

# Risk interrelationship among multiple primary tumors

## A case report and review of literature

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### Abstract

**Rationale:** Along with advanced management in oncology, great progress has been recently achieved in the studies of multiple primary tumors. Several reports have studied the coexistence between lymphoma and either renal cell carcinoma (RCC) or Warthin tumor. However, the level of coexistence between these cases remains unclear due to the absence of a distinct link between them.

**Patient concerns:** We present a unique case of multiple primary tumors (lymphoma, RCC, and Warthin tumor) in an 80-year-old man and a review of the literature on the coexistence of RCC with lymphoma and lymphoma with Warthin tumor.

**Diagnosis:** With a history of RCC, the patient had a freely movable lump under his left ear, and the pathological report indicated Hodgkin lymphoma and Warthin tumor.

**Intervention:** RCC and Warthin tumor of the patient were surgically treated, followed by 2 cycles (14 days per cycle) of Epirubicin 40 mg day 1, Bleomycin 8 mg day 1, Vincristine 2 mg day 1, and Dacarbazine 500 mg day 1. The chemotherapy protocol was then changed to Epirubicin 40 mg day 1, Vincristine 2 mg day 1, and Dacarbazine 500 mg day 1 for 7 cycles.

**Outcomes:** After the last day of chemotherapy, the patient showed a complete response.

**Lessons:** To the best of our knowledge, this paper is the first to report a case of multiple primary tumors with a complete response. For their early detection, favorable prognosis, and correlation identification, we suggest a transitive relation between these coexisting tumors. Therefore, similar studies should be conducted.

**Abbreviations:** HD = Hodgkin disease, NHL = non-Hodgkin lymphoma, RCC = renal cell carcinoma.

**Keywords:** coexistence, lymphoma, multiple primary tumors, renal cell carcinoma, warthin tumor

### 1. Introduction

The number of patients with multiple malignancies has grown continuously.<sup>[1]</sup> Currently, the frequency of multiple primary tumors is estimated to be between 2% and 17%.<sup>[2]</sup> In the United States, the number of people with cancer is expected to reach more than 3 million by 2050.<sup>[3]</sup> According to a Norwegian cohort study, the relative risk of secondary tumors among patients with primary malignancies is 31% compared with that in nonprimary tumor patients.<sup>[4]</sup> Among a large American cohort of 756,467

patients, 8% of the surviving patients had been affected by cancer more than once from 1975 to 2001.<sup>[5]</sup>

Patients with Hodgkin disease (HD) are susceptible to secondary solid tumors, and renal cell carcinoma (RCC) is the least common secondary malignancy post-treatment of HD (O/R ratio 1.5).<sup>[6]</sup> Other studies reported the same association in small cohorts.<sup>[6–8]</sup> By contrast, the relative risk of non-Hodgkin lymphoma (NHL) in patients with RCC is significantly higher than that of RCC in patients with NHL (1.86 and 2.67, respectively; Table 1).<sup>[6,9]</sup> Similarly, the current study shows the history in the association of lymphomas with Warthin tumor (Table 2).

Earlier reports on RCC–lymphoma or lymphoma–Warthin tumor were described in 1979 and 1996 and suggested a sporadic relationship between these tumors.<sup>[7,10]</sup> Eventually, an evolutionary risk relationship has been established between these 2 tumors. Given the hazardous effect and the increasing incidence of tumors, their precise interrelationship should be defined to facilitate their classification and early detection. Considering the literature review and our unique case of multiple primary tumors (RCC, HD, and Warthin tumor, marked as “x,” “y,” and “z,” respectively), we interpreted this transitive relation, defined as relation R, to always imply xRz when xRy and yRz are combined.<sup>[11]</sup>

### 2. Case presentation

The patient provided informed consent for the publication of his clinical and histological data. This study was approved by the

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**Table 1****Coexisting cases of RCC: Lymphoma (synchronous and metasynchronous).**

Author	Reference	Year of publication	Year of registration	Number of patients/gender	Lymphoma type	Distinct risk relation*
Tihan	[7]	1996	1985–1995	15 (total); 4/M 11/F	Diffuse large cell 3 Diffuse small lymphocytic 6 Follicular 3 Diffuse mantle zone 1 Follicular large cell 1 Diffuse mixed 1	—
Anderson	[9]	1998	1954–1995	41 (total); 32/M 9/F	Follicular small cleaved cell 9 Diffuse large cell 12 Small lymphocytic 9 Follicular mixed cell 2 Follicular large cell 1 Peripheral T cell 1 Mantle cell lymphoma 1 Mucosal associated lymphoid tissue 2 Diffuse small cleaved cell lymphoma 1 Diffuse mixed cell lymphoma 1 Non-Hodgkin lymphoma 2	Immune-dysregulation
Yagisawa	[8]	2001		3/M	Gamma/delta T-cell lymphoma 1 Follicular lymphoma 1 Mucosa-associated lymphoid tissue 1	Immunological association (bronchial asthma, idiopathic thrombocytopenic purpura, and mesangioproliferative glomerulonephritis)
Beisland	[4]	2006	1987–1993	12/NA	Non-Hodgkin lymphoma (NA)	—
Lossos	[1]	2011	First registry (1973–2006) +Author registry	1039/NA/ 10 (total); 8/M 2/F	NHL (NA) Diffuse large cell 5 Mantle cell lymphoma 3 Follicular lymphoma 1 Marginal zone lymphoma 1	—
Uz	[18]	2016	2016	1/M	Chronic lymphoid lymphoma 1	Cytokines, immunomodulators

\* Other than (genetics, familial, chemoradiotherapy, smoking, hormonal), F=female, M=male, NA=not available, NHL = non-Hodgkin lymphoma, RCC = renal cell carcinoma.

Institutional Ethics Committee of Second Affiliated Hospital of Dalian Medical University (Dalian, China).

On May 2015, an 80-year-old Chinese old man who complained about a painless lump under his left ear for half a month was admitted to our clinic. The lump was approximately the size of an ordinary egg. During this period, the patient was not feeling any pain, and the density of the freely moving mass was increasing gradually. As a treatment plan to cure the lump, he was taking some antibiotics and antivirus medicines at home. No other signs or symptoms were found. The patient had a history of RCC with complete total nephrectomy (T3NXM0) through surgical treatment 5 years ago. He also had both well-controlled primary hypertension and primary gout disease 15 and 2 years ago, respectively. He had been smoking 7 to 8 cigarettes/d since

the age of 50 and declared the absence of any other past medical or surgical history. During the physical examination, the face of the patient was not symmetrical, and normal facial expressions were observed. A 5 × 4 cm protruding lump with a distinct shape was found near the left parotid gland. In addition, the lump was soft and smooth when touched. It also had a clear border and good movement and was not fixed or tethered to neighboring tissues. No signs of inflammation of the other normal salivary glands were observed.

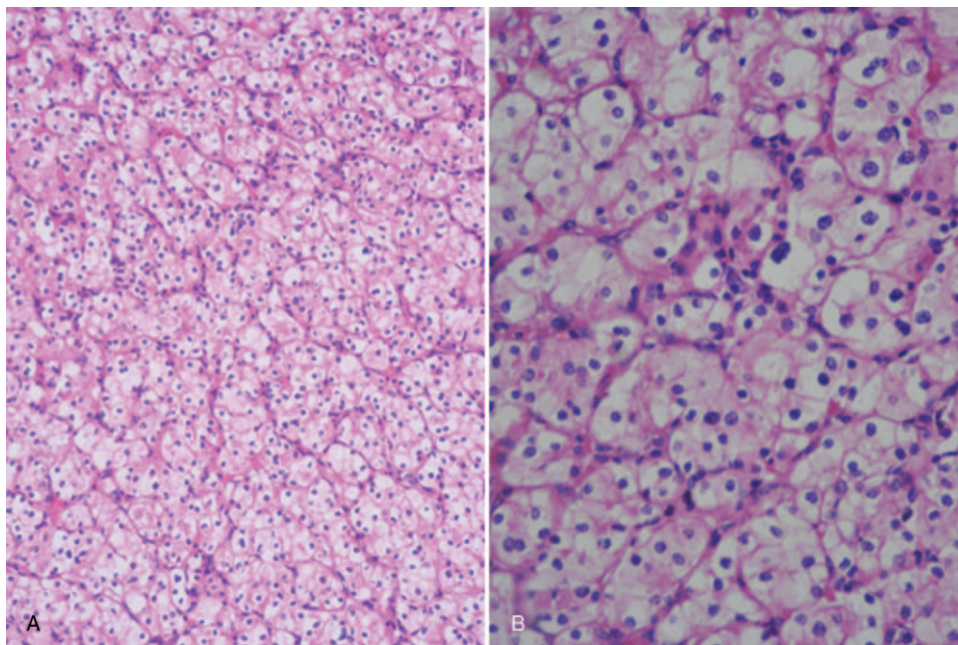
### 3. Interventions and outcomes

After a month, the patient underwent superficial parotid resection, and the left deep neck mass (left neck nodule) and

**Table 2****Coexisting cases of lymphoma-WT (synchronous and metasynchronous).**

Author	Reference	Year of publication	Number of patients/gender	Lymphoma type	Age, y	Distinct risk relation*
1. Colby	[10]	1979	1/M	Follicular lymphoma 1	NA	—
2. Liu	[16]	2013	1/M	Hodgkin lymphoma 1 (lymphocytic rich cell)	78	Histomorphological and immunohistochemical of lymphoid tissue in WT
3. Arcega	[14]	2015	1/M	Mantle cell lymphoma 1	77	Karyotyping lymphoid stroma in WT
4. Di Napoli	[17]	2015	1/M	Hodgkin lymphoma (Nodular lymphocytic predominant)1	73	—

\* Other than (genetics, familial, chemoradiotherapy, smoking, hormonal), F=female, M=male, NA=not available, WT=warthin tumor.



**Figure 1.** (A, B) Typical appearance of clear cell renal cell carcinoma (hematoxylin and eosin, original magnification; (A)  $\times 200$  and (B)  $\times 400$ ).

lymph nodes were examined and resected (size:  $2.5 \times 2.0 \times 4.0$  and  $2.0 \times 2.0 \times 1.5$  cm; HD:  $2.5 \times 2.5 \times 3.0$  and  $1.5 \times 2.0 \times 1.5$  cm, respectively). The parotid nodule ( $3.0 \times 4.0 \times 4.5$  cm) indicated a Warthin tumor. The patient was not advised to take adjuvant chemotherapy due to the comorbidities mentioned above. Within a month, the patient experienced fatigue, fever (maximum of  $37.9^\circ\text{C}$ ), cough, and expectoration. He underwent symptomatic treatment but obtained no benefits. On October 20, 2015, he underwent computed tomography scan, and it showed bilateral maxillary sinusitis, hyperdensity in the left parotid and soft tissue masses in the posterior part of the parotid gland, multiple enlarged lymph nodes under bilateral submandibular region, multiple enlarged lymph nodes in the retroperitoneal and hepatic hilar regions, brain atrophy, bilateral coronary artery calcification, and postoperative nephrectomy. The ultrasound presented enlarged lymph nodes in the bilateral neck and supraclavicular regions and their maximum size was  $21.8 \times 16$  mm. Multiple enlarged lymph nodes with a maximum size of  $22.4 \times 12.5$  mm were found in the bilateral axillary area. The echo in bilateral groin lymph nodes was observed on the left side ( $14.2 \times 5.2$  mm) and on the right side ( $12.5 \times 4.6$  mm).

According to the staging studies, no apparent sign of metastasis or bone marrow involvement was observed. The patient was subsequently diagnosed with Stage IIIA HD (mixed cellularity type). On November 3, 2015, the patient was advised to take 2 cycles of Epirubicin 40 mg day 1, Bleomycin 8 mg day 1, Vincristine 2 mg day 1, and Dacarbazine 500 mg day 1 (14 days per cycle). Considering the performance status and other comorbidities, we changed the chemotherapy protocol to Epirubicin 40 mg day 1, Vincristine 2 mg day 1, and Dacarbazine 500 mg day 1 for 7 cycles.

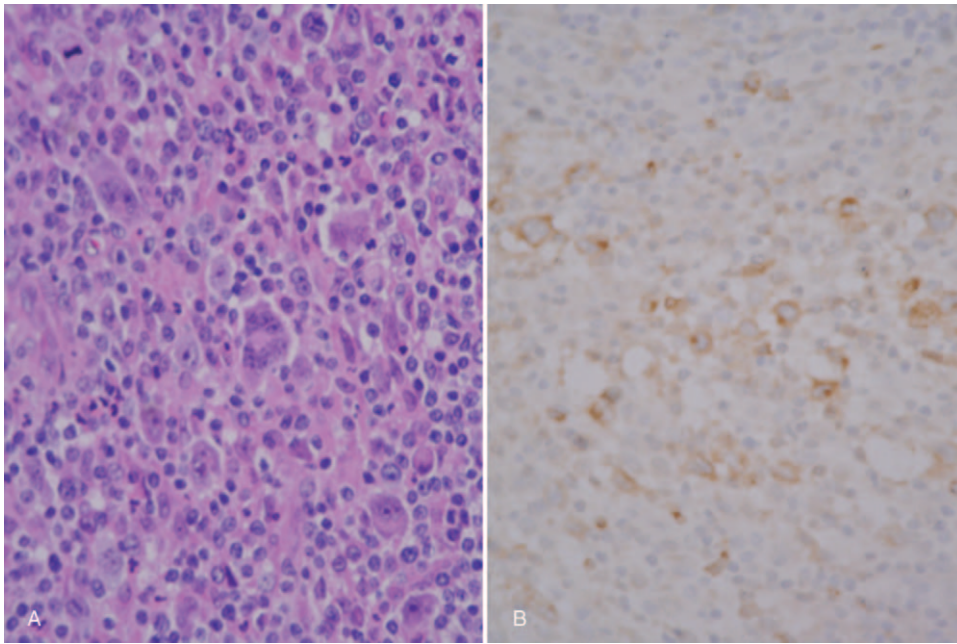
The last date of chemotherapy was on February 29, 2016. According to the Revised International Workshop criteria of response, the patient had a complete response.

#### 4. Pathological findings

The kidney tissue was architecturally diverse, with solid, alveolar, and acinar patterns. The cytoplasm was clear and surrounded by a distinct cell membrane. The tumor contained a regular network of small, thin-walled blood vessels and diagnosed as a clear cell type of RCC (Fig. 1). The left neck nodule histologically showed that the lymph node capsule was partially thickened, and the structure of the lymph node was damaged. In the background of granulomas, lymphocytes, and fibrosis, several heterotypic R-S cells were observed. Immunophenotyping revealed that CD30 (+), CD19 (–), PAX-5 poor (+), CD20 (–), CD15 (–), CD45 (–), CD10 (–), BCL-6 (–), MUM-1 (+), Ki-67 (+), EBER ISH (–), and EBV (+) under HD diagnosis showed a mixed cellularity type (Fig. 2). The parotid nodule was composed of epithelial and lymphoid components. Meanwhile, the epithelium was composed of 2 layers of cells with the stroma containing prominent lymphoid tissue with mature lymphocytes and germinal centers and was diagnosed with Warthin tumor (Fig. 3).

#### 5. Discussion

Many secondary tumors have been linked to RCC, particularly lymphoma, and yet this issue remains poorly understood.<sup>[1,6,9]</sup> A total of 15 cases of RCC–lymphoma association was first recorded in 1996,<sup>[7]</sup> and the first attempt to explain this phenomenon came from Anderson in 1998. He proposed that an immune dysregulation in the primary malignancy predisposes the patient to secondary tumors.<sup>[9]</sup> Likewise, Yagisawa et al in 2001 hypothesized the existence of immune dysregulation mechanisms, such as bronchial asthma, idiopathic thrombocytopenic purpura, and mesangioproliferative glomerulonephritis, in patients with coexisting lymphoma and RCC.<sup>[8]</sup> Long after, 1 hypothesis in 2006 predicted the chromosomal mutations occurring in RCC and NHL: 17p deletions, 7, 3p trisomy, and

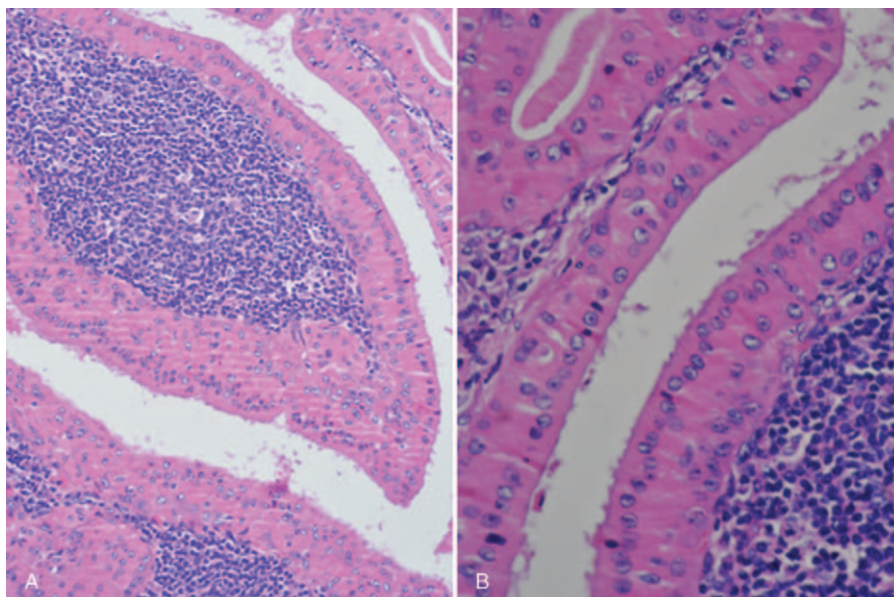


**Figure 2.** (A, B) Hodgkin lymphoma, mixed cellularity type in the background of granulomas and CD30+ (A:  $\times 400$ , B:  $\times 200$ ), respectively.

p53 mutations.<sup>[4]</sup> Overall, these data highlight the importance of adequate care, including long-term medical surveillance for patients with a history of lymphoma, given the increased risk of secondary primary malignancies. NHL with RCC has been reported more frequently than HD with RCC,<sup>[2]</sup> whereas other studies described an increase in secondary tumors after HD within 10 years during a median follow-up.<sup>[6]</sup>

One previous study has reported an increased risk of secondary malignancies in patients who have cancer in the head and neck regions.<sup>[12]</sup> Warthin tumor is the most common (approximately accounting for 80–85%) salivary gland tumor, which is mostly

located in the parotid gland.<sup>[13]</sup> The average age of the onset of Warthin tumor is 62 years, and it is rarely seen before the age of 40. Smoking has been suggested as the major risk factor of Warthin tumor.<sup>[14]</sup> In 1953, the male-to-female ratio was 10:1. This ratio significantly decreased to 1.2:1 in 1996 and was attributed to the increased number of female smokers.<sup>[14]</sup> Distinct lymphoid components are seen from the lesions of the salivary glands and occur in both types of benign and malignant tumors.<sup>[15]</sup> Intraparenchymal nodal tissues are contained within the normal parotid gland. Nonetheless, most of the parotid lymphomas do not have a nodal origin.<sup>[6]</sup> Most salivary gland



**Figure 3.** (A, B) Typical features of Warthin tumor with prominent lymphoepithelial components and oncocystic cells (hematoxylin and eosin, original magnification; A:  $\times 200$ , B:  $\times 400$ ).

HDs have been proven to be secondary to nodal disease outside the parenchymal nodal tissue of salivary glands.<sup>[15]</sup> Among the literature review of 23 cases of Warthin tumor associated with lymphoma, Liu et al suggested that the lymphoid stroma of Warthin tumor is a part of the systemic lymphoid tissue, and that may be a reason for lymphoma association.<sup>[16]</sup> In 2015, Arcega et al reported an unusual case of mantle cell lymphoma inside the lymphoid tissue of Warthin tumor and confirmed a reciprocal translocation (11; 14) (q13; q32) within the lymphoid tissue of Warthin tumor.<sup>[14]</sup> Similar to our case of simultaneous association of Warthin tumor and cervical lymph nodes, Di Napoli et al reported 1 case, like the other 2 of 3 reported cases in the literature, whereas only 1 case of association was reported as an intraparotid lymph node.<sup>[17]</sup>

## 6. Conclusions

According to our unique case and the literature, we found the complete response in tumors with early diagnosis. Considering that many researchers have reported that the relation of RCC with HD and HD with Warthin tumor could be caused by shared or nonshared common risk factors, we should pay more attention to the coexistence of RCC and Warthin tumor as a transitive relation. However, we also found a complete response either in RCC before (only surgically treated) or in the coexistence of the HD stage IIIA and Warthin tumor, even in old age and associated medical events. According to previous reports and the present study on RCC with lymphoma and other lymphomas with Warthin tumor, we can observe the transitive relation between RCC and Warthin tumor. To allow early diagnosis and the level of correlation among the primary tumors, oncologists should consider their transitive relationship either in demonstrated or not demonstrated shared risk factors.

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