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Malignancies in Patients with IgG4-Related Diseases in Head and Neck Regions

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Immunoglobulin G4-related disease (IgG4-RD) is a recently recognized disease, characterized by high serum IgG4 concentrations and IgG4-producing plasma cell expansion with fibrotic or sclerotic changes in affected organs. Recent work has focused on the relationship between IgG4-RD and malignancies, but there is no report of malignancies associated with IgG4-RD in head and neck regions. The aim of this study was to analyze the clinicopathological characteristics of malignancies in patients with IgG4-RD in head and neck regions. We retrospectively analyzed 26 patients with IgG4-RD (12 men and 14 women aged 60.6 ± 11.6 years). The mean follow-up period was 26.6 months (from 12 to 96 months). These patients were divided into single-lesion group (n = 12) with IgG4-RD only in head and neck regions and multiple-lesion group (n = 14) with IgG4-RD in other regions. There was no significant difference in serum IgG4 concentrations between the single-lesion group (459.4 ± 336.4 mg/dL) and the multiple-lesion group (908.0 ± 739.2 mg/dL) (P = 0.07), whereas the IgG4/IgG ratio was significantly lower in the single-lesion group (22.8 ± 11.0%; n = 11) compared with the multiple-lesion group (31.7 ± 15.0%; n = 11, P = 0.02). Among the 26 patients, two patients (7.7%), both in the multiple-lesion group, developed life-threatening malignancies (salivary duct carcinoma in the submandibular gland and lymphoma in the orbital tissue). All physicians need to keep in mind the possible coexistence of malignancies in patients with IgG4-RD with high IgG4/IgG ratio and multiple lesions at the time of diagnosis.

Keywords: head and neck regions; IgG4-related diseases; lymphoma; malignancy; salivary duct carcinoma
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Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a recently recognized disease entity characterized by high serum IgG4 concentrations and IgG4-producing plasma cell expansion with fibrotic or sclerotic changes in affected organs (Hamano et al. 2001; Kamisawa et al. 2015). The common involvement sites of IgG4-RD included the salivary gland (Yamamoto et al. 2006a; Takano et al. 2017), the orbit (Ohshima et al. 2012), the sinonasal region (Ikeda et al. 2010), the thyroid (Watanabe et al. 2013), the pituitary gland (Yamamoto et al. 2006b), and the ear (Schiffenbauer et al. 2012). For physicians, it is mandatory to discriminate enlarged lesion(s) related with IgG4-RD and malignant tumor(s).

The underlying mechanism of IgG4-RD involves predominance of T helper (Th) 1 and T cytotoxic type (Tc) 1 cells, overexpression of IL-17, tumor growth factor (TGF)-β, and periostin in the affected site(s) in persistent chronic inflammation (Ohta et al. 2012a, b, 2013). Recent studies have also suggested that Epstein-Barr virus might play an important role in pathogenesis of IgG4-RD (Furukawa et al. 2015). However, the mechanism responsible for the onset and systemic involvement of IgG4-RD still remains a mystery. Recent work has focused on the relationship between IgG4-RD and malignancies (Yamamoto et al. 2012; Wallace et al. 2016; Ahn et al. 2017). However, there has been no previous report of malignancies with IgG4-RD in head and neck regions. We therefore analyzed the incidence, the types and the details in the clinical course of malignancies in patients with IgG4-RD in head and neck regions.

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Materials and Methods

Twenty-six patients with IgG4-RD who had visited Yamagata University Hospital or Tohoku Medical and Pharmaceutical University were enrolled in present study. These patients (12 men, 14 women, aged 60.6 ± 11.6 years) have met the diagnostic criteria for IgG4-RD: (1) enlargement of the affected organs; (2) elevated levels of serum IgG4 (> 135 mg/dl); and/or (3) abundant infiltration of IgG4-positive plasma cells and fibrosis (Kamisawa et al. 2015). Their mean follow-up period was 26.6 months (from 12 to 96 months). They were divided into single-lesion group, with IgG4-RD in the head and neck regions only, including lacrimal and/or salivary glands, and a multiple-lesion group, with IgG4-RD also in other regions, including extra-lacrimal and extra-salivary glands.

Serum concentrations of IgG (n = 22) and IgG4 (n = 26) were measured in patients with IgG4-RD, as described previously (Takano et al. 2017). In brief, concentrations of serum IgG subclasses were measured by using BS-NIA IgG1-4 (The Binding Site, San Diego, USA), and those of IgG were measured with a Behring nephelometer (Dade Behring, Deerfield, IL, USA).

IgG, IgG4, CD20, CD79a and cytokeratin (CK) were immunohistochemically examined by using a labeled streptavidin-biotin-complex method as described previously (Kamisawa et al. 2015, Furukawa et al. 2015). In brief, 10-μm sections were taken from paraffin-embedded tissue blocks and then deparaffinized and rehydrated. Monoclonal or polyclonal antibody to IgG, IgG4, CD20, CD79a or CK (CK-MNF116) was applied as a primary antibody respectively, and the sections were incubated at 4°C overnight. The sections were treated with biotinylated goat anti-rabbit IgG or anti-mouse IgG (Dako Cytomation, Glostrup, Denmark) as the secondary antibody and incubated for 1 h at room temperature. Histofine MAX-PO(R) (Nichirei Bioscience, Tokyo, Japan) detection reagent with diaminobenzidine substrate was used in accordance with the manufacturer's instructions. The ratio of IgG4 positive cells to total IgG positive cells per field was expressed as follows: (–) negative; +, > 50%; and ++, > 60%.

Data were analyzed by Student's *t*-test, Wilcoxon's rank-sum test, and the Mann-Whitney *U*-test in SPSS v. 20 software (IBM, Chicago, IL, USA). Differences with a corrected P value of < 0.05 were considered significant. Data are presented as mean ± SD.

The study was approved by the Tohoku Medical and Pharmaceutical University Hospital Review Board and the Yamagata University Institutional Review Board.

Results

Clinical characteristics of patients with IgG4-RD of the head and neck regions

Twelve patients (46%) had IgG4-RD only in head and neck region (single-lesion group), and 14 (54%) had IgG4-RD also in other regions (multiple-lesion group). The multiple-lesions group included eight patients (57%) with auto-immune pancreatitis (AIP), two patients (14%) with lung pseudotumor (IP), one patient (7%) with retroperitoneal fibrosis, one patient (7%) with AIP and IP, one patient

Table 1. Clinical features of patients with IgG4-RD in head and neck regions.

Age	Sex	Lacrimal gland	Salivary duct	AIP	Other organs	Malignances	IgG4 (mg/dL)	IgG4/IgG (%)	IgG4 (+)
47	F		+				664	30.7	ND
74	F		+				1,440	37.4	+
53	M		+				210	13.4	+
65	F		+				111	8.6	++
68	F		+				557	32.2	++
66	F		+				681	35.8	ND
61	M		+				286	NA	++
85	M		+				436	22.3	ND
50	F		+				279	18.9	++
64	F		+				276	15.9	++
48	F	+	+				210	10.9	++
38	F	+	+				223	16.6	ND
69	F		+		IP		625	24.6	ND
66	M		+		IP		234	NA	++
71	F	+	+		RF		822	37.9	++
41	M	+	+		CKD		511	14.4	+/–
77	M		+	+			353	NA	++
56	F		+	+			631	NA	++
56	M	+	+	+			1,750	57.7	++
60	F	+	+	+			369	22.0	ND
62	M	+	+	+			548	23.9	++
58	M	+	+	+	IP		1,180	41.0	++
52	M	+	+	+			971	40.3	+/–
70	F	+		+			819	46.5	++
46	M	+	+	+		+	2,820	55.0	++
73	M	+	+	+	TN	+	322	13.7	++

The data of IgG4 and IgG4/IgG from patients with IgG4-RD are shown. The number of positive cells of IgG4 positive cells/total IgG positive cells per field are expressed as follows: (–) negative; +, > 50%; and ++, > 60%. Single-lesion group included 12 patients with IgG4-RD in lacrimal and/or salivary glands, shown as first 12 patients. The concentrations of IgG were not available from four cases, as indicated by NA (not applicable).

AIP, autoimmune pancreatitis; TN, tubulointerstitial nephritis; RF, retroperitoneal fibrosis; IP, inflammatory pseudotumor of the lung; MS, maxillary sinus; CKD, chronic kidney diseases; ND, not done.

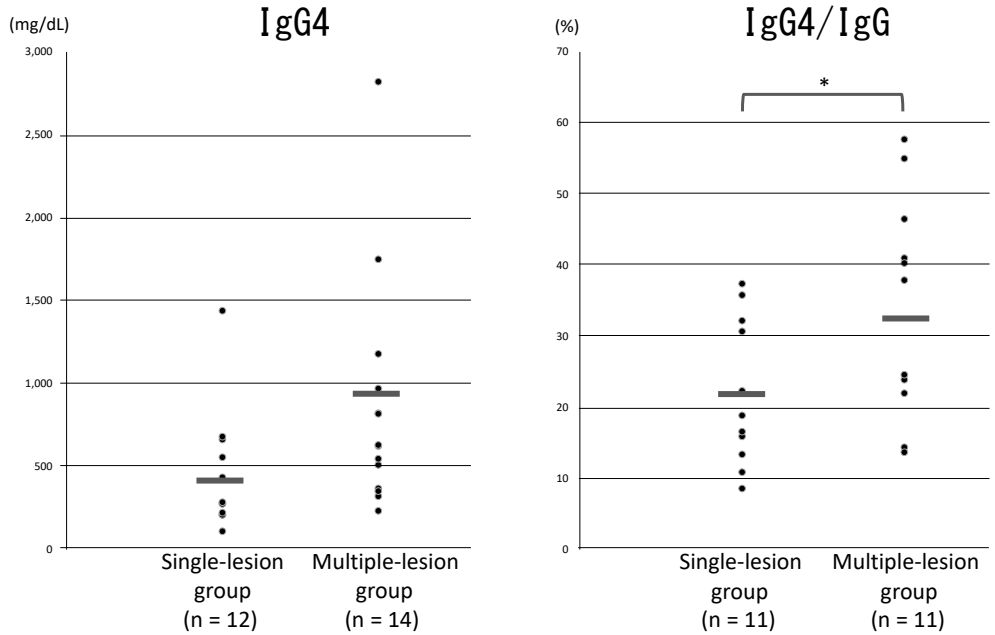

Fig. 1. IgG4 and IgG4/IgG.
Serological data of IgG4 (n = 26, left) and IgG4/IgG ratio (n = 22, right) in single-lesion group and multiple-lesion group.
*Significantly different (P = 0.02).

(7%) with chronic kidney disease, and one patient (7%) with API and tubulointerstitial nephritis (Table 1). There was no significant difference in serum IgG4 concentration between the single-lesion group (459.4 ± 336.4 mg/dL) and the multiple-lesion group (908.0 ± 739.2 mg/dL) (P = 0.07; Fig. 1, left). The IgG4/IgG ratios waere 22.8 ± 11.0% in the single-lesion group and 31.7 ± 15.0% in the multiple-lesion group, with a significant difference (P = 0.02; Fig. 1, right).

Malignancies in patients with IgG4-related diseases in head and neck regions

The detail of malignancies in patients with IgG4-RD in head and neck regions was analyzed. Two patients (7.7%) developed life-threatening malignancies (salivary duct carcinoma in the submandibular gland and lymphoma in the orbital tissue). Both patients with malignancies belonged to the multiple-lesion group. Serological data showed that IgG4 levels were 591.1± 411.2 mg/dL in the non-malignancy group (24 patients) and its mean value was 1,571 mg/dL (322 mg/dl and 2,820 mg/dl) in the two cancer patients. The IgG4/IgG ratio was 27.6 ± 13.2% in the non-malignancy group (20 patients), and its mean value was 34.4% (13.7% and 55.0%) in the two cancer patients. The details of two cancer patients are described below.

Case 1

A 73-year-old man noticed bilateral submandibular masses 14 years ago. He was admitted to our hospital with a right submandibular mass gradually enlarging from 3 years ago. Bilateral submandibular and orbital swelling 3 cm round and tumor immobility were observed. The serological data showed IgG4 of 322 mg/dl, IgG of 2,350 mg/dl, and IgG4/IgG ratio of 13.7%. Computed tomography (CT) and positron emission tomography (PET) revealed a right submandibular mass and enlargement of bilateral orbital, submandibular, renal, pancreatic, prostatic, and mediastinal lymph nodes (Fig. 2a-c). Total resection of the right submandibular gland was performed and immunostaining revealed prominent infiltration of IgG4-bearing plasma cells and fibrosis in the submandibular gland, and an intraductal growth pattern with comedo-type necrosis in the tumor (Fig. 2d, e). The patient was diagnosed with IgG4-RD and salivary duct carcinoma. Additional treatment with selective neck lymph node dissection (I-V) and post-operative radiotherapy (43.2 Gy) were performed. There was no recurrence 5 years postoperatively.

Case 2

A 46-year-old man was admitted to the ophthalmology department with bilateral conjunctival hyperemia and swelling of both eyelids. Magnetic resonance imaging (MRI) showed bilateral orbital tumors (Fig. 3a). Orbital biopsy revealed marginal-zone B-cell lymphoma (Fig. 3b-d). He was treated with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) chemotherapy. Four years after the initial treatment, he developed a tumor at the site of the right exterior orbital lesion. Biopsy was performed and histological examination indicated no recurrence. Five years after the initial treatment, PET demonstrated abnormal accumulation in the left parotid gland and submandibular and bilateral mediastinal lymph nodes. He was referred

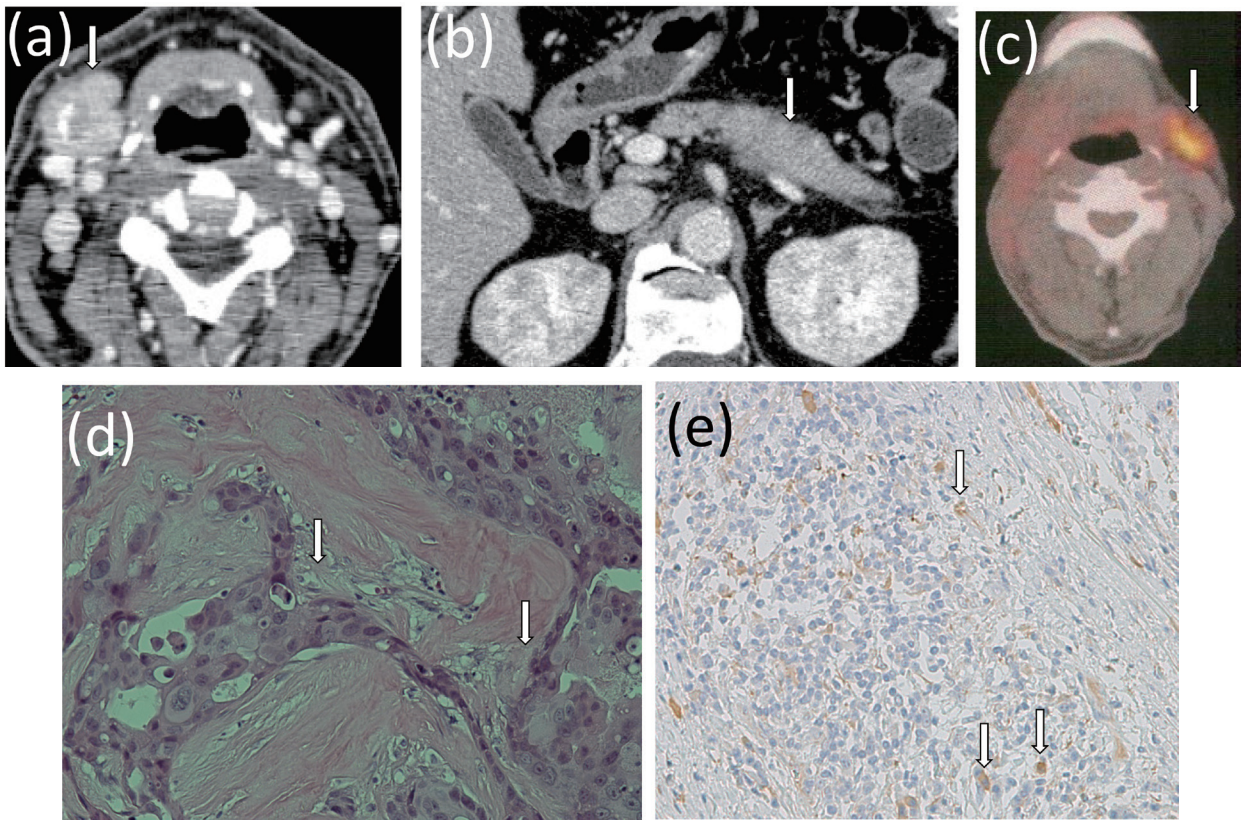

Fig. 2. Clinicopathological findings of Case 1.
Preoperative axial contrast-enhanced CT showing (a) a well-defined, slightly enhanced, nonhomogeneous soft-tissue-density mass with calcification in the right submandibular gland and (b) enlargement of the pancreas (arrow). (c) PET revealed the accumulation in the right submandibular gland (arrow). The accumulation was also observed in pancreas, prostate, and kidney (data not shown). (d) Submandibular gland tissue with comedo-type necrosis (arrow), atrophic glands adjacent fibrosis (hematoxylin and eosin, × 200). (e) Immunohistochemistry of submandibular gland tissue showing positive IgG4 staining of plasma cells surrounding atrophic glands (arrow) (× 100).

to our department for submandibular biopsy. Histological examination revealed no recurrence and observation was continued. Swelling of both eyelids was observed 9 years after the initial treatment. CT showed enlargement of bilateral orbital, submandibular, renal, pancreatic, prostatic, mediastinal, and epigastric-part lymph nodes (Fig. 3e-h). The serological data showed IgG4 of 2,820 mg/dl, IgG of 5,127 mg/dl, and IgG4/IgG ratio of 55%. Total resection of the right submandibular gland was performed. Immunostaining revealed that most of the plasma cells expressed IgG4, with no recurrence of marginal-zone B-cell lymphoma. The patient was initially treated with oral prednisolone (30 mg/day). After the treatment, the swelling of the orbit was resolved.

Discussion

Knowledge of IgG4-RD in head and neck regions is important for physicians, since the salivary and lacrimal glands are the most frequently involved sites, and early detection helps to prevent potentially life-threatening systemic involvement (Takano et al. 2017). Here, 14 (53.8%) of our 26 patients with IgG4-RD in head and neck regions had potentially life-threatening systemic involvement (AIP, retroperitoneal fibrosis, or inflammatory pseudotumor of the lung) after the initial swelling of the salivary and/or lacrimal glands. A previous study (Carruthers et al. 2015) reported that the mean serum IgG4 level was higher in patients with multi-organ IgG4-RD (699 mg/dL) than that in patients with single-organ IgG4-RD (233 mg/dL). By contrast, there was no significant difference in serum IgG4 concentration between the single- and multiple-lesion groups in the present study. However, the serum IgG4/IgG ratio was higher in the multiple-lesion group. These results allow us to speculate that not only IgG4 but also IgG4/IgG ratio might be additional biomarkers for prediction of the risk for systemic involvement of IgG4-RD.

Concerning the relationship between IgG4-RD and malignancies (Yamamoto et al. 2012; Wallace et al. 2016; Ahn et al. 2017), previous studies showed malignancies in 13.9% (Shiokawa et al. 2013) and 17.9% (Schneider et al. 2017) of IgG4-RD in the case of AIP. Our results found malignancies in two patients (7.7%) with IgG4-RD in head and neck regions, high IgG4/IgG and multiple lesions. Malignancies in patients with IgG4-related diseases in head and neck regions were lymphoma and salivary duct carcinoma in present study. It is well known that chronic persis-

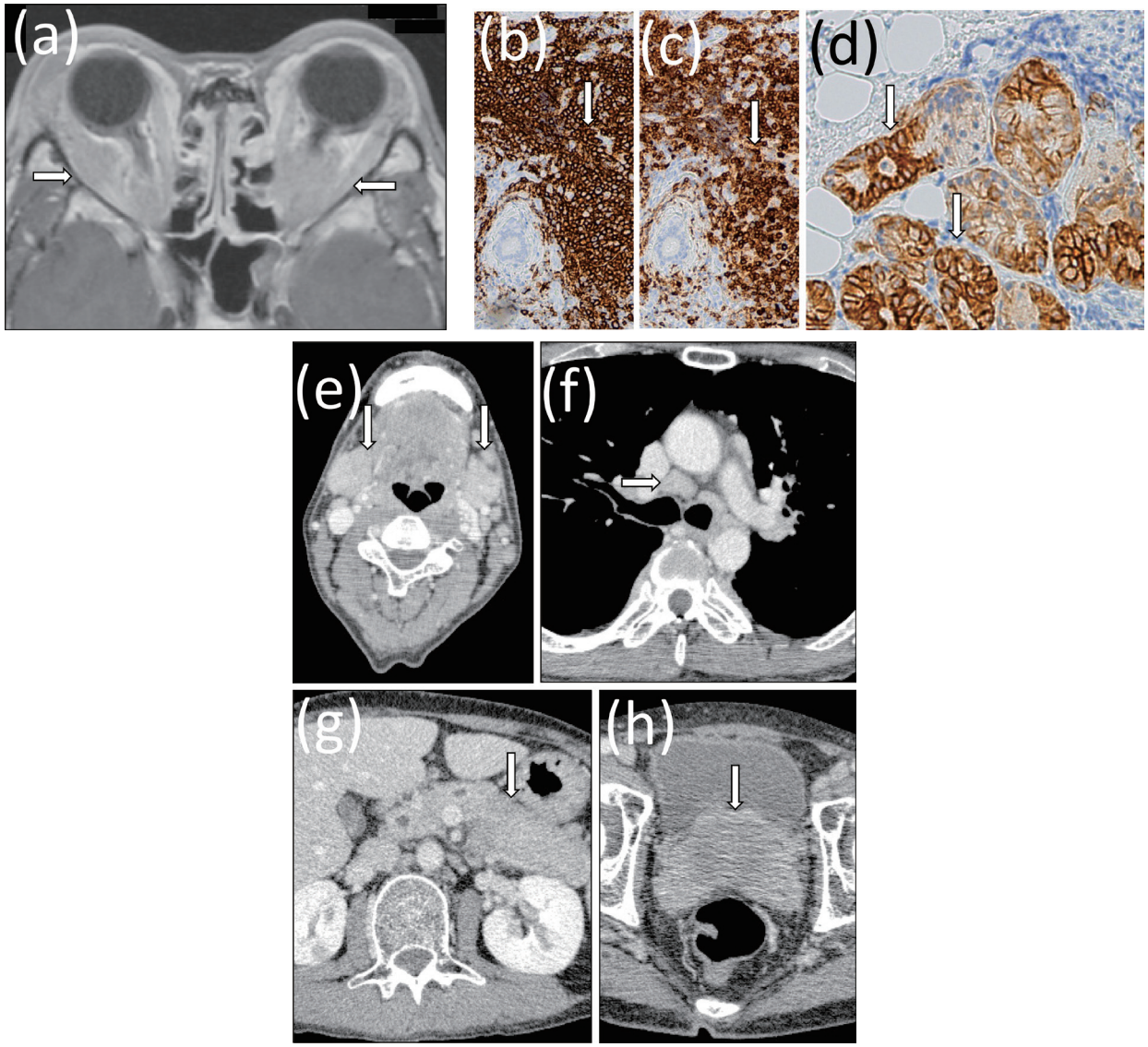

Fig. 3. Clinicopathological findings of Case 2.
(a) Preoperative axial MRI showing well defined bilateral orbital masses (arrow). Positive immunohistochemistry of orbital tumor with CD20 (× 100) (b), CD79a (× 100) (c), and CK-MNF116 (× 200) (d). Arrow indicates lymphoepithelial lesion of each staining image. Axial enhanced CT shows the enlargement of bilateral submandibular glands (e, arrow), mediastinal and epigastric-part lymph nodes (f, arrow), the pancreas (g, arrow), and the prostate (h, arrow).

tent inflammation can induce B cell activation and mucosa associated lymphoid tissue lymphoma (Furukawa et al. 2015). In Sjögren syndrome, antigenic activation of B cells, together with oncogenic events, including p53 inactivation and bcl-2 activation, may play important roles in B cell monoclonal proliferation and malignant transformation (Ohta et al. 2013). These findings may allow us to speculate that chronic persistent inflammation caused by IgG4-RD might also develop the lymphoma in head and neck region. The precise mechanism responsible for the onset of salivary duct carcinoma in IgG4-RD still remains unclear. More cases are needed to confirm the relationship between IgG4-RD in head and neck regions and malignancies.

It is essential to discriminate enlarged organs and malignant tumors. All physicians should pay careful attentions for patients with IgG4-RD with high IgG4/IgG ratio and categorized to multiple-lesion group. In conclusion, to our knowledge, this is the first report of malignancies in patients with IgG4-RD in head and neck regions. All physicians need to keep in the mind the possible coexistence of malignancies in patients with IgG4-RD at the time of diagnosis and during long-term follow-up.

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Conflict of Interest

The authors declare no conflict of interest.

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