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Adult onset xanthogranuloma of the eyelid

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ABSTRACT

Purpose: To report a rare case of an eyelid lesion in an adult, with histological features of juvenile xanthogranuloma (JXG).
Observations: Juvenile xanthogranuloma primarily affects the skin of infants and young children. It infrequently can involve the structures of the eye and orbit and rarely occurs in individuals beyond the second decade of life. We present a case of adult onset xanthogranuloma (AXG) involving the eyelid of a 29-year-old female. This lesion required management with multiple treatment modalities.
Conclusions: This is a rare example of an eyelid xanthogranuloma in an adult. As such, JXG-like lesions should be included as a differential diagnosis for lesions of the eye and orbit in adults. Surgical management may be required if there is no response to intralesional steroids.

1. Introduction

Juvenile xanthogranuloma (JXG) is a rare disease belonging to a subgroup of cutaneous non-Langerhans cell histiocytosis. Clinically, the lesion presents as a yellow/orange stromal mass. It is characterized histologically by an infiltrate of epithelioid to foamy histiocytes and multinucleate Touton giant cells.[1] Typically, lesions affect the skin, however the eye is the most frequently affected extra-cutaneous site.[2] Ophthalmic involvement can occur at the orbit, eyelid, iris, retina, choroid and the optic nerve, with the majority of cases being diagnosed within the first year of life.[3] Surgical excision is often successful at producing recurrence free outcomes, however cases have been reported of multiple resection attempts for recurrent disease.[4] Ocular JXG-like lesions rarely occur in the third decade or later in life and are defined as adult onset xanthogranuloma (AXG). Here we present a case of solitary xanthogranuloma in an eyelid of a 29-year-old female patient.

2. Case presentation

A 29-year-old Indian female patient with a 2-week history of a non-tender mass on the left upper eyelid was referred to an outreach ophthalmology service in remote Western Australia. She reported a small erythematous mass initially, which increased in size over the 2-week period despite the regular use of warm compresses. She denied any changes to her vision or trauma to the eyelid and was otherwise well with no constitutional symptoms. She had no significant past ocular history and her only medical history of note was iron deficiency anaemia. She had no previous history of malignancy or similar lesions elsewhere.

On examination, she had a swollen left eyelid. Eyelid eversion revealed a smooth, homogenous mass which measured approximately 1cm × 1cm (Fig. 1A). The mass was firm and rubbery on palpation and was not tender. Her visual acuity was 6/9.5 bilaterally and intraocular pressures were normal. She had full and equal range of extraocular muscle movement and her pupils were equal and reactive to light with no evidence of an RAPD. She was normotensive and afebrile.

Given the clinical appearance, this was managed initially as a pyogenic granuloma with intralesional triamcinolone (kenacort).

The patient was reviewed one month after initial treatment with intralesional triamcinolone. Despite slight initial improvement after injection, she re-developed significant eyelid swelling with intermittent pain and blurred vision. Her visual acuity was 6/12 bilaterally and she continued to use warm compresses twice per day. On examination, she had a persistent lesion, which was managed with incisional biopsy and

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intralesional triamcinolone.

The histopathologic examination revealed portions of a mass of mainly histiocytic cells including epithelioid histiocytes and touton-type multinucleated giant cells; the latter characterized by central wreath like arrangement of round to oval nuclei and abundant peripheral lipidized foamy cytoplasm (Fig. 2A). There was a smaller component of admixed lymphocytes, plasma cells and polymorphonuclear cells. By immunohistochemistry the constituent histiocytic cells were positive for common histiocytic markers (CD163 and CD68) (Fig. 2B), and negative for S100 and specific Langerhans cell markers including CD1A and Langerin. The lesion extended to the peripheral and deep aspects of the specimen.

The overall immunomorphological features were those of a juvenile xanthogranuloma, albeit occurring in an adult.

The patient was reviewed at one and three weeks following excision and the lesion had re-grown on the upper eyelid. She was commenced on topical steroid drops and had a re-excision of the lesion one month post initial incisional biopsy. She had no recurrence of the lesion at three months after the second excision, and her eyelids had returned to normal.

3. Discussion

The histiocytoses are a group of rare conditions characterized by an accumulation of cells derived from macrophages and dendritic lineages.[5] Histiocytes of the skin include macrophages and $CD14^{+}$ dendritic cells located in the dermis, and Langerhans cells located predominantly in the epidermis.[6,7] Langerhans cells share properties of both macrophages and dendritic cells and are capable of migrating to lymph nodes as antigen presenters.[8]

In 1987, an initial classification of this collection of diseases grouped them into three categories, Langerhans cell (LCH), non-Langerhans cell (N-LCH) related or malignant (M) histiocytoses.[6] Since then, a greater understanding of the molecular mechanisms contributing to the pathogenesis of these conditions led to a revision of the classification to reflect their clinical, immunohistochemically and genetic features.[5] This resulted in a new classification with the following categories; Langerhans (L), cutaneous and mucocutaneous (C), malignant (M), Rosai-Dorfman Disease (R) and haemophagocytic lymphohistiocytosis (H).[6]

Juvenile and adult onset xanthogranuloma, histologically and immunohistochemically identical lesions, are placed in category C with solitary reticulo-histiocytoma (SRH). SRH can be easily distinguished from xanthogranuloma on histologic examination, showing nodular proliferation of polygonal mononuclear or multimutated histiocytes with large nuclei, prominent nucleoli and characteristically abundant dense ground-glass eosinophilic cytoplasm. Erdheim-Chester disease (ECD), often an extra-cutaneous form of histiocytosis with common involvement of the bone, shares some histological and immunohistochemical features with juvenile and adult onset xanthogranuloma; however, it is classified into the L group due to frequent MAPK (mitogen-activated protein kinase) pathway somatic mutations (mainly *BRAF* mutation) similar to Langerhans cell histiocytosis.[6] Clinically, ECD is a systemic and much more significant disease compared to JXG, with multi organ system involvement and a median survival of 10.42 years.[9] Eye and orbital involvement in ECD is rare, but often results in profound visual and ophthalmic sequelae.[10] Langerhans cell histiocytosis (LCH) and Rosai-Dorfman disease (RDD) can be readily distinguished from JXG/AXG on histological and immunohistochemical grounds via expression of CD1A/Langerin in LCH and S100 in RDD. Necrobiotic xanthogranuloma (NXG) is a further type of non-Langerhans histiocytosis which can histologically mimic xanthogranuloma, particularly the adult onset form. This condition shows a predilection for periorbital skin, often in older individuals (average age sixth decade), and is highly associated with systemic paraproteinemia. Histologically, NXG is characterized by a palisading xanthogranulomatous inflammatory infiltrate encompassing areas of necrobiotic collagen and often contains cholesterol clefts and large bizarre foreign body type giant histiocytic cells.

Clinically, juvenile and adult xanthogranulomas tend to manifest as cutaneous lesions only and are solitary in up to 80% of cases.[11] The characteristic lesion is well demarcated, firm and yellow/orange in colour, most commonly affecting the head and neck region. Less common patterns of cutaneous involvement in the form of lichenoid, plaque and generalised lesions can also occur.[12] Up to 85% of cases arise within the first year of life, making adult onset JXG exceedingly rare.[13] Extracutaneous lesions of JXG have been reported, with the eye being the most frequently described. In children with cutaneous JXG, eye involvement is reported to occur in 0.3–10% of cases.[14] Systemic JXG is rare and is defined as cutaneous/sub-cutaneous nodules with two or more organ systems affected. There are rare reports of CNS, liver, spleen and lung involvement.[15] In a single centre study of 30 patients, the iris was the most frequently involved ophthalmic structure, accounting for 68% of cases, followed by conjunctival and eyelid lesions contributing to 19% and 6% of cases respectively.[16] This has been reflected in other series,[17,18] however one study found the eyelid to be the most commonly affected site.[2] Common clinical findings with eye involvement include redness, iris and conjunctival lesions and hyphaemia (typically in iris tumors).[16] An association with neurofibromatosis type 1, Niemann-Pick disease, juvenile myelomonocytic leukemia and urticaria pigmentosa has been established in some studies.[19,20]

Adult onset xanthogranuloma affecting the eyelid is exceedingly rare. Chalfin and Lloyd's description of a right upper eyelid lesion in a 24 year old Caucasian male in 1998 is the only previous case report of a solitary adult-onset xanthogranuloma of the eyelid.[21] This lesion was managed with an excisional biopsy. Two case series concerning eye involving JXG include patients with eyelid involvement presenting in

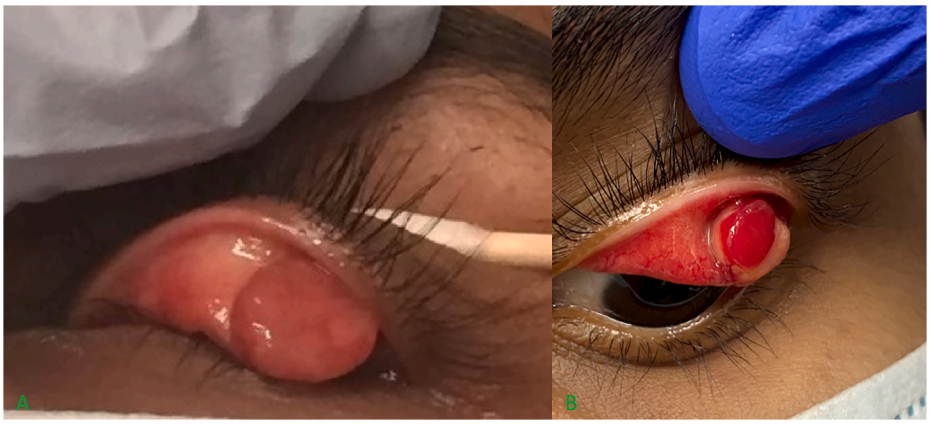

Fig. 1. A) Eyelid lesion on first presentation, B) Lesion at time of re-presentation, 3 weeks following initial treatment.

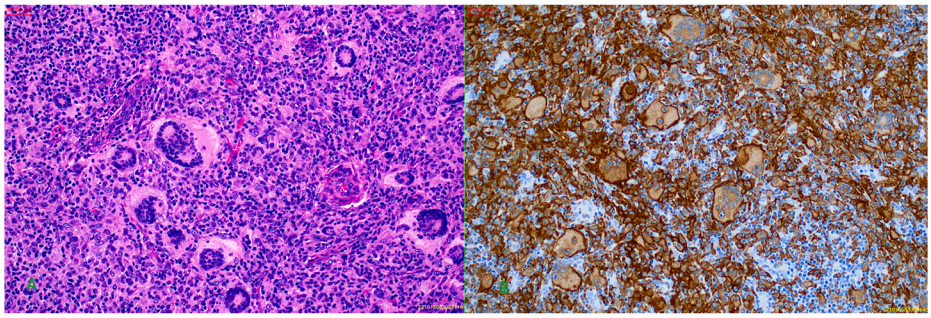

Fig. 2. A) A microscopic histology image of the lesion showing portions of a histiocytic proliferation including epithelioid and touton type multinucleated histiocytes with a component of admixed other inflammatory cells, mainly lymphocytes (H&E image), B) The lesional cells show diffuse positive staining (brown) with CD163, a common histiocytic immunomarker (IHC for CD163).

their third and fifth decades, however these do not elaborate on the clinical features of these presentations.[3,22] Several individual case reports have discussed adult-onset JXG arising in other ophthalmic structures including the iris,[23] limbus[24–27] and orbit.[28–30]

Corticosteroids are the mainstay of treatment for juvenile xanthogranuloma involving the eye. Typically, these are topical or intra-lesional injection, however periocular and oral routes have also been used with success. Excisional biopsy has been utilised primarily for tumors involving the conjunctiva, eyelid and orbit.[16] There have also been reports of low-dose radiation and observational management. Recurrence of these lesions is rare, with most series of eye involving JXG reporting no recurrence after 15–27 months.[3,16] Recurrence requiring multiple surgical excisions to achieve regional tumor control has been reported. Nishina et al.[31] describe excision of a mass of JXG and associated subcutaneous tissue, including orbital septum, and reconstruction with a pre-auricular skin graft resulting in two year recurrence free follow up. Mansour et al.[4] report re-excision of a right lower eyelid lesion in a 12-year-old girl, following recurrence after five previous excisions. The repeat excision was also taken to the orbital septum and followed by local cryotherapy to the area. In this case the masses recurred five months later and the patient had to undergo low dose radiation therapy.

4. Conclusion

In summary, we report a case of histologically typical xanthogranuloma with several unusual and unique clinical features including the age of onset, its location on the eyelid and lack of response to treatment with intralesional steroid. Although benign in nature, the local control of such lesions can be challenging at times. It should also be emphasized that, despite the common designation "juvenile", clinicians should consider rare cases of xanthogranuloma in the differential diagnosis of eyelid masses in an older population.

Patient consent to publication

Informed written consent to publication of the following information was obtained from the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

Author contribution

James Wiffen: Conceptualisation, Roles/Writing – original draft, review and editing. **Amy Kalantary:** Conceptualisation, Roles/Writing – original draft, review and editing. **Nima Mesbah Ardakani:** Conceptualisation, Roles/Writing – original draft, review and editing. **Angus Turner:** Conceptualisation, Supervision, Writing – review and editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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