Original Contribution

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Association Between Immunoglobulin G4-Related Ophthalmic Disease and Nonlymphoid Malignancy Case Series and Comprehensive Review of the Literature

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Background: Immunoglobulin G4-related disease (IgG4-RD) and immunoglobulin G4-related ophthalmic disease (IgG4-ROD) complicated with nonlymphoid malignancy (NL-malignancy) are rare. No exact relationship between IgG4-RD and NL-malignancies has been established yet, and there have been few reports of different types of IgG4-ROD and related malignancies.

Methods: We retrospectively reviewed medical records of patients diagnosed with IgG4-RD and NL-malignancy, whichever occurred first, from January 2015 to March 2021. In addition, the literature on the relationship between IgG4-ROD and NL-malignancy was reviewed.

Results: There were 115 patients diagnosed with IgG4-RD, and 10 patients were enrolled in the study with NL-malignancy. Three patients were diagnosed with IgG4-ROD. One patient reported a previous history of cancer, and the other 2 patients developed cancer at or after the diagnosis of IgG4-RD. The 3 patients' cancers were located in the lung, gastrointestinal tract, and thyroid.

Conclusions: There may be potential malignancy occurrence during follow-up of IgG4-RD patients, especially among elderly patients. In addition, IgG4-RD could be a paraneoplastic syndrome at or before the diagnosis of malignancy.

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This study was approved by the BFH Ethics Committee and was conducted following the latest iteration of the Declaration of Helsinki (version:2020-P2-314-01). Participants were given written informed consent (version V1.0 /2020-01-01) before inclusion in the study. All blood samples were collected as part of routine treatment for this study.

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Immunoglobulin G4-related disease (IgG4-RD) is a chronic systemic inflammatory disease that has received modest attention in the last decade. It is corticosteroid responsive and often presents with tumor-like lesions in single or multiple affected organs clinically, dense lymphoplasmacytic tissue infiltration with abundant IgG4-positive plasma cells, and elevated serum IgG4 levels serologically (1). Although several previous studies have reported that IgG4-RD might be triggered by cancer (2,3), other research suggests that cancer is one of the complications of IgG4-RD (4).

Approximately 60%–90% of patients with IgG4-RD have multiple organs involved. It has strong predilections for the major salivary glands, the pancreas, and the biliary tree. IgG4-related ophthalmic disease (IgG4-ROD) was reported in 23% of IgG4-RD patients (5). The ocular adnexal was affected most commonly, including the lacrimal gland, infraorbital nerve, extraocular muscles, and orbital fat (6). Optic nerve involvement is rare (7,8). Recently, Lemaitre et al reported an unusual IgG4-ROD patient with bilateral orbital involvement and optic perineuritis who developed colon cancer subsequently (9). They demonstrated the plausibility of IgG4-ROD being a paraneoplastic syndrome of colon cancer rather than an independent disease. Researchers from Asia (10,11),

America (12), and Europe (3) have reported that IgG4-RD patients have a higher prevalence or incidence of cancer. Gastrointestinal tract cancer was commonly reported in Chinese IgG4-RD patients (11). A possible link between IgG4-RD and cancer remains to be established.

To previous reports (13), malignancies associated with IgG4-RD were classified as either lymphoma or nonlymphoid malignancy (NL-malignancy). Lymphoma was the most frequent malignancy associated with IgG4-RD (10,12). NL malignancies were relatively rare in IgG4-RD and undetermined. In this article, we present 10 IgG4-RD patients with NL-malignancy, 3 of them were diagnosed with IgG4-ROD. The literature on the relationship between IgG4-ROD and NL-malignancy is also reviewed.

METHODS

This study was approved by our institutional review board. We retrospectively reviewed medical records of inpatients diagnosed with IgG4-RD and NL-malignancy based on the whole hospital, whichever occurred first, from January 2015 to March 2021 in Beijing Friendship Hospital, Capital Medical University. The diagnosis of the IgG4-RD was based on the 2019 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for IgG4-RD: Cases met the classification criteria for IgG4-RD if the entry criteria were met, no exclusion criteria were present, and the total points were (numerical weight) ≥20 (14) (see **Supplemental Digital Content 1**, **Supplemental Table 1**, http://links.lww.com/WNO/A618).

IgG4-ROD were diagnosed according to "Diagnostic criteria for IgG4-related ophthalmic disease, 2014 (15)" (see **Supplemental Digital Content 1**, **Supplemental Table 2**, http://links.lww.com/WNO/A618).

Malignancies were diagnosed histopathologically by biopsy or analysis of resected specimens according to the International Classification of Disease (ICD-10) criteria. Patients with IgG4-RD and NL-malignancy diagnosed concurrently were defined as having NL-malignancy within 1 year's duration of IgG4-RD diagnosis.

All patients had previously consented to use their medical records for research purposes. Cases with lymphoma and insufficient clinical information were excluded from our study.

RESULTS

Through a maintained database and referrals from various clinical specialities, of the 115 patients with IgG4-RD, 10 patients (4 males and 6 females) were identified as having NL-malignancy and enrolled in the study. Six patients had diabetes mellitus. Four patients reported a previous history of cancer, and the other 6 patients developed cancer at or after the diagnosis of IgG4-RD. Three patients had cancers in the gastrointestinal tract (2 cases of gastric cancer and 1 case of colon cancer). Two patients had thyroid cancer. The remaining 5 patients' cancers were located in the renal, breast, lung, larynx, and bladder. The clinical data of 10

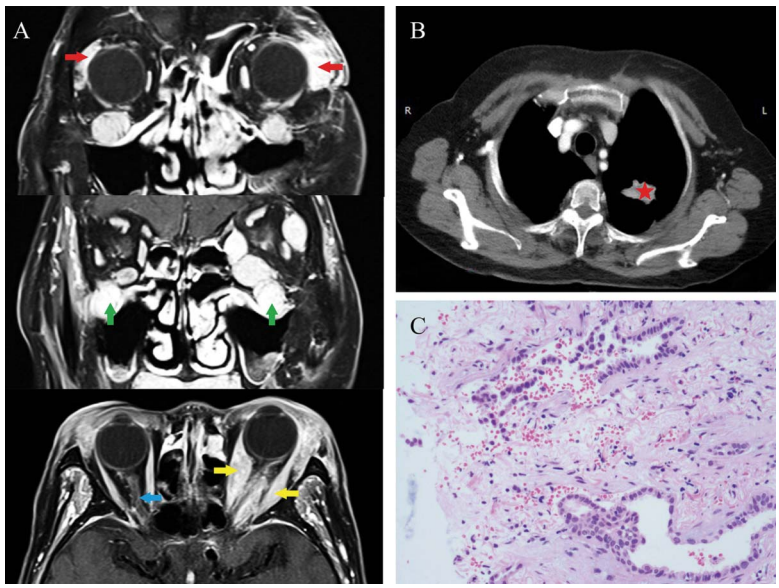

FIG. 1. A. MRI of the orbits. The bilateral lacrimal gland (*red arrow*), infraorbital nerve (*green arrow*), multiple extraocular muscles (yellow arrow), and orbital fat are enlarged. In addition, the bilateral optic nerve sheath is enhanced (blue arrow). **B**. CT of the lung. A spiculated nodule (40 × 20 mm, red star) with the pleural indentation in the left upper lobe. **C**. Lung biopsy (10 × 10). Alveolar and adenoid structure, epithelium atypical moderately, immunohistochemical staining: CK7(+), TTF-1(+), CK5/6(−), D2-40(−), calretinin (−), Glut-1(−), and Ki67:5% (+).

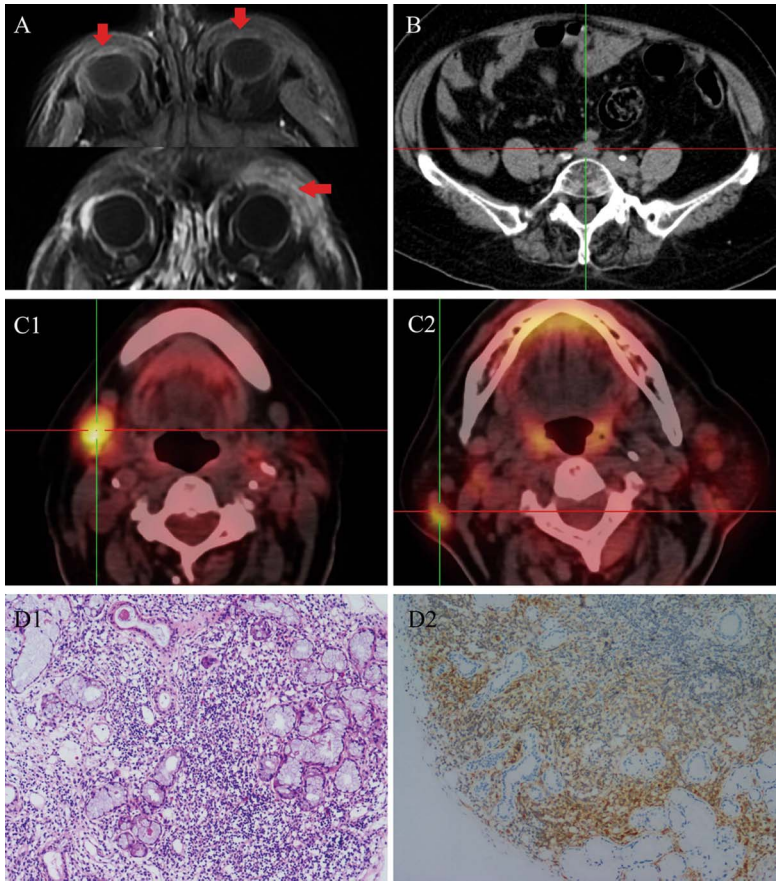

FIG. 2. **A**. MRI of the orbits. The left lacrimal gland is enlarged, and bilateral eyelids exhibit swelling (red arrow). **B**. CT of the abdomen. Postoperative state (colectomy and regional lymph node resection). **C**. 18F-FDG-PET of patient 2. High accumulation in the right submandibular nodule (C1) and right parotid gland (C2), with maximum SUV of 6.9 and 4.3, respectively. **D**, Biopsy of the lower lip (10 × 10). Severe lymphoplasmacytic infiltration and fibrosis (D1). IgG4-positive plasma cells (>50/HPF). Immunohistochemical staining: IgG4+/IgG+ ratio was 40% (D2).

IgG4-RD patients with NL-malignancy were summarized in Table 1. Three patients were diagnosed as having IgG4-ROD with NL-malignancy (Figs. 1–3).

Case Presentation

Patient 1 is an 82-year-old woman, who visited the ophthalmologic department for markedly swelling orbits for half a year. She complained of the sensation of having a foreign body and puffiness around her left eye. Her visual acuity was 20/25 in the right eye and 20/50 in the left eye. Intraocular pressure (IOP) and fundus were within normal ranges. Physical examination revealed enlarged lachrymal glands. MRI of the orbits showed enlargement of the bilateral lacrimal gland, infraorbital nerve, multiple extraocular muscles, and orbital fat. Her bilateral optic nerve sheath was also enhanced. This patient exhibited markedly elevated IgG4 levels of 4,570 mg/dL (reference range, 3–201 mg/dL) and total IgG levels of 4,100 mg/dL (reference range, 600–1,500 mg/dL). Thyroid function tests were normal, making thyroid eye disease unlikely. Diagnosis of IgG4-ROD was definite. Six years ago, she (at the age of 76) visited our hospital because of cough, sputum production, and dyspnea. A chest computed tomography (CT) scan showed a 40mm x 20 mm spiculated nodule with the pleural indentation in the upper lobe of her left lung. Hilar and mediastinal lymphadenopathies were identified. A percutaneous lung biopsy was performed, which revealed adenocarcinoma. She was diagnosed with lung adenocarcinoma at cT2N3M1, stage IV. She was subsequently treated with pemetrexed plus cisplatin, gemcitabine plus cisplatin, and gefitinib/anlotinib.

Patient 2 is a 79-year-old woman who presented with a 2-year history of the right-sided submandibular lump (12.5 × 17 × 16 mm) and right eyelid/conjunctive swelling that appeared to improve. She complained of tearing and puffiness around both eyes when consulted by ophthalmologists. MRI of the orbits showed enlargement of the left lacrimal gland and swelling of bilateral eyelids. An 18F-fluorodeoxyglucose-positron emission tomography (18F-FDG-PET) scan revealed high accumulation in her right submandibular nodule and right parotid gland, with maximum standardized uptake value (SUV) of 6.9 and 4.3, respectively. The lower lip biopsy

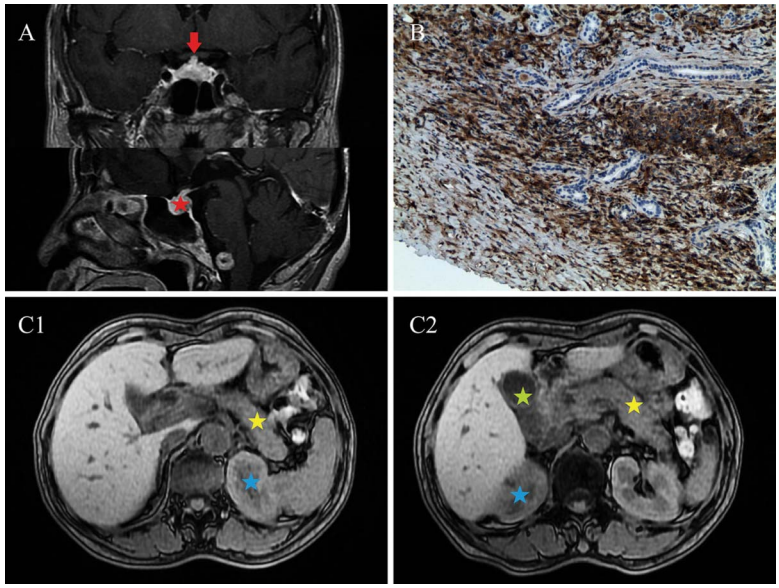

FIG. 3. A. MRI of the cranial. A circumferential optic nerve sheath enhancement in the optic chiasm (*red arrow*), and enlarged pituitary gland (12 × 13 × 16 mm red star). **B**, A biopsy of the submandibular gland. Severe lymphoplasmacytic infiltration, and the presence of numerous IgG4+ plasma cells (20/40×HPF), CD138(+), CD38(+), and IgG (+). **C**. MRI of the abdomen. The pancreas (yellow star) and bilateral kidney (blue star) are enlarged diffusely. The lower biliary ducts are smoothly narrowed, and the upper choledochus and cholecyst are dilated (green star).

showed severe lymphoplasmacytic infiltration, fibrosis, and the presence of numerous IgG4-positive plasma cells (>50/HPF). Immunohistochemical staining revealed an IgG4+/IgG+ ratio of 40%. The serology demonstrated elevated IgG4 levels of 1,070 mg/dL and normal total IgG levels of 1,630 mg/dL. Other immunological test results were negative for rheumatoid factor and antinuclear antibodies. The patient was diagnosed with IgG4-related Mikulicz syndrome. Her background included a 10-year history of colon cancer. A total colectomy and regional lymph node resection were performed. Tumor markers were negative until this study.

Patient 3 is a 60-year-old woman. She was referred for further evaluation of a bilateral submandibular swelling present for several years. She complained of dry eye and vision decrease when consulted by ophthalmologists. Her visual acuity was 20/20 in the right eye and 20/32 in the left eye. IOP and eye fundus examination were normal. A cranial MRI showed a circumferential optic nerve sheath enhancement in the optic chiasm likely because of optic nerve sheath infiltration by the enlarged pituitary gland (12 mm × 13 mm × 16 mm). MRI examination of the abdomen revealed a diffusely enlarged pancreas and biliteral kidney. Her lower biliary ducts were smoothly narrowed, and her upper choledochus was dilated. A biopsy of the submandibular gland revealed severe lymphoplasmacytic infiltration and the presence of numerous IgG4-positive plasma cells (20/40× HPF), CD138(+), CD38(+), and IgG (+). Total serum IgG and IgG4 were elevated to 2,230 mg/dL and 2,690 mg/dL, respectively. Diagnosis of IgG4-RD was made by characteristic pathology and radiology imaging of multiple organs, including the pancreas, bile ducts, kidneys, submandibular gland, optic nerve, basilar artery wall, thyroid, and pituitary gland. At the same time, a nodule was incidentally found in the left lobe of her thyroid. Fine needle aspiration cytology revealed a thyroid papillary carcinoma cytometry. Her thyroid-stimulating hormone levels were 6.36 uIU/mL (reference range, 0.49–4.91uIU/mL). Free triiodothyronine and free thyroxine were within the normal limit. She accepted cyclophosphamide therapy. Her syndromes in ocular were released so as other organs after and with no evidence of recurrence right now.

Literature Review

To date, 12 patients of IgG4-ROD with NL-malignancy have been reported within the English literature. Their clinical characteristics and histopathology are summarized in Table 2 (9,11,12,16–18). The most common NL-malignancy associated with IgG4-ROD was colon cancer and breast cancer (2 patients, respectively). The remaining 8 solid tumors were located in the parotid gland, submandibular gland, lipoblastoma, thyroid, cervix, prostate, lung, and tongue. Four patients reported a previous history of cancer, and the other 8 patients developed cancer at or after the diagnosis of IgG4-ROD.

DISCUSSION

The immunologic pathogenesis of IgG4-RD is complex. Autoimmunity or infection may trigger the immune reaction of T helper cell type 2 (Th2) cells, followed by predominate interleukins 4, 5, 10, and 13, which activate B cells and transform growth factor b (TGF-b).

TABLE 1. Clinical data of IgG4-RD patients with NL-malignancy

	Sex/Age	Organ Involvement	Pharmacotherapy	DM	HbAlc	IgG4-RD	Diagnosis Cancer	Treatment of CA	IgG4(mg/dL) (3–201)	IgG(mg/dL) (700–1,600)
Patient 1	F/82	Lacrimal gland, infraorbital nerve, multiple extraocular muscles, and optic nerve	None	N	5.5	6Y after CA	Lung adenocarcinoma (cT2N3M1 IV)	Pemetrexed + cisplatin, gemcitabine + cisplatin, and gefitinib/ anlotinib	4,570	4,100
Patient 2	F/79	Lacrimal gland, salivary glands, submandibular gland, parotid, gland, and retroperitoneal fibrosis	Methylprednisolone	Y	6.5	10Y after CA	Colonic cancer	Surgical resection	1,070	1,630
Patient 3	F/60	Optic nerve, lacrimal gland, pancreas, pituitary gland, thyroid, aortic wall, bile duct, and renal	Cyclophosphamide	Y	8.9	Concurrent	Thyroid papillary and carcinoma	Loss to follow-up	2,690	2,230
Patient 4	F/43	Bladder	Methylprednisolone	Y	5.1	2Y before CA	Thyroid cancer	Surgical resection	376	2,560
Patient 5	F/66	Submandibular gland	Methylprednisolone	N	4.8	1Y before CA	Gastric cancer (cT4aNxM1 IV)	Palliative care	381	1,290
Patient 6	M/79	Pancreas and retroperitoneal fibrosis methylprednisolone	Y	7.4	2Y before CA	Gastric cancer (pT2N1M0IIA)	Surgical resection + capecitabine	328	1,070	
Patient 7	M/67	Pancreas, bile duct, and retroperitoneal fibrosis	Methylprednisolone + cyclophosphamide	Y	9.5	1Y before CA	Renal cancer (ccRCC, stage 2)	Surgical resection	2,250	2,680
Patient 8	M/38	Pancreas and colon	None	N	8.9	10Y after CA	Larynx cancer	Surgical resection	351	2,970
Patient 9	M/64	Pancreas and bile duct	Prednisone	Y	5.7	12Y after CA	Bladder cancer	Surgical resection	3,010	2,737
Patient 10	M/83	Pancreas, bile duct, and parotid gland	None	N	5.8	Concurrent	Breast cancer	Surgical resection + lelrozol + exemestane	1,300	1730

IgG4-RD, IgG4-related disease; NL-malignancy, nonlymphoid malignancy; CA, cancer; F, female; M, male; ccRCC, clear cell renal cell carcinoma.

TABLE 2. Clinical characteristics and histopathology summary of IgG4-ROD with NL-malignancy in previous literature

Author, Publish Year	Sex/Age	IgG4-ROD	IgG4-RD Diagnosis	Solid Tumor	IgG4(mg/dL)	IgG (mg/dL)	Available Specimens Immunohistochemical
Jespal Gill, 2008	M/75	Lacrimal gland, salivary gland, submandibular gland, and chronic sclerosing sialadenitis	Concurrent	Parotid gland (salivary duct carcinoma)	341	1,630	IgG and IgG4: >100/ HPF; IgG4+ /IgG+ :> 40%
	F/71	Orbit, parotid, submandibular, and skin	3Y after CA	Breast CA	>135	NA	NA
Zachary S. Wallace	F/34	Orbit and lymphadenopathy,	9Y after CA	Cervix CA	>135	NA	NA
	M/61	Orbital, aorta, and pancreas	4Y after CA	Prostate CA	>135	NA	NA
Yuan-Hung Wu, 2017	M/67	Orbit mass and medial rectus muscle	11Y after CA	Tongue squamous cell carcinoma	780	1,500	IgG4+ /IgG+: >50%
Stephanie Lemaitre, 2018	M/78	Orbit, lateral and medial rectus; muscles; optic nerve; and lymph node	2Y before CA	Colonic adenocarcinoma (stage IV)	71	NA	IgG4+ / IgG+: 42.2%
Ryoukichi Ikeda, 2019	M/73	Lacrimal gland, salivary duct, pancreas, submandibular, renal, pancreatic, prostatic, and mediastinal lymph nodes	Concurrent	Submandibular gland (salivary duct carcinoma)	322	2,350	IgG4+ /IgG+:> 60%
HanqiTang, 2020	M/42	Lacrimal gland and parotid gland	2Y after CA 3Y before CA	Lipoblastoma	263	NA	NA
	M/49	Lacrimal gland, pancreas, parotid gland, lung, prostate, and lymph nodes	1Y before CA	Thyroid carcinoma	1000	NA	NA
			Concurrent	Lung CA	1730	NA	NA
	F/69	Lacrimal gland, parotid gland, salivary gland, and sinus	4Y before CA	Colon CA	5,800	NA	NA
	M/79	Lacrimal gland and pancreas		Breast CA	1,000	NA	NA
	F/50	Lacrimal gland and parotid gland					

M, male; F, female; Y, year; CA, cancer; NA, not available; HPF, high-power field; IgG4-RD, IgG4-related disease; NL-malignancy, nonlymphoid malignancy; IgG4-ROD, IgG4-related ophthalmic disease.

Conceivably, TGF-b is a key molecule in diffuse fibrosis and directs B cells to produce IgG4 potently. As a result, regulatory T cells (Treg) are activated, and increased serum IgG4 and infiltrated IgG4-positive plasma cells/lymphocytes lead to the damage of organs. The increased production of Th2-dominated cytokine, IgG4, and Treg are responsible for IgG4-RD (19).

The ocular adnexal was the most common involvement site of IgG4-RD (6). As seen in patients 1 and 2, the disease manifests as mass lesions in the orbits and lacrimal glands, characterized by eyelid swelling. Infraorbital nerve enlargement is a specific sign associated with IgG4-ROD. Histological analysis revealed that the epineurium was inflamed, whereas the endoneurium and perineurium were unaffected (20). IgG4-related compressive optic neuropathy, caused by enlarged orbital structures, was found by orbital imaging in 9.2% of the IgG4-ROD cases (7). Patient 3 was diagnosed with perineuritis. Meningeal infiltration of the optic nerve was found by imaging because of the inflammation of the optic nerve sheath involved by IgG4-related hypophysitis but not direct infiltration of the optic nerve. Simultaneously, the enlarged pituitary gland caused compressive optic neuropathy at the optic chiasma. Commonly, compressive optic neuropathy often affects the unilateral optic nerve.

NL-Malignancy has an unclear association with IgG4-RD. They could share several risk factors. Treg cells not only lead to IgG4-RD but also play a role in the progression and metastasis of various malignant tumors (21). TGF-b is overexpressed in the severe fibrotic area and invasion front of papillary carcinoma. Patients might be diagnosed with malignancy before, concurrently, or after the diagnosis of IgG4-RD**.** Huggett et al (3) found malignancy occurred in 11% of autoimmune pancreatitis (AIP) or IgG4-RSC patients shortly before or after IgG4-RD was diagnosed.

The most common malignancies associated with IgG4-RD were reported in different geographic regions and research designations: prostate cancer (American, Wallace et al (12).and Sekiguchi et al (22)), lung cancer (Japanese, Hirano et al (23)), lymphoma(Korean, Ahn et al (10)), and colorectal cancer (Chinese Tang et al (11)). In our research, we reported 8 kinds of NL-malignancies. Gastric cancer and thyroid cancer were the most common.

Previous studies (12,22) reported that 10% and 16% of IgG4-RD patients had a history of malignancy. A history of malignancy was 3 times more likely in IgG4-RD patients compared with case-controlled patients. First, cancer may trigger autoantigen expression and develop IgG4-RD. Second, anticancer therapies, such as radiation chemotherapy and immunotherapy, might increase the risk of IgG4-RD development (12). In addition, immune checkpoint inhibitors promote the recruitment of B cells to IgG4 by inhibiting the PD-1/PD-L1 pathway and enhancing T follicular helper cells (24). Third, IgG4 antibodies, Treg cells, and IL-10 activated in IgG4-RD seem to suppress antitumor immune responses and implicate tumor-immune escape directly (25).

On the other side, malignancies were concurrent or followed in 10.4% of the IgG4-RD patients in a report. The standardized incidence ratio is approximately 3.5 times higher than that in the general population at diagnosis or during a follow-up period (2). For example, adenocarcinomas in the pancreas and salivary gland are complications of AIP and IgG4-related sclerosing sialadenitis (16). IgG4-RD is a predisposing condition. It may create immunological environments favorable for cancer development (21). IgG4-RD onset at age >65 is a risk factor for cancer development due to a deficiency in anticancer immune surveillance among the elderly. Furthermore, another risk factor reported by Hirano et al (23) was diabetes mellitus (DM). Six of 10 patients had DM in our report.

The relationship between IgG4-RD and malignant lymphomas was more closely than NL-malignancies. Malignant lymphoma possibly arising from IgG4-RD was proven histologically. It was hard to distinguish IgG4-RD from lymphoma in the contiguous lesions. IgG4-RD could represent a chronic inflammatory background for the development of malignant lymphomas. Marunaka et al (26) have observed that IgG4-ROD and ocular marginal zone B-cell lymphoma with IgG4+ cells showed the same expression pattern of cytokines mRNA.

Treatment regimens of IgG4-RD have not yet been standardized. Patients generally respond well to corticosteroids and immunosuppression, but their IgG4-RD typically recurs as soon as corticosteroids are reduced or withdrawn (4). Cases of spontaneous remission have also been reported. Furthermore, given the side effects of steroids and the poor general condition of the patients, wait-and-see management may be more appropriate in IgG4-RD patients with malignancy.

In addition, patients with malignancies might develop IgG4-ROD and patients with IgG4-ROD might cause malignancies occurrence or shortly. So attention to ocular symptoms should be paid to the IgG4-ROD by both ophthalmologists and physicians. Early treatment of IgG4-ROD was crucial. Ocular symptoms were diverse. If not controlled, persistent dry eye disease because of the lacrimal glands involved or visual loss because of the mass effect of orbital involvement would seriously decline patients' quality of life. Further studies focused on classification, severity assessments for ophthalmic lesions, treatment guidelines, and even the pathogenesis of IgG4-ROD.

CONCLUSIONS

In conclusion, we report rare cases of IgG4-RD and IgG4-ROD complicated with NL-malignancies. Accordingly, it is important to carefully screen for potential malignancy occurrence during follow-up examinations of IgG4-RD patients, especially elderly patients. It is still too early to

draw a definitive relationship between IgG4-RD and NL-malignancy. The mechanism responsible for the development of IgG4-RD requires further research.

STATEMENT OF AUTHORSHIP
Conception and design: H. Li; Acquisition of data: Y. Hou; Analysis and interpretation of data: Q. Su, J. Li, H. Zhou, Y. Hou; Drafting the manuscript: Y. Hou; Revising the manuscript for intellectual content: H. Li, Y. Hou; Final approval of the completed manuscript: H. Li.

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REFERENCES

1. **Deshpande V**, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, Klöppel G, Heathcote JG, Khosroshahi A, Ferry JA, Aalberse RC, Bloch DB, Brugge WR, Bateman AC, Carruthers MN, Chari ST, Cheuk W, Cornell LD, Fernandez-Del Castillo C, Forcione DG, Hamilos DL, Kamisawa T, Kasashima S, Kawa S, Kawano M, Lauwers GY, Masaki Y, Nakanuma Y, Notohara K, Okazaki K, Ryu JK, Saeki T, Sahani DV, Smyrk TC, Stone JR, Takahira M, Webster GJ, Yamamoto M, Zamboni G, Umehara H, Stone JH. Consensus statement on the pathology of IgG4-related disease. Mod Pathol : official J United States Can Acad Pathol Inc. 2012;25:1181–1192.
2. **Yamamoto M**, Takahashi H, Tabeya T, Suzuki C, Naishiro Y, Ishigami K, Yajima H, Shimizu Y, Obara M, Yamamoto H, Himi T, Imai K, Shinomura Y. Risk of malignancies in IgG4-related disease. Mod Rheumatol. 2012;22:414–418.
3. **Huggett MT**, Culver EL, Kumar M, Hurst JM, Rodriguez-Justo M, Chapman MH, Johnson GJ, Pereira SP, Chapman RW, Webster GJM, BarnEs E. Type 1 autoimmune pancreatitis and IgG4-related sclerosing cholangitis is associated with extrapancreatic organ failure, malignancy, and mortality in a prospective UK cohort. Am J Gastroenterol. 2014;109:1675–1683.
4. **Hart PA**, Kamisawa T, Brugge WR, Chung JB, Culver EL, Czakó L, Frulloni L, Go VLW, Gress TM, Kim MH, Kawa S, Lee KT, Lerch MM, Liao WC, Lohr M, Okazaki K, Ryu JK, Schleinitz N, Shimizu K, Shimosegawa T, Soetikno R, Webster G, Yadav D, Zen Y, Chari ST. Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis. Gut. 2013;62:1771–1776.
5. **Wallace ZS**, Deshpande V, Stone JH. Ophthalmic manifestations of IgG4-related disease: single-center experience and literature review. Semin Arthritis Rheum. 2014;43:806–817.
6. **McNab AA**, McKelvie P. IgG4-Related ophthalmic disease. Part II: clinical aspects. Ophthalmic Plast Reconstr Surg. 2015;31:167–178.
7. **Hwang G**, Jin SY, Kim HS. IgG4-related disease presenting as hypertrophic pachymeningitis and compressive optic neuropathy. Joint bone Spine. 2016;83:601–602.
8. **Takahashi Y**, Kitamura A, Kakizaki H. Bilateral optic nerve involvement in immunoglobulin G4-related ophthalmic disease. J Neuroophthalmol. 2014;34:16–19.
9. **Lemaitre S**, Esquerda GM, Guardiola AC, Agustin JT, Sanda N, González-Candial M. Colon cancer and IgG4-related disease with orbital inflammation and bilateral optic perineuritis: a case report. Medicine. 2018;97:e12197.
10. **Ahn SS**, Song JJ, Park YB, Lee SW. Malignancies in Korean patients with immunoglobulin G4-related disease. Int J Rheum Dis. 2017;20:1028–1035.
11. **Tang H**, Yang H, Zhang P, Wu D, Zhang S, Zhao J, Peng L, Chen H, Fei Y, Zhang X, Zhao Y, Zeng X, Zhang F, Zhang W. Malignancy and IgG4-related disease: the incidence, related factors and prognosis from a prospective cohort study in China. Scientific Rep. 2020;10:4910.
12. **Wallace ZS**, Wallace CJ, Lu N, Choi HK, Stone JH. Association of IgG4-related disease with history of malignancy. Arthritis Rheumatol. 2016;68:2283–2289.
13. **Yamamoto M**, Takahashi H, Shinomura Y. IgG4-related disease and malignancy. Intern Med. 2012;51:349–350.
14. **Wallace ZS**, Naden RP, Chari S, Choi HK, Della-Torre E, Dicaire JF, Hart PA, Inoue D, Kawano M, Khosroshahi A, Lanzillotta M, Okazaki K, Perugino CA, Sharma A, Saeki T, Schleinitz N, Takahashi N, Umehara H, Zen Y, Stone JH. The 2019 American College of Rheumatology/European League against rheumatism classification criteria for IgG4-related disease. Ann Rheum Dis. 2020;79:77–87.
15. **Goto H**, Takahira M, Azumi A. Erratum to: diagnostic criteria for IgG4-related ophthalmic disease. Jpn J Ophthalmol. 2015;59:201.
16. **Gill J**, Angelo N, Yeong ML, McIvor N. Salivary duct carcinoma arising in IgG4-related autoimmune disease of the parotid gland. Hum Pathol. 2009;40:881–886.
17. **Wu YH**, Wang LC, Yen SH, Yu WK, Kao SC, Kau HC, Tsai CC, Liu CJL. Change of serum IgG4 in patients with ocular adnexal marginal zone B cell lymphoma associated with IgG4-related ophthalmic disease after treatment. J Ocul Pharmacol Ther. 2017;33:543–548.
18. **Ikeda R**, Kurakami K, Ohta N, Suzuki T, Saito Y, Kusano Y, Yamazaki M, Tateda Y, Kitaya S, Kakehata S, Takahashi H, Satoh K. Malignancies in patients with IgG4-related diseases in head and neck regions. Tohoku J Exp Med. 2019;249:285–290.
19. **Sato Y**, Notohara K, Kojima M, Takata K, Masaki Y, Yoshino T. IgG4-related disease: historical overview and pathology of hematological disorders. Pathol Int. 2010;60:247–258.
20. **Ohshima KI**, Sogabe Y, Sato Y. The usefulness of infraorbital nerve enlargement on MRI imaging in clinical diagnosis of IgG4-related orbital disease. Jpn J Ophthalmol. 2012;56:380–382.
21. **Harada K**, Nakanuma Y. Cholangiocarcinoma with respect to IgG4 reaction. Int J Hepatol. 2014;2014:803876.
22. **Sekiguchi H**, Horie R, Kanai M, Suzuki R, Yi ES, Ryu JH. IgG4-Related disease: retrospective analysis of one hundred sixty-six patients. Arthritis Rheumatol (Hoboken, NJ). 2016;68:2290–2299.
23. **Hirano K**, Tada M, Sasahira N, Isayama H, Mizuno S, Takagi K, Watanabe T, Saito T, Kawahata S, Uchino R, Hamada T, Miyabayashi K, Mohri D, Sasaki T, Kogure H, Yamamoto N, Nakai Y, Yoshida H, Ito Y, Akiyama D, Toda N, Arizumi T, Yagioka H, Takahara N, Matsubara S, Yashima Y, Koike K. Incidence of malignancies in patients with IgG4-related disease. Intern Med (Tokyo, Japan). 2014;53:171–176.
24. **Umehara H**, Okazaki K, Kawano M, Tanaka Y. The front line of research into immunoglobin G4-related disease - do autoantibodies cause immunoglobin G4-related disease? Mod Rheumatol. 2019;29:214–218.
25. **Trampert DC**, Hubers LM, van de Graaf SFJ, Beuers U. On the role of IgG4 in inflammatory conditions: lessons for IgG4-related disease. Biochim Biophys Acta Mol basis Dis. 2018;1864:1401–1409.
26. **Marunaka H**, Orita Y, Tachibana T, Miki K, Makino T, Yoshino T, Nishizaki K, Sato Y. Diffuse large B-cell lymphoma of the lacrimal sac arising from a patient with IgG4-related disease. Mod Rheumatol. 2018;28:559–563.