Original Article

Xanthogranulomatous epididymo-orchitis: A single-institutional case series and systematic review

Garima Vijayvergiya, Hanni Vasudev Gulwani*, Shariq Ul Hasan[1]

Departments of Pathology and [1]Urosurgery, Bhopal Memorial Hospital and Research Centre, Bhopal, Madhya Pradesh, India

*E-mail: hannigulwani@yahoo.com

ABSTRACT

Introduction: Xanthogranulomatous inflammation is a rare nonneoplastic and chronic inflammatory process, characterized by proliferation of foamy macrophages resulting in damage and necrosis of the affected tissue. Involvement of the testis/epididymis by the disease is a rare event.

Methods: A case series of four male patients diagnosed with xanthogranulomatous epididymitis/orchitis (XGEO) at our institute was reviewed. In addition, a systematic review of XGEO was carried out using PRISMA Guidelines 2020. Twenty-nine articles describing 38 patients of XGEO were included in the study.

Results: XGEO usually has a subacute or chronic presentation and affects male individuals in the 5th or 6th decades of life. The disease is also known to occur in the pediatric age group. The patients present with swelling, tenderness, or pain in the scrotal region. Bilateral involvement has also been documented. Thirty patients were known to have one or more causal risk factors including diabetes mellitus (23.7%), spinal cord injury/neuropathic bladder (7.9%), prostatectomy (7.9%), trauma (4.1%), and transurethral resection of prostate procedure (4.1%). Complications observed were scrotal fistula, adhesions, and abscess formation. Radiological features reported are nonspecific and include heterogeneous echotexture, hypoechoic areas, and/or scrotal wall collections. Bacterial microorganisms isolated from the affected tissue demonstrated the presence of *Escherichia coli, Pseudomonas aeruginosa,* and *Staphylococcus aureus.* Histological subtypes of XGEO are diffuse and focal. In the diffuse subtype, which is more common, there is extensive parenchymal destruction by inflammatory process accompanied by widespread ischemic necrosis.

Conclusion: The mainstay of treatment in XGEO cases is surgical excision preferably orchidectomy. Conservative management has been attempted in young individuals and in patients with focal XGEO, but there is limited supporting evidence. We present data of four cases along with detailed systematic review of the disease examining its clinicopathological behavior and associated risk factors followed by operative approach.

INTRODUCTION

Xanthogranulomatous inflammation (XGI) is a rare nonneoplastic and chronic inflammatory process, characterized by damage and necrosis of the affected tissue that is replaced with foamy macrophages.[1] The kidney and gallbladder are the most commonly affected organs; other less affected sites include urinary bladder, appendix, and liver.[2-5] Rarely involved organs include male and female genital tract, wherein testes, prostate, epididymis, ovary, uterus, and fallopian tube may be infiltrated by XGI.[6] Four cases of xanthogranulomatous epididymitis/orchitis (XGEO) diagnosed at our institute were described. In addition, a systematic review and detailed analysis of XGEO and funiculitis was done. The data for this rare entity are available in medical literature only as case reports and case series.

Access this article online	
Quick Response Code:	Website: www.indianjurol.com
	DOI: 10.4103/iju.iju_270_22

Received: 28.07.2022, **Revised:** 05.11.2022,

Accepted: 10.12.2022, **Published:** 29.12.2022

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

MATERIALS AND METHODS

The institutional ethics committee approved the retrospective study. All the orchidectomy specimens submitted for histopathology and diagnosed as XGEO, between January 2000 and January 2022, were screened for inclusion in the study. Testicular and epididymal biopsies were excluded from the study. Two histopathologists independently reviewed the cases and confirmed the diagnosis based on the morphological features of the XGEO. A total of four cases were identified that are described in detail. Xanthogranulomatous involvement of prostate was not included in the study.

Retrospective data were collected from the patient's record files and analyzed for various clinical parameters including patient's age, ethnicity, clinical presenting signs and symptoms, laboratory investigations, serum tumor markers, radiological findings, perioperative findings, postoperative management, gross and microscopic histopathological examination, and follow-up of the patient.

Surgical specimens were fixed in 10% neutral buffered formalin. All the tissue sections were stained with routine hematoxylin and eosin stain and special stains such as Ziehl–Neelsen, lepra stain, periodic acid-Schiff (PAS), and Gomori's silver methenamine stains. The immunohistochemical study was carried out using 3-µm-thick sections on poly-L-lysine-coated slides by standard horseradish peroxidase technique. Primary antibodies against CD-68 (Ready to use-RTU; Thermo scientific, Monoclonal antibody, USA) and placental alkaline phosphatase (PLAP; RTU; Leica Biosystem; New UK) were performed in all the cases.

In addition, a comprehensive search of medical English literature was performed using the PRISMA guidelines 2020[7] [Figure 1]. An extensive systematic review search was conducted in PubMed, Web of Science (Clarivate Analytics), Ovid (Medline), and Google Scholar. The articles included were case reports, case series, and letters to the editor containing all the information including the clinical presentation, diagnosis, and treatment of the disease.

RESULT

Case 1

A 58-year-old hypertensive male presented with chief complaints of mild fever, swelling, and pain in the right scrotal region for 15 days. He was a known case of diabetes mellitus (DM), on oral hypoglycemics. The swelling was tender with reddened skin on physical examination. The routine hematology, biochemical investigations, and serum tumor markers were within normal limits. Ultrasonography (USG) scrotum showed 2–3 loculated heteroechoic areas likely suggestive of abscess. Minimal

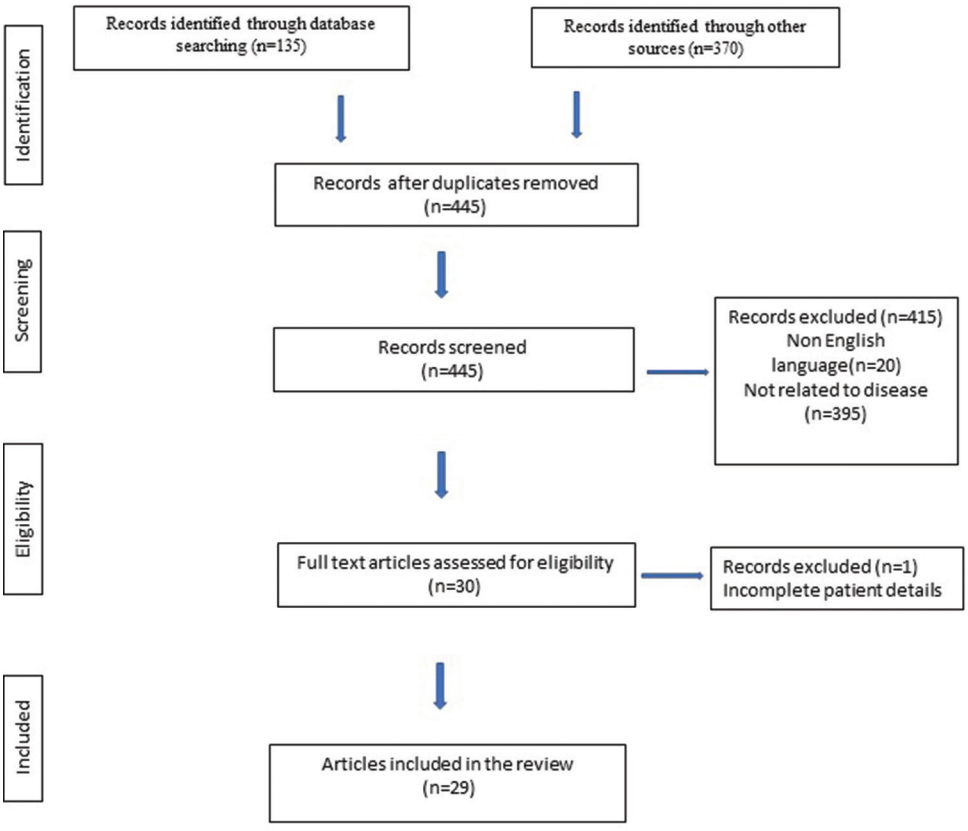

Figure 1: Flowchart of systematic literature review

right-sided hydrocele with internal septations was also noted [Figure 2a]. right orchidectomy was performed. Intraoperatively, pus was present in the right scrotal cavity that was sent for culture and sensitivity. The culture grew coagulase-positive *Staphylococcus aureus*. On gross examination, testicular tissue was shrunken and exhibited necrotic and yellowish areas. Microscopic examination showed diffuse replacement of testicular parenchyma and epididymis by sheets of foamy histiocytes admixed with numerous lymphocytes and plasma cells along with neutrophilic abscess formation. Inflammation was also extending to the adjacent paratesticular fibrofatty tissue. The report suggested a diagnosis of xanthogranulomatous epididymo-orchitis with superadded acute infection.

Case 2

A 43-year-old male presented with complaints of right-sided scrotal swelling associated with pain and fever for 10 days. On physical examination, there was right-sided scrotal enlargement with mild tenderness and raised temperature. The left testis was unremarkable. He was started on oral antibiotics for 1 week without any symptomatic relief. He did not have any history of urinary complaints or physical trauma. His white blood cell count was raised to 15,200/cumm. On routine biochemistry investigations, HbA1c was elevated (11.4%) and random blood sugar was >250 mg/dl. He was diagnosed to have type 2 DM and was started on oral metformin. Urine culture was negative. USG of the scrotum showed moderate amount of loculated collection with fine echoes and edematous thickening of the right-sided scrotal wall likely suggestive ofa Septated hydrocele or a Pyocele. Right orchidectomy was performed. Intraoperative findings revealed a thickened edematous sac filled with pus and necrotic testis [Figure 2b]. On gross examination, the testis was shrunken and necrotic. Firm yellowish nodular deposits were observed in the right testis and epididymis [Figure 2c]. On microscopic examination, sheets of foamy histiocytes were observed in the epididymis that were admixed with plasma cells, eosinophils, and lymphocytes [Figure 3a and b]. Immunohistochemical stain for CD68 was performed that highlighted the foamy histiocytes [Figure 3c]. These findings were suggestive of xanthogranulomatous epididymitis.

Case 3

A 46-year-old male presented with complaints of left-sided testicular swelling for 2 months. The patient did not have a history of urinary symptoms, trauma, sexual contact, or diabetes. On physical examination, the lesion was firmly adhered to scrotal skin. The right testis was unremarkable. Routine hematology, biochemical investigations, and serum tumor markers were within normal limits. Contrast-enhanced computed tomography revealed a left testicular mass suggestive of neoplastic etiology with intra-abdominal lymphadenopathy. Inguinal orchidectomy with excision of the adhered scrotal skin was performed. Gross examination revealed replacement of testicular tissue by necrotic and firm yellowish white areas. Microscopic examination showed almost complete destruction of testicular parenchyma and epididymis by inflammatory infiltrate comprising many foamy histiocytes, plasma cells, lymphocytes, few neutrophils, and eosinophils along with multinucleated giant cells. At places, granulation tissue formation was evident. Most of the seminiferous tubules (ST) were hyalinized with thickened basement membrane. There were areas of fibrosis and lymphoid aggregates [Figure 4a]. The inflammation was extending up to the dermoepidermal junction of the scrotal skin with fat necrosis in surrounding

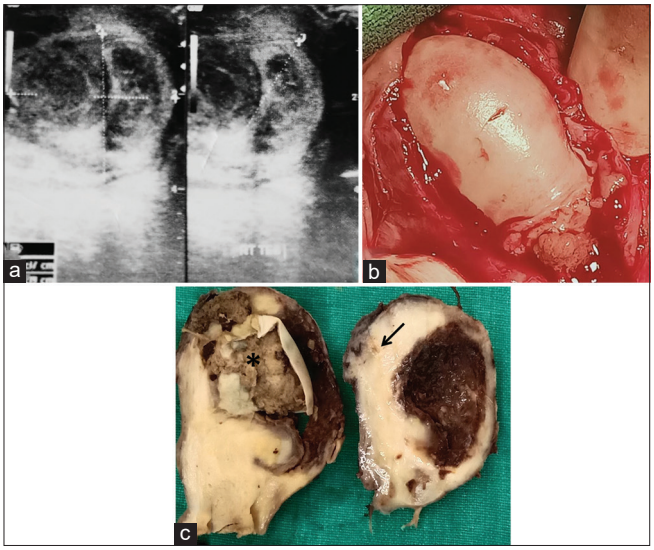

Figure 2: (a) USG shows heterogeneous hypoechoic areas with diffuse involvement of testis, (b) intraoperative photograph shows pus collection in the scrotal cavity and epididymis, (c) gross photograph of resected orchidectomy specimen showing necrotic and shrunken testis (marked with asterix) surrounded by thickened fibrotic and yellowish-white deposits in paratesticular region (marked with arrow). USG: Ultrasonography

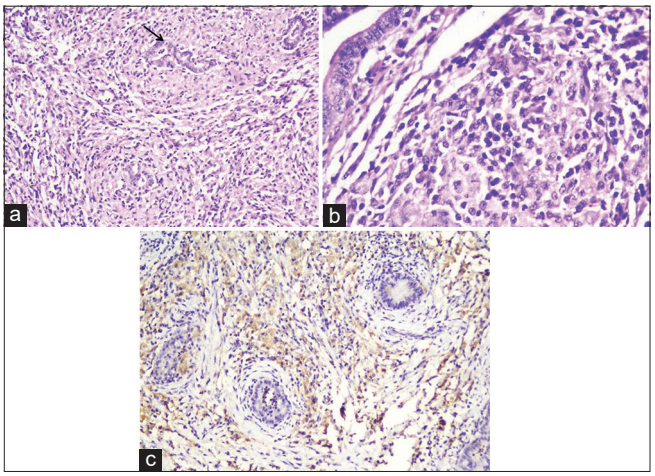

Figure 3: (a) Photomicrograph of case with xanthogranulomatous epididymitis showing interstitial proliferation of foamy histiocytes resulting in compression of the epididymal tubules (marked with arrow; H and E, ×20), (b) high-power view demonstrating presence of plasma cells, and lymphocytes amidst collections of foamy histiocytes (H and E, ×40), (c) immunohistochemical stain for CD68 highlighting the foamy histiocytes (×20)

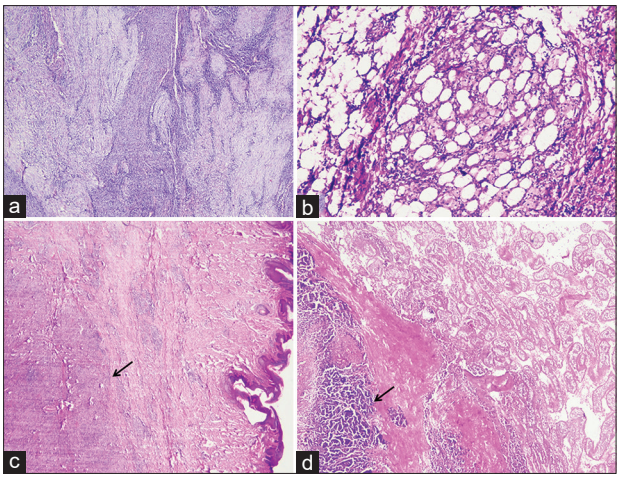

Figure 4: Representative image from XGEO case showing (a) areas of extensive fibrosis replacing the parenchymal tissue (H and E, ×4), (b) fat necrosis evident in paratesticular region (H and E, ×20), (c) XGI (marked with arrow) extending to the dermoepidermal junction of the scrotal skin (H and E, ×4), (d) widespread Ischemic necrosis involving testicular parenchyma and neutrophilic abscess formation (marked with arrow; H and E, ×4). XGEO: Xanthogranulomatous epididymitis/orchitis, XGI: Xanthogranulomatous inflammation

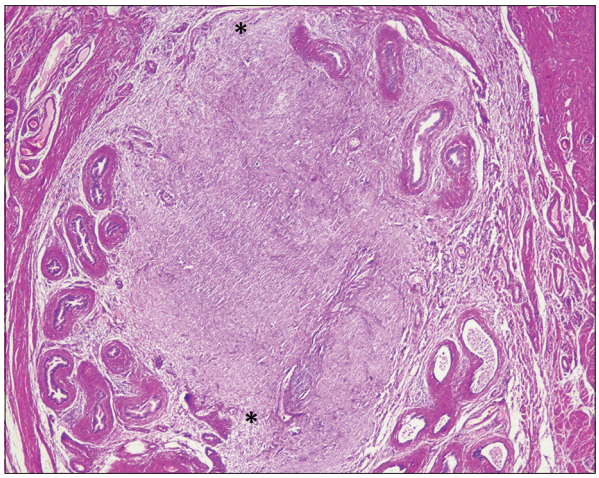

Figure 5: A case of focal XGE-low power photomicrograph showing a well-circumscribed nodular deposit of foamy macrophages replacing the epididymal tubules (boundaries marked with asterix; H and E, ×2). XGI: Xanthogranulomatous inflammation

adipose tissue [Figure 4b and c]. Extensive ischemic necrosis of testicular parenchyma was noted along with the presence of neutrophilic abscesses [Figure 4d]. These findings were suggestive of xanthogranulomatous epididymo-orchitis.

Case 4

A 65-year-old male with advanced-stage prostatic carcinoma underwent bilateral inguinal orchidectomy for hormonalmanipulation. Routine hematology and biochemical investigations were within normal limits. Both the testes and left epididymis were grossly unremarkable. The right epididymis revealed a focal firm yellowish nodular area measuring 0.5 cm × 0.3 cm. Section examined from the epididymal nodule revealed collection of foamy histiocytes admixed with few lymphocytes and plasma cells [Figure 5]. The histologic findings were consistent with incidental focal xanthogranuloma of the epididymis. There was no evidence of any primary or secondary malignancy in resected specimen.

All the above cases were analyzed by two independent histopathologists. Other differential diagnoses were ruled out. Special stains were performed in all cases that included Ziehl–Neelsen stain for acid-fast bacilli, PAS, and silver stain for fungal organisms and lepra stain. There was no evidence of any organism or malignancy after meticulous slide analysis in any of the cases described above. The postoperative course was uneventful in all the cases and the follow-up period ranged from 6 months to 4 years.

DISCUSSION

XGI is a chronic suppurative destructive disease process that involves host factors, stasis, and microbiological organisms, leading to localized proliferation of macrophages.[6,8] XGI of male genital organs has been rarely reported in medical literature and it may affect testicles, epididymis, spermatic cord, and prostate.[2] The first case of xanthogranulomatous epididymitis was reported in 1987 by Wiener *et al.*[9]

XGEO is a rare disease process with a description of 38 cases reported in 29 articles in medical literature.[1,2,6,8-32] The details of demographics and clinical profile of the patients are summarized in Table 1. Most of these cases have been reported from the Asian continent (n = 18), followed by Europe (n = 13), North America (n = 3), Africa (n = 2), and 1 case each from South America and Australia. Most patients presented during the 5th and 6th decades with a median age being 52 years (range 13–93 years); 2 (5.3%) were pediatric (<18 years) and 36 (94.7%) were adults. Although there is a predilection for middle-aged adults.; the disease may even affect adolescent boys.[24,25] The youngest case reported was a 13-year-old boy.[24] In the present study, all the males were of Indian origin and in the 5th and 6th decades of life. The most common presenting symptom reported among these cases was testicular swelling (84.2%), followed by pain (65.7%), fever (21%), and discharging sinus (14.6%). Subacute (10 days–1 month; 47%) and chronic (2 month–1 year; 31.5%) presentations were more frequent than acute (1–7 days; 18.4%). Predisposing risk factors described were the presence of DM (23.7%),[12,13,19,21,24-26] spinal cord injury/neuropathic bladder (7.9%),[10,12] prostatectomy (7.9%),[11,12] trauma (4.1%),[25,27] and transurethral resection of prostate (TURP) procedure (4.1%).[5,31] Two of the four patients in the present study had DM and one of them had been earlier operated for prostatic carcinoma. The disease may rarely be detected incidentally, as was observed in one of our cases in which prophylactic bilateral orchidectomy was done as a part of hormonal treatment for prostate

Table 1: Data from the 29 studies included in the systematic review

	Authors name and year	Number of cases	Country	Age (years)	Laterality and site	Symptom onset	Associated factors	Microorganisms in pus culture	Type of surgery
1	Wiener *et al.*, 1987[9]	1	United State	60	Bilateral epididymis	Chronic (2 months)	DM	*E. coli* and *B. fragilis*	Bilateral epididymectomy
2	Vaidyanathan *et al.*, 2000[10]	1	United Kingdom	21	Left testis, epididymis and spermatic cord	Acute	Spinal cord injury/neuropathic bladder, recurrent UTI	NS	Orchidectomy
3	Matsuoka *et al.*, 2001[11]	1	Japan	70	Right epididymis	Acute (5 days)	Prostatectomy	*P. aeruginosa*	Orchidectomy
4	Hajri *et al.*, 2001[12]	7	France	30–75	Left testis and epididymis	Subacute	DM	No organism	Orchidectomy
					Left testis and epididymis	Subacute	DM	No organism	Orchidectomy
					Left testis and epididymis	Subacute	DM	No organism	Orchidectomy
					Left testis and epididymis	Subacute	Prostatectomy	No organism	Orchidectomy
					Left testis and epididymis	Subacute	Prostatectomy	No organism	Orchidectomy
					Right testis and epididymis	Subacute	Spinal cord injury/neuropathic bladder	No organism	Orchidectomy
					Right testis and epididymis	Subacute	NA	No organism	Orchidectomy
5	Nistal *et al.*, 2004[13]	2	Spain	58	Left spermatic cord	NA	DM	Actinomycosis	Orchidectomy
				79	Left testis and epididymis	NA	NA	*E. coli*	Orchidectomy
6	Demirci *et al.*, 2004[14]	1	Turkey	21	Left testis	Subacute (15 days)	NA	NS	Orchidectomy with hemiscrotectomy
7	Yap *et al.*, 2004[15]	1	United State	64	Left testis	Acute (2 days)	NA	NS	Orchidectomy
8	Salako *et al.*, 2006[16]	1	Nigeria	24	Left testis	Chronic (9 months)	UTI	NS	Orchidectomy
9	Al-Said *et al.*, 2007[17]	1	Qatar	44	Right testis	Subacute (3 weeks)	NA	Mixed growth	Orchidectomy
10	Hill *et al.*, 2008[18]	1	United State	68	Left testis, epididymis	Acute (1 week)	BCG installation instrumentation or ischemia	*E. coli*	Orchidectomy
11	Kang *et al.*, 2007[19]	3	Korea	93	Left epididymis	Subacute (15 days)	NA	NS	Orchidectomy with hemiscrotectomy
				68	Right epididymis	Acute (1 day)	Benign prostatic hyperplasia	NS	Right epididymectomy and vasectomy
				53	Left epididymis	Subacute (20 days)	DM	NS	Left orchidectomy
12	Persec *et al.*, 2008[20]	1	Croatia	72	Right epididymis	Subacute (10 days)	UTI, arterial hypertension	*E. coli*	Right orchidectomy
13	Rifat Mannan *et al.*, 2009[21]	1	Kuwait	65	Left testis	Chronic (1 year)	DM	NS	Orchidectomy
14	Val-Bernal *et al.*, 2010[22]	1	Spain	52	Left testis and epididymis	Chronic (4 months)	NA	NS	Orchidectomy with hemiscrotectomy
15	Val-Bernal *et al.*, 2012[8]	1	Spain	55	Bilateral testis and epididymis	Chronic	Spinal cord injury or neuropathic bladder	*P. aeruginosa* or *E. coli*	Bilateral orchidectomy
16	Çakır *et al.*, 2011[23]	1	Maltya	34	Right testis and epididymis	Chronic (4 months)	NA	NS	Right orchidectomy
17	Rapetto *et al.*, 2012[24]	1	Italy	13	Bilateral testis, epididymis and spermatic cord	Chronic (2 months)	NA	NS	Frozen biopsy specimen
18	Ezer *et al.*, 2013[25]	1	Turkey	14	Right testis and epididymis	Subacute (10 days)	Trauma	*P. aeruginosa*	Scrotal orchidectomy and hemiscrotectomy
19	Parihar and Sharma, 2016[26]	1	India	61	Bilateral testis, epididymis, spermatic cord	Chronic (2 months)	DM	NS	Bilateral orchidectomy
20	Alazab *et al.*, 2017[5]	1	Jordan	69	Right testis	Chronic (6 months)	TURP procedure	NS	Orchidectomy
21	Yamashita *et al.*, 2017[27]	1	Japan	28	Left testis	Subacute (1 month)	Trauma	NS	Enucleation

Contd...

Table 1: Contd...

	Authors name and year	Number of cases	Country	Age (years)	Laterality and site	Symptom onset	Associated factors	Microorganisms in pus culture	Type of surgery
22	Ting *et al.*, 2018[28]	1	USA	66	Right epididymis	Chronic (1 year)	Immunocompromised HIV/TB	NS	Partial epididymectomy and bilateral hydrocelectomy
23	Somani *et al.*, 2019[29]	1	India	20	Left testis	Chronic (3 months)	NA	NS	Orchidectomy
24	Gongora *et al.*, 2019[30]	1	Brazil	55	Right testis	Chronic (1 year)	DM hypertension	NS	Orchidectomy
25	Hama *et al.*, 2019[1]	1	Iraq	70	Right testis	Subacute (1 month)	DM	*E. coli*	Orchidectomy
26	Sharma *et al.*, 2019[2]	1	India	60	Left testis	Chronic (1 year)	NA	NS	Orchidectomy
27	Murshed *et al.*, 2020[31]	1	Qatar	42	Left testis, epididymis	Subacute (1 month)	NA	NS	Simple orchidectomy along with drainage of scrotal wall abscess
28	Bapir *et al.*, 2022[6]	1	India	35	Right testis, epididymis	Subacute (3 weeks)	NA	*E. coli*	Orchidectomy
29	PattenPattenden *et al.*, 2022[32]	1	Australia	77	Right testis	Acute	Recurrent UTI	*E. coli*	Simple right orchidectomy plus abscess drainage

E. coli = *Escherichia coli*, *B. fragilis* = *Bacteroides fragilis*, *P. aeruginosa* = *Pseudomonas aeruginosa*, NA = Not available, NS = Not specified, DM = Diabetes mellitus, UTI = Urinary tract infection, BCG = Bacillus Calmette–Guérin, TURP = Transurethral resection of prostate, TB = Tuberculosis

cancer. Physical examination findings in patients revealed tenderness in 37%, erythema in 21%, and palpable mass in 15.8% of cases. The swelling was indurated in 17% of the cases. Unilateral involvement was more common (left [53%] > right [37%]). Bilateral testicular involvement with paratesticular extension is uncommon but has been described in four cases.[5,8,9,24] Of these, two had poorly controlled type 2 DM and another one had spinal cord injury with neuropathic bladder. XGI involvement of the testis is usually a chronic destructive process that leads to extensive necrosis of testicular parenchyma and/or surrounding structures. However, in some of the cases, focal involvement may be seen (13.1%).[9,13,27,28] One of the cases in our series also revealed focal XGI involving epididymis.

Laboratory and radiological findings

Routine hematology and biochemistry investigations revealed leukocytosis in 23.7% and raised CRP levels in 15.8% of the patients. Other laboratory parameters and serum tumor markers were within normal limits. In our case series, one of the patients also showed leukocytosis. USG of the scrotum is usually performed as an initial radiological investigation. CT/MRI is performed in cases with strong suspicion of malignancy. USG findings were available in 29 out of 38 reported cases. The findings observed were heterogeneous echotexture (50%), hypoechoic areas (28.9%), scrotal wall collection (10.8%), hydrocele (10.8%), reduced vascularity (7.9%), and calcifications (7.9%). The greatest dimension of lesion size varied from 1.5 cm to 10.9 cm (mean: 3.6 cm). One case each was suggested as torsion of testis[30] and epidermoid cyst.[27] Suspicion of malignancy was suggested in 21% of cases on USG. CT scan was performed in three of these cases and MRI in two cases. In the present study, two of the cases showed heterogeneous hypoechoic areas on USG and one of the cases was suspicious of malignancy even on CT scan. Superadded acute infection may result in abscess formation and increased vascularity on USG. Imaging features are not diagnostic of XGEO, since similar findings may be observed in several other benign, infective, and neoplastic conditions.

Pathophysiology

Even though the etiopathogenesis of XGI is not very clear. ; some contributing factors are obstruction, immune system dysfunction, and abnormal lipid metabolism. DM (23.7%) remains one of the most common predisposing risk factors in patients with XGEO.[12,13,19,21,24-26] It is well known that diabetes leads to weakened immune response with leukocyte dysfunction, phagosome abnormality, and lesser chemotaxis, resulting in proliferation of organisms.[33]

Mechanical obstruction has been proposed as one of the major causative host factors. Obstruction of the epididymis or spermatic cord may lead to stasis with extravasation of sperms. Sperms initiate the immune response and macrophages reach the site of stasis to start the disease

process. Around 13% of patients with XGEO were reported to have a prior history of TURP or prostatectomy, which may also predispose to obstruction of male genital tract.[8,11,12,31] Similarly, mechanical obstruction of the urinary tract causes urinary tract infection along with resultant retrograde reflux of urine into the male genital system, leading to initiation of inflammatory process. Some of the authors have supported infective etiology as an initial cause, leading to accumulation of histiocytes. Eight cases reported isolation of *Escherichia coli* in culture and 3 cases showed the presence of *Pseudomonas aeruginosa*.[1,6,8,9,11,13,17,18,20,25,32] Although Gram-negative bacterial infection is common, in one of our cases, Gram-positive *Staphylococcus aureus* was isolated in culture. Role of *Staphylococcus aureus* in the pathogenesis of xanthogranulomatous adrenalitis has also been emphasized by one of the authors.[34] Blunt trauma in the testis may lead to XGEO through the invasion of macrophages in response to trauma-induced hematoma[25,27] Testicular ischemia secondary to hypertensive arteriosclerosis in adults and in children after endarteritis has also been reported in cases with XGEO. At the site of tissue damage, there is an increased expression of monocyte chemoattractant protein-1 (MCP-1) and interleukin 6 (IL-6). MCP-1, a key chemokine, initiates chemotaxis due to which migration and accumulation of macrophages occurs at the site.[35] Other inflammatory cells including lymphocytes and plasma cells also accompany the macrophages. It has been documented in orbital xanthogranulomatous disease that TIMP signaling pathway is activated in macrophages by stimulating the phosphorylation of JAK2 and STAT3. The authors also reported an increased level of IL-17 and interferon-gamma in the affected tissues.[36]

Histopathology

On gross examination, the testis was shrunken in most of the cases due to ischemic necrosis, whereas in some of the cases, enlargement was noted. Firm yellowish spots (28.9%) were observed in the affected area including testis and/or epididymis. In addition, there were areas of cystic change (7.8%). Predominant involvement of the testis was observed in 12 cases, followed by isolated XGI of the epididymis in 7 cases. Focal XGI of the spermatic cord was seen in 1 case.[13] Extensive involvement affecting testis, epididymis, and spermatic cord was observed in 3 cases.[10,24,26] Diffuse XGEO was noted in 15 cases.

Characteristic histomorphologic features were infiltration in interstitial tissue with compression of ST or epididymal tubules, destruction of testicular parenchyma, and replacement by diffuse proliferation of sheets of foamy macrophages. Accompanying inflammatory cells were lymphocytes (92%), plasma cells (65.85%), neutrophils (47%), and eosinophils (10.5%). Multinucleated giant cells were observed in 23.6% of the cases. Other morphological findings observed were fibrosis (29%), necrosis (26%), microabscess formation (26%), and inflammatory granulation tissue (5%). Extension of inflammation to paratesticular soft tissues was observed in 18% of the cases. Testicular atrophy with hyalinization of ST and reduction or loss of spermatogenesis and replacement by Sertoli cells was observed in 7.9% of the cases.

XGI results in the formation of abscess cavities, which are predominantly lined by foamy macrophages intermixed with inflammatory cells, including lymphocytes, plasma cells, and neutrophils. These macrophages contain lipid-rich material that gives a yellowish appearance on gross examination.[8] The inflammatory process is usually initiated in the interstitium and results in destruction of native parenchymal tissue with compression of adjacent seminiferous/epididymal tubular structures.[31] Although XGI is considered as a benign and chronic inflammatory disease, superadded bacterial infection may lead to multiple microabscess formation that exacerbates the condition.

Differential diagnosis

The more common diseases that need to be considered in the differential diagnoses include bacterial epididymo-orchitis, tubercular epididymo-orchitis, genitourinary sarcoidosis, hernia with hydrocele, and testicular neoplasm. Clinical workup to rule out tubercular epididymo-orchitis should be carried out especially for cases in developing countries. The theoretical role of seeding of cancer to skin and lymph nodes has resulted in a limited role of fine needle aspiration cytology (FNAC) in testicular malignancies.[37] FNAC has, however, proved to be an essential tool for the diagnosis of tubercular epididymo-orchitis as documented in several case reports and thus prevention of inadvertent orchidectomy.[38,39] Cytopathological diagnosis of xanthogranulomatous pyelonephritis and cholecystitis through USG-guided FNAC has been reported in literature and FNA could prove a useful tool for preoperative diagnosis of XGEO as well.[40]

Benign histiocytic proliferation may be observed in lesions such as Rosai–Dorfman disease, malakoplakia, tuberculosis, leprosy, and idiopathic granulomatous orchitis.[5,22]

Management

A trial of broad-spectrum intravenous and/or oral antibiotics (3rd generation cephalosporin) for 1–3 weeks was given to 19 patients in view of clinical suspicion of infective epididymo-orchitis. In two of our cases, preoperative antibiotics was given. Surgical exploration was planned in the patients when no improvement was noted despite medication. Operative procedures performed in reported cases were as follows: orchidectomy was done in 28 patients, orchidectomy with scrotal abscess drainage was carried out in 2 patients, orchidectomy with hemiscrotectomy was performed in 4 patients, epididymectomy in 1 patient, partial epididymectomy with bilateral hydrocelectomy in 1 patient, epididymectomy and vasectomy in 1 patient, and enucleation

of mass in 1 patient. Intraoperative findings observed were collection of pus forming abscesses (34.2%), scrotal fistula formation with involvement of scrotal skin (15.7%), and paratesticular adhesion (13.1%). Intraoperative frozen section was submitted in three patients. The youngest boy (aged 13 years) in the study analysis was diagnosed to have inflammatory xanthogranulomatous orchitis with bilateral involvement on frozen section examination.

The diagnosis of XGEO is unexpected. Although orchidectomy is a definitive treatment, especially in extensive and diffuse lesions of XGEO, cases with focal or nodular involvement may be managed conservatively. In one of the case reports from Italy, conservative management was attempted in a 13-year-old boy with bilateral lesions on USG.[24] He was kept on regular follow-up and USG scan performed after 2 years revealed marked reduction in size of the lesion. In another instance, focal XGO followed blunt testicular trauma. Enucleation of the lesion was successfully performed, salvaging the testis.[27] The role of pathologist remains crucial since the intraoperative diagnosis provided on frozen sectioning can guide the operating surgeon to plan the extent of resection.[17,24,28] Postoperative follow-up ranging from 2 months to 4 years was available in 23 patients and was uneventful in all including the cases in the present study.

CONCLUSION

Despite the rarity of the reported cases of XGEO in medical literature, the actual prevalence of the disease may be higher. The worldwide incidence of type 2 DM has risen and this metabolic condition poses a significant risk among males for the development of XGEO. Careful histopathological examination with adequate sampling is the gold standard for confirmation of diagnosis. Not every patient is a candidate for orchidectomy and conservative measures can be attempted for management in selected cases.

REFERENCES

1. Hama Amin Said S, Abdalla RY, Aghaways I, Abdullah AM. Xanthogranulomatous orchitis: Review of the published work, and report of one case. Urol Case Rep 2019;27:100908.
2. Sharma P, Ramteke P, Satapathy A, Ray MD. Xanthogranulomatous orchitis presenting as a scrotal mass in an elderly male: Malignancy or mimicker? Clin Med Insights Case Rep 2019;12:1179547619890295.
3. Kim SW, Yoon BI, Ha US, Sohn DW, Cho YH. Xanthogranulomatous pyelonephritis: Clinical experience with 21 cases. J Infect Chemother 2013;19:1221-4.
4. Azari FS, Kennedy GT, Bormann B, Braslow B, Tondon R, Lee K 4th. A contemporary analysis of xanthogranulomatous cholecystitis in a Western cohort. Surgery 2021;170:1317-24.
5. Alazab RS, Ghawanmeh HM, Al-Okour RK, Alshammari A, Lafi T, Al-Karasneh AI, *et al.* Xanthogranulomatous orchitis: Rare case with brief literature review. Urol Case Rep 2017;13:92-3.
6. Bapir R, Ali RM, Hussien DA, Omar DA, Kakamad FH, Salih AM, *et al.* Xanthogranulomatous epididymo-orchitis: A case report with review of the literature. Int J Surg Case Rep 2022;92:106832.
7. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
8. Val-Bernal JF, Argueta L, Fernández-Flórez A, Correas MA, Val D, Garijo MF, *et al*. Bilateral xanthogranulomatous orchitis in a tetraplegic patient. Pathol Res Pract 2012;208:62-4.
9. Wiener LB, Riehl PA, Baum N. Xanthogranulomatous epididymitis: A case report. J Urol 1987;138:621-2.
10. Vaidyanathan S, Mansour P, Parsons KF, Singh G, Soni BM, Subramaniam R, *et al.* Xanthogranulomatous funiculitis and epididymo-orchitis in a tetraplegic patient. Spinal Cord 2000;38:769-72.
11. Matsuoka K, Yano H, Inoue M, Iida S, Hirabayasi Y, Noda S. Xanthogranulomatous epididymitis. BJU Int 2001;87:275-6.
12. Hajri M, Amna MB, Derouich A, Ayed M, Zermani F, Jilani SB. [Xanthogranulomatous orchitis. Report of 7 cases]. Ann Urol (Paris) 2001;35:237-9.
13. Nistal M, Gonzalez-Peramato P, Serrano A, Regadera J. Xanthogranulomatous funiculitis and orchiepididymitis: Report of 2 cases with immunohistochemical study and literature review. Arch Pathol Lab Med 2004;128:911-4.
14. Demirci D, Ekmekçioglu O, Soyuer I, Emirdogan M. Xanthogranulomatous orchitis with scrotal fistulas. Int J Urol 2004;11:686-8.
15. Yap RL, Jang TL, Gupta R, Pins MR, Gonzalez CM. Xanthogranulomatous orchitis. Urology 2004;63:176-7.
16. Salako AA, Olasode BJ, Eziyi AK, Osasan SA. Xanthogranulomatous orchitis in an adult Nigerian. Int J Urol 2006;13:186-8.
17. Al-Said S, Ali A, Alobaidy AK, Mojeeb E, Al-Naimi A, Shokeir AA. Xanthogranulomatous orchitis: Review of the published work and report of one case. Int J Urol 2007;14:452-4.
18. Hill JR, Gorgon G, Wahl SJ, Armenakas NA, Fracchia JA. Xanthogranulomatous orchitis in a patient with a history of instrumentation and bacillus Calmette-Guérin therapy. Urology 2008;72:3.e11-3.
19. Kang TW, Lee KH, Piao CZ, Yun KJ, Joo HJ, Park KS, *et al.* Three cases of xanthogranulomatous epididymitis caused by *E. coli*. J Infect 2007;54:e69-73.
20. Persec Z, Bulimbasic S, Persec J, Ljubanovic D, Bartolin Z, Patrlj L, *et al*. Xanthogranulomatous epididymitis: Clinical report and immunohistochemical analysis. Wien Klin Wochenschr 2008;120:366-9.
21. Rifat Mannan AA, Kahvic M, Abu Sara Y, Bharati C. An unusual case of extensive xanthogranulomatous orchitis in a diabetic patient. Med Princ Pract 2009;18:418-21.
22. Val-Bernal JF, González-Márquez P, Ramos-Barseló E, Portillo JA. Concurrent xanthogranulomatous orchiepididymitis and seminoma in the same testis. Pathol Int 2010;60:55-8.
23. Çakır A, Şamdancı E, Beytur A, Nurkabul Z, Aydın NE. Xanthogranulomatous epididymo-orchitis. Inonu Uni Med Faculty Journal 2011;18:126-8.
24. Repetto P, Bianchini MA, Ceccarelli PL, Roncati L, Durante V, Biondini D, *et al.* Bilateral xanthogranulomatous funiculitis and orchiepididymitis in a 13-year-old adolescent boy. J Pediatr Surg 2012;47:e33-5.
25. Ezer SS, Oguzkurt P, Temiz A, Bal N, Hicsonmez A. Xanthogranulomatous orchiepididymitis: A very uncommon cause of scrotal mass in childhood. Urology 2013;82:228-30.
26. Parihar A, Sharma S. Bilateral xanthogranulomatous orchiepididymitis in a diabetic patient. J Clin Diagn Res 2016;10:L01-2.
27. Yamashita S, Umemoto H, Kohjimoto Y, Hara I. Xanthogranulomatous orchitis after blunt testicular trauma mimicking a testicular tumor: A case report and comparison with published cases. Urol J 2017;14:3094-6.
28. Ting J, Jin Q, Biles M, Berry SA, Shah M, Herati AS. Xanthogranuloma of the epididymis. Urol Case Rep 2018;17:50-2.
29. Somani K, Singh P, Verma S, Tandon T. An unusual case of

xanthogranulomatous orchitis: A tumor mimic. Apollo Med 2019;16:174-6.
30. Gongora E Silva RF, Pinto IC, Constantino EC, Querichelli AF, Spessoto LC, Fácio FN Jr. Xanthogranulomatous orchitis: Case report of a rare condition. AME Case Rep 2019;3:4.
31. Murshed KA, Taha NM, Ben-Gashir M. A case of xanthogranulomatous orchitis and its preoperative diagnostic challenges. Urol Case Rep 2020;32:101248.
32. Pattenden TA, Morton A, Keller A. Xanthogranulomatous orchitis: A rare case of testicular mass. Urol Case Rep 2022;43:102111.
33. Delamaire M, Maugendre D, Moreno M, Le Goff MC, Allannic H, Genetet B. Impaired leucocyte functions in diabetic patients. Diabet Med 1997;14:29-34.
34. Reed CT, Adams K, Shenoy V. Xanthogranulomatous adrenalitis: A case report of a diabetic, 55-year-old male. Endocr Pathol 2015;26:229-31.
35. Bartoli F, Gesualdo L, Niglio F, Gentile O, Penza R, Leggio S, *et al.* Xanthogranulomatous pyelonephritis is associated with higher tissue expression of monocyte chemotactic protein-1. Eur J Pediatr Surg 2007;17:365-9.
36. Ding X, Cao Y, Xing Y, Ge S, Lin M, Li J. TIMP-1 mediates inflammatory and immune response to IL-6 in adult orbital xanthogranulomatous disease. Ocul Immunol Inflamm 2020;28:288-97.
37. Shah VB, Shet TM, Lad SK. Fine needle aspiration cytology of epididymal nodules. J Cytol 2011;28:103-7.
38. Garbyal RS, Gupta P, Kumar S, Anshu. Diagnosis of isolated tuberculous orchitis by fine-needle aspiration cytology. Diagn Cytopathol 2006;34:698-700.
39. Shenoy VP, Viswanath S, D'Souza A, Bairy I, Thomas J. Isolated tuberculous epididymo-orchitis: An unusual presentation of tuberculosis. J Infect Dev Ctries 2012;6:92-4.
40. Krishnani N, Dhingra S, Kapoor S, Pandey R. Cytopathologic diagnosis of xanthogranulomatous cholecystitis and coexistent lesions. A prospective study of 31 cases. Acta Cytol 2007;51:37-41.

How to cite this article: Vijayvergiya G, Gulwani HV, Ul Hasan S. Xanthogranulomatous epididymo-orchitis: A single-institutional case series and systematic review. Indian J Urol 2023;39:58-66.