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Adult orbital xanthogranuloma: long-term follow-up of treated cases

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BACKGROUND: Adult orbital xanthogranulomatous disease (AOXGD) is a group of rare disorders. Four subtypes are identified: adult-onset xanthogranuloma (AOX), adult-onset asthma and periocular xanthogranuloma (AAPOX), necrobiotic xanthogranuloma (NBX), and Erdheim-Chester disease (ECD). Therapy options vary and little is known about the long-term effect of the treatment. In this study, we will describe the clinical behaviour, effect of treatment, and long-term outcome in a consecutive series of patients with AOXGD.

METHODS: This is a descriptive, retrospective study with a long follow-up term of 21 patients with histologically proven AOXGD, treated between 1989 and 2021 in the Rotterdam Eye Hospital and Erasmus MC University Medical Center.

RESULTS: Twenty-one patients with histologically proven AOXGD were included. The follow-up ranged from 2–260 months (median of 67 months). Six of the nine patients with AOX were treated with surgery alone, with recurrence in two. Three received systemic therapy, with recurrence in one. All four patients with AAPOX received systemic treatment, the disease recurred in two. Two patients with NBX were treated with surgery alone, with recurrence in one. Four required additional therapy with recurrence in two. Both patients with ECD required systemic therapy.

CONCLUSIONS: Recognition of AOXGD is important, in particular, because of the potential severe systemic locations in the different subtypes. Surgical excision might be a sufficient therapy for patients with AOX. Patients with AAPOX, NBX, and ECD warrant systemic therapy. Currently, there is no conclusive evidence for a superior treatment strategy, but further studies are necessary to investigate treatment options.

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INTRODUCTION

Adult orbital xanthogranulomatous disease (AOXGD) is a group of rare orbital and ocular adnexal disorders within the spectrum of type II Non-Langerhans cell histiocytosis (non-LCH). Hallmark histopathological characteristics consist of CD1a- and S100-negative foamy histiocytes, Touton giant cells and fibrosis [1]. Based on clinical features and systemic associations, four subtypes are identified [2].

Adult-onset xanthogranuloma (AOX) is a rare entity and may present as a solitary xanthogranulomatous eyelid or orbital lesion [3, 4].

Adult-onset asthma and periocular xanthogranuloma (AAPOX) presents with lesions similar to AOX but is associated with late-onset asthma. In addition, it may be associated with IgG4-related disease (IgG4-RD) and some cases may show reactive lymphadenopathy or lymphoma [3–9].

Necrobiotic xanthogranuloma (NBX) is one of the most frequently reported subtypes and is characterized by the presence of necrobiosis in adnexal and frequently accompanying skin lesions [4]. Systemic findings include monoclonal gammopathy and associated hematologic malignancies [4, 10–14].

Erdheim-Chester disease (ECD) is a lymphohistiocytic disorder of the orbit, often with systemic infiltration, affecting the long bones and visceral organs such as lungs and heart. The orbital lesions in ECD tend to have a more diffuse involvement than the other subtypes of AOXGD. Because of the extensive involvement and the progressive and therapy-resistant lesions, ECD is the most devastating subtype. The clinical course is potentially fatal [2, 4, 15].

To date, mostly small series on AOXGD have been published [3, 16–22]. AOXGD is a rare condition and there are no formal management guidelines. Therapy options vary, with no current consensus and little is known about the long-term efficacy and side-effects in these patients. In this study, we will evaluate the clinical course, effect of treatment and long-term outcome in a consecutive series of patients with histologically proven AOXGD treated at the Rotterdam Eye Hospital and Erasmus MC University Medical Center.

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Table 1. Patient characteristics, therapy and outcome.

Patient	Age range	Sex	Diagnosis	Localisation	Medical history	Therapy	Recurrence	Survival	Follow-up (months)
1	30 s	M	AOX	LUE, LG	None	Debulking	No	Yes	4
2	50 s	M	AOX	RLE, EOM	None	Debulking	No	Yes	6
3	40 s	M	AOX	DO, EOM	None	Debulking	Yes, after 4 months	Yes	98
4	50 s	F	AOX	LUE, sublingual	None	Debulking	Yes after 60 months	Yes	74
5	60 s	F	AOX	RUE	Hypertension, TIA	Debulking	No	Yes	19
6	80 s	F	AOX	LUE	Hypertension	Debulking	No	Yes	5
7	40 s	M	AOX	DO	None	Debulking, prednisolone 35 mg/day, azathioprine 150 mg/day	No	Yes	15
8	80 s	F	AOX	RUE, RLE, EOM, LG, sinus	Hypertension, psoriasiform dermatitis	Prednisolone 60 mg/day. After recurrence prednisolone 60 mg/day and azathioprine 50 mg/day	Yes, after 48 months	Yes	120
9	70 s	M	AOX	RUE, LN	TIA, CVA, CEA, DM	Debulking, prednisolone 20 mg/day, and azathioprine 100 mg/day	No	Yes	7
10	50 s	M	AAPOX	RUE, RLE, LUE, LLE, EOM, LG, LN	IgG4-RD, constrictive lung disease, lung adenocarcinoma	Prednisolone 60 mg/day, debulking	No	Yes	113
11	50 s	F	AAPOX	RUE, LUE, LG	Asthma	Debulking, prednisolone 60 mg/day, and methotrexate 10 mg/week	No	Yes	138
12	40 s	F	AAPOX	RUE, RLE, LUE, LLE, EOM, LG, LN	Asthma, fibromyalgia, hypercholesterolemia, iron-deficiency anaemia	Debulking, prednisolone 60 mg/day, and azathioprine 75 mg/day. Switch to mycophenolic acid 1440 mg/day	Yes, after 30 months	Yes	142
13	60 s	F	AAPOX	RUE, RLE, LUE, LLE, EOM, LG	Asthma, M. Graves, TED, corneal melt	Debulking, prednisolone 30 mg/day, and mycophenolic acid 720 mg/day. After recurrence prednisolone 30 mg/day and mycophenolic acid 360 mg/day	Yes, after 12 months	Yes	108
14	40 s	M	NBX	RUE, RLE, LUE, LLE, LG, LN,	Primary sclerotic cholangitis, IgG4-RD	Debulking	Yes, after 48 months	Yes	260
15	70 s	F	NBX	LLE, LN	Hypertension, COPD, tuberculosis	Debulking, prednisolone 25 mg/day, and azathioprine 100 mg/day	No	Yes	18
16	40 s	F	NBX	LUE, LLE	None	Debulking, and subcutaneous triamcinolone 4–12 mg/injection	Yes, after 6 months	Yes	28
17	60 s	M	NBX	RLE Skin, parotid gland	CLL, thymoma, hypertension, hypercholesterolemia	Debulking	No	Yes	40
18	50 s	F	NBX	RUE, LG, LN, skin	Hypertension, hypercholesterolemia	Debulking. Side effects of prednisolone 30 mg/day, and methotrexate 20 mg/week. Dexamethasone 6 mg/day without effect, switch to azathioprine 150 mg/day. Due to recurrence, switch to mycophenolate mofetil 3 g/day, without effect. Switch to cyclophosphamide 2 g/month, without effect. Treatment was ceased.	Yes, after 34 months	Yes	84
19	50 s	M	NBX	RUE, LUE	M. Graves, T-cell lymphoma, pneumococcal sepsis, EBV infection	R-CHOP	No	Yes	4

Table 1. continued

Patient	Age range	Sex	Diagnosis	Localisation	Medical history	Therapy	Recurrence	Survival	Follow-up (months)
20	40 s	M	ECD	DO, bone, brain, periaortic, retroperitoneal	None	Debulking, prednisolone 70 mg/day, methotrexate 10 mg/week, cyclosporine 200 mg/day, octreotide 300 mcg/day, cyclophosphamide 150 mg/day, etanercept 50 mg/week radiotherapy 34 Gy, gammaglobulines 140 g/month, ^{177}Lutetium-octreotate 5.6GBq, azathioprine 100 mg/day	No	Deceased due to CVA	120
21	50 s	M	ECD	RUE, RLE, LUE, LLE, bone, skin	Hypertension, diabetes mellitus	Intravenous methylprednisolone 1 g for 3 days, and prednisolone 60 mg/day	Yes, after 1 month	Yes	3

AAPOX adult onset asthma and periocular xanthogranuloma, *AOX* adult onset xanthogranuloma, *CEA* carotid endarterectomy, *CLL* chronic lymphocytic leukaemia, *COPD* chronic obstructive pulmonary disease, *CVA* cerebral vascular accident, *DO* diffuse orbit, *EBV* Epstein-Barr virus, *ECD* Erdheim-Chester disease, *EOM* extra-ocular muscle, *F* female, *IgG4-RD* IgG4-related disease, *LG* lacrimal gland, *LLE* left lower eyelid, *LN* lymph nodes, *LUE* left upper eyelid, *M* male, *N/A* not applicable, *NBX* necrobiotic xanthogranuloma, *R-CHOP* rituximab/cyclophosphamide/hydroxydaunorubicine/oncovin/prednisolone, *RLE* right lower eyelid, *RUE* right upper eyelid, *TED* thyroid eye disease, *TIA* transient ischemic attack

MATERIALS AND METHODS

This is a descriptive, retrospective study with a long follow-up term of 21 patients with histologically proven AOXGD, treated between 1989 and 2021 in the Rotterdam Eye Hospital and Erasmus MC University Medical Center.

Patients were diagnosed with one of four subsets that make up AOXGD based on clinical features and systemic associations. AOX usually present as a solitary lesion. AAPOX is more often bilateral and associated with late-onset asthma. NBX is characterized by the presence of necrobiosis in the biopsy. ECD has a more diffuse involvement with systemic lesions.

Data including baseline demographics, clinical parameters, ophthalmic features, treatment, recurrence, and survival were retrospectively collected from medical records. If both sides were affected, we recorded the clinical findings of the most affected eye. If both eyes were equally affected, the right eye was noted. A minimal follow-up time of three months was required to establish remission. Clinically significant improvement needed to be observed in two to four weeks. If this was seen, additional treatment followed. Patients experienced ophthalmic symptoms, including pain, swelling, redness, proptosis, subjective change in vision. Remission was judged by examining these soft tissue signs and ophthalmic features. The Kaplan-Meier method was used to indicate the proportion of patients with recurrence-free survival. Therapy was a success when the soft tissue signs or ophthalmic features improved. Defined as a relapse was recurrence of these ophthalmic symptoms. A subset of the earlier treated patients was included in previous reports [4, 23, 24].

Patients with inconclusive histopathological diagnoses or no follow-up appointment were excluded.

Haematoxylin and eosin slides were reviewed by an ophthalmic pathologist for correct histopathological diagnosis and evaluated for Touton giant cells, foamy histiocytes, lymphocytic infiltrate, fibrosis and necrobiosis.

The study was approved by the Medical Ethics Committee of the Erasmus MC University Medical Center Rotterdam (MEC-2021-0510) and conducted according to the criteria set by the declaration of Helsinki. Informed consent was not obtained, since this was a retrospective study and histopathological findings were determined via post-determination on stored tissue.

RESULTS

Patient characteristics

Twenty-one patients with histologically proven AOXGD were included (Table 1). Of these patients, nine were diagnosed with AOX (age range 31–82 years), four with AAPOX (age range 45–68 years), six with NBX (age range 49–67 years), and two with ECD (age range 47–80 years). Of these 21 patients, 11 were female. The follow-up ranged from 2–260 months (median of 67 months).

Ophthalmic features

Patients presented with a median best corrected visual acuity (BCVA) of the (most) affected eye of 0.8 (range 0.16–1.25), a median intra-ocular pressure (IOP) of 16 mmHg (range 13–20), and a median Hertel value of the affected eye of 20 mm (range 16–26). These values were not significantly different after treatment ($p > 0.05$, paired *t*-test).

Histopathology

In AOXGD, subtypes share common histopathologic features. All showed xanthoma cells. Touton giant cells and lymphocytic infiltrates were present all but one patient. All patients diagnosed with NBX showed necrobiosis. This was not found in patients with AOX, AAPOX, or ECD. Immunohistochemistry was not performed in all patients.

Adult-Onset Xanthogranuloma

All nine patients with AOX showed unilateral symptoms (Table 1). Periorbital involvement was seen in seven patients. In 5 patients there was also orbital involvement, this included infiltration of extraocular muscles, the lacrimal gland, or diffuse infiltration. Three patients had associated systemic involvement, including the lymph nodes, sinus, and a sublingual xanthogranulomatous lesion. The median follow-up time was 15 months (range 4–120). The age of presentation ranged van 31–82 years.

Six patients were treated with debulking surgery alone. Recurrence occurred in two of these patients after 4 and

60 months, respectively (Fig. 1). One patient did not require additional therapy. The second patient required additional debulking surgery, but no systemic therapy. Two patients were treated with debulking surgery, prednisolone, and azathioprine without recurrence. One patient was treated with prednisolone and after recurrence with prednisolone and additional azathioprine with good results. After debulking surgery some side effects were noted, like diplopia, ptosis, and lagophthalmos. One patient reported nausea from the azathioprine 50 mg fairly quickly after commencement and this subsided after cessation.

Adult-onset asthma and periocular xanthogranuloma

All four patients with AAPOX had bilateral involvement. Three patients showed involvement of both upper- and lower eyelids. In one patient, only the upper eyelids were affected. All patients had infiltration of the lacrimal gland and three showed involvement of the extraocular muscles and two patients had lymphadenopathy. The median follow-up time was 126 months (range 108–142).

Three of the four patients were treated with debulking surgery and prednisolone. Two of these patients also received additional systemic therapy, one with methotrexate and one with azathioprine.

Two patients received mycophenolic acid with a good response, although both patients had recurrent disease after 12 and 30 months, respectively.

One patient received prednisolone only, this was insufficient regarding the proptosis, and additional debulking surgery, orbital decompression, and reconstructive eyelid surgery was performed.

One patient developed a corneal ulcer due to lagophthalmos and disfunction of the lacrimal gland after surgery. Two patients reported side effects of the systemic therapy. One patient reported muscle aches weeks after commencement with mycophenolic acid. This subsided spontaneously. Another patient reported weight loss and joint pain weeks after commencement with mycophenolic acid, this subsided after cessation. One patient was concurrently diagnosed with IgG4-RD.

Necrobiotic xanthogranuloma

In two of the six patients with NBX the involvement was bilateral. Four patients showed periorbital involvement, two patients showed infiltration of the lacrimal gland. All but two patients showed systemic manifestations, including the skin, lymph nodes, and parotid gland. The median follow-up time was 34 months (range 2–260).

Two patients were treated with debulking surgery alone, with recurrence of the eyelid lesions in one after 48 months. A second debulking surgery was performed in this patient with satisfactory results. One patient received debulking surgery and systemic prednisolone with azathioprine with no recurrence. One patient received debulking surgery and subcutaneous triamcinolone. After recurrence a new triamcinolone injection was given with good response. In one patient the treatment was eventually ceased due to either side effects or no effect of the treatment, including prednisolone, methotrexate, dexamethasone, azathioprine, mycophenolate mofetil, and cyclophosphamide. Two patients developed hematologic malignancies: one patient developed chronic lymphatic leukaemia 12 months and a thymoma 18 months after the initial NBX diagnosis. The other patient was almost simultaneously diagnosed with angioimmunoblastic T-cell lymphoma with lymphadenopathy, spleen, and liver involvement and was directly treated with R-CHOP. This patient passed away as a result of the angioimmunoblastic T-cell lymphoma. One patient was diagnosed with IgG4-RD 20 years after the first xanthogranulomatous lesion.

Two patients developed ectropion after debulking surgery.

Erdheim-chester disease

Both patients with ECD showed bilateral ophthalmic symptoms. One patient had bone and skin lesions. This patient was treated with intravenous methylprednisolone and oral prednisolone, but showed little response and the symptoms worsened one month after the methylprednisolone. Due to moving house the care for this patient was continued in a hospital elsewhere. The second patient had extensive systemic ECD with infiltration in multiple bones and periaortic, retroperitoneal and intracerebral lesions. This patient experienced multiple orbital flare-ups whilst using prednisolone. The patient received methotrexate, cyclosporine, octreotide and cyclophosphamide, etanercept, external beam radiation, immunoglobulin therapy without an obvious effect. A trial with ^{177}Lutetium-octreotate was started, but was ineffective. However, after this treatment and additional follow-up therapy with prednisolone and azathioprine, the inflammation did not relapse for several years. Unfortunately, this patient passed away

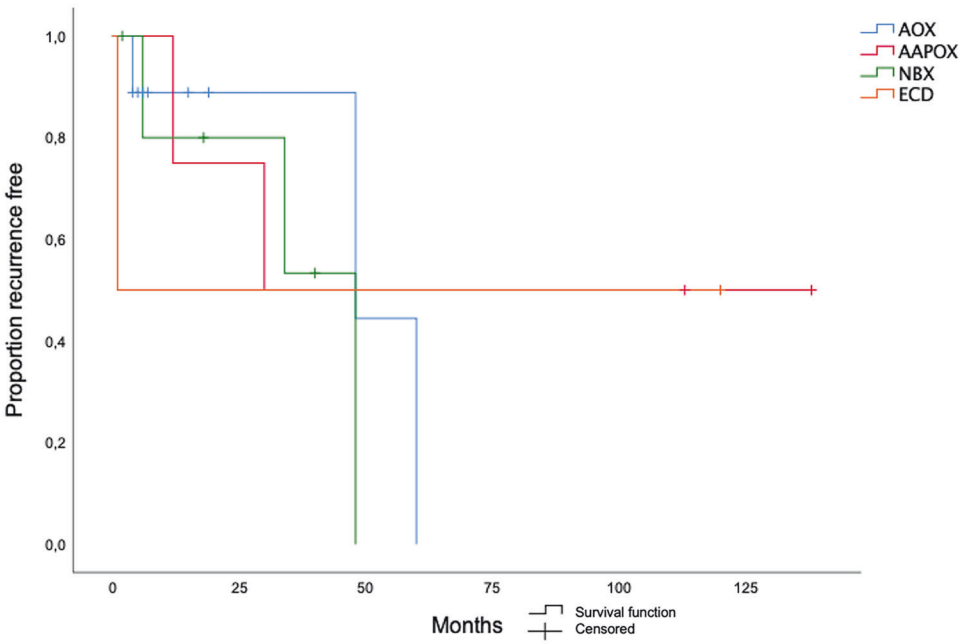

Fig. 1 Kaplan-Meier curve of the proportion of patients with recurrence-free survival. AAPOX adult-onset asthma and periocular xanthogranuloma, AOX adult onset xanthogranuloma, ECD Erdheim-Chester disease, NBX necrobiotic xanthogranuloma.

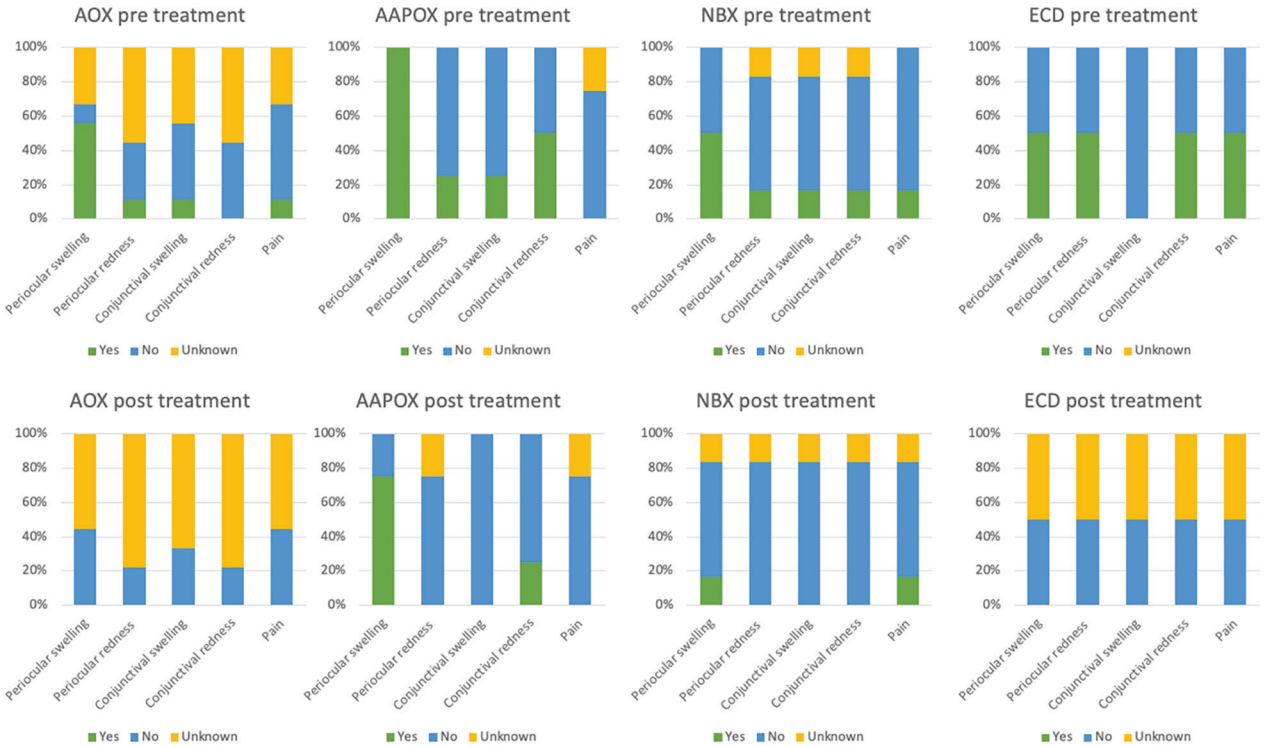

Fig. 2 Ophthalmic soft tissue signs before and after treatment. AAPOX adult-onset asthma and periocular xanthogranuloma, AOX adult onset xanthogranuloma, ECD Erdheim-Chester disease, NBX necrobiotic xanthogranuloma.

due to a massive cerebrovascular event caused by a floating thrombus in his carotid artery, complicated by sepsis, kidney insufficiency, ileus and multiple thrombo-embolic events during the hospitalization.

The ECD was clinically and radiologically stable for years, without signs of cardiac involvement. Therefore, the cerebrovascular event did not seem to be directly related to his ECD and was dedicated to cardiovascular disease.

Soft Tissue Signs

Before the treatment, 13 patients showed periocular swelling, four periocular redness, three conjunctival swelling and four conjunctival redness. Three patients experienced pain before treatment. After treatment, four patients experienced periocular swelling, one conjunctival redness, and one patient still had pain. None of the patients showed periocular redness or conjunctival swelling after treatment (Fig. 2). Unfortunately, not all soft tissue signs were documented before and after treatment.

Reconstructive surgery

Six patients required reconstructive surgery after the primary treatment of AOXGD. Of these patients three patients were treated with debulking surgery only and developed eyelid malposition: one ptosis and two ectropion. Two patients were treated with debulking surgery and additional systemic therapy. One of these patients required a ptosis correction and a lower eyelid correction with scleral inlay. The other patient required ectropion correction.

One patient received prednisolone, but this was insufficient for the proptosis. This patient required orbital decompression and lower eyelid reconstruction with scleral inlays.

DISCUSSION

This series of patients with AOXGD is of considerable size with the longest follow-up time to date. This study showed that the clinical course of patients with AOXGD varies greatly, depending on the subtype.

In this series, the ophthalmic parameters like vision, intra-ocular pressure, or exophthalmos did not differ before or after treatment, but the soft tissue signs improved. Treatment depended on clinical symptoms and differed between the subtypes of AOXGD. Various treatment strategies have been described, without consensus. Surgery and systemic therapy both come with possible side effects [25].

For the treatment of AOX and AAPOX without systemic conditions, surgical debulking alone may be effective. However, complete resection might not be feasible due to the infiltrative nature of the lesions and despite the excision the lesion may recur [25]. In this study, we found that in patients with AOX surgery might be sufficient for some and therefore spare them systemic treatment with possible side effects. Patients with AAPOX showed that surgery alone was insufficient and all patients required systemic therapy. AOX, AAPOX, NBX, and ECD have similar histopathological features, although necrobiosis typically (and by definition) is only present in NBX. The subtypes may represent a spectrum disease [1]. Perhaps the presence of systemic involvement and bilaterality might indicate disease more likely to require additional systemic therapy. However, both AOX and AAPOX could result in sight-threatening disease and this might be an indication for systemic therapy, regardless of systemic involvement. It is of note that the patients with AOX required systemic therapy less often and in lower doses than patients with AAPOX. Most patients with NBX and both patients with ECD required systemic therapy.

No difference is seen in the development of eyelid malposition in patients who received additional systemic therapy compared to debulking surgery alone.

The retrospective design of the current study is subject to limitations. First, there is some missing data because not all parameters could be collected from the medical records available. Second, in our cohort, all patients showed progressive incapacitating symptoms that all required treatment. In this

light, the natural history of this set of diseases could not be evaluated.

AOX is a rare non-LCH and presents with infiltration of the orbital and periorbital tissues. It may present at any adult age and has no systemic involvement [3]. Treatment often exists of surgical excision [3, 4]. In our series, 22% required additional systemic therapy and 50% showed recurrence. One patient with AOX was diagnosed with IgG4-RD years later and still has regular follow-up appointments to this day. AOX might be associated with IgG4-RD [26–28]. It is well recognized that many inflammatory diseases have raised IgG4-positive plasma cells on histopathology and this is a common finding in AOXGD [24, 27]. However, histomorphologic features also need to meet the Boston Consensus Criteria for the diagnosis IgG4-RD can be made [29].

AAPOX presents similarly to AOX, but is associated with late-onset asthma [17]. AAPOX may also be associated with lymphadenopathy, lymphoma or IgG4-RD [3–9, 30, 31]. In this series, one patient had concurrent IgG4-RD, and two patients lymphadenopathy. Despite showing a similar presentation as AOX, the treatment of patients with AAPOX required more than surgery alone as compared to the treatment of most AOX patients. The disease recurred in two of the four patients. In the literature, systemic steroids alone showed a good response in some cases, but often with disease recurrence upon tapering [32].

NBX is a subtype of non-LCH, histopathologically characterized by the presence of necrobiosis in the lesions. NBX is associated with extra-orbital lesions and with monoclonal gammopathy or other hematologic malignancies [4, 10–14]. In concurrence with the literature, patients with NBX in this study showed lesions of the skin, parotid gland, and lymph nodes. Further, two patients were diagnosed with a hematologic malignancy, one with chronic lymphatic leukaemia and one with T-cell lymphoma. Most patients required systemic treatment. Recurrence occurred in three patients. One patient in this series was repeatedly treated with intralesional steroids, with reports of varying success in the literature [33, 34].

ECD is the most devastating subtype of non-LCH and well described in the literature. The lesions are more often diffuse intra-orbital compared to other subtypes of AOXGD. The long bones and several organs can be involved in about 80% of the patients. The orbital lesions tend to be therapy resistant, as seen in both patients [2, 4, 15]. The clinical course was fatal in one patient.

Treatment of AOXGD with steroid-sparing agents have been described with various success rates. Treatment with methotrexate and azathioprine showed some success, however, multiple patients could not tolerate the side effects and discontinued the treatment [20, 23]. Cyclophosphamide has been used in recalcitrant NBX with conflicting results [35, 36]. In our patients, cyclophosphamide was ineffective. Side effects of steroid-sparing therapy in this study were also noted and included fatigue, weight loss, muscle aches, and nausea.

Since the prognosis and associated systemic conditions vary between the subtypes, a thorough diagnostic work-up is warranted. Imaging of the orbit is made to localize the lesion. A biopsy should be obtained and histopathologic examination should focus on foamy histiocytes, lymphocytes, Touton giant cells, fibrosis, and necrobiosis in patients with NBX. Immunohistochemically, the foamy histiocytes are generally positive for common histiocytic markers such as CD14, CD68 and CD163 and negative for S100 and CD1a [37]. AOXGD lesions tend to be indurated, deeper and more diffuse than xanthelasma palpebrarum. Histopathology of xanthelasma palpebrarum also shows large foamy histiocytes, but very few other cells and generally no Touton giant cells [2, 38]. Due to sampling error, NBX can be missed when necrobiosis is not present in the biopsy.

The patients in this study received a SPECT or FDG-PET scan to search for any systemic lesions, lymphoma of lymphadenopathy. A full blood work needs to be performed, with emphasis on signs for monoclonal gammopathy and hematologic malignancies.

There has been debate whether histiocytosis is of a reactive or neoplastic nature. The mitogen-activated protein kinase (MAPK) pathway is a cellular signalling pathway that regulates cell proliferation and survival. Genes might undergo mutations that may activate signalling elements that lead to autonomous growth and transformation [39]. Multiple mutations involving BRAF V600E, MEK1, MEK2, ARAF, KRAS, and NRAS genes in the MAPK pathway have been found in patients with histiocytic and related disorders including ECD, AAPOX, and juvenile xanthogranuloma [40–46]. Treatment targeted against BRAF- or MAPkinase mutations have been shown effective in various histiocytic disorders and might indicate a possible role for targeted therapy in the treatment of AOXGD.

CONCLUSION

AOXGD are rare and diagnosis and treatment might pose challenges. Due to its rarity, optimal treatment guidelines have not been established for AOXGD. Recognition of these disorders is important for the sometimes-severe systemic associations in the different subtypes. A complete diagnostic work-up is necessary, including full-body imaging and blood work. The prognosis depends on the subtype of AOXGD and treatment and surveillance must be tailored to this and to the individual patient. Surgical debulking might be sufficient therapy for patients with AOX. Patients with AAPOX, NBX, and ECD need systemic therapy. Currently, there is no conclusive evidence that one treatment strategy is superior than the other. Therefore, further studies are necessary to investigate treatment options.

SUMMARY

What was known before

- Adult orbital xanthogranulomatous disease is a group of rare type II Non-Langerhans cell histiocytosis with four subtypes.
- Due to its rarity, optimal treatment guidelines have not been established.

What this study adds

- Surgical debulking might be sufficient therapy for patients with adult-onset xanthogranuloma.
- Patients with adult-onset asthma and periocular xanthogranuloma, necrobiotic xanthogranuloma and Erdheim-Chester disease need systemic therapy.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

All authors were involved in the design of the study. RV evaluated all haematoxylin and eosin slides for the correct histopathological diagnosis. SD, GH, and DP performed the analyses. SD wrote the manuscript. DP, JvL, RM, GH, RdK, and PvH advised and reviewed the manuscript. All authors conform that neither this manuscript nor part of it has been published and is not under consideration for publication elsewhere.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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