular pain, with recurrence on right 16 months after initial diagnosis	Labs: (+) ANA; U/S: avascularity of bilateral testes	Fibrinoid necrosis of small and medium sized arteries with severe inflammatory infiltrate and near obstruction of arterial lumen	Bilateral orchiectomy	Asymp- and disease free at 22 months	Recurrent testicular PAN
Mukamel, 1995 [16]	28, 35/isolated testicular PAN	Right painful testicular swelling and mass	Labs: all (-); U/S: intratesticular hyper- and hypoechogenic areas (1); normal with hydrocele (1)	Intratesticular hemorrhage and fibrosis, segmental fibrinoid necrosis, thrombosis, and perivascular fibrosis of small arteries; some aneurysmal dilatation	Orchiectomy only	Asymp- and disease free at 2 - 3 years	Isolated testicular PAN

Table 1. A Selected Review of the Literature on Testicular Polyarteritis Nodosa [3-18] - *(continued)*

Study, date	Patient age/ final Dx	CC	Labs and ultrasound	Pathology	Tx	Sx after tx	Significance
Warfield, 1994 [17]	19/isolated testicular PAN	Left testicular pain and swelling with recurrence in right testicle 12 months later	Labs: elevated ESR and CRP, (-) ANCA; U/S: heterogeneous echo pattern including areas suggestive of cystic change	Gross: scattered areas of hemorrhage of lower pole of testis; Microscopic: patchy, necrotizing vasculitis affecting medium and small arteries; fibrinoid necrosis of walls and transmural infiltrate of PMNs and lymphocytes	Left orchiectomy + cyclophosphamide × 1month, azathioprine and oral prednisone with short-term increase after recurrence on right side, long-term low dose prednisolone	Recurrence of sx at 12 months; asymp- and disease free at 18 months	Recurrence of sx while on systemic therapy
Fleischmann, 2007 [18]	21/isolated testicular PAN + metastatic mixed germ cell tumor	Left painful scrotal swelling	Labs: N/A; U/S: enlarged left epididymis and calcifications	Mixed germ cell tumor of left testis; circumferential, transmural fibrinoid necrosis, inflammatory infiltrates composed of neutrophils and monocytes in or around the walls of small to medium-sized arteries	Orchiectomy only	Asymp- and disease free at 2 years	Isolated PAN presenting with mixed germ cell tumor

ANA: anti-nuclear antibody; ANCA: anti-nuclear cytoplasmic antibody; Asymp-: asymptomatic; Avg: average; Bx: biopsy; CRP: C-reactive protein; C/W: consistent with; ESR: erythrocyte sedimentation rate; PAN: polyarteritis nodosa; Sx: symptoms; Tx: treatment; U/S: ultrasound.

20], there is also a case of minocycline-induced systemic PAN with a short course of prednisone and hydroxychloroquine alone for complete symptom resolution [3]. To better characterize and quantify the severity of symptoms, Fraenkel-Rubin et al used the Birmingham Vasculitis Activity Scale (BVAS), a 56 point assessment of disease activity, in order to determine if a patient with testicular vasculitis needs systemic therapy [13, 21]. Based on this scale, a low BVAS score indicates a localized disease while high BVAS means a systemic disease which requires steroid therapy with or without orchiectomy. Our patient displayed systemic symptoms and scored moderately high on BVAS, and his testicular pain had been well managed with prednisone 60 mg once a day taper without any surgical intervention at his 1-month follow-up.

Surveillance is paramount to monitor for symptom recurrence and progression. Although our patient's hematuria had completely resolved at the time of testicular biopsy, further systemic signs and recurrence of testicular pain would mandate both additional imaging work and possible orchiectomy, respectively. Lastly, due to the complexity of this clinical condition, close communication and collaborative efforts between urology and rheumatology are crucial in monitoring symptoms and coordinating treatment options.

Conclusions

Minocycline-induced PAN can present with constitutional symptoms and testicular pain among patients using the acne treatment. Although it is uncommon, it is important to consider systemic vasculitis as a possible diagnosis when a patient presents with acute testicular pain along with musculoskeletal symptoms. Optimal management of these patients requires close collaboration amongst urologists and rheumatologists for accurate tissue diagnosis and close surveillance.

Conflict of Interest

There is no conflict of interest to disclose.

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Abbreviations

ANA: anti-nuclear antibody; ANCA: anti-nuclear cytoplasmic antibody; Avg: average; BP: blood pressure; BUN: blood urea nitrogen; BVAS: Birmingham Vasculitis Activity Scale; Bx: biopsy; CBC: complete blood count; CRP: C-reactive protein; CT: computed tomography; C/W: consistent with; ESR: erythrocyte sedimentation rate; HSP: Henoch-Schonlein purpura; MPO: myeloperoxidase; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; PAN: polyarteritis

nodosa; RBCs/HPF: Red blood cells per high power field; Sx: symptoms; Tx: treatment; U/S: ultrasound

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