Case Report

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 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. 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. 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.

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
recurrence of his testicular pain, abdominal pain, or hematuria. Following discharge, he is asymptomatic and has not had any recurrence of disease after 1 to 3 years of follow-up [11, 13, 15, 16, 17]. Three to four cycles in addition to the prednisone. Two months 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 cycles. The patient 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 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 aneurism 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 hepatitis 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, orchectomy 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 orchectomy alone without any recurrence of disease after 1 to 3 years of follow-up [11, 13, 15, 16, 17].

![Figure 1](image1.jpg)

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

![Figure 2](image2.jpg)

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).
<table>
<thead>
<tr>
<th>Study, date</th>
<th>Patient age/ final Dx</th>
<th>CC</th>
<th>Labs and ultrasound</th>
<th>Pathology</th>
<th>Tx</th>
<th>Sx after tx</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gervaise, 2014 [4]</td>
<td>28/systemic PAN</td>
<td>Right testicular pain</td>
<td>Labs: mildly elevated CRP; U/S: no Doppler flow in right testis with numerous hypoechogenic areas and some areas of normal parenchyma</td>
<td>Gross: heterogeneous in appearance with alternating areas of ischemia without necrosis and healthy parenchyma w/ acute vasculitis</td>
<td>IV prednisolone and cyclophosphamide</td>
<td>Asymp-</td>
<td>Diagnosis of testicular vasculitis on CT angio: thrombosis of distal testicular artery, no confirmed biopsy</td>
</tr>
<tr>
<td>Bing, 2012 [5]</td>
<td>46/systemic PAN</td>
<td>Left flank pain with gross hematuria after running</td>
<td>Labs: elevated ESR and CRP, anemia, (-) ANA, (-) ANCA; renal U/S: left-sided, upper pole, pelvi-calyceal distension and peri-nephric edema</td>
<td>N/A</td>
<td>Glucocorticoid, cyclophosphamide, methotrexate</td>
<td>Asymp- and disease free at 2 years</td>
<td>Diagnosis based on presence of aneurysms on left renal angiogram</td>
</tr>
<tr>
<td>Toepfer, 2011 [6]</td>
<td>55/systemic PAN</td>
<td>Left testicular pain, with recurrence on the right 3 weeks after initial evaluation, recurrent systemic ischemic events</td>
<td>Labs: all (-); U/S: decreased blood flow</td>
<td>Testicular specimens: interstitial hemorrhage and focal atrophy; Abdominal wall bx: thrombotic vasculopathy with leukocytoclastic vasculitis</td>
<td>Bilateral orchiectomy, methylprednisone + cyclophosphamide</td>
<td>Recurrence of ischemic events at 3 weeks and 5 weeks; asymp- after systemic tx at 6 months</td>
<td>Asynchronous testicular necrosis as initial sign of systemic PAN</td>
</tr>
<tr>
<td>Ahmad, 2010 [7]</td>
<td>65/systemic PAN</td>
<td>Left testicular pain and swelling, developed frank painless hematuria during workup</td>
<td>Labs: (+) ANCA, elevated ESR; U/S: mycotic aneurysmal lesions of the testicle</td>
<td>N/A</td>
<td>Glucocorticoid</td>
<td>“Clinically well”</td>
<td>Left renal hematoma on CT scan, small aneurysms found in both kidneys on angiography</td>
</tr>
<tr>
<td>Meeuwissen, 2008 [8]</td>
<td>72, 61, 28/ systemic PAN</td>
<td>Testicular pain preceding systemic symptoms (1), concurrent systemic sx and testicular pain (2)</td>
<td>Labs: elevated ESR, CRP, (-) ANCA, (-) ANA, anemia; U/S: heterogeneous, enlarged testes</td>
<td>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</td>
<td>Orchiectomy, methylprednisolone taper (after onset of systemic symptoms)</td>
<td>Asymp- and disease free at 16 months - 80 months</td>
<td>Testicular involvement as prominent sign of PAN</td>
</tr>
<tr>
<td>Kolar, 2007 [9]</td>
<td>29/systemic PAN</td>
<td>Right scrotal pain + systemic sx</td>
<td>Labs: elevated ESR, CRP, (-) ANCA; U/S: enlarged and swollen right epididymis with reduced blood flow; reduced testicular artery flow</td>
<td>N/A</td>
<td>Glucocorticoids + cyclophosphamide</td>
<td>N/A</td>
<td>Improved testicular artery flow after systemic treatment without need for orchiectomy</td>
</tr>
</tbody>
</table>
### Table 1. A Selected Review of the Literature on Testicular Polyarteritis Nodosa [3-18] - (continued)

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

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 orchietomy. 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 orchietomy, 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; MRI: magnetic resonance imaging; PAN: polyarteritis nodosa; Sx: symptoms; Tx: treatment; U/S: ultrasound.
nodosa; RBCs/HPF: Red blood cells per high power field; Sx: symptoms; Tx: treatment; U/S: ultrasound

References