EXTENDED REPORT

Adult xanthogranulomatous disease of the orbit and ocular adnexa: new immunohistochemical findings and clinical review

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Background/aims: Adult xanthogranulomatous disease involving the ocular tissues is rare and poorly understood. Adult onset xanthogranuloma (AOX), adult onset asthma and periocular xanthogranuloma (AAPOX), necrobiotic xanthogranuloma (NBX), and Erdheim-Chester disease (ECD) are the four syndromes within this disorder, which is diagnosed by characteristic histopathology. Experience with eight cases prompted a multi-institutional effort to study the histopathology, immunohistochemistry, clinical findings, and systemic associations in this disorder.

Methods: 22 cases, including histopathological slides, were compiled. Published reports were identified by an English language Medline search (1966–2005) and review of reference citations. Each case in this series and the literature was classified as one of four syndromes and then analysed for age onset, sex, skin xanthoma, orbital location, immune dysfunction, internal organ and bone lesions, treatment, and outcome. The histopathology in each of these cases was reviewed by two pathologists. Immunohistochemical stains (CD3, CD4, CD8, L26) were performed in 14 cases where unstained slides were available.

Results: 137 cases were compiled. There was no sex or age difference between syndromes. AOX, AAPOX, NBX affect the anterior orbit, ECD tends to be diffuse and intraconal. Skin lesions are found in all the syndromes. Immune dysfunction was noted in all cases of AAPOX and NBX; 11% of NBX and all ECD patients had internal organ disease. Treatment included surgery, corticosteroids, other chemotherapeutic agents, radiotherapy, and combinations of these. No AOX or AAPOX deaths occurred; 66% of ECD patients died. All 22 cases had xanthoma cells; most had Touton giant cells. Lymphocytes were present in all cases and occurred as aggregates (mostly in AAPOX) or diffuse populations mixed with fibroblasts (mostly in ECD). Immunohistochemistry revealed the majority of these to be CD8+. Necrosis was most marked in NBX.

Conclusion: Adult xanthogranuloma of the orbit is rare, making prospective evaluation or meta-analysis impossible. The best treatment is unknown but seems to be with multiagent chemotherapy guided by histopathological, immunohistochemical, and systemic findings.

Adult xanthogranulomatous disease involving the ocular or orbital tissues is rare and constitutes a group of entities with varying manifestations that are poorly understood. These are non-Langerhans histiocytic disorders (type II) that are diagnosed histopathologically by the presence of foamy histiocytes, Touton giant cells, and varying degrees of fibrosis and, in some entities, necrosis. Personal experience with eight cases prompted us to organise a multi-institutional effort to study the histopathology, immunohistochemistry, clinical findings, and systemic associations of this group of disorders, which included a comprehensive review of the English language literature.

METHODS

Clinical case series and review of published articles

Twenty two cases were collected, eight from the University of British Columbia and 14 from other institutions; eight of the latter have been previously reported. Based on systemic associations, there are four syndromes that comprise the disorder of adult xanthogranuloma^{1–3}:

- Adult onset xanthogranuloma (AOX) (solitary lesion without systemic findings)

- Adult onset asthma and periocular xanthogranuloma (AAPOX)
- Necrobiotic xanthogranuloma (NBX)
- Erdheim-Chester disease (ECD).

We classified each case as one of these four syndromes and then analysed for onset age, sex, location of the orbital/adnexal lesion, skin xanthomas, internal organ involvement, bone lesions, immune dysfunction (including asthma, para-proteinaemia, lymphadenopathy, and other lymphoproliferative disorders), treatment, and outcome.

A search was conducted using the Medline database (1966–2005) for English language publications, and all identified articles and their reference citations were reviewed. Each case of orbital xanthogranulomatous disease was classified and analysed in the same fashion as our case series. Data obtained from reported cases and from our cases were then pooled and analysed.

Abbreviations: AAPOX, adult onset asthma and periocular xanthogranuloma; AOX, adult onset xanthogranuloma; ECD, Erdheim-Chester disease; MGUS, monoclonal gammopathy of undetermined significance; NBX, necrobiotic xanthogranuloma

Table 1 Number, mean age, and sex distribution of patients with orbital xanthogranuloma

Syndrome	Pooled age data	Sex distribution*								
		Our series			Literature†			Pooled data		
		Males	Females	Total	Males	Females	Total	Males	Females	Total
AOX	50 (15) range 38–79	3	0	3	0	5	5	3	5	8
AAPOX	46 (13) range 22–74	7	4	11	7	3	10	14	7	21
NBX	57 (14) range 20–85‡	2	2	4	30	38	68	32	40	72
ECD	53 (13) range 17–77	3	1	4	21	11	32	24	12	36
Total	¶	15	7	22	58	57	115	73	64	137

* χ^2 testing showed no sex preference (χ^2 observed = 6.34, $p = 0.095$).

†References 1–3, 6–12, 15–25, 28–30, 33–35, 38–43, 60–62.

‡Does not include Ugurlu *et al*'s series (mean 57, range 26–79) or Robertson and Winkelmann's series (mean 54, range 39–73).^{6,7}

¶Nominal logistic regression showed no significant difference in mean age ($p = 0.059$).

Table 2 Anatomical location of ocular adnexal/orbital lesions

Syndrome	Our series			Literature*		
	Preseptal/ anterior	Intermediate	Diffuse/apical/ intracranial	Preseptal/ anterior	Intermediate	Diffuse/apical/ intracranial
AOX	3/3			2/4		2/4
AAPOX	10/11	1/11		10/10		
NBX	4/4			8/9†	1/8	
ECD			4/4	1/16		15/16‡

*References 1–3, 6–12, 15–25, 28–30, 33–35, 38–43, 60–62.

†Unable to determine from Robertson and Winkelmann's or Mehregan and Winkelmann's series (NBX).^{7,8}

‡Unable to determine number from Veyssier-Belot's series (ECD).²⁸

Statistical analysis

For each syndrome, the mean age and standard deviation were determined and analysed using nominal logistic regression. A p value <0.05 was considered significant. The sex distribution of all the cases was analysed using the χ^2 test.

Histopathology and immunohistochemistry

Haematoxylin and eosin as well as Masson's trichrome stained slides were obtained for all 22 cases and reviewed by two pathologists. All slides were specifically evaluated for foamy histiocytes, Touton giant cells, lymphocytic infiltrate, and presence of fibrosis and necrosis. The immunohistochemical examination focused on the lymphocyte population and included CD3 (T cell), CD4 (T helper cell), CD8 (T suppressor cell, cytotoxic), and L26 (B cell). This was performed on 14 of the cases where additional unstained slides were available.

RESULTS

Clinical case series and review of published reports

Between this case series and published reports, 137 cases of adult xanthogranulomatous disease of the orbit and adnexa were compiled, including eight classified as AOX, 21 as AAPOX, 72 as NBX, and 36 as ECD (table 1). Four cases of periorbital xanthogranuloma were unclassifiable and were not included in this analysis.^{4,5} Nominal logistic regression using the pooled data revealed no significant difference in the mean age of patients with each syndrome ($p = 0.059$). The average age of patients with NBX in this study was similar to that of reported series.^{6,7} There was no sex preference (χ^2 observed = 6.34, $p = 0.095$) (table 1).

Patients classified as AOX, AAPOX, and NBX typically had preseptal and anterior orbital involvement (table 2, figs 1, 2, 4). Intraconal involvement was evident in two cases of AOX, one of AAPOX, and one of NBX (fig 3). In contrast, all but one patient with ECD had diffuse intraconal disease (fig 5). Eyelid skin lesions were noted in all syndromes: four of eight AOX (50%), 20 of 21 AAPOX (95%), 53 of 62 NBX (85%), and

15 of 36 ECD (42%). Overall, 72% (92 of 127) had periorbital skin manifestations (table 3). Evidence of immune dysfunction was denoted by the presence of asthma, lymphadenopathy, paraproteinaemia or other lymphoproliferative lesions including multiple myeloma, lymphoma, and chronic lymphocytic leukaemia (table 4). All AAPOX and NBX cases had evidence of immune dysfunction. In AAPOX, the dysfunction tended to be asthma and reactive (benign) lymphadenopathy; other lymphoproliferative disorders included our case of Burkitt's lymphoma and one report of non-Hodgkin's lymphoma. In NBX, immune dysfunction was usually paraproteinaemia, either monoclonal gammopathy of undetermined significance (MGUS) or multiple myeloma.⁸ Other lymphoproliferative disorders in NBX included a single case each of non-Hodgkin's lymphoma, Hodgkin's disease and lymphosarcoma.^{6,7,9} By our criteria, there was no evidence of immune dysfunction in AOX and only one case of ECD had evidence of immune dysfunction.¹⁰

All ECD cases had internal organ dysfunction, including pericardial or pleural effusions, retroperitoneal involvement,

Figure 1 Adult onset xanthogranuloma. (A) Clinical photograph of a 42 year old white male with 8 year history of bilateral, yellow, palpable, firm, rubbery masses restricting lid elevation. He was treated with surgical debulking and had no evidence of systemic disease. (B) Computed tomography scan showing homogeneous infiltration of the preseptal and anterior orbital tissues including the lacrimal gland. Reproduced with permission.

Figure 2 Adult onset asthma and periocular xanthogranuloma. (A) Clinical photograph of a 46 year old white male with 3 year history of bilateral, rubbery, yellow lid lesions, and facial fullness. Associated findings included three separate lymph node biopsies showing reactive change, 20 years earlier, adult onset asthma diagnosed 15 years earlier, submandibular and cervical lymphadenopathy (arrow), allergic sinusitis with nasal polyps, and autoimmune thyrotoxicosis. The patient was treated with 2000 cGy in 10 fractions to both orbits with worsening condition. Cyclosporin 250 mg/day and prednisone 10 mg/day led to improvement, but 1 year later he developed Burkitt's lymphoma. (B) During bone marrow suppressive treatment he had resolution. (C) He has done well when maintained on prednisone 8 mg/day at 2 year follow up. (D and E) Computed tomography scan at initial presentation showing bilateral infiltration of the extraocular muscles, lacrimal glands, and lids and at 2 year follow up. Reproduced with permission.

Figure 3 Adult onset asthma and periocular xanthogranuloma. (A) Clinical photograph of a 74 year old Indian male with bilateral, progressive proptosis, firm, periocular xanthogranuloma, limited ocular movements, and decreased vision. Associated findings included adult onset asthma. (B) The patient had return of vision and reduction in lesion size after corticosteroid and cyclosporin treatment. (C) CT scan showed diffuse, irregular anterior and extraconal infiltrates. Reproduced with permission.

Figure 4 Necrobiotic xanthogranuloma. (A and B) Clinical photograph of a 69 year old white female with 1 year history of yellow, subcutaneous and subconjunctival infiltrates, pain, diplopia, tearing, and blurred vision. Associated findings included elevated IgG at 31.7 g/l (8–18 g/l) and a similar leg lesion. She was initially treated with prednisone 40 mg/day and then maintained on 5 mg/day without change for 6 years. (C) Computed tomography scan showed prominent, enhancing, soft tissue masses around each globe, a thickening medial rectus muscle, and increased fat density on the right. Reproduced with permission.

perinephric and mediastinal infiltrations, diabetes insipidus, brain and dural masses and hepatosplenomegaly (table 4). Eight of 71 (11%) patients with NBX had clinically identifiable internal organ lesions, including one patient with pancreatitis in our series. One AAPOX case had a low testosterone level. No patient with AOX had known internal organ disease.^{11–12} Bone lesions were present in 29 of 33 (89%) patients evaluated for such; all had ECD (table 4).

The treatment modalities employed were surgery, administration of corticosteroids and/or other chemotherapeutic agents, radiation, and combinations of these. Surgery alone was effective in AAPOX (6/8, 75%) and one case of NBX, whereas corticosteroids were useful in some cases of AAPOX (2/2), NBX (8/24, 33%), and ECD (7/24, 29%). Other immunosuppressive agents were beneficial in 31 of 52 cases

(60%). In our series, the most frequent beneficial agents were cyclosporin and cyclophosphamide. In some reports, management, including cyclophosphamide, melphalan, chlorambucil, vincristine, vinblastine, interferon, etoposide, methotrexate, etanercept, gammaglobulin, clofazimine, and doxorubicine, led to improvement. Radiation was effective in four of six (67%) NBX cases. Despite treatment, two of our patients died (one each with NBX and ECD). Of patients reported in the literature, those with NBX had a 90% survival rate at 15 years⁶ whereas 21 of the 32 (66%) patients with ECD died. No death was reported among patients with AOX or AAPOX. Based on immunohistochemical evidence of T cell influx, two of our patients were treated successfully in a novel way using corticosteroids, cyclophosphamide (B cell suppression), and cyclosporin (T cell suppression).

Figure 5 Erdheim-Chester disease. (A) Clinical photograph of a 67 year old Asian female with 4 month history of bilateral, progressive, painless vision loss, proptosis, and decreased extraocular movements. Associated findings included long bone sclerosis and hypertension secondary to retroperitoneal/perinephric fibrosis. The patient was treated with methylprednisolone, 1 g every other day for three doses, followed by prednisone 40 mg/day and cyclophosphamide 100 mg/day. She had initial improvement in vision but then declined to no light perception on the right and hand motions on the left. The patient died 4 months after presentation. (B) Contrasted computed tomography scan showing bilateral, intraconal, homogeneous, mildly enhancing masses with smooth margins. The extraocular muscles are obscured, and the optic nerves are displaced superomedially and appear thin. Reproduced with permission.

Histopathology and immunohistochemistry

All cases studied histopathologically had xanthoma cells and most had Touton giant cells infiltrating the tissue. In cutaneous specimens, the infiltrate extended deeply into subcutaneous tissue and orbicularis muscle. The lesions were poorly circumscribed, especially when xanthoma cells were admixed with inflammatory cells and fibroblasts (fig 6).

Lymphocytes were observed in all cases and occurred in two patterns: aggregates or a diffuse population admixed with proliferating fibroblasts. The lymphoid aggregates varied in size and number, from large and numerous to absent, and were most abundant in AAPOX (fig 6B). They had typical germinal centres; small “burnt out” or ill defined germinal centres were not a feature. Secondary follicles exhibited the usual immunohistochemical profile of B cells within germinal centres and a T cell rich population in the perifollicular zone.

The diffuse population of lymphocytes was intimately admixed with proliferating fibroblasts. This population was seen in all the syndromes but was most frequent in ECD, which had more areas of fibrosis and fewer follicles than the other syndromes. Immunohistochemistry showed the majority of these diffuse lymphocytes to be CD8 positive suppressor cells with little evidence of influx of CD4 helper/inducer cells or B cells (table 5, fig 6D–E). Other inflammatory cells, especially eosinophils and plasma cells were seen but were never the dominant population. Angiocentric inflammation was not present in any case.

Necrosis was most marked in the cases of necrobiotic xanthogranuloma, represented by geographic areas of necrosis surrounded by a palisade of epithelioid histiocytes, and seen only in one case of AAPOX (fig 6C).

DISCUSSION

In 1987, the Histiocyte Society Writing Group classified histiocytic disorders into three categories: class I (Langerhans cell histiocytosis-histiocytosis X spectrum), class II (histiocytoses of mononuclear phagocytes other than Langerhans cells) (table 6), and class III (malignant histiocytic disorders).¹³ Adult xanthogranulomatous disease, which falls within class II, is uncommon, generally affects middle aged individuals without sex predilection (table 1), and can present as subcutaneous, subconjunctival and periocular xanthochromic infiltrates with varying mass formation.

Adult ocular adenexa/orbit xanthogranuloma are often associated with other systemic manifestations. These are the basis for classification into the four syndromes: adult onset xanthogranuloma (AOX), adult onset asthma with periocular xanthogranuloma (AAPOX), necrobiotic xanthogranuloma (NBX) and Erdheim-Chester disease (ECD). NBX is the most frequently reported followed by ECD, AAPOX, and AOX (table 1).

AOX is an isolated xanthogranulomatous lesion without systemic involvement (figs 1 and 6A). There are two reports of this condition that were termed adult onset juvenile xanthogranuloma of the orbit.¹² Juvenile xanthogranuloma is a separate non-Langerhans histiocytic disorder that occurs as a self limited, corticosteroid sensitive and usually focal subcutaneous disease of childhood^{11 14} (table 6).

AAPOX is a syndrome (periocular xanthogranuloma associated with asthma) that was described by Jakobiec *et al.*¹ In addition to asthma, cases of APPOX in our series had lymphadenopathy and often increased IgG levels (polyclonal), suggesting an underlying stimulation and proliferation of B cell populations (figs 2, 3, 6B). Our search for reported cases identified four additional cases with associated asthma and one with an increased IgG level (polyclonal) and lymphadenopathy.^{15–17}

NBX is characterised by the presence of subcutaneous skin lesions in the eyelids and anterior orbit, which also may occur throughout the body. Although skin lesions are seen in all the syndromes, those in NBX have a strong propensity to ulcerate and fibrose. Frequent systemic findings include paraproteinaemia and multiple myeloma^{2 6–9 18–25} (figs 4, 6C). Internal organ involvement occurs in NBX, but is often found only at autopsy.⁸

ECD, the most devastating of the adult xanthogranulomas, is characterised by dense, progressive, recalcitrant fibrosclerosis of the orbit and internal organs, including the mediastinum, pericardium and pleural, perinephric,^{26 27} and retroperitoneal spaces. While the orbit/adenexal xanthogranuloma tends to be anterior in AOX, AAPOX, and NBX, it is often diffuse in ECD and leads to visual loss (fig 5, table 2). Bone involvement is common and death frequent despite aggressive therapies^{3 10 28–43} (figs 5, 6D–E).

While the majority of published cases were able to be classified as one of the four syndromes, there are four

Table 3 Periocular skin findings

Syndrome	Our series	Literature*	Pooled data
AOX	3/3	1/5	4/8
AAPOX	10/11	10/10	20/21
NBX	3/4	50/58†‡	53/62
ECD	1/4	14/32¶	15/36
Total	17/22	75/105	92/127

*References 1–3, 6–12, 15–25, 28–30, 33–35, 38–43, 60–62.
†In Ugurlu *et al*'s series, 11 of 26 patients (42%) had ulceration (NBX).⁶
‡In Robertson and Winkelmann's series, all 16 patients also had skin lesions elsewhere (NBX).⁷
¶In Veyssier-Belot *et al*'s series, 11 cases were noted to have xanthoma-like lesions on the eyelids. There were cases with skin lesions elsewhere but the number is not specified (ECD).²⁸

Table 4 Systemic findings associated with orbital xanthogranuloma.

Syndrome	Immune dysfunction				Paraproteinaemia		Lymphadenopathy		Other lymphoproliferative*		Pooled	Internal organ dysfunction		Bony lesions	
	Asthma										Pooled				
	Our series	Literature†	Our series	Literature†	Our series	Literature	Our series	Literature†	Our series	Literature†		Our series	Literature†	Our series	Literature†
AOX	0/3	0/5	0/1	0/5	0/3	0/5	0/3	0/5	0/3	0/5	0/8	0/3	0/5	0/1	0/4
AAPOX	8/11	10/10	3/5	2/9	7/11	1/9	1/7	0/10	1/7	0/10	21/21	1/11	0/10	0/1	0/7
NBX	1/4	3/21	2/4	54/54	1/4	2/2	2/4	7/56	2/4	7/67¶	71/71	1/4	7/67¶	0/1	0/1
ECD‡	0/4	1/30	0/3	0/3	0/4	0/30	0/3	0/30	0/3	0/30	1/34	4/4	32/32	3/4	26/27

*Includes lymphoma, multiple myeloma, and lymphadenopathy.

†References 1–3, 6–12, 15–25, 28–30, 33–35, 38–43, 60–62.

‡In Veyssier-Belot *et al*'s series of ECD, one patient had a myeloproliferative disorder but did not have orbital disease.²⁸¶In Mehregan and Winkelmann's series, many internal organ lesions in NBX were noted to be silent, found only at autopsy.⁸

published reports that fall between AOX and AAPOX/NBX. These patients had periocular xanthogranuloma and other blood dyscrasias including thrombocytopenia, paraproteinaemia and monoclonal gammopathy of undetermined significance.^{4, 5}

The xanthogranulomas have a histopathological appearance that is common to all forms, and thus they cannot be subclassified on histopathological grounds alone. The histopathological hallmarks are the presence of non-Langerhans lipid laden histiocytes and Touton giant cells (fig 6). Non-Langerhans histiocytes tend to be s100, MAC387, and LeuM1 negative, and positive for Ln3 and KiM1p.⁴⁴ Lymphocytic infiltration, fibrosis, and necrosis are also present but these can vary within the same specimen and between cases and, moreover, change with time and treatment. Although these features are common to all adult xanthogranuloma, certain features can suggest a specific syndromic association. For instance, necrosis (necrobiosis) with palisading epithelioid histiocytes is most often seen in NBX whereas large lymphoid aggregates with germinal centers are often found in cases of AAPOX (fig 6C and B). ECD exhibits florid fibrosis with fewer follicles and more dispersed lymphocytes and lipid laden histiocytes (fig 6D). These histopathological differences may correlate with the associated findings in each of the syndromes. NBX tends to have clinical ulcerative lesions, which correlates with necrobiosis. AAPOX is associated with lymphadenopathy and B cell dysfunction (including asthma and paraproteinaemia) and histologically has B cell lymphoid aggregates. The fibrosclerosis seen ECD is responsible for the internal organ and orbital mass effect seen clinically.

While clinical and histopathological description are useful academic endeavours, ultimately, we hope to positively affect the treatment of patients with adult xanthogranuloma. But, the rarity of this disease precludes prospective investigation or meta-analysis, making the outcome of therapy extremely difficult to evaluate because of conflicting reports and the multiple modalities used in all these syndromes. Current treatment regimens are often ineffective, especially in ECD. Two of our patients, with NBX and ECD respectively, died; 21 of 32 reported patients with ECD died between 3 months and 15 years after diagnosis.^{3, 10, 28–39, 41–43} The best results seem to have been obtained with multiagent chemotherapy, with or without radiation or surgery. While comprehensive examination establishes the degree of the disease, a thorough understanding of the histopathology and immunohistochemistry are necessary to guide therapy.

To this end, we found the dominant diffuse lymphocytic infiltrate was T cells (CD3 positive) with a subset of CD8 (cytotoxic) cells in areas of fibrosis and lipophage accumulation (fig 6E). In other disorders (such as Graves' disease, myelofibrosis, parabronchiolitis, sclerosing orbital inflammation and retroperitoneal and mediastinal fibrosis),^{45–58} granulomatous inflammation with fibroplasia appears to be activated by T cells; therefore, we treated two of our patients with ciclosporin and cyclophosphamide. In addition, there may be a rationale for systemic B cell suppression in the management of AAPOX and NBX. Myra *et al* have had a unique case of ECD with a monocytosis with specific cytokine activation that responded to cladribine, a purine analogue toxic to monocytes.⁵⁹ Further developments in immunohistochemistry, selective immunotherapeutic and chemotherapeutic agents, and a better characterisation of the histiocytes may lead to better treatment options. Because the best reported results were obtained with multiagent chemotherapy, and because of our success with ciclosporin combined with cyclophosphamide and our new immunohistochemical findings, we recommend that clinical features be correlated with histopathological B and T cell findings when choosing an immunosuppressive agent for treatment.

Figure 6 Pathology. (A) Haematoxylin and eosin stain (20× magnification) of case of AOX showing foamy histiocytes and Touton giant cells (arrow). (B) Haematoxylin and eosin stain (10× magnification) of AAPOX case with prominent follicle formation. (C) Haematoxylin and eosin stain (10× magnification) of NBX case demonstrating necrobiosis (arrow). (D) Haematoxylin and eosin stain (10× magnification) of ECD case demonstrating foamy histiocytes and Touton giant cells with lymphocytic infiltrate and fibrosis. (E) CD8 stain (20× magnification) of ECD case showing predominance of CD8+ cells.

Table 5 Stromal immunohistochemistry of 14 patients diagnosed with orbital xanthogranuloma

Case number	CD3 (T cell)	CD4 (T helper cell)	CD8 (suppressor, cytotoxic)	L26 (B cell)
Adult onset xanthogranuloma (AOX)				
1	+2	+2	0	0
2	+3	0	+2	0
3	+3	+1	+3	+1
Adult onset asthma and periocular xanthogranuloma (AAPOX)				
4	+3	0	+3	0
5	+3	0	+3	0
6	+3	0	+2	+1
7	+3	+1	+2	0
8	+2	0		
9	+3	+1	+3	0
12	+3	0	+3	0
13	+3	0	+3	0
Necrobiotic xanthogranuloma (NBX)				
15	+4	0	+4	0
16	+2	0	+2	0
Erdheim-Chester disease (ECD)				
22	+3	0	+2	+1
Average	2.9	0.4	2.5	0.2

Table 6 Non-Langerhans disorders of histiocytes

- Xanthogranulomatous disease of adults
- Juvenile xanthogranuloma
- Benign cephalic histiocytosis
- Papular xanthoma
- Multicentric reticulohistiocytosis
- Xanthoma disseminatum
- Reticulohistiocytoma
- Generalised eruptive histiocytoma
- Sinus histiocytosis with massive lymphadenopathy
- Self healing reticulohistiocytosis
- Indeterminate cell histiocytosis

Data from Zelger *et al.*⁴⁴

disease is so rare, a prospective evaluation of treatment will not be possible. Nevertheless, our understanding of xanthogranulomatous disease will be advanced by comprehensive assessment for systemic manifestations, and histopathological study of tissue specimens. New treatments may be guided by complete histopathological and immunohistochemical examination including study of B and T cell populations and perhaps cytokines. These syndromes emphasise the importance of the systemic context in the study of orbital disorders.

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CONCLUSION

The diagnosis of adult xanthogranulomatous disease is based on characteristic histopathological findings. Because this

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REFERENCES

- Jakobiec F, Mills M, Hidayat A, et al. Periocular xanthogranulomas associated with severe adult-onset asthma. *Trans Am Ophthalmol Soc* 1993;**91**:99–129.
- Bullock J, Bartley G, Campbell R, et al. Necrobiotic xanthogranuloma with paraproteinemia. *Ophthalmology* 1986;**93**:1233–6.
- Alper M, Zimmerman L, LaPiana F. Orbital manifestations of Erdheim-Chester disease. *Trans Am Ophthalmol Soc* 1983;**81**:64–85.
- Tang WK, Lee KC, Chong LY. Three patients with orbital xanthogranuloma and non-progressive haematological abnormalities. *Australas J Dermatol* 2003;**44**:185–9.
- Malhotra R, Porter RGB, Selva D. Adult orbital xanthogranuloma with periosteal infiltration. *Br J Ophthalmol* 2003;**87**:120–1.
- Ugurlu S, Bartley GB, Gibson LE. Necrobiotic xanthogranuloma: long-term outcome of ocular involvement. *Am J Ophthalmol* 2000;**129**:651–7.
- Robertson D, Winkelman R. Ophthalmic features of necrobiotic xanthogranuloma with paraproteinemia. *Am J Ophthalmol* 1984;**97**:173–83.
- Mehregan D, Winkelman R. Necrobiotic xanthogranuloma. *Arch Dermatol* 1992;**128**:94–100.
- Reeder C, Connolly S, Winkelman R. The evolution of Hodgkin's disease and necrobiotic xanthogranuloma syndrome. *Mayo Clin Proc* 1991;**66**:1222–4.
- van der Lee I, Elbers J. A patient with diabetes insipidus and periorbital swellings; Erdheim-Chester disease. *Neth J Med* 1999;**55**:76–9.
- Nasr A, Johnson T, Hidayat A. Adult onset primary bilateral orbital xanthogranuloma. Clinical, diagnostic and histopathologic correlations. *Orbit* 1991;**10**:13–22.
- Rouhiainen H, Nerdrum K, Puustjarvi T, et al. Xanthogranuloma juvenile—a rare cause of orbital swelling in adulthood. *Ophthalmologica* 1992;**204**:162–5.
- Moschella SL. An update of the benign proliferative monocyte-macrophage and dendritic cell disorders. *J Dermatol* 1996;**23**:805–15.
- Zimmerman LE. Ocular lesions of juvenile xanthogranuloma. Nevoxanthoendothelioma. *Am J Ophthalmol* 1965;**60**:1011–35.
- Miszkiel KA, Sohaib SA, Rose GE, et al. Radiological and clinicopathological features of orbital xanthogranuloma. *Br J Ophthalmol* 2000;**84**:251–8.
- Mencia-Gutierrez E, Gutierrez-Diaz E, Madero-Garcia S. Juvenile xanthogranuloma of the orbit in an adult. *Ophthalmologica* 2000;**214**:437–40.
- Hammond MD, Niemi EW, Ward TP, et al. Adult orbital xanthogranuloma with associated adult-onset asthma. *Ophthalm Plast Reconstr Surg* 2004;**20**:329–32.
- Rose GE, Patel BC, Garner A, et al. Orbital xanthogranuloma in adults. *Br J Ophthalmol* 1991;**75**:680–4.
- Char D, LeBoit P, Ljung B, et al. Radiation therapy for ocular necrobiotic xanthogranuloma. *Arch Ophthalmol* 1987;**105**:174–5.
- Cornblath W, Dotan S, Trobe J, et al. Varied clinical spectrum of necrobiotic xanthogranuloma. *Ophthalmology* 1992;**99**:103–7.
- Finan M, Winkelman R. Necrobiotic xanthogranuloma with paraproteinemia. *Medicine* 1986;**65**:376–88.
- Finelli L, Ratz J. Plasmapheresis, a treatment modality for necrobiotic xanthogranuloma. *J Am Acad Dermatol* 1987;**17**:351–4.
- Kossard S, Winkelman RK. Necrobiotic xanthogranuloma with paraproteinemia. *J Am Acad Dermatol* 1980;**3**:257–70.
- Novak P, Robbins T, Winkelman R. Necrobiotic xanthogranuloma with myocardial lesions and nodular transformation of the liver. *Hum Pathol* 1992;**23**:195–6.
- Tucker NA, Discepolo MJ, Blanco G, et al. Necrobiotic xanthogranuloma without dermatologic involvement. *Can J Ophthalmol* 1997;**32**:396–9.
- Murray D, Marshall M, England E, et al. Erdheim-Chester disease. *Clin Radiol* 2001;**56**:481–4.
- Scheer M, Hon M, Fruauff AA, et al. Perinephric xanthogranulomatosis: CT diagnosis and confirmation by CT-guided percutaneous biopsy. *J Clin Imaging* 2000;**24**:64–7.
- Veyssier-Belot C, Cacoub P, Caparros-Lefebvre D, et al. Erdheim-Chester disease: clinical and radiologic characteristics of 59 cases. *Medicine* 1996;**75**:157–69.
- Amrith S, Low C, Cheah E, et al. Erdheim-Chester disease: a bilateral orbital mass as an indication of systemic disease. *Orbit* 1999;**18**:99–104.
- Bancroft L, Berquist T. Erdheim-Chester disease: radiographic findings in five patients. *Skeletal Radiol* 1998;**27**:127–32.
- Chetrit J, Paradis V, Dargere D, et al. Chester-Erdheim disease: a neoplastic disorder. *Hum Pathol* 1999;**30**:1093–6.
- Gothardt M, Welcke U, Brandt D, et al. The role of bone scintigraphy in patients with Erdheim-Chester disease. *Clin Nucl Med* 2000;**25**:414–20.
- Kenn W, Stabler A, Zachoval R, et al. Erdheim-Chester disease: a case report and literature overview. *Eur Radiol* 1999;**9**:153–8.
- Kenn W, Eck M, Allolio B, et al. Erdheim-Chester disease: evidence for a disease entity different from Langerhans cell histiocytosis? Three cases with detailed radiological and immunohistochemical analysis. *Hum Pathol* 2000;**31**:734–9.
- Miller R, Sheeler L, Bauer T, et al. Erdheim-Chester disease: case report and review of the literature. *Am J Medicine* 1986;**80**:1230–7.
- Molnar C, Gottschalk R, Gallagher B. Lipid granulomatosis: Erdheim-Chester disease. *Clin Nucl Med* 1988;**13**:736–41.
- Ono K, Oshiro M, Uemura K, et al. Erdheim-Chester disease: a case report with immunohistochemical and biochemical examination. *Hum Pathol* 1996;**27**:91–95.
- Rozenberg I, Wechsler J, Koenig F, et al. Erdheim-Chester disease presenting as malignant exophthalmos. *Br J Radiol* 1986;**59**:173–7.
- Sheidow T, Nicolle D, Heathcote J. Erdheim-Chester disease: two cases of orbital involvement. *Eye* 2000;**14**:606–12.
- Shields JA, Karciglu Z, Shields C, et al. Orbital and eyelid involvement with Erdheim-Chester disease. *Arch Ophthalmol* 1991;**109**:850–4.
- Tien R, Brasch R, Jackson D, et al. Cerebral Erdheim-Chester disease: persistent enhancement with Gd-DTPA on MR images. *Radiology* 1989;**172**:791–2.
- Valmaggia C, Neuweiler J, Fretz C, et al. A case of Erdheim-Chester disease with orbital involvement. *Arch Ophthalmol* 1997;**115**:1467–8.
- Wright A, Hermann R, Parisi J. Neurological manifestations of Erdheim-Chester disease. *J Neurol Neurosurg Psychiatry* 1999;**66**:72–5.
- Zelger B, Cerio R, Orchard G, et al. Juvenile and adult xanthogranuloma. A histological and immunohistochemical comparison. *Am J Surg Pathol* 1994;**18**:126–35.
- Postlethwaite AE. Role of T cells and cytokines in effecting fibrosis. *Int Rev Immunol* 1995;**12**:247–58.
- Jelaska A, Strehlow D, Korn JH. Fibroblast heterogeneity in physiological conditions and fibrotic disease. *Springer Sem Immunopathol* 2000;**21**:385–95.
- Jimenez SA, Saitta B. Alterations in the regulation of expression of the alpha-1(I) collagen gene (COL1A1) in systemic sclerosis (scleroderma). *Springer Sem Immunopathol* 2000;**21**:397–414.
- Le Bousse-Kerdiles MC, Martyre MC. Myelofibrosis: pathogenesis of myelofibrosis with myeloid metaplasia. French INSERM Research Network on Myelofibrosis with Myeloid Metaplasia. *Springer Sem Immunopathol* 2000;**21**:491–508.
- Pinzani M. Liver fibrosis. *Springer Sem Immunopathol* 2000;**21**:475–90.
- Eckes B, Kessler D, Aumailley M, et al. Interactions of fibroblasts with the extracellular matrix: implications for the understanding of fibrosis. *Springer Sem Immunopathol* 2000;**21**:415–29.
- Fonseca C, Abraham D, Black CM. Lung fibrosis. *Springer Sem Immunopathol* 2000;**21**:453–74.
- Chizzolini C. T lymphocyte and fibroblast interactions: the case of skin involvement in systemic sclerosis and other examples. *Springer Sem Immunopathol* 2000;**21**:431–50.
- Chizzolini C. Introductory note to: fibrosis year 2000. *Springer Sem Immunopathol* 2000;**21**:377–82.
- Bellinghausen I, Brand U, Steinbrink K, et al. Inhibition of human allergic T-cell responses by IL-10-treated dendritic cells: differences from hydrocortisone-treated dendritic cells. *J Allerg Clin Immunol* 2001;**108**:242–9.
- Wahl SM, Allen JB. T lymphocyte-dependent mechanisms of fibrosis. *Prog Clin Biol Res* 1988;**266**:147–60.
- Holgate ST, Djukanovic R, Howarth PH, et al. The T cell and the airway's fibrotic response in asthma. *Chest* 1993;**103**:1255–85.
- Fukuzawa M, Okada A, Shearer GM. Effect of FK 506 on CD4+ and CD8+ T-cell function in vivo. *Transplant Proc* 1991;**23**:2945–7.
- Bierer BE. FK 506 and rapamycin: molecular probes of T-lymphocyte activation. *Transplant Proc* 1991;**23**:2850–5.
- Myra C, Sloper I, Tighe PJ, et al. Treatment of Erdheim-Chester disease with cladribine: a rational approach. *Br J Ophthalmol* 2005;**89**:844–6.
- Karciglu ZA, Sharara N, Boles TL, et al. Orbital xanthogranuloma clinical and morphologic features in eight patients. *Ophthalm Plast Reconstr Surg* 2003;**19**:373–81.
- Serratrice J, Granel B, de Roux C, et al. "Coated aorta": a new sign of Erdheim-Chester disease. *J Rheumatol* 2000;**27**:1550–3.
- Shaudig U, Al-Samir K. Upper and lower eyelid reconstruction for severe disfiguring necrobiotic xanthogranuloma. *Orbit* 2004;**23**:65–76.