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Frequency And Unusual Clinical Manifestation Of Orbital Xanthogranulomas: An Overview

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Abstract

Objective: To assess the frequency and clinical characteristics of orbital xanthogranulomas, focusing on their unusual presentations and impact on bone structure in a South Asian population.
Methods: This is a retrospective study conducted at Al-Shifa Trust Eye Hospital, a tertiary care hospital in Rawalpindi, Pakistan. The study included patients diagnosed with orbital xanthogranulomas between July 2001 and July 2023. The variables collected included patient demographics (age, gender), presenting symptoms, duration of symptoms before presentation, clinical features, diagnostic modalities used (e.g., CT scans, histopathology), treatment modalities, and follow-up outcomes.
Results: Between July 2001 and July 2023, 1250 orbital lesions were identified. Out of these, a total of 6 patients were diagnosed with orbital xanthogranuloma.
The presenting symptoms for these 6 patients included proptosis in 5 cases, loss of vision in 5 cases, and redness of the eyes in 1 case. In four patients, bony erosions were seen preoperatively. The most commonly involved bone was the roof of the orbit. In one patient, osteosclerosis of the knee and elbow joint was reported. The mean duration of symptoms before presentation was 1.8 years, ranging from 3 months to 5 years. The mean age at presentation was 38 years (range, 3 – 70 years). Recurrence was seen in only one patient.
Conclusion: In conclusion, our findings indicate that orbital xanthogranulomas, while rare, constitute a noteworthy proportion of lesions with bony erosions. These tumours manifest with diverse clinical features, complications, and systemic associations, making them complex to diagnose and manage effectively.
MeSH Keywords: xanthogranuloma, Orbital inflammation, Erdheim-Chester disease, asthma.

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1. Introduction

Orbital xanthogranulomas are a rare but clinically significant group of disorders manifesting yellowish masses in the orbital region.[1] These disorders are categorised as class II non-Langerhans histiocytic proliferations, underscoring their distinct pathophysiological processes separate from more common histiocytic disorders.[2] Orbital xanthogranulomas have four subtypes: adult-onset xanthogranuloma (AOX), adult-onset asthma and periocular xanthogranuloma (AAPOX), necrobiotic xanthogranuloma (NBX), and Erdheim-Chester disease (ECD).[3] It remains uncertain whether late-onset juvenile xanthogranuloma (JXG) should be classified as a subtype of adult-onset xanthogranuloma (AOX) or if it constitutes a separate clinical entity. Each subtype has distinct clinical presentations and systemic associations guiding treatment decisions. These lesions can present with various symptoms, including proptosis, vision loss, and ocular discomfort, posing significant challenges for diagnosis and management.[3]
The various clinical forms of AOX, AAPOX, NBX, and ECD exhibit significant histopathological similarities. These morphological commonalities may indicate that different clinical manifestations are linked through shared immunological pathways. Xanthogranulomatous disease in the periorbital area is characterised by the presence of foamy histiocytes, Touton giant cells, and varying degrees of fibrosis; in the case of NBX, necrobiosis is also a notable feature.[4]
A well-documented association exists between NBX and plasma cell dyscrasia. However, plasma cells are not typically the predominant inflammatory type.[5]
Due to their rarity and the potential for significant morbidity, early and accurate diagnosis followed by appropriate management is crucial for improving patient outcomes.[6]
The aetiology of orbital xanthogranulomas needs to be better understood. These lesions may be linked to systemic conditions such as hyperlipidemias, diabetes mellitus, or blood disorders, including IgG

monoclonal gammopathy, plasmacytosis, cryoglobulinemia, chronic lymphocytic leukaemia, and asthma.[3] Therefore, a comprehensive systemic evaluation is essential. Periorbital lesions are typically managed with chemotherapy, radiotherapy, steroidal injections, or local excision. However, due to the rarity of this condition, treatment approaches are primarily based on anecdotal evidence and often yield inconsistent results. While local excision may prove successful in some instances, surgical debulking can result in recurrence in others.[6]

Despite the clinical importance of orbital xanthogranulomas, there needs to be more literature on its prevalence, especially in South Asia. This gap in the literature highlights a crucial need for focused research in specific geographical settings to understand better the presentation, progression, and outcomes associated with this condition. This study aims to fill this gap by examining the frequency of orbital xanthogranulomas at Al-Shifa Trust Eye Hospital, a tertiary care hospital in Rawalpindi. We aim to present data on patient demographics, clinical features, diagnostic modalities, treatment outcomes, and follow-up, providing valuable insights into the presentation and management of this rare condition in a specific geographical setting.

2. Materials & Methods

This is a retrospective study conducted at Al-Shifa Trust Eye Hospital, a tertiary care hospital in Rawalpindi, Pakistan. The Institutional Review Board approved the study, and all procedures were carried out by the Declaration of Helsinki.

In the study, participants were selected based on specific inclusion and exclusion criteria to ensure clarity and relevance of the data. Inclusion criteria included patients diagnosed with orbital xanthogranuloma based on histopathological findings between July 2001 and July 2023, encompassing all ages and genders and those who had received any treatment. Only patients with available follow-up data to assess treatment outcomes were included. Exclusion criteria comprised patients without definitive histopathological confirmation of orbital xanthogranuloma, those with incomplete medical records or lacking detailed follow-up information, and individuals with concurrent orbital disorders or prior orbital surgeries for conditions other than xanthogranuloma.

Medical records of the patients were reviewed to extract relevant data. We meticulously documented variables, including age, laterality, applied treatment protocols, and patient responses to these treatments, and observed recurrence rates across the groups. Histopathological analyses were conducted to evaluate the presence of fibrosis and to classify the diagnosis at the initial biopsy. Statistical analyses were performed using SPSS version 27, ensuring rigorous data handling and analysis. Quantitative variables were expressed as means and standard deviations. Categorical variables were presented as frequencies and percentages, facilitating a clear understanding of data distribution and demographic details.

All patients in this retrospective study underwent orbitotomy for orbital lesions. All patients underwent requisite imaging procedures, and their diagnoses were substantiated through histopathological analysis. The diagnosis of orbital xanthogranuloma was confirmed histopathologically in all cases. Immunohistochemistry was performed in selected cases to differentiate it from other similar conditions.

Information was collected on the treatment modalities used, including surgical procedures and medical therapies. Follow-up data were obtained from medical records, including symptom resolution, recurrence, and complications.

3. Results

Between July 2001 and July 2023, 1250 orbital lesions were identified. Out of these, a total of 6 patients were diagnosed with orbital xanthogranuloma. These included 3 cases of Adult Onset Xanthogranuloma (AOX), 2 cases of Juvenile Xanthogranuloma (JXG) and one case of Erdheim-Chester Disease (ECD) as described in Table 1. Detailed information on patient demographics, clinical characteristics, treatment outcomes, and follow-up are presented in Table 2.

The presenting symptoms for these 6 patients included proptosis in 5 cases, loss of vision in 5 cases, and redness of the eyes in 1 case. In four patients, bony erosions were seen preoperatively. The lesions were mostly extraconal, and the superior orbit was the most frequent location. The most involved bone was the roof of the orbit. In one patient, osteosclerosis of the knee and elbow joint was reported. The mean duration of symptoms before presentation was 1.8 years, ranging from 3 months to 5 years. The mean age at presentation was 38 years with a standard deviation of 26.26 (range, 3 – 70 years).

All 6 patients underwent anterior orbitotomy and were followed up for a minimum of six months. The outcomes varied, with some experiencing near-complete resolution of symptoms and others facing complications such as severe ptosis and loss of vision. Recurrence was seen in only one patient.

Figure 1: Adult onset xanthogranuloma (A) Patient at presentation showing left inferior globe displacement (B) CT scan showing bone destruction (C) one-year post-surgery (D) yellowish fragmented nature of the lesion.

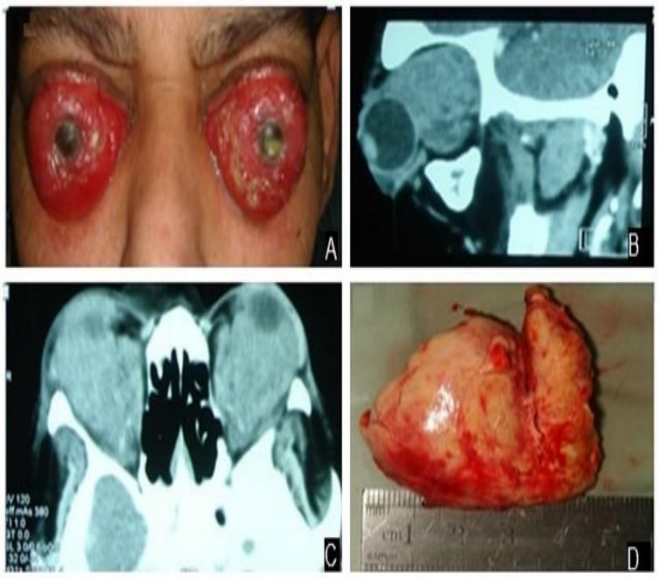

Figure 2: Erdheim Chester disease (A) patient at presentation (B) sagittal and (C) axial CT scan of the orbit showing the lesion occupying most of the orbit (D) yellowish mass removed from the right orbit.

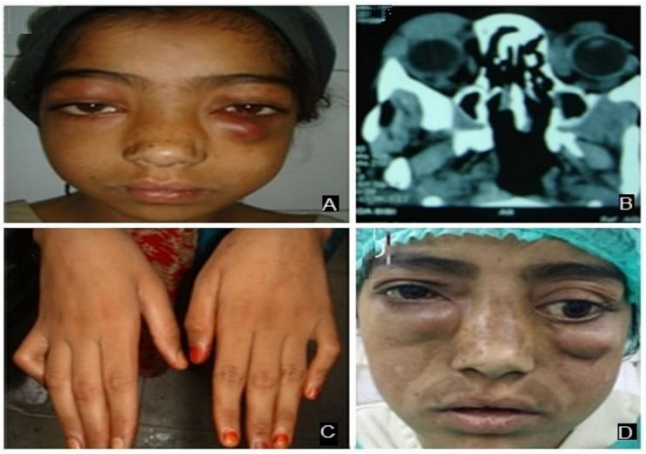

Figure 3: Patient with juvenile xanthogranuloma (A) preoperative photograph at first presentation (B) CT scan showing lesion in the orbits (C) bilateral flexion deformity of little fingers (D) preoperative photograph at recurrence 8 years after.

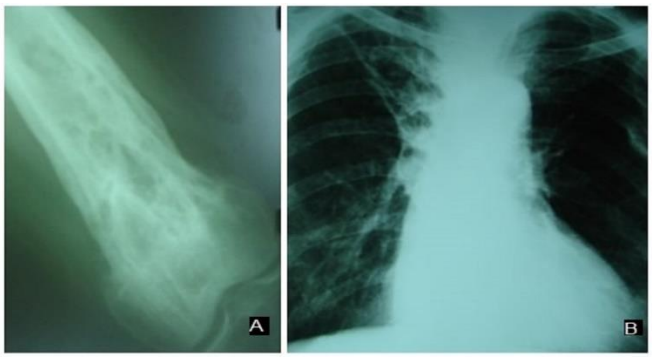

Figure 4: X-ray (A) femur, showing sclerosis (B) chest, showing hila and paratracheal streaky densities suggestive of fibrosis.

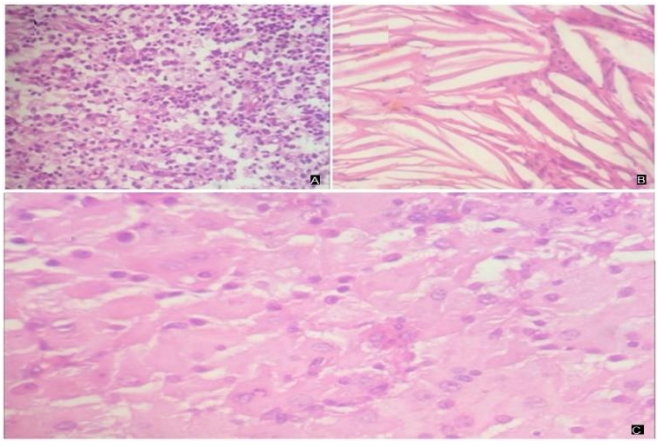

Figure 5: Haematoxylin and eosin slides show (A) dense lymphohistiocytic proliferation with (B) cholesterol clefts and (C) multinucleated giant cells.

Table 1: Frequency of each subtype confirmed on histopathology in 6 patients with orbital xanthogranuloma

Subtype	Frequency	Per cent
JXG[a]	2	33.3
AOX[b]	3	50.0
ECD[c]	1	16.7

Adult orbital xanthogranulomatous disease is an infrequent condition affecting individuals between 17 and 85, with no apparent gender predilection.7 Adult-onset xanthogranuloma, the least common entity among AOXGDs, manifests as an isolated xanthogranulomatous lesion without significant systemic involvement. It typically occurs in individuals aged 38 to 79, showing no gender preference. Recognizing this subtype is crucial as it is often self-limiting, requiring less aggressive treatment than other AOXGD subtypes.[3]

Table 2: Patient demographics, clinical features, treatment and follow-up in 6 patients with orbital xanthogranuloma.

Case	Sub type	Age/sex	Laterality	Clinical features	Systemic disease	Imaging features	Treatment	Prognosis or outcome
1	JXG [a]	03Y F	Unilateral	Painless proptosis with a down displacement of the globe	None	Circumscribed extraconal superior orbital mass	Excisional biopsy	No recurrence
2	JXG [a]	12Y F	Bilateral	Bilateral multiple swellings in the anterior orbits and periorbita	None	Bilateral circumscribed lesions in the anterior orbits	Excisional biopsy	Bilateral recurrence after 8 years. Disease stable after 18 months post re-excision
3	AOX [b]	35Y M	unilateral	Painless mass in superior orbit with inferior globe displacement. Blurred vision	None	Extraconal superior orbital mass associate with the destruction of roof of the orbit	Excisional biopsy	Stable after 2 years
4	AOX [b]	70Y M	Unilateral	Painless proptosis	None	Extraconal superior orbital lesion associated with the destruction of the roof of the orbit	Excisional biopsy	Stable after one year
5	ECD [c]	55Y M	Bilateral	Painful bilateral marked proptosis associated with exposure keratopathy and loss of vision	Osteoscler osis with Knee and elbow joint pains	Bilateral intraconal mass lesion abutting both eyeballs with marked proptosis. Streaky densities around the hila and paratrachea are suggestive of fibrosis. Osteosclerosis of knee and joint.	Debulking and systemic steroid.	Bilateral post-operative severe ptosis. Lost to follow-up after one year without recurrence
6	AOX [b]	53YM	Unilateral	Painless mass in superior orbit with inferior globe displacement. Blurred vision	None	Extraconal superior orbital lesion associated with the destruction of roof of the orbit	Excisional biopsy	Stable after six months

a= Juvenile Xanthogranuloma, b= Adult-onset Xanthogranuloma. c= Erdheim Chester disease

4. Discussion

Necrobiotic xanthogranuloma is characterized by subcutaneous skin lesions prone to ulceration and fibrosis. It primarily affects adults aged 20 to 85, with no distinct gender bias. Frequently associated systemic findings include paraproteinemia and multiple myeloma.[8]

Erdheim-Chester disease, an idiopathic condition, involves lymphohistiocytic infiltration in the orbit and various internal organs. It primarily affects males (male to female ratio, 2:1) between 17 and 77 years of age. This condition often presents with significant systemic involvement, leading to potentially fatal outcomes such as cardiomyopathy, severe lung disease, or chronic renal failure. Bilateral diffuse orbital masses should raise concern for this serious systemic disease.[9,10]

Adult-onset asthma and periocular xanthogranuloma, a rare entity with only 21 reported cases, present with bilateral yellow-orange, elevated, indurated xanthomatous eyelids and/orbital masses. It typically affects individuals aged 22 to 74, with a higher incidence in males. The underlying mechanism linking adult-onset asthma and periocular xanthogranuloma remains poorly understood, indicating a systemic immunologic derangement. Association with lymphoproliferative disorders and internal organ dysfunction has been reported.[11]

The clinical presentation often involves extensive eyelid and periocular infiltration, causing a significant mass effect that can impair vision. While visual acuity is

generally preserved, exposure keratopathy and dry eye conditions may arise in rare cases.[12]

Our study on orbital xanthogranulomas in a South Asian population presents some interesting contrasts and parallels with a similar multicenter cohort study on necrobiotic xanthogranuloma (NXG) done by Nelson CA, Zhong CS, Hashemi DA, et al.[9] While the multicenter study predominantly involved a Western cohort with a mean age of 61.6 years and a notable female predominance, our study identified a younger mean age of 38 years and no significant gender bias in the incidence of orbital xanthogranulomas. This disparity could highlight underlying genetic or environmental factors affecting the epidemiology of these histiocytic disorders in different geographic regions.

Moreover, our findings regarding the clinical management and outcomes of orbital xanthogranulomas echo some aspects of the NXG study. In both studies, the complexity of the diseases necessitates a multifaceted treatment approach, often involving surgical interventions, which in our study showed favourable outcomes similar to the high response rates to various treatments reported in the multicenter study. Additionally, both studies underscore the necessity for ongoing surveillance and a multidisciplinary management approach due to the potential for systemic involvement and recurrence, as evidenced by the multicenter study's focus on long-term hematologic surveillance following paraproteinemia and other systemic conditions associated with NXG.

Management of orbital xanthogranulomas remains largely empirical, with various treatment modalities including surgery, steroids, chemotherapy, and radiotherapy. In our study, all patients underwent surgical excision and were followed up for at least one year. Only one patient experienced recurrence, aligning with other reports that suggest surgery can be effective in many cases. However, the efficacy of other treatments like systemic steroids and radiotherapy remains variable. Detiger et al.'s long-term follow-up of AOXGD patients highlighted the variable outcomes and recurrence rates associated with different treatment modalities, such as surgical and systemic therapies. Similarly, our study discusses the diverse clinical manifestations of orbital xanthogranulomas and the subsequent impact on treatment efficacy. While Detiger et al. found that surgical excision may be sufficient for AOX, systemic treatments were necessary for other subtypes like AAPOX, NBX, and ECD, which aligns with our findings that emphasize the need for a tailored approach based on the specific subtype and individual patient characteristics. The recurrence observed in both studies indicates the necessity for ongoing monitoring and possibly developing more effective long-term management strategies.

Information on the prevalence of orbital xanthogranuloma is scarce, and the condition is generally regarded as rare. However, the proportion of orbital xanthogranulomas among these tumours is noteworthy and diverges from commonly held views that consider it rare. This could indicate a higher prevalence in our demographic or an underdiagnosis in other settings.

The varied clinical presentation, ranging from proptosis to vision loss, highlights the need for a comprehensive diagnostic approach. The mean duration of symptoms before presentation was 1.8 years, suggesting that earlier diagnosis could prevent complications. Given that almost all patients presented with palpable orbital masses and a majority had vision-related complaints, clinicians should have a high index of suspicion for orbital xanthogranuloma in similar cases.

Limitations and Future Directions

While the study provides valuable insights, it is limited by its retrospective nature and the relatively small number of cases. Larger, prospective studies are needed to validate these findings and to explore the potential factors contributing to the high frequency of orbital xanthogranuloma in our setting. Further research could also focus on the efficacy of various treatment modalities and long-term outcomes.

5. Conclusion

Our study demonstrates that orbital xanthogranulomas, while rare, are significant causes of orbital lesions with bone involvement in the South Asian demographic. These tumours exhibit diverse clinical manifestations and complications, underscoring the need for vigilant diagnosis and multidisciplinary management. Further research is essential to deepen understanding and improve treatment outcomes for this challenging and complex condition.

INSTITUTIONAL REVIEW BOARD

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A.M - Conception of study
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A.M, F.T, S.A - Analysis/Interpretation/Discussion
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