Coexistence of IgG4-Related Disease with Synchronous Parotid and Lung Cancers: Diagnostic and Therapeutic Challenges

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ABSTRACT

IgG4-related disease (IgG4-RD), a chronic inflammatory disorder with multi-organ involvement, presents diagnostic and therapeutic challenges. While rare malignancies are reported with IgG4-RD, concurrent dual cancers remain undocumented. A 65-year-old male patient with right parotid enlargement underwent radical resection, which confirmed parotid carcinoma and IgG4-RD. During adjuvant radiotherapy and glucocorticoid therapy, a second tumour, lung adenocarcinoma, was diagnosed. To avoid the risks of immune-related adverse events, the use of glucocorticoids was reduced, and PD-1 inhibitors were withheld in the early stages. Despite first-line treatment, the patient's lung cancer progressed. After six months, second-line chemotherapy and anti-PD-1 therapy were initiated, during which hormone therapy was discontinued. The patient succumbed within a month thereafter. This case highlights the need to identify imaging and pathological features of IgG4-RD with malignancies, balance therapies, and optimise anti-cancer strategies.

Key Words: *IgG4-related disease, Dual primary cancers, Parotid gland cancer, Lung cancer*.

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INTRODUCTION

IgG4-related disease (IgG4-RD) is an immune-mediated fibro-inflammatory condition characterised by elevated serum IgG4 and organ enlargement or nodular lesions.[1] Previous studies in Japan and the United States have shown that the incidence of IgG4-RD is less than 1/1000, and it is a rare disease in China.[2,3] Moreover, mortality risk for IgG4-RD patients is 2.5- fold higher than that of the general population.[2] Studies demonstrate that malignancy prevalence in IgG4-RD patients exceeds that of the general population.[4] Its aetiology remains unclear, with diagnosis guided by the 2020 Japanese criteria.[5] Management includes glucocorticoids, immunosuppressants, biologics, and surgical intervention in selected cases, though high recurrence rates complicate management.[3,6]

Insufficient clinician awareness frequently leads to its misdiagnosis as malignancy, causing significant organ damage.[7,8] IgG4-RD also coexists with cancers (*e.g.*, colorectal, lung, pancreatic, breast, parotid, and bladder),[9] though synchronous dual primary parotid and lung carcinomas remain unreported. Synchronous multiple primary malignant neoplasms (MPMN) are clinically uncommon and pose significant therapeutic challenges.

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This study addresses the diagnostic and therapeutic complexities of this rare dual disease and retrospectively analyses the characteristics of IgG4-RD to provide clinical management references.

CASE REPORT

A 65-year-old male had undergone prior surgeries: left parotidectomy for a parotid mixed tumour 10 years ago and bilateral submandibular gland excision for chronic sclerosing sialadenitis four years ago. He has now presented with a newly detected right parotid mass for two months.

Physical examination revealed a firm 5 × 4 × 3 cm^3 right parotid nodule. Ultrasound, CT, and MRI showed bilateral parotid diffuse lesions (suggestive of Mikulicz disease) with multiple right parotid nodules (Figure 1A), accompanied by widespread lymphadenopathy, suggestive of chronic inflammation. Serum IgG4 was markedly raised (10,866.1 mg/L).

Initial multidisciplinary team (MDT) consensus-guided resection of the nodule was subsequently converted to radical parotidectomy based on intraoperative pathology. Histopathological analysis showed ductal carcinoma in the right parotid gland (Figure 1B (1,2)). Chronic sclerotic inflammation of the salivary gland showed plasma cell expression of IgG and IgG4, with an IgG4/IgG ratio of >0.4 (Figure 1C). Combined with a significant rise in the serum IgG4, the diagnoses were established as: Right parotid salivary duct carcinoma, pT2N2bM0, stage IVA and IgG4-RD. Postoperative FDG^{18}-PET-CT revealed bilateral cervical (SUVmax 2.4; likely inflammatory), mediastinal and hilar lymphadenopathy (SUVmax 7.5, suspected IgG4-RD), and a left upper lung nodule (2.9 × 1.9 cm, SUVmax 7.4; suspected IgG4-RD or infectious lesion) (Figure 1D).

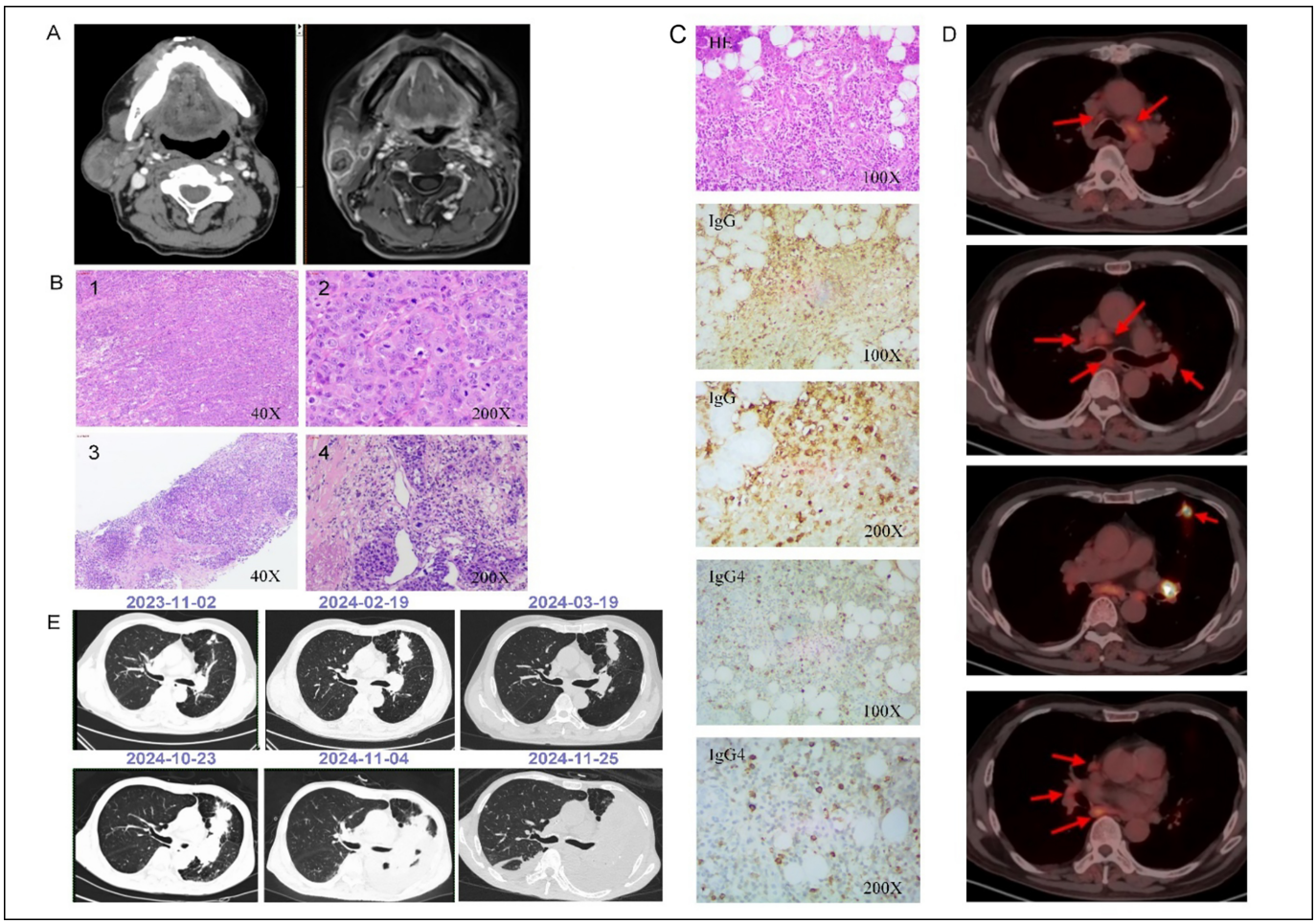

Figure 1: Imaging and pathological examination results of the patients with IgG4-RD combined with parotid gland cancer and lung cancer. (A) Enhanced CT (left) and MRI (right) showing nodules and enlargement of the right parotid gland. (B) The pathology of parotid salivary gland carcinoma (1-2). The pathology of lung adenocarcinoma (3-4). (C) The pathology of chronic sclerotic salivary adenitis of the right parotid gland, as well as the IHC expression of IgG and IgG4; IgG4/IgG >40%. (D) PET-CT showing the metabolism of the left pulmonary nodules and mediastinal lymph nodes. (E) The lesion of the lung mass progresses over time.

Table I: The clinical characteristics of one patient with IgG4-RD combined with a malignant tumour and three patients with IgG4-RD alone.

Characteristics	IgG4-RD with tumour (1 case)	IgG4-RD without tumour (3 cases)
Gender (Male/Female)	Male, 100%	Male, 3 cases 100%
Age (years)	65	Median: 63.5, range 44-87
Smoking history	Yes, 100%	Yes, 3 cases 100%
Diabetes	No, 0%	No, 3 cases 0%
Autoimmune disease	No, 0%	No, 3 cases 0%
Serum IgG4 (mg/L)	10866	Median: 10762, range 1318-30956
Serum IgG (g/L)	24.4	Median: 24.45, range 13.7-67.4
Involved organs	Parotid gland, lymph nodes	Bile duct, lymph nodes; Lymph nodes; Lymph nodes
Treatment regimen	Glucocorticoid, 100%	Glucocorticoid, 3 cases, 100%
Follow-up time (months)	12	6; 13; 1
Final outcome	Death	Death; death; survival

IgG4 levels decreased postoperatively (5,896 mg/L). The patient was started on prednisone, iguratimod, and hydroxychloroquine for IgG4-RD, alongside adjuvant radiotherapy delivered to the tumour bed (66 Gy/30 fractions) and high-risk lymphatic areas (54 Gy/30 fractions). A follow-up was arranged for the pulmonary nodular lesions.

During radiotherapy, new respiratory symptoms emerged. CT demonstrated a progressive left upper lobe lesion (4.3 × 2.5→5.1 × 2.4 cm) with raised tumour markers CA19-9 (59.9 U/ml), CA12-5 (105 U/ml), CA72-4 (8.77 U/ml), and IgG4 (>16,000 mg/L). CT-guided biopsy confirmed lung adenocarcinoma without driver mutations and negative for IgG4 staining (Figure 1B (3-4)), immunohistochemical findings: CK7 (+), the AR part of (+), TTF-1 (-), NapsinA (-), P63 (-), CK5/6 (-), P40 (-), P53 (+), Ki-67 about 90% (+), IgG (-), IgG4 (-), CD138 epithelia cells (+). Final diagnosis: lung adenocarcinoma with bone metastases (cT3N3M1b, stage IVA, AJCC 8th edition).

Given the coexistence of IgG4-RD, PD-1 inhibitors were withheld due to the risks of immune-related adverse events. Initial management comprised six cycles of pemetrexed/carboplatin chemotherapy, plus five cycles of bevacizumab, followed by three-weekly maintenance bevacizumab and

palliative bone radiotherapy. IgG4-RD therapy continued concurrently, with no parotid carcinoma recurrence. Seven months later, widespread metastases developed involving the bone, liver, adrenal glands, abdominal nodes, and retroperitoneal nodes. Tumour obstruction of the left main bronchus led to respiratory failure. Second-line treatment was changed to albumin-bound paclitaxel plus sintilimab; anti-IgG4-RD therapy was discontinued. Follow-up imaging demonstrated systemic progression (Figure 1E). The patient refused further treatment and passed away one month later.

Subsequently, IgG4-RD cases at our hospital were reviewed. After excluding incomplete records, four male patients were analysed: one with IgG4-RD-associated malignancy (previously described) and three with isolated IgG4-RD (Table I). Comparative analysis revealed no significant intergroup differences in age (65 *vs*. 63.5 years), serum IgG4 (10,866 *vs*. 10,762 mg/L), comorbid autoimmune conditions and diabetes (0% both), or glucocorticoid use (100% both). All were male smokers with lymph node involvement. Outcomes were poor: three died from disease progression (one malignancy-related). These findings suggest that IgG4-RD patients, especially elderly smokers, may benefit from regular tumour surveillance. The authors advise incorporating parotid ultrasound and low-dose thoracoabdominal CT into routine follow-up. Limitations include a small sample size (n = 4); validation requires larger cohorts.

DISCUSSION

IgG4-RD is an autoimmune disease that is associated with tumours. Literature review shows that IgG4-RD can coexist with many tumours, such as lymphoma, salivary gland cancer, lung cancer, breast cancer, pancreatic cancer, oesophageal cancer, gastric cancer, prostate cancer, bladder cancer, cholangiocarcinoma, and colon cancer.[9,10] These tumours may occur either before or after the onset of IgG4-RD. Studies indicate that the incidence of malignant tumours in patients with IgG4-RD is higher than that in the general population.[4] Additionally, environmental changes, smoking, and blue-collar-related occupations are associated with an increased risk of developing IgG4-RD.[2,3] A study in the Italian population suggested that close monitoring of newly diagnosed IgG4-RD patients is necessary during the first 36 months, as IgG4-RD can present as a paraneoplastic syndrome in some patients.[4]

This first reported case of IgG4-RD with synchronous parotid carcinoma and lung adenocarcinoma reveals critical management challenges. Such overlapping inflammatory and neoplastic features frequently cause misdiagnosis, necessitating multidisciplinary consensus, extensive sampling, and PET-CT integration.[8,10,11] Treatment conflicts arise between glucocorticoids (accelerating tumour progression) and checkpoint inhibitors (contraindicated initially due to immune-risk). Therefore, PD-1 inhibitors were only used during second-line treatment, but the patient's tumour progressed rapidly afterwards, suggesting that the IgG4-RD microenvironment may affect the efficacy.

Persistently high IgG4 levels were consistent with rapid tumour progression in this case. Emerging evidence suggests that increased IgG4 in the cancer microenvironment may inhibit antibodymediated anticancer responses and help cancer evade local immune attack and indirectly promote cancer growth.[12,13] Notably, the patient's history included submandibular gland resection, revealing chronic sclerosing sialadenitis on pathology, and this chronic, untreated immune dysregulation may have contributed to oncogenesis. The retrospective analysis (n = 4) demonstrated 100% mortality in IgG4-RD patients with malignancies *versus* 67% in IgG4-RD alone, predominantly affecting elderly male smokers. Consequently, we propose incorporating parotid ultrasound and low-dose thoracoabdominal CT into routine follow-ups for high-risk IgG4-RD patients.

This case highlights diagnostic challenges arising from overlapping features and suggests that sustained IgG4 elevation may be linked to carcinogenesis; caution should be exercised with PD-1 inhibitors in IgG4-RD patients, and surveillance for malignancy is crucial for the high-risk groups. Clinical deficiencies include delayed recognition and insufficient intensification of therapy despite elevated IgG4.

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PATIENT'S CONSENT:
The patient described in this case had passed away. Therefore, the Ethics Committee of Guangzhou Red Cross Hospital granted a waiver of informed consent for both the study and the publication of this report (Approval No. 2025-084-01).

COMPETING INTEREST:
All authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
JF: Designed the study, collected the data, and drafted and revised the manuscript.
QY: Collected the data and critically reviewed the manuscript.
LW, LL: Designed the study and critically revised the manuscript.
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