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Case Series

Xanthogranulomatous orchitis: a case series

Tanvi R. Sambhus, Swati Sharma*, Kanthilatha Pai, Mary Mathew

Department of Pathology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India

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***Correspondence:**
Dr. Swati Sharma,
E-mail: swati.sharma@manipal.edu

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ABSTRACT

Xanthogranulomatous orchitis (XGO) is a sporadic disorder that has no definite aetiology and is a mimicker of several conditions, most significant of which are testicular neoplasms. We present a case series of three cases. The first case presented with swelling in his scrotum. The second case presented with similar symptoms and had prior history of trauma to the scrotum. Both cases were clinically diagnosed with testicular tumour. The third case was a referred case of left chronic orchitis with sinus tract. All three patients underwent high inguinal orchidectomy. Regardless of clinical work-up and diagnoses, upon histopathological evaluation, all three cases were diagnosed with XGO. This study explores the variety of risk factors and aetiologies that may result in XGO.

Keywords: Inflammation, Lipid, Macrophages, Necrosis, Testis, Xanthogranulomatous

INTRODUCTION

Xanthogranulomatous orchitis (XGO) is rare. A non-neoplastic inflammatory condition of the testis, it can be difficult to distinguish from testicular tumours.[1] Histologically, it is characterized by parenchymal destruction and cellular infiltration by sheets of lipid-laden macrophages (xanthoma cells) along with a granulomatous reaction composed of neutrophils, plasma cells, multinucleated giant cells with or without areas of necrosis.

CASES SERIES

Case 1

A 50-year-old patient presented to the surgery outpatient department (OPD) with a right sided scrotal swelling for one month. Nil comorbid. There was no expansile cough impulse. Scrotal examination showed a non-tender right sided swelling with no rise in local temperature. The swelling was cystic with a positive fluctuation sign. Total leucocyte count and platelet count was elevated. Random blood sugar and fasting blood sugar was incidentally elevated (the patient was not a known diabetic). Scrotal ultrasound (USG) and doppler suggested a chronic hematoma in the right testis with right hydrocele. The differentials given were hematoma and carcinoma. The patient underwent right orchidectomy.

Grossly, the testis weighed 85 grams and measured 8×6×4 centimetres. Cut section of the testis showed a uniloculated cyst with a thickened corrugated wall measuring 4.5×4 centimetres filled with pultaceous material with? Testis identified peripherally in the wall. Microscopy revealed a thickened and fibrotic hydrocele sac with extensive ulceration of tunica replaced by a mat of necrotic debris admixed with neutrophils, plasma cells, foamy macrophages, and eosinophils with proliferating capillaries. Moderate transmural inflammation was seen which extended into the interstitium. Features of atrophy with smaller calibre seminiferous tubules showing a thickened hyalinized basement membrane, marked reduction of germ cell complement with predominance of Sertoli cells and internalisation of Leydig cells were seen. Interstitial fibroblastic proliferation was also noted along

with dense lymphoplasmacytic infiltrate, foam cells and an occasional giant cell. The inflammation was seen extending into the vasa efferentia and epididymis with cystic dilation of a few glands. A histologic diagnosis of XGO with infected? Hydrocele sac was given.

Case 2

A 68-year-old asthmatic with history of chronic constrictive pericarditis presented to the surgery OPD with right testicular pain and swelling for 18 days. He had a history of bilateral varicocele due to chronic left scrotal abscess and fibrosis for which he had undergone left scrotal exploration and orchidectomy four years prior to the present complaint. Workup for a right testicular neoplasm was done. General and systemic examination was normal. There was an elevated erythrocyte sedimentation rate and platelet count. Total leucocyte count was within normal limits. A pre-diabetic level of glycated haemoglobin was seen although the patient was not a known diabetic. Urinalysis revealed a white blood cell count of 2+ and a red blood cell count of 3+. Urine culture did not show growth. Aerobic culture from the site of the old scar showed growth of *Escherichia coli* (E. coli).

USG showed an ill-defined, partially exophytic, heteroechoic lesion involving the lower half of the right testis with internal vascularity suggestive of a neoplasm and right grade four varicocele. Right inguinal orchidectomy with excision of scrotal skin was done. Intraoperatively, an exophytic growth was seen in the right testis infiltrating the scrotal skin along the old scar. Pus was present at the base of the scrotum.

Gross examination showed a nodule over the scrotal skin weighing 53 grams measuring 6.5×5×4 centimetres. Cut section showed a well circumscribed white fibrous area along with yellow fatty and necrotic areas. The testis weighed 66 grams and measured 6.5×4.5×3 centimetres. Macroscopy showed a unifocal tumour composed of homogenous grey white areas, haemorrhagic specs and focal necrotic areas was seen (Figure 1). On microscopy, the scrotal skin nodule showed focally preserved stratified squamous layer overlying extensively oedematous fibrocollagenous and fibromuscular stroma with preserved adnexal structures, scattered lymphoplasmacytic infiltrate and congested blood vessels. The testis showed extensive xanthogranulomatous change comprising sheets and clusters of macrophages, histiocytes, lymphocytes, plasma cells, eosinophils, neutrophilic aggregates, and multinucleated foreign body giant cells surrounded by areas of neutrophilic necroinflammatory infiltrate and congested thin and thick wall vessels. Also seen were sclerosed seminiferous tubules, Leydig cell hyperplasia, interspersed rete testis and epididymis. There was no evidence of malignancy (Figure 2-4). A diagnosis of XGO with foreign body giant cell response was given along with oedematous serosal nodule.

Figure 1: Cut section of the testis shows homogenous grey-white areas, haemorrhagic specs, and focal necrotic areas.

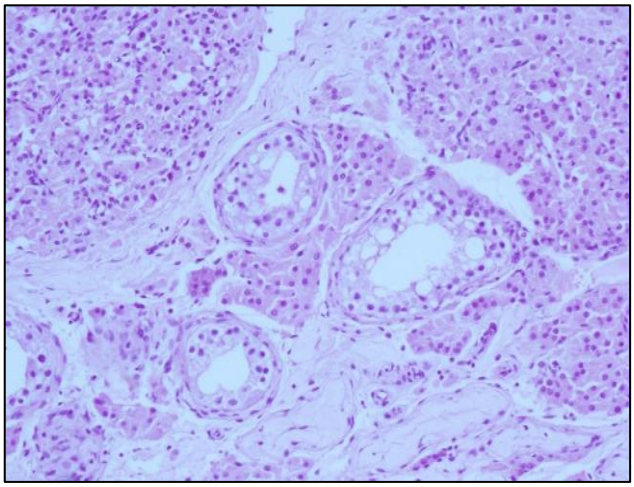

Figure 2: Hyperplastic Leydig cells with sclerosed seminiferous tubules (H and E, 100×).

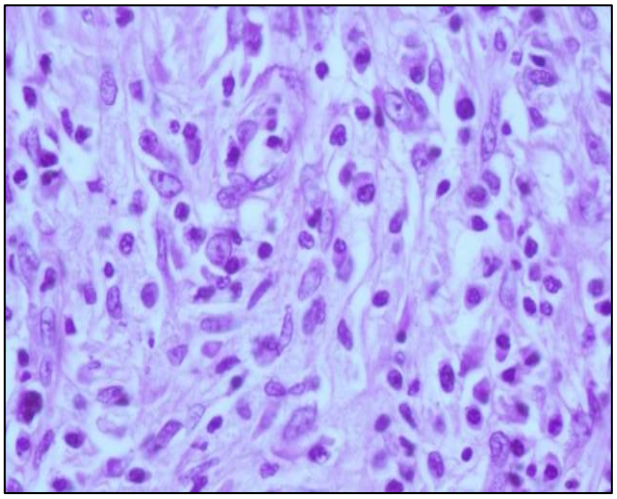

Figure 3: Granulomas surrounded by mixed inflammatory infiltrate H and E (400x).

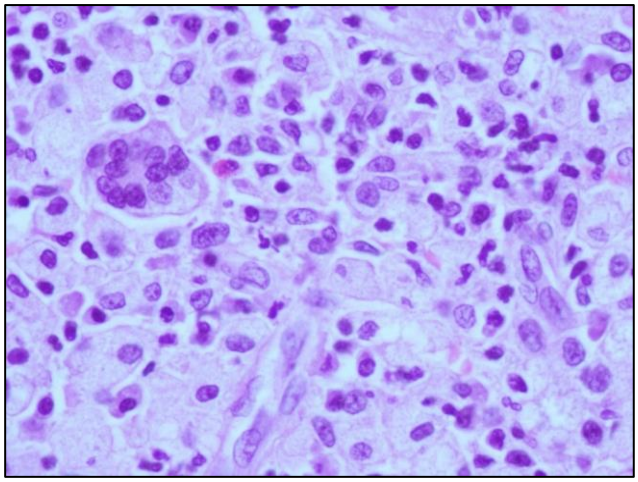

Figure 4: Giant cells with lipid-laden macrophages and inflammatory infiltrate H and E (400x).

Case 3

A sample of a referred case of a 60-year-old patient was sent to our pathology lab with a diagnosis of left chronic orchitis with sinus tract. No further clinical details were available. Grossly, the testis measured 11×7×5 centimetres. On cut section, a cystic lesion with extensive areas of grey white friable necrotic tissue measuring 6.2×4.5×5 centimetres, shows focally preserved testicular parenchyma was seen. A separately sent skin covered mass weighed 33 grams, and measured 6×5×3 centimetres. Cut section showed a tract measuring two centimetres in length surrounded by fibrous, necrotic, and haemorrhagic areas.

Histopathology revealed a fibrocollagenous stroma with dense inflammatory infiltrate, composed of sheets of foamy histiocytes, neutrophils and lymphoplasmacytic with areas of infarction, necroinflammatory debris, foci of calcification, cholesterol clefts and fibrous stroma. Also seen were hyalinized seminiferous tubules with Leydig cell proliferation, surrounded by foamy histiocytes. Foci of rete testis were seen. The tract showed keratinized stratified focally acanthotic squamous epithelium, overlying the dermis showing dense inflammatory infiltrate composed of neutrophils, lymphoplasmacytic and eosinophils with cholesterol clefts, ectatic and proliferating vessels in a fibrotic stroma. No granuloma was observed in the section studied. (Acid fast stain, Fite stain-negative).

DISCUSSION

Xanthogranulomatous inflammation (XGI) is an inflammatory, non-neoplastic disease that destroys and effaces normal structures of affected organs.[2] Testicular XGI is rare and was first reported in 2003 by Yap et al.[3] It has been reported to affect patients aged anywhere between 14 years to 70 years.[4,5] Cases have been reported across the globe in Asia, the Americas, Southwestern Europe, and Western Africa. XGI is commonly seen in the kidneys and gall bladder. Other organs that may be involved include the liver, appendix, urinary bladder, ovaries, prostate, epididymis, spermatic cord, and the testicles.[6]

The aetiology of XGO remains obscure and the exact pathogenesis of this condition is controversial.[7,2] Most theories and proposed mechanisms arise from the literature of XGI of the kidneys, a more familiar disease which is well-studied and widely reported. Rami et al expressed a relationship between impaired host immune response and persistent chronic inflammatory process in the presence of partial or complete obstruction. This process is influenced by lipid accumulation in macrophages as a consequence of abnormal lipid metabolism, immunological defect in macrophages, foreign materials, persistent chronic infection and local response to the tumour.[2] In contrast, Shimpei et al suggested ascending or haematogenous infection as the main cause of this condition. Nevertheless, a clear pathogenesis is still unknown.[8] Salako et al reported this condition to be associated with a self-immune reaction as a result of sperm extravasation, not clinically distinguishable from a neoplasm, however, exact aetiology remains elusive.[9]

Several risk factors have been implicated in the development XGO. One is a partial or complete obstruction of the spermatic cord which may be mechanical or functional. Mechanical obstruction may occur because of surgical procedures done on nearby structures. Alazab et al reported a case of a patient who had undergone a transurethral prostatectomy three years prior to the development of XGO.[2] Functional obstruction can be seen due to neuropathy as seen in spinal cord injury. Fernando et al reported a case of a patient with post-traumatic tetraplegia at C6 level who developed XGO twelve years post injury. The patient had neuropathic bladder, sphincter overactivity and loss of co-ordination with bladder function. Risk factors for tetraplegic patients developing XGO are reflux of urine into the vas deferens and indwelling urethral catheter both of which were present in this case. Spinal cord injury leads to dyssynergic voiding. As a result, there is high pressure reflux of urine into the vas caused by external urethral sphincter dyssynergia. Urethro-vasal reflux of infected urine is a sequel of indwelling catheter which stimulates detrusor muscle contractions and striated sphincter. This leads to retrograde extension from the urinary tract by common urinary pathogens (ascending infection).[10] Another report was of a patient who had a history of transurethral bladder resection for recurrent bladder carcinoma and later developed XGO.[7]

Ischemia to the testis is a significant risk factor. Testicular ischemia secondary to atherosclerosis may contribute to XGO in older patients. In younger patients, ischemia may be related to endophlebitis or endarteritis.[4] Blunt trauma to the testis is another risk factor for XGO.

Shimpei et al and Semire et al reported cases where each patient experienced blunt trauma to the scrotum and then developed XGO.[4,8] There were no signs of infection or obstruction, and urinalysis was normal. Shimpei explained two mechanisms: first, that macrophages infiltrate the hematoma caused by blunt trauma leading to XGO and secondly, that macrophages infiltrate the necrotic tissue which is produced because of blood vessel damage. There is a need for further study of these mechanisms.[8] The second case in the present study had a history of scrotal exploration and orchidectomy on the opposite side. This may have caused trauma to the affected side which may have led to the development of XGO. Another risk factor is chronic infective inflammation. XGI is an extensively damaging process of the testes which represents a phase in chronic suppurations where there is a localized proliferation of macrophages containing abundant phagocytic material. This occurs because of host microorganism interactions and stasis. The macrophages are associated with gram negative infection[10], most common of which is *E. coli*. Other associated organisms are *Pseudomonas aeruginosa*, *Bacteroides fragilis*, Actinomyces and bacillus Calmette-Guerin (after treatment of bladder cancer).[4,7] These microorganisms are typically negative on culture and pose a problem in identifying the inciting infective agent. This may perhaps be linked with preceding antibiotic therapy and the chronicity of the inflammation.[11] In the present study, the second case displayed growth of *E. coli* on aerobic culture from the wound from previous surgery. Sexually transmitted infections and urethral manipulation may also be implicated in the occurrence of XGO.[9]

Some conditions predispose to XGO such as genitourinary disease and DM. Diabetics are frequently immunocompromised and show a global dysfunction of polymorphonuclear neutrophils.[12] Leucocyte dysfunction in DM impairs the ability of phagocytes to effectively neutralize microorganisms. Xanthomatous reaction occurs consequently. This process is also seen in malakoplakia.[11] In the present study, two patients, although not known to be diabetics, showed elevated blood sugar levels which may have been a contributory factor in the development of XGO.

USG features characteristically show a heterogenous, hypoechoic mass or mixed echotexture with absent internal vascularity replacing the entire testis.[6,10,11] There may be areas of necrosis and purulent secretions along with thickening of cord or epididymis. These features may suggest an abscess or a neoplasm.[4] In the present study, the first case showed features suggestive of a hematoma in the testis with hydrocele. The second case showed a heteroechoic lesion with internal vascularity significant of a neoplasm. Hama et al reported multiple hypoechoic lesions suggesting multiloculated right testicular abscess with moderate hydrocele on ultrasound. Chest radiography and computed tomography (CT) of the abdomen do not show suspicious features.[3,9,11] Contrast enhanced CT may show features similar to that of USG with contrast studies showing moderate heterogeneous enhancement.[14] Magnetic resonance imaging may show a round tumour with a distinct boundary between the tumour and normal testicular tissue.[8] Conversely, it may also be seen as a complex cystic mass.[3] XGO is indistinguishable from neoplasm on radiology and a diagnosis cannot be made using this method alone.

An aggressive approach with partial or total transinguinal orchidectomy of the affected testis is the definitive course of treatment in most reported cases. This is because severe tissue destruction occurs because of tumorous XGI. Also, since the possibility of neoplasm is high, scrotal approach is not recommended. There are occasional cases where scrotal approach was used. Semire et al reported a case where scrotal approach was preferred as findings from the initial biopsy showed inflammatory cells and tumour markers were normal. The scrotum showed an abscess and fistulous lesions.[4] In the present study, all three cases underwent high inguinal orchidectomy.

Grossly, testes appear yellow on cut section with areas of necrosis. There is destruction of testicular parenchyma. Microscopy classically shows diffuse replacement of seminiferous tubules and interstitium by sheets of lipid-laden histiocytes (xanthoma cells), along with a granulomatous reaction composed of lymphocytes, neutrophils, macrophages, plasma cells and multinucleated giant cells. Areas of necrosis may or may not be present. Concurrent presence of malignancy may be present as reported by Val-Bernal et al wherein seminoma cells were present surrounded by a pseudocapsule which was continuous with XGO.[13] Pooja Sharma reported asteroid bodies in the cytoplasm of most of the giant cells and stated that extensive sampling or orchidectomy specimen should be done to exclude occult germ cell tumour. She also asserted that burnout seminomas or seminomas with a prominent granulomatous reaction may be misdiagnosed as idiopathic granulomatous orchitis and in such cases, germ cell neoplasia in situ must be looked for in residual seminiferous tubules. Concurrent malignancy was not identified in all three cases in the present study.

There are several conditions of which XGO is a mimic. Malacoplakia is a chronic granulomatous inflammation commonly affecting the genito-urinary tract. Microscopically, it is composed of clusters of von Hansemann's histiocytes which are foamy histiocytes with ample eosinophilic, granular cytoplasm and the pathognomonic Michealis-Gutmann bodies (laminated/ round/ targetoid basophilic spherules measuring between 1 µm and 10 µm in histiocytes).[15] This condition is most commonly associated with *E. coli*. All of our cases showed absence of Michealis-Gutmann bodies on microscopy which ruled out malacoplakia. Rosai-Dorfman disease depicts emperipolesis: histiocytes which have phagocytized mononuclear cells, typically positive

for S-100. No such cells were seen in All of our cases which rules out this condition. Infective orchitis can be caused by a multitude of organisms and can may appear like XGO. However, these infections usually subside with antibiotic therapy. Furthermore, tests for special stains can be performed. Acid fast staining can be performed to test for tuberculous orchitis. Fite stain can be performed to visualize for lepromatous bacilli. Periodic acid Schiff and Gomori Methenamine Silver staining can be done to observe various fungi. All these stains would be negative in XGO.

Finally, testicular tumours pose as the most significant differential for XGO. Generally, elevated serum tumour markers point towards testicular tumours although some tumours may not express these. Tumour markers were not performed in the cases in the present study. In XGO, histiocytes test positive for cluster of differentiation (CD) 34, CD68 and CD163 on immunohistochemistry. They test negative for S-100 which helps rule out Rosai-Dorfman disease. There is no literature on XGO related to prognosis of this disease. Further studies need to be done to ascertain the prognosis in this condition.

CONCLUSION

XGO is a rare, pseudoneoplastic condition with few reported cases in literature. Pre-operatively, it is seldom diagnosed as it is indistinguishable from testicular tumours solely based on physical and radiologic findings. Other aetiologies of scrotal masses must be excluded before a diagnosis of XGO is considered owing to the rarity of this pathologic finding. Focal XGO and epidermoid cyst have similar presentations. Testis salvage surgery should be taken into consideration is epidermoid cyst is suspected, noting the possibility of XGO. Adequate pathologic sampling with careful histopathologic examination is the gold standard for excluding neoplastic growths and confirming this diagnosis. Relying solely on imaging is not a substitute for surgical exploration and excision of abnormal cells and necrotic tissue as inflammation may be present with or without neoplasm. Due to the aggressive nature of this disease, total or partial orchidectomy with or without hemiscrotectomy is the recommended treatment of choice. Further studies are to ascertain the etiology of this disorder.

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