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Synchronous double primary lymphoma and thyroid cancer

A single-institution retrospective study

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Abstract

Synchronous double primary malignancies of lymphoma and thyroid cancer are rare. In this retrospective study, we investigated the pathology, clinical characteristics, and treatment outcomes of patients with synchronous lymphoma and thyroid cancer.

Of the 1156 newly diagnosed lymphoma patients treated in our hospital between January 1, 2016 and February 1, 2021, 8 cases had lymphoma complicated with thyroid cancer. The clinical data and treatment strategies of 8 cases with synchronous lymphoma and thyroid cancer were retrospectively analyzed.

The median age of patients was 56 (25–64) years. All the 8 patients were female and papillary thyroid cancer. Only 1 patient had peripheral T-cell lymphoma, and the other 7 were B-cell lymphoma. Seven of 8 patients had normal free triiodothyronine and free thyroxine at the time of diagnosis. Seven thyroid cancer patients received total thyroidectomy and levothyroxine and the remaining 1 patient has a plan for surgery. At the last follow-up, 7 patients with B-cell lymphoma are alive; the patient with peripheral T-cell lymphoma complicated with thyroid cancer died due to lymphoma progression.

Synchronous lymphoma and thyroid cancer are more predominant in women. Histologically, B-cell lymphomas and papillary thyroid cancer subtypes are more common. Attention should be paid to the presence of thyroid nodules in the diagnosis of lymphoma. Biopsy or ultrasound-guided fine needle aspiration of the suspicious thyroid nodule should be performed to exclude thyroid malignancy.

Abbreviations: CR = complete remission, DLBCL = diffuse large B-cell lymphoma, DPM = double primary malignancies, HL = Hodgkin lymphoma, MALT = mucosa-associated lymphoid tissue, PET-CT = positron emission tomography-computed tomography.

Keywords: double primary malignancies, lymphoma, thyroid cancer

1. Introduction

Double primary malignancies (DPM) are rare, although their incidence has been increasing in recent years.[1] In patients with DPM, 2 different types of primary malignant tumors occur at the same time or successively.[1] Cases with no history of invasive tumors are classified as the index type.[2] DPM are classified as metachronous or synchronous depending on the time interval between the 2 tumors. Both lymphoma and thyroid cancer are quite common individually, lymphoma of the thyroid gland is also frequently found, while their joint presentation is more unusual. Secondary thyroid malignancies are well known to be associated with previous chemotherapy and radiotherapy of Hodgkin lymphoma (HL) patients. Secondary thyroid cancer development may result from genetic predisposition to cancer, exposure to environmental risk factors, or previous treatment with genotoxic agents.[3] Nevertheless, the synchronous presentation of these 2 types of malignancies is exceptional. The clinical characteristics and treatment outcomes of synchronous lymphoma and thyroid cancer remain unclear. The topic of synchronous thyroid cancer and lymphoma has been noted by Morata et al since 1997[4] and a few cases have been published subsequently. However, most of the previous studies are case reports, the clinical features of synchronous presentation of these 2 types of

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malignancies need further explanation. In this study, we retrospectively analyzed the clinical characteristics and treatment outcomes of 8 cases of synchronous lymphoma and thyroid cancer diagnosed in our hospital.

2. Materials and methods

2.1. Diagnosis

The study was reviewed and approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. We retrospectively analyzed data from 1156 patients with malignant lymphoma receiving treatment in Union Hospital, Tongji Medical College of Huazhong University of Science and Technology from January 1, 2016 to February 1, 2021. The diagnosis was achieved by pathological examination of biopsies, which included routine pathomorphological evaluation and immunohistochemical staining. Lymphoma diagnosis and classification were based on the World Health Organization 2016 classification criteria of lymphoma,[5] whereas thyroid cancer diagnosis and staging were based on the World Health Organization criteria.[6] The Ann Arbor staging system was used for lymphoma staging. Patients with early-stage classical HL were stratified as favorable and unfavorable based on the National Comprehensive Cancer Network and the European Organization for Research and Treatment of Cancer, and those with nonHodgkin lymphomas were stratified according to the international prognostic index. According to the international standards developed by Warren and Gates in 1932,[7] DPM was defined as the presence of 2 primary malignant tumors with different pathological characteristics, cases with recurrent or metastatic lesions of the primary tumor were not considered DPM. On the basis of the time interval between the development of 2 tumors, DPM cases were classified as metachronous (>6 months) or synchronous (<6 months). A total of 8 patients met the diagnostic criteria for synchronous double primary lymphoma and thyroid cancer. Data on the general health condition, onset time, past medical history, family history, pathological characteristics, imaging findings, laboratory findings, and treatment outcomes were reviewed.

2.2. Treatment

Patients with early-stage gastric mucosa-associated lymphoid tissue (MALT) lymphoma were treated with radiotherapy alone. Patients with aggressive lymphoma were treated with systemic immunochemotherapy, and those with early-stage or bulky disease received consolidation radiotherapy. Patients with recurrent/refractory lymphoma were treated with salvage chemotherapy, radiotherapy, and targeted therapy according to the specific condition. Patients with thyroid cancer underwent thyroidectomy and were given levothyroxine replacement therapy after the operation.

2.3. Evaluation of treatment response

Response to lymphoma treatment was evaluated by positron emission tomography-computed tomography (PET-CT) or enhanced CT of neck, chest, abdomen, and pelvis. According to the 2014 Lugano criteria,[8] cases were classified as complete remission (CR), partial remission, stable disease, or progressive disease.

2.4. Follow-up

Patient follow-up data were obtained by reviewing electronic medical records or telephone communication. The last follow-up was on May 30, 2021. The follow-up time was defined as the time from the patient's first visit until the last follow-up. The overall survival time was defined as the time from diagnosis until the time of death or last follow-up.

3. Results

3.1. Patient characteristics

Among 1156 newly diagnosed malignant lymphoma cases, 8 were synchronous double primary lymphoma and thyroid cancer cases, the crude incidence rate of synchronous thyroid cancer in lymphoma patients was $138.41/10^5$·year. The median age of patients was 56 (25–64) years. All the 8 patients were female and only 1 patient had a history of Hashimoto thyroiditis. One of the patients had a family history of cancer. Three of 8 patients confirmed lymphoma and thyroid cancer by surgery simultaneously, while other 5 patients were detected to have thyroid nodules during treatment for lymphoma, and thyroid cancer was confirmed by puncture biopsy. One patient had history of Hashimoto thyroiditis. The general health condition of 8 patients is summarized in Table 1.

3.2. Pathology and examination

From the point of view of lymphoma, 5 of 8 cases were diffuse large B-cell lymphoma (DLBCL), and the remaining were gastric

Table 1

Overview of 8 patients of synchronous double primary lymphoma and thyroid cancer.

Case	Gender	Age (yr)	First	Second	Familial history	Thyroiditis	Interval time (mo)	Survival	OS (mo)
1	Female	47	DLBCL	PTC	Yes	No	0	Alive	39
2	Female	59	DLBCL	PTMC	No	No	0	Alive	23
3	Female	57	DLBCL + FL3b	PTC	No	No	0	Alive	27
4	Female	55	PTCL NOS	PTC	No	No	0	Dead	2
5	Female	53	MALT lymphoma	PTMC	No	No	4	Alive	23
6	Female	25	DLBCL	PTMC	No	Yes	0	Alive	44
7	Female	58	PTC	HL	No	No	0	Alive	5
8	Female	64	DLBCL	PTC	No	No	4	Alive	6

DLBCL = diffuse large B cell lymphoma, FL = follicular lymphoma, HL = Hodgkin lymphoma, MALT = mucosa associated lymphoid tissue, OS = overall survival, PTC = papillary thyroid carcinoma, PTCL NOS = peripheral T cell lymphoma not otherwise specified, PTMC = papillary thyroid microcarcinoma.

MALT lymphoma, HL, and peripheral T-cell lymphoma. Only 1 of 8 cases were indolent lymphoma, and other 7 cases were aggressive lymphoma. There were 3 cases of germinal center B-cell (GCB) type and 2 cases of non-GCB type of DLBCL respectively. Six of the 8 patients had stage I-II disease, and 2 had stage-IV disease. From the point of view of thyroid cancer, 3 were papillary thyroid microcarcinoma, the other 5 cases were papillary thyroid carcinoma. Seven patients had lymph node metastasis of thyroid cancer and had normal free triiodothyronine and free thyroxine at the time of diagnosis. Two patients were found an abnormal of thyroid stimulating hormone. Elevated antithyroglobulin antibodies were found in 5 patients.

3.3. Treatment

Lymphoma patients no. 2, no. 3, no. 6, and no. 8 (early-stage DLBCL) achieved CR after 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone and local consolidation radiotherapy. Patient no. 1 was a female patient with advanced-stage DLBCL treated with second-line lenalidomide plus Ifosfamide, carboplatin, etoposide chemotherapy after relapse. The patient is in CR with lenalidomide as maintenance therapy. Patient no. 5 was a female patient with early-stage gastric MALT and achieved CR after local radiotherapy. patient no. 4 had advanced-stage peripheral T-cell lymphoma and died of the progression of lymphoma after 2 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. Patient no. 7 was diagnosed as HL and thyroid cancer simultaneously at December 9, 2020, she is receiving doxorubicin, bleomycin, vincristine, and dacarbazine regimen at the end of follow-up, and consolidation radiotherapy is expected to take place after CR. Seven patients underwent total thyroidectomy and had levothyroxine after surgery and the remaining 1 patient has a plan for surgery. The pathology, examination, and treatment of these 7 patients are summarized in Table 2.

3.4. Follow-up

Up to the follow-up time, 7 patients with B-cell lymphoma were alive, with the longest survival time being 44 months. The patient with peripheral T-cell lymphoma had a survival time of only 2 months, which was the shortest survival time in this cohort. No recurrence of thyroid cancer was found in follow-up examination for 7 patients.

4. Discussion

DPM are rare, with a reported incidence of 0.73% to 11.7% in a retrospective cohort of 1,104,269 cancer patients, and with a higher prevalence in the elderly.[9] A population-based study showed a significantly higher risk (8.29%) of second primary malignancies in patients with mantel cell lymphoma than in the general population.[10] The increasing incidence of DPM may be due to the rising numbers of cancer survivors, long-term side effects of chemotherapy and radiotherapy, and the interaction between genetic and environmental risk factors. Population aging may have also contributed to the increase in DPM incidence of recent years. Advances in early tumor detection and regular patient follow-up have led to an increase in the number of diagnosed cancers.

The presentation of lymphoma with a second primary tumor is most commonly seen during follow-up of patients with HL. The most frequent secondary tumors are breast, lung, and thyroid cancers. The occurrence of secondary thyroid cancer in HL patients is usually metachronous. Radiotherapy at the early stage of lymphoma is recognized to be associated with the future occurrence of secondary thyroid cancer.[11] Similar study showed that previous radiotherapy of the head, neck, and upper diaphragm may be risk factors for thyroid cancer development in HL patients.[3] Usually, the second primary thyroid cancers are differentiated follicular or papillary carcinomas and have a good prognosis. However, some thyroid cancers are poorly differentiated and have a poor prognosis.[12] Recent evidence suggests no significant difference between the prognosis of primary thyroid cancer and that of thyroid cancer secondary to HL.[13]

There are few reports on the prognosis of thyroid cancer associated with other tumors, Al-Qahtani et al had reported that differentiated thyroid cancers patients with second primary malignancies had lower ten-year disease-free survival (56.1% vs 95.5%) and overall survival (71.7% vs 97.8%) than patients without second primary malignancies.[14] To our knowledge, rarely has any study to date investigated the association between synchronous thyroid cancer and lymphoma, most of previous reports are case reports. A summary of these reports is shown in Table 3.[15–25] Consistent with previous findings, all the 8 patients in our study were female and had papillary thyroid cancers. The phenomenon that these DPM occurs more frequently in women may be related to the fact that thyroid cancer is more common in women than man.

Table 2

Clinical information of 8 patients of synchronous double primary lymphoma and thyroid cancer.

	Lymphoma					Thyroid cancer								
Cases	Subtypes	Stage	Risk	LDH (U/L)	Treatment	Subtypes	Greatest dimension (cm)	Lymph nodes	Extra thyroidal invasion	FT3 (p mol/L)	FT4 (p mol/L)	TSH (μIU/mL)	Anti-TG (IU/mL)	Treatment (thyroidectomy)
1	DLBCL-ABC	IV	IPI 2	217	Chemo + Radio	PTC	1.2	9/12	Capsule	3.8	19	0.083↓	0.67	Total
2	DLBCL-ABC	II	IPI 0	164	Chemo + Radio	PTMC	0.84	2/25	No	3.9	9.9	0.86	13.25↑	Total
3	DLBCL&FL3b-GCB	II	IPI 0	195	Chemo + Radio	PTC	1.2	5/31	No	4.1	11.5	1.59	7.78↑	Total
4	PTCL NOS	IV	IPI 3	185	Chemo	PTC	2.0	19/47	Capsule	3.2	14.7	1.81	6.82↑	Total
5	MALT	I	IPI 0	184	Radio	PTMC	0.84	2/27	No	4.8	13	3.07	1.89	Total
6	DLBCL-GCB	II	IPI 1	318↑	Chemo	PTMC	0.6	3/24	No	4.6	12.7	2.44	1.82	Total
7	cHL	II A	Favorable	169	Chemo + Radio	PTC	1.1	1/25	Capsule	2.5	11.1	1.18	5.12↑	Total
8	DLBCL-GCB	II	IPI 1	149	Chemo + Radio	PTC	1.9	NA	NA	3.4	8.0↓	10.02↑	681.88↑	Plan to surgery

ABC = activated B cell, Anti-TG = antithyroglobulin antibodies, Chemo = chemotherapy, cHL = classical Hodgkin lymphoma, DLBCL = diffuse large B cell lymphoma, FL = follicular lymphoma, FT3 = free triiodothyronine, FT4 = free thyroxine, GCB = germinal center B cell, IPI = international prognostic index, LDH = lactic dehydrogenase, MALT = mucosa associated lymphoid tissue, NA = not available, PTC = papillary thyroid carcinoma, PTCL NOS = peripheral T cell lymphoma not otherwise specified, PTMC = papillary thyroid microcarcinoma, Radio = radiotherapy, TSH = thyroid stimulating hormone.

Table 3

Clinical characteristics of reported cases of synchronous thyroid cancer and lymphoma in the literature.

			Lymphoma			Thyroid cancer			
Author/published year	Age (yr)	Gender	Diagnosis	Stage	Treatment	Diagnosis	Thyroiditis	Treatment	OS (mo)
Lin et al/1998	25	Female	B-NHL	NA	Chemo	PTC	NA	Partial thyroidectomy	NA
Cheng et al/2012	59	Male	MALT	Early-stage	Surgery	PTC	Hashimoto	Total thyroidectomy + ^{131}I	>84
Xie et al/2014	41	Male	DLBCL	NA	Chemo + Radio	PTC	Hashimoto	Partial thyroidectomy	>2
Shen et al/2015	25	Female	MALT	NA	Chemo	PTC	Hashimoto	Total thyroidectomy + ^{131}I	>24
Trovato et al /2017	66	Female	DLBCL	Early-stage	Chemo	PTC	Hashimoto	Total thyroidectomy	>24
Ahmed et al/ 2017	61	Female	CLL/SLL	NA	NA	PTC	NA	Total thyroidectomy	NA
Liu et al/2018	37	Female	DLBCL	Early-stage	Chemo	PTC	NA	Thyroidectomy	>12
Popivanov et al/2018	48	Female	FL	Advanced- stage	Chemo	PTC	NA	Total thyroidectomy + ^{131}I	>24
Liu et al/2018	17	Female	cHL	IIA	Chemo + Radio	PTC	NA	Total thyroidectomy + ^{131}I	NA
Li et al/2019	22	Female	cHL	II	NA	PTC	NA	NA	NA
Chen et al/2019	37	Female	DLBCL	Early-stage	Chemo	PTC	NA	Partial thyroidectomy	>12
Liu et al/2019	53	Female	ALK (+) ALCL	IV	Chemo	PTC	NA	Thyroidectomy	NA

ALK = anaplastic lymphoma kinase, ALCL = anaplastic large cell lymphoma, B-NHL = B cell nonHodgkin lymphoma, Chemo = chemotherapy, cHL = classical Hodgkin lymphoma, CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma, DLBCL = diffuse large B cell lymphoma, FL = follicular lymphoma, MALT = mucosa associated lymphoid tissue, NA = not available, OS = overall survival, PTC = papillary thyroid carcinoma, Radio = radiotherapy.

Our study indicated that the crude incidence rate of synchronous thyroid cancer in lymphoma patients was 138.41/10^5·year, which was nearly 10 times higher than the incidence of thyroid cancer in the general population in China.[26–28] The pathogenesis and etiology of DPM remain unclear and are possibly influenced by various factors, including genetic background, hormones, environmental carcinogens, diet, alcohol, and smoking. Forkhead-box (FOX) gene family members are highly expressed in cancers, including DLBCL and thyroid cancer. Furthermore, FOX genes are involved in gene transcription and DNA repair.[29] Therefore, aberrant expression of FOX genes may be a common driver of lymphoma and thyroid cancer. The published studies have demonstrated that oncogenic BRAF mutation is present in 60% of papillary thyroid cancer cases.[30] Additionally, detection of BRAF V600E mutations is helpful in the diagnosis of classical hairy cell leukemia.[31] These findings suggested that BRAF mutation may be another driver mutation of these DPM, which need further exploration.

It is well known that patients with Hashimoto thyroiditis are at higher risk of developing thyroid cancer. Similarly, 40% to 85% of primary thyroid lymphoma patients have a history of chronic thyroiditis or Hashimoto thyroiditis.[16] In a study of 214 patients with DLBCL received routine thyroid ultrasound, Yue et al[32] found that 18.7% of patients had Hashimoto thyroiditis, and 8.4% had thyroid imaging reporting and data system score of 4 suggestive of malignancy; thyroid cancer was confirmed in 6 patients by thyroid biopsy. In a different study, among 17 lymphoma patients with second primary solid tumors, 7 patients had papillary thyroid cancer; 2 of 7 patients had a history of chronic thyroiditis.[33] Previous studies (listed in Table 3) showed that 4 out of 12 patients with synchronous lymphoma and thyroid cancer had a history of Hashimoto thyroiditis. These results suggest that the pathogenesis of lymphoma and thyroid cancer may be related to Hashimoto thyroiditis. Hence, lymphoma patients with a history of chronic thyroiditis or Hashimoto thyroiditis should be closely monitored for thyroid cancer.

The baseline PET-CT scan of patient no. 3 and no. 8 indicated hypermetabolic lesions in the thyroid gland; although immunochemotherapy significantly reduced the size of cervical lymph nodes, no change was observed in these thyroid lesions. Thyroid cancer was confirmed by thyroid color doppler ultrasound and puncture biopsy. Lymphoma can involve in multiple lymph nodes and extranodal organs, including the gastrointestinal tract, thyroid gland, breast, and bones. Since it is impossible to evaluate biopsies from every suspicious lesion at the initial diagnosis, some DPM cases may go undetected. Therefore, a comprehensive baseline examination is critical. Papajík evaluated 209 patients with newly diagnosed nonHodgkin lymphoma. PET-CT findings indicated solid tumors in 6 patients (2.9%), suggesting that PET-CT is of great value in the early diagnosis of double primary malignancies.[34] Color doppler ultrasound also plays a vital role in the diagnosis of thyroid cancer. Typical imaging findings include fine sand-like calcification, cystic necrosis, and adenoid manifestations. The use of ultrasonography to diagnose thyroid cancer provided a sensitivity of 97.4% and specificity of 33.3%.[35] Therefore, for the clinical symptoms that can't be explained by a single tumor, the possibility of DPM should be taken into account, and a comprehensive examination should be conducted to prevent missed diagnosis. For the lesions that are changed inconsistent with other sites after treatment, a scrupulous re-biopsy of suspicious lesions is suggested to improve the accuracy of DPM diagnosis.

Currently, there is no standardized treatment for DPM because of its rarity. Pathological types, stage, age, performance status, and clinical characteristics should be taken into account in clinical decision making. There are significant differences in the biological behavior and prognosis of aggressive lymphoma and thyroid cancer. Patients with aggressive lymphoma progress rapidly and respond well to systemic immunochemotherapy, whereas differentiated thyroid tumors are often inert and surgical resection is the first choice in thyroid cancer patients. Therefore, the thyroidectomy of differentiated thyroid cancer should be prioritized behind immunochemotherapy of lymphoma. Local management, such as surgical resection or radiotherapy, is recommended for early-stage indolent lymphoma, whereas systemic immunochemotherapy is needed for advanced-stage indolent lymphoma. Both indolent lymphoma and differentiated thyroid tumors develop slowly. Hence, the treatment approach relies on clinical symptoms. Usually, the tumor that bring symptoms to patients needs to be preferred.

The prognosis of DPM strongly depends on the tumor and pathological types. More than 90% of thyroid tumors are well-differentiated and progress slowly. After surgical resection, the

prognosis of patients is relatively good, even in patients with regional lymph node metastasis. On the other hand, the prognosis of lymphoma varies immensely. Staging, risk factors, age, and previous treatment are key factors affecting the prognosis. The prognosis of most lymphomas is worse than that of differentiated thyroid carcinoma, so the survival time of patients with double thyroid malignancies depends on the disease condition of lymphoma.

In conclusion, this descriptive study describes our single-center experience with 8 synchronous lymphoma and thyroid patients. We found that B-cell lymphoma and papillary thyroid cancer were the most common histologic subtypes and female were predominant than man. This article is written to draw more attention to this synchronized presentation and avoid missed diagnosis. Considering the small number of cases, the clinical characteristics and potential pathogenesis of these patients need further exploration.

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