CASE REPORT

Adult-onset Xanthogranuloma Overlapping with IgG4-related Ophthalmic Disease: A Case Report

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An adult xanthogranulomatous disease of the orbit (AXDO) is a subset of non-Langerhans cell histiocytosis. IgG4-related disease (IgG4-RD) is a fibroinflammatory condition affecting multiple organs. The authors reported a case of 47-year-old woman of adult-onset xanthogranuloma (AOX) associated with IgG4-related ophthalmic disease (IgG4-ROD). She had yellow plaques with swelling of both periorbital areas for many years. Histopathological findings showed foamy histiocytes in the dermis with Touton giant cells along with inflammatory infiltrate of lymphocytes, plasma cells, and histiocytes with prominent germinal centers which were consistent with AOX. There were areas of increased fibrosis along with increased number of IgG4+ plasma cells and elevated serum IgG4 level which fulfill criteria of IgG4-RD diagnosis. There was no evidence of IgG4-RD in other organs. She was prescribed oral methotrexate with resulted in minimal improvement. Diagnosis of IgG4-RD in the setting of overlapping with dermatologic diseases is crucial because systemic work up is warranted.

Keywords: IgG4-related disease; IgG4-related ophthalmic disease; Periorbital xanthogranuloma; Adult-onset xanthogranuloma

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An adult-onset xanthogranuloma (AOX) is a type of adult xanthogranulomatous disease of the orbit (AXDO) which is a subset of non-Langerhans cell histiocytosis(1). IgG4-related ophthalmic disease (IgG4-ROD) is a subset of IgG4-related disease (IgG4-RD) which commonly involves the lacrimal gland and periorbital soft tissue(2). Concomitant AOX with IgG4-ROD cases were reported(3). Here, the authors reported another case of AOX overlapping with IgG4-ROD.

Case Report

A 47-year-old woman had swelling eyelids for 12 years with minimal improvement after surgical corrections. Previous investigations revealed bilateral lacrimal gland tumor from computed tomography (CT) of the orbit and dacryoadenitis from lacrimal gland biopsy. The lesions were initially improved after oral prednisolone 60 mg/day, but recurrence occurred after tapering. After a 5-year course of treatment, she lost to follow-up.

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Subsequently, she noticed progressive painless swelling with newly developed yellowish discoloration of periorbital areas leading to our hospital visit. Her past medical history was allergic rhinitis without asthma. She denied any systemic symptoms.

Physical examination showed yellow plaques with swelling of both periorbital areas (Figure 1a). Visual acuity and extraocular movement were normal. ENT examination showed nasal polyp on both sides. Examination of other systems was normal.

A histological examination from the left lower eyelid demonstrated discrete collections of foamy histiocytes throughout the dermis with Touton giant cells (Figure 2a-d). The orbital septum showed an inflammatory infiltrate of lymphocytes, plasma cells, and histiocytes. Prominent germinal centers and areas of increased fibrosis were detected (Figure 2e-h). Immunohistochemistry revealed infiltration of IgG4+ plasma cells which a ratio of IgG4+/IgG+ cells 90% and IgG4+ plasma cells 40/HPF (Figure 2i, j). Serum IgG4 level was 413.6 mg/dL. Complete blood count, blood chemistry, thyroid function, and serum protein electrophoresis were normal. Repeat CT of the orbit was done (Figure 1b, c). No evidence of pancreatic enlargement and retroperitoneal fibrosis on abdominal CT.

The final diagnosis was adult-onset xanthogranuloma (AOX) associated with IgG4-related ophthalmic disease (IgG4-ROD). Due to concerning about long term side effects of systemic corticosteroids, methotrexate was use as a steroid -sparing agent. At the time of writing manuscript, oral methotrexate dose was 25 mg weekly but there was

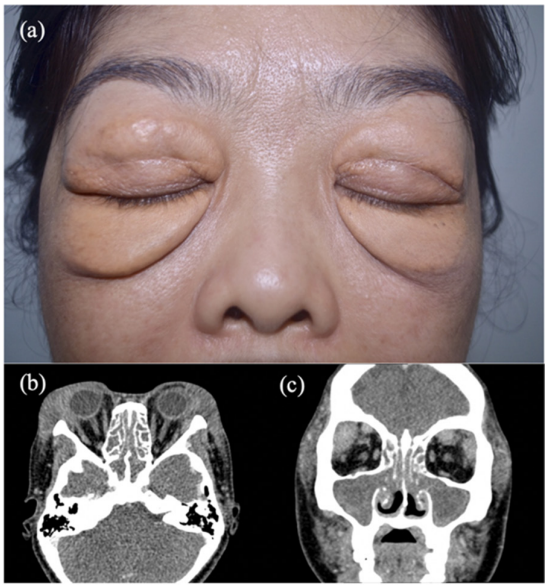

Figure 1. (a) Bilateral, symmetrical, ill-defined yellow, soft plaques without ulceration on upper and lower eyelids accompanied by swelling of periorbital areas of both eyes. (b, c) CT of the orbit showed enhancing soft tissue lesion of the bilateral extraconal compartment and both lacrimal glands, accompanied by pansinusitis.

a slight improvement. There was no adverse effect from treatment.

Discussion

An adult xanthogranulomatous disease of the orbit (AXDO) is a subset of non-Langerhans cell histiocytosis which classic histological findings include interstitial infiltrate of foamy histiocytes and an inflammatory infiltrate composed of lymphocytes, plasma cells, and Touton giant cells[1]. Four clinical forms of AXDO are: (i) adult-onset xanthogranuloma (AOX), the isolated cutaneous form without systemic involvement; (ii) adult-onset asthma and periocular xanthogranuloma; (iii) necrobiotic xanthogranuloma characterized by necrobiotic collagen on histology and associated paraproteinemia; and (iv) Erdheim-Chester disease, the fatal form with systemic involvement[1].

IgG4-related disease (IgG4-RD) is a fibroinflammatory condition affecting multiple organs. IgG4-ROD commonly involves the lacrimal gland and periorbital soft tissue[2]. The revised comprehensive diagnostic criteria for IgG4-RD are (i) clinical examination of swelling or mass; (ii) serum IgG4 >135 mg/dL; (iii) Two out of three histopathological criteria of (a) lymphoplasmacytic infiltration and increased fibrosis, (b) infiltration of IgG4+ plasma cells which a ratio of IgG4+/IgG+ cells >40% and IgG4+ plasma cells >10/HPF, and (c) Typical tissue fibrosis or obliterative phlebitis[4]. Around 80% of IgG4-ROD cases had extra-ophthalmic manifestations including sialadenitis, autoimmune

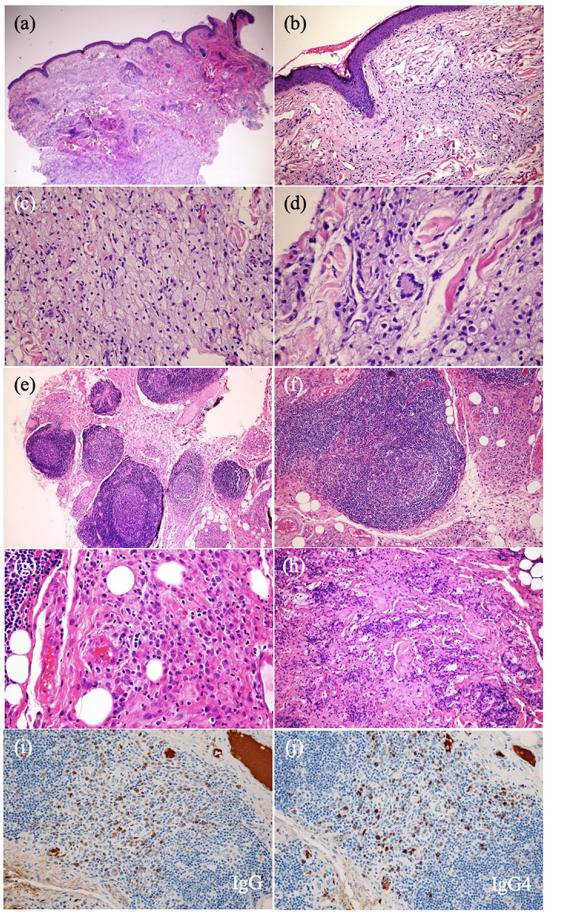

Figure 2. (a-d) skin from the left lower eyelid showed discrete collections of foamy histiocytes throughout the dermis with Touton giant cells. (e-g) orbital septum showed inflammatory infiltrate of lymphocytes, plasma cells, and histiocytes with prominent germinal centers. (h) areas of increased fibrosis. Haematoxylin and eosin, original magnification (a, e) x40; (b, f, h) x100; (c) x400; (d, g) x1,000. (i, j) The number of IgG4+ plasma cells was 40/HPF with a ratio of IgG4+/IgG+ cells 90%. (original magnification x400).

pancreatitis, sclerosing cholangitis, Riedel thyroiditis, and retroperitoneal fibrosis[2].

Few cases of AOX with IgG4-ROD were reported[3]. The significance of infiltrated IgG4+ plasma cells in periorbital xanthogranuloma is needed to be determined. One case series showed increased IgG4+ plasma cells were detected in 8 of 16 cases with histologically confirmed orbital xanthogranuloma. Only 2 of them had systemic diseases[5]. Periorbital xanthogranuloma may occur simultaneously with or it can be a xanthogranulomatous variant of IgG4-RD. The proposed mechanism was the fibroinflammatory process from IgG4-RD resulting in fat necrosis, subsequent engulfment of fat by macrophage, and foam cell formation[6].

Treatment of AOX and IgG4-RD is quite similar. Systemic glucocorticoid is the first line therapy[1,2].

Methotrexate is commonly used as steroid-sparing agents for both diseases. Other medications for IgG4-RD include azathioprine, mycophenolate mofetil. B-cell depleting therapy rituximab is effective in IgG4-RD[2]. Relapse is common during treatment[2].

Conclusion

The authors report a rare case of definite adult-onset xanthogranuloma associated with IgG4-related ophthalmic disease. Diagnosis of IgG4-RD in the setting of overlapping with dermatologic diseases is crucial because systemic involvement could occur.

What is already known on this topic?

An adult xanthogranulomatous disease of the orbit (AXDO) is a subset of non-Langerhans cell histiocytosis. IgG4-related disease (IgG4-RD) is a fibroinflammatory condition affecting multiple organs. These conditions were considered as separated entities.

What this study adds?

There are increasing reports of overlapping between adult-onset xanthogranuloma (AOX) associated with IgG4-related ophthalmic disease (IgG4-ROD). Whether these conditions were separated entities or in the same spectrum is needed to be determined.

Ethics approval

This report was approved by Center for Ethics in Human Research, Khon Kaen University (HE641634).

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Conflicts of interest

The authors declare no conflict interests.

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