

Letters to the Editor

Presence of Immunoglobulin Heavy Chain Rearrangement in So-Called IgG4-Related Plasma Cell Granuloma of the Eyelid

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TO THE EDITOR

So-called inflammatory pseudotumor (IPT) affects almost all major organs.¹ The histological appearance of IPT varies from fibrohistiocytic proliferation to plasma cell-dominated lesions. The latter are composed of numerous plasma cells, lymphocytes, and histiocytes as well as mesenchymal cells, that is, plasma cell granuloma (PCG). Recently, Zen *et al.* demonstrated that some of the pulmonary PCGs represent an immunoglobulin G4 (IgG4)-related sclerosing disease.²⁻⁴ We report here a unique case of IgG4-related PCG of the eyelid.

An 85-year-old man had a history of bronchial asthma for several years. He presented with a right upper eyelid mass, and under a diagnosis of squamous cell papilloma underwent tumor resection in May 2008. The surgical tissue was diagnosed as an inflammatory granulation tissue. Preoperative patient laboratory examination results were within normal limits. Serum IgG4 level was not examined. Two years later, he also presented with a left upper eyelid mass, and mass resection was performed under the diagnosis of chalazion. There was no other evidence of disease and the patient remained free of disease on examination 12 months later.

Histologically, initial and recurrent lesions presented similar findings. In a low- power field, both lesions were charac-

terized by chronic inflammatory processes, and irregular fibrosis and/or sclerosis were not prominent (Fig. 1a). In a high-power field, these lesions demonstrated severe infiltration of mature plasma cells, plasmacytoid cells, and small lymphocytes with scattered eosinophils (Fig. 1b). Scattered Russell bodies (intracytoplasmic inclusions) were present in both lesions (Fig. 1b), but there were no centrocyte-like (CCL) cells, Dutcher bodies (intranuclear inclusions), or amyloid deposition. A few isolated small lymphocytes and mature plasma cells invaded into the Meibomian gland epithelium. However, there was no lymphoepithelial lesion (LEL) (Fig. 1b). Elastica-van Gieson staining demonstrated that there was no obliterative phlebitis or arteritis.

Immunohistochemical studies were performed using the antigen retrieval method on the Histofine Histostainer (Nichirei Bioscience Inc., Tokyo, Japan) according to the manufacturer's instructions. Staining for CD20, CD3, and CD5 showed the mixed nature of the small lymphocytes. There were no CD43⁺ B-cells in either lesion. *In situ* hybridization (ISH) and immunohistochemical studies of κ -chain and λ -chain demonstrated polyclonality of the plasma cells and plasmacytoid cells in both lesions (Figs. 1c & 1d). There were numerous IgG-positive plasma cells with scattered IgA- or IgM-positive plasma cells. However, IgG4⁺ cells comprised more than 40% of the IgG⁺ plasma cells (Figs. 1e & 1f). There were no LELs detected even by immunostaining for cytokeratin in any of the two lesions (Fig. 1g). CD23 immunostain demonstrated no residual follicular dendritic cell network in both lesions. On ISH study, there were no Epstein-Barr virus (EBV)-encoded small RNA (EBER)⁺ cells in either lesion.

By polymerase chain reaction (PCR) for *immunoglobulin heavy chain (IgH)* gene, a discrete band of amplified *IgH* gene was found for the recurrent lesion,⁵ while for the initial lesion, only germline bands were detected (Fig. 1h).

IgG4 is the least common of the 4 subclasses of IgG4,

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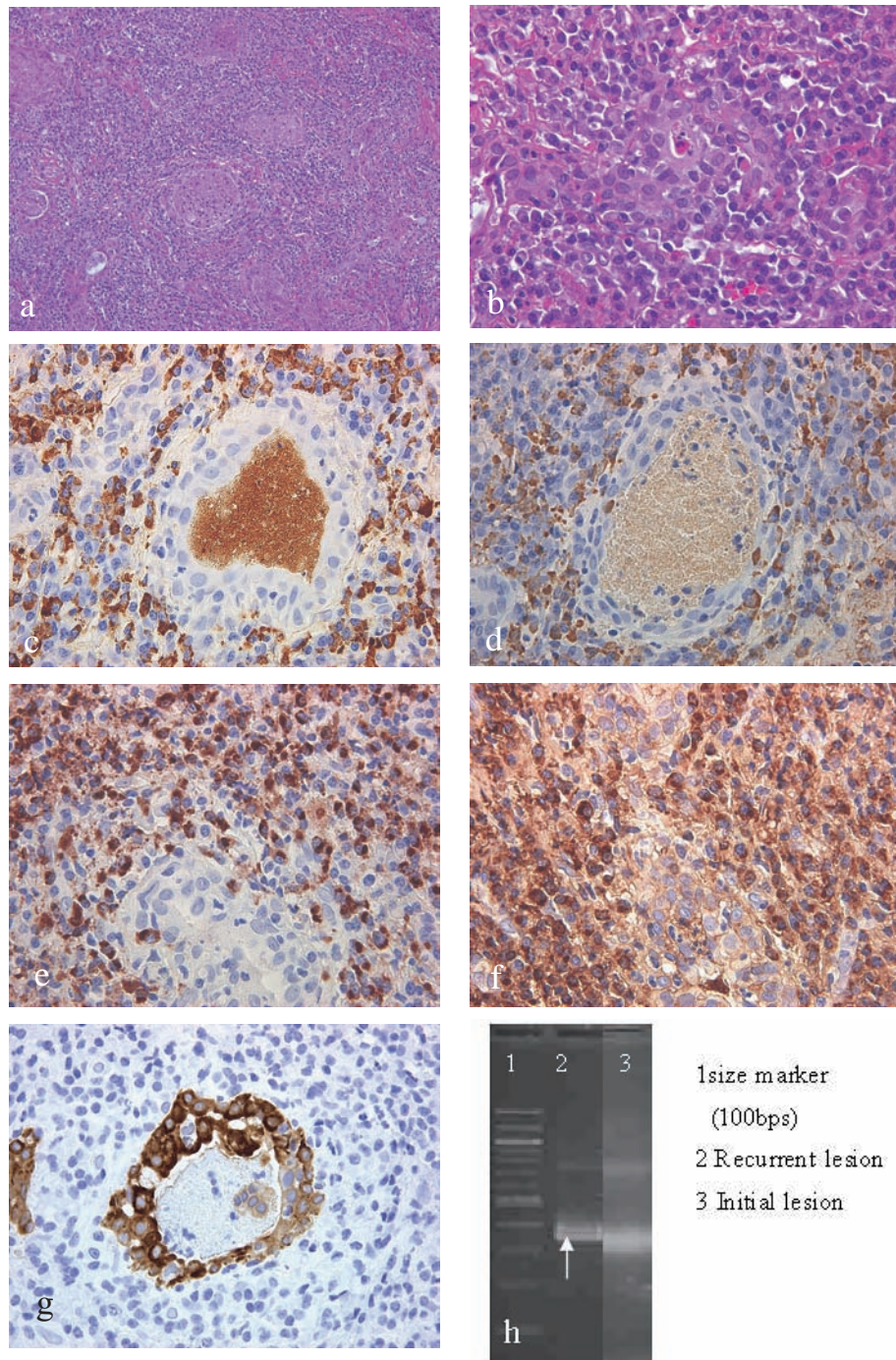


Fig. 1. Histological findings of recurrent lesion. (*1a*) In a low-power field, the lesion was characterized by chronic inflammatory processes, and irregular fibrosis and sclerosis were not prominent. H & E stain, $\times 10$. (*1b*) In a low-power field, the lesion demonstrated severe infiltration of mature plasma cells, plasmacytoid cells, and small lymphocytes with scattered eosinophils. A few isolated small lymphocytes and mature plasma cells invaded into the Meibomian gland epithelium (*arrow*). H & E stain, $\times 40$. (*1c & 1d*) Immunohistochemical studies of κ -chain and λ -chain demonstrated polyclonality of the plasma cells and plasmacytoid cells (*1c*, κ -chain; *1d*, λ -chain). $\times 40$. (*1e & 1f*) IgG4-positive cells (*1e*) comprised more than 40% of the IgG⁺ plasma cells (*1f*) $\times 40$. (*1g*) There were no lymphoepithelial lesions detected even by immunostaining for cytokeratin. $\times 20$. (*1h*) By polymerase chain reaction for *immunoglobulin heavy chain (IgH)* gene, a discrete band of amplified *IgH* gene was found for the recurrent lesion (*arrow*), while for the initial lesion, only germline bands were detected.

namely, IgG1, IgG2, IgG3, and IgG4, normally constituting only 3% to 6% of the entire IgG fraction.^{3,4} IgG4-related disease is a recently recognized entity characterized clinically by tumor-like enlargement of one or more exocrine glands or other extranodal sites by lymphoplasmacytic infiltrates and sclerosis, and accompanied by increased IgG4⁺ plasma cells in the tissues and elevated IgG4 titer in the serum.^{3,4,6} The most common components of IgG4-related disease are autoimmune pancreatitis, chronic sclerosing sialoadenitis of submandibular gland, and chronic sclerosing dacryoadenitis.^{3,4,6}

The serum IgG4 level was not examined in this case. However, immunohistochemical study demonstrated that IgG4⁺ cells comprised more than 40% of the IgG⁺ plasma cells in both lesions.^{3,4,6} Overall, given the histopathological and immunohistological findings, both lesions were considered IgG4-related ocular adnexal lesions.⁷

Histologically, IgG4-related ocular lesions are classified in 3 types: (i) reactive lymphoid hyperplasia, (ii) sclerosing inflammation, and (iii) lymphoplasmacytic lesion. The histological findings of PCG are similar to those of lymphoplasmacytic lesion, and the present case appears to involve lymphoplasmacytic lesions.⁸

An association between malignant lymphoproliferative disorders and IgG4-related disorders has been reported in several papers.^{3,6} The majority of them were ocular adnexal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type.^{3,6} Occasionally, MALT showed prominent plasma cell differentiation.⁹ In this case, there were no characteristic histological and immunohistochemical findings of MALT-type lymphoma in both lesions, including (i) absence of CCL-cells, Dutcher bodies, and CD43⁺ B-cells, (ii) polytypic nature of the plasma cells and plasmacytoid cells in both lesions, and (iii) absence of LELs.¹⁰ However, interestingly, by the PCR study for *IgH* gene, a discrete band of amplified *IgH* gene was found for the recurrent lesion.

One of the authors (M. K.) recently reported one case of PCG of the lung containing a fraction of monoclonal B-cells as determined by PCR reaction.¹¹ As previously suggested, it remains unclear whether this demonstrated *IgH* gene rearrangement could be a sign of prelymphomatous stage (incipient MALT lymphoma arising from IgG4-related disorder) or merely represents an exaggeration of normal B-cell clonal response.^{10,11} However, this patient has undergone only a short follow-up to date. To clarify this issue, further study is needed.

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financial interests.

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