

# A Case of Warthin's Tumor Together with IgG4-Related Sialadenitis

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**How to cite this paper:** Aoki, R., Ito, R., Ohashi, A., Niwa, R., Matsuyama, M., Oka, S., Kawaguchi, N., Sakakima, T., Kodama, D., Watanabe, N., Okamoto, D., Naiki, T. and Tanaka, T. (2024) A Case of Warthin's Tumor Together with IgG4-Related Sialadenitis. *Open Journal of Pathology*, 14, 81-89.

<https://doi.org/10.4236/ojpathology.2024.143010>

**Received:** June 28, 2024

**Accepted:** July 22, 2024

**Published:** July 25, 2024

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## Abstract

Warthin's tumor is the second most frequent neoplasm next to pleomorphic adenoma in the salivary gland. The tumor contains the epithelial oncocytic cells with the presence of rich-mitochondria and their surrounding abundant lymphocytes. A relatively new disease entity of IgG4-related disease frequently occurs in the salivary gland. However, the coexistence of Warthin's tumor and IgG4-related disease is scarcely observed. We have recently experienced a rare case of Warthin's tumor with IgG4-related sialadenitis. A 51-year-old man presented to our hospital, complaining of a mass with right submandibular tenderness and spontaneous pain. A computed tomography scan of the cervical region revealed a suspicion of lymph node proliferative disease, including malignant lymphoma. Elevated serum levels of IL-2R: 1843 U/ml (reference value 122 - 496 U/ml), IgG: 3430 mg/dl (reference value 861 - 1747 mg/dl), and IgG4: 3140 mg/dl (reference value 11 - 121 mg/dl) were observed. Other laboratory data showed within normal ranges. The cervical tumor was diagnosed as Warthin's tumor by the findings of fine-needle aspiration cytology and biopsy examination. Immunohistochemistry revealed numerous IgG4- and IgG-positive cells with fibrosis surrounding the epithelial component of Warthin's tumor, suggesting IgG4-related sialadenitis. Finally, we diagnosed the cervical tumor as Warthin tumor with IgG4-related sialadenitis. This is the second report describing a case of Warthin's tumor with possible involvement of IgG4-related sialadenitis.

## Keywords

Warthin's Tumor, Sialadenitis, IgG4-Related Disease, Immunohistochemistry

## 1. Introduction

Warthin's tumor is the second most common tumor of the parotid gland after pleomorphic adenoma, accounting for about 15% of all parotid tumors [1] [2]. The site of occurrence is restricted to the parotid gland and surrounding lymph nodes, with a high frequency of simultaneous or ectopic multiple or bilateral occurrences [3] [4]. The tumor usually presents as a painless mass, but may be painful when the lesion is associated with inflammation [5]. Whether Warthin's tumor is a true neoplasm that occurs as a clonal growth or nonneoplastic developmental malformation remains controversial, but we proposed that it is neoplastic [6]. Histopathologically, Warthin's tumor is defined by tubular, cystic, and papillary proliferation of highly cylindrical oncocyte-like cells with eosinophilic granular sporulation. The tumor is well-demarcated by fibrous tissue from the surrounding normal salivary gland tissue [7] [8]. The stroma of tumor is occupied by mature, non-atypical small lymphocytes with lymphoid follicles, although the amount of the stroma varies from case to case. Cytological diagnosis can be made by observation of a two-cell pattern of lymphocytes and epithelial cells [9] [10]. On the Papanicolaou staining smears, oncocyte cells appear with light green stained granular cytoplasm, often being with eosinophilic changes that stain orange G. Numerous lymphocytes are observed in the background. Fine needle aspiration cytology (FNAC) is a useful technique for the pre-operative diagnosis of Warthin's tumor [11]-[13].

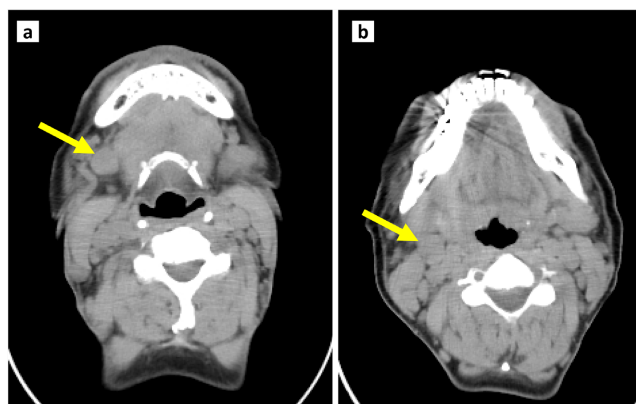
IgG4-related disease (IgG4-RD) is a disease concept that originated in Japan in 2001, when Hamano *et al.* first reported elevated serum IgG4 levels in autoimmune pancreatitis (AIP) [12]. In addition to autoimmune abnormalities and high levels of serum IgG4, this unique disease shows fibrosis, IgG4 plasma cell infiltration, phlebitis obliterans in the lesion. The disease has been reported in various regions other than pancreas. They include salivary/lacrimal glands, liver, bile duct, and retroperitoneal cavity. The pathogenesis of IgG4-RD is still unknown. When focused on the salivary gland, it has been suggested that Mikulicz disease and Sjogren's syndrome should be included in the IgG4-related dacryoadenitis and sialadenitis (IgG4-DS), which is a subtype of IgG4-RD. A unilateral sclerosing submandibular gland inflammation, Kuttner tumor, is also an IgG4-RD. Thus, it is possible that IgG4-RD (IgG4 sialadenitis) commonly occurs in the salivary glands. However, since the first report by Aga *et al.* [14], where Warthin's tumor associated with IgG4-related sialadenitis, there were no case reports.

We report here our experience with the second case of Warthin's tumor with IgG4-associated sialadenitis. Our goal is to determine the association between IgG4 and development/growth of Warthin's tumor by IHC findings of p53 and p16.

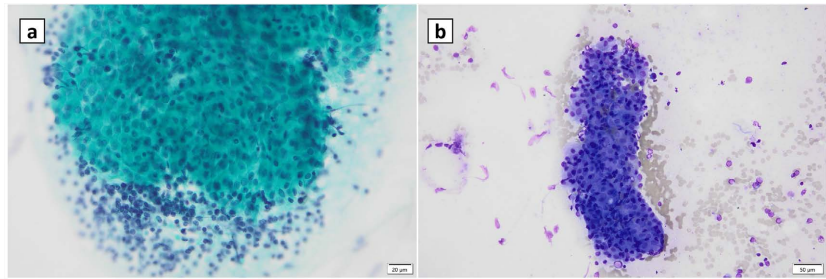
## 2. Case Presentation

A 51-year-old Japanese man with a mass of tenderness and spontaneous pain

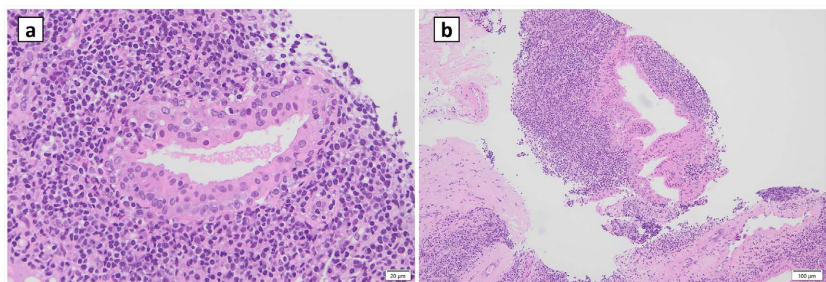
under the right jaw presented to the Department of Otorhinolaryngology of our hospital. Flexible fiberoptic nasopharyngolaryngoscopy showed mucosal swelling of the pharyngeal larynx, mainly swelling of the tonsils of the root of the tongue. Cervical computed tomography (CT) showed enlarged right submandibular and parotid glands, swelling of surrounding lymph nodes and increased density of peri-lymphatic fat tissue (**Figure 1(a)** and **Figure 1(b)**). In addition, mild lymph node enlargements were found in the bilateral pulmonary hilum, mediastinum, supraclavicular fossa lymph nodes, and abdominal para-aortic region. These findings led us to suspect lymph node proliferative disease, such as malignant lymphoma. Laboratory test reported that serum IL-2R: 1843 U/ml (reference value 122 - 496 U/ml), IgG: 3430 mg/dl (reference value 861 - 1747 mg/dl), and IgG4: 3140 mg/dl (reference value 11 - 121 mg/dl). Other measures were normal ranges. Flow cytometry showed “T lymphocyte predominance” and “poor culture” by karyotyping (G-banding). Antinuclear antibodies and immunoelectrophoresis (M protein) were negative. These findings suggested IgG4-sialadenitis or malignant lymphoma. To diagnose the lesion, fine needle aspiration cytology (FNAC) and biopsy were performed in the parotid gland. On the Papanicolaou-stained specimen, a cluster of slightly atypical epithelial cells were present in a background of numerous small to large lymphocytes and foam cells. The cytoplasm of the epithelial cell clusters was stained light green and acidic (**Figure 2(a)**). May-Grünwald-Giemsa-stained specimens showed clusters of epithelial cells with numerous large and small lymphocytes and foam cells. There was no evidence of metachromasia. These cytological findings suggested Warthin’s tumor (**Figure 2(b)**). Fine needle biopsy for accurate diagnosis showed the presence of oncocytes-like glandular structures with lymphoid tissue growth (**Figure 3(a)**, **Figure 3(b)**). Immunohistochemical staining revealed numerous IgG and IgG4-positive cells in the surrounding lymphoid tissue, the latter being predominant (**Figure 4(a)**, **Figure 4(b)**). Additionally, p53 (**Figure 5(a)**) and p16 (**Figure 5(b)**) were positive in the columnar epithelium of the



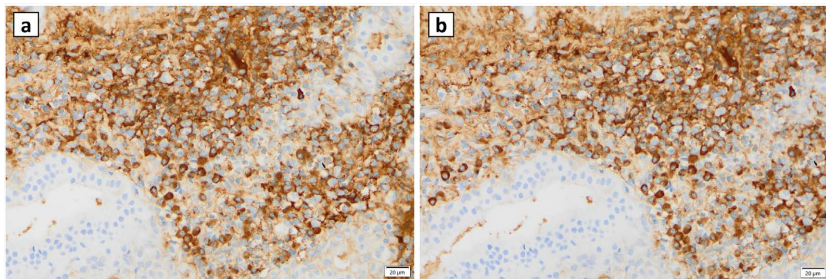
**Figure 1.** Computed tomography (CT) scan examination. (a) The right submandibular gland (arrow) and its surrounding lymph node are enlarged. The surrounding fat tissue density is elevated. (b) A mass (arrow) is found in the deep lobe of the parotid gland. Axial view.



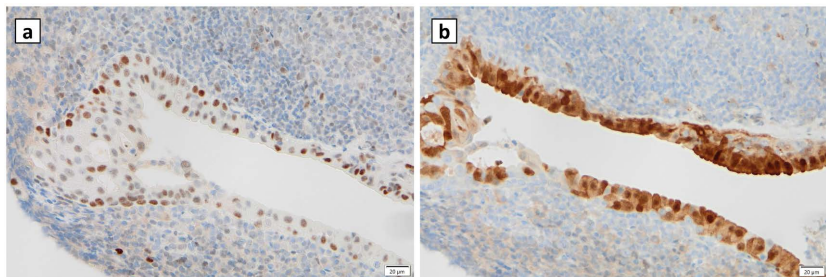
**Figure 2.** FNA cytology of the enlarged right submandibular gland. (a) Small cohesive sheets of oncocytes with abundant granular cytoplasm with central round nucleus/prominent nucleolus are observed. (b) Numerous lymphocytes with granular debris in the background, and there are no metachromatic features. (a) Papanicolaou stain, Bar = 20  $\mu$ m and (b) May-Grünwald Giemsa stain, Bar = 50  $\mu$ m.



**Figure 3.** Histopathology of the enlarged right submandibular gland biopsy. (a) Papillary cystic structure lined by bilayered oncocytic epithelial cells and its surrounding by a lymphoid stroma, suggesting Warthin's tumor. (b) Inflammatory cell infiltration, including plasma cells, and fibrosis around the tumor are noted. Hematoxylin and eosin (H&E), (a) bar = 20  $\mu$ m, (b) bar = 100  $\mu$ m.



**Figure 4.** Immunohistochemistry of Warthin's tumor. Positivity of (a) IgG and (b) IgG4 in the surround lymphoid stroma. Bars = 20  $\mu$ m.



**Figure 5.** Immunohistochemistry of the Warthin's tumor shows positive reactivity of (a) p53 and (b) p16 in the surrounding lymphoid tissue. Bars = 20  $\mu$ m.

Warthin's tumor. The pathological diagnosis was Warthin's tumor with IgG4-related sialadenitis. He was given oral predonine (10 mg) and predonisolone (2 mg) daily for 12 months, his symptoms improved significantly, and the right submandibular and parotid masses decreased in size. The patient is free from disease(s) for over 13 months followed-up.

### 3. Discussion

A benign epithelial salivary tumor, Warthin's tumor, also known as papillary cystadenoma lymphomatosum or monomorphic adenoma, or adenolymphoma is one type of salivary adenoma. Histologically, Warthin's tumor is structured of two components, epithelial tissue that often lines cystic formations and lymphoid tissue in the tumor stroma. Depending on the proportions of the epithelial component and lymphoid stroma, Warthin's tumor is categorized in 4 types [15]: "typical", "stroma-poor", "stroma-rich", and "metaplastic". This case was considered to be "typical" subtype of Warthin's tumor, as shown in **Figure 3**. Accurate cytological diagnosis by fine needle aspiration (FNA) is straightforward when three characteristic components are present: oncocytes, either isolated or associated in clusters, lymphocytes and lymphoid cells and often an inflammatory/necrotic-like substance [6] [9] [10] [16]. Cytological features of FNA cytology in this case showed typical cytological findings of Warthin's tumor, as given in **Figure 2**. However, bilateral, multicentric or multiple and infrequently occurred extra-salivary localizations of Warthin's tumor are associated with further cytopathological diagnostic difficulties [6]. In addition, a rare possibility of malignant transformation of the epithelial or lymphoid component of Warthin's tumor as well as possible association with other primary tumors remains a challenge in accurate cytopathological and histological diagnosis of Warthin's tumor [6]. Our case is easy to be diagnosed as Warthin's tumor by FNA biopsy and cytology.

A rare systemic chronic fibroinflammatory condition, immunoglobulin G4-related disease (IgG4-RD), is characterized by tumor-like tissue infiltrations with a numerous lymphocytes and IgG4-secreting plasma cells, storiform fibrosis, and often, but not always, an elevated serum level of IgG4. The disease results in swelling, scarring, and dysfunction of the organ affected [17] [18]. The systemic nature of this disease has been recognized only in the 21st century by Hamano *et al.* [12] in Japan. The disease can affect almost every organ, usually pancreas, biliary ducts, salivary glands, orbits, kidneys, and lymph nodes [17]-[19]. Despite the growing recognition of this new condition, adequate epidemiological data, and unified evidence-based guidelines for IgG4-RD diagnosis and management are still lacking. Our knowledge about IgG4-RD prevalence and manifestation in Europe and other Western countries is limited, as the majority of clinical data analysis has been performed in Asia, mostly Japan [20]. Diagnosis of IgG4-RD is based on a set of clinical, serological, and pathological criteria [19], and the histological picture is critical for diagnosis, but the diag-

nostic process of IgG4-RD is challenging, as it takes time and referrals to many different specialists to establish the correct diagnosis. Presently, the pathophysiological mechanisms underlying IgG4-RD have not yet been fully established. The increase of IgG4 itself appears to be a reactive phenomenon rather than the primary disease driver. Similar case of ours has recently been reported by Aga *et al.* [14]. They suggested an association between Warthin's tumor and IgG4-RD [14]. In addition, serum IgG4 level in the patients with Warthin's tumor were higher than those with pleomorphic adenoma [21]. It therefore can speculate that IgG4-producing plasma cells may influence the tumor microenvironment by secreting platelet-derived growth factor, which activates local PDGF-receptor expressing fibroblasts and myofibroblasts, resulting in uncontrolled fibrosis [22], and contributes to the development/growth of Warthin's tumor, although the exact mechanism(s) are not known [23] [24].

Other interesting findings of this case were that the epithelium of the Warthin's tumor showed immunohistochemically positivity of p16 and p53. p16 is a tumor suppressor protein encoded by the cyclin-dependent kinase inhibition 2A (CDKN2A) gene. In immunostaining, p16 positivity is generally a biomarker for HPV infection-related malignancies, such as cervical and pharyngeal cancers. On the other hand, p53 is a tumor suppressor gene product that promotes or suppresses the transcription of various proteins, thereby conferring resistance to various cellular stresses. p53 maintains genomic stability and is involved in DNA repair, apoptosis and cellular senescence [25]. Mutant p53 proteins not only lose their tumor suppressor activity, but often acquire additional oncogenic functions that confer growth and survival advantages to the cell [26]. In the immunohistochemical study of p16 and p53, 12 cases of Warthin's tumor were negative results in all cases, suggesting that no evidence of abnormal staining for tumor suppressor gene protein products (p16 and p53) [27]. Our findings of immunohistochemistry suggests in this case that p16 and p53 immunohistochemical staining, we found positive nuclei in the columnar cells of Warthin's tumor, suggesting that certain DNA damage might occur. It is interesting to clarify the role of IgG4 in development and/or growth of salivary glands, such as Warthin's tumor.

#### 4. Conclusion

We experienced the second case of Warthin's tumor with IgG4-RD in the parotid tumor. This case was diagnosed by FNA cytology, histopathology, and immunohistochemistry. The association of IgG4-RD with Warthin's tumor observed in this case is suggestive that IgG4-producing plasma cells may play a certain role in tumor microenvironment. Studies with larger case series are needed to render the possibility evaluable.

#### Consent

Agreement by a document was obtained from the patient before writing this case

report.

### Ethical Approval

This was obtained from the Ethical Committee of our hospital before writing this case report (Ethical Approval No. 824).

### Conflicts of Interest

The authors declare that they have no competing interests.

### Authors' Contributions

R.A., wrote the manuscript, collected the data, and made the cytological diagnosis, visualization and reference collection; A.O., R.N., N.K., M.M., made the cytological diagnosis; R.I., S.O., collected the data; D.K., N.W., made the pathological diagnosis; D.O., clinically diagnosed and treated the patient; T.N., supervision; T.T., made substantial contributions to the interpretation of data and manuscript review. All authors read and approved the final manuscript.

### Funding

This research received no external funding.

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