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Clinical analysis of lymphoma with malignant solid tumor simultaneously: a retrospective case series

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Abstract

This study aimed to investigate the clinical features and potential pathogenesis of lymphoma complicated with malignant solid tumors. Clinical data from 35 patients treated at Yantai Yuhuangding Hospital between January 2018 and March 2023 were retrospectively analyzed. Among 1726 lymphoma patients, 35 (2.03%) were found to have solid tumors, including 22 males and 13 females, with a median age of 62 years (range: 49–83 years). The lymphoma subtypes included 14 cases of diffuse large B-cell lymphoma (DLBCL), 8 cases of small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), 7 cases of marginal zone lymphoma (MZL), 3 cases of peripheral T-cell lymphoma (PTCL), 2 cases of follicular lymphoma (FL), and 1 case of Waldenström macroglobulinemia (WM). The solid tumors included 9 cases of papillary thyroid carcinoma (PTC), 8 cases of colorectal cancer (CRC), 7 cases of lung cancer (LC), 5 cases of gastric cancer (GC), 2 cases of prostate cancer (PCa), and 1 case each of breast cancer (BC), clear cell renal cell carcinoma (ccRCC), pharyngeal squamous cell carcinoma (PSCC), and bladder cancer (BLCA). Lymphoma with solid tumors is rare, often affecting elderly males. Non-Hodgkin's lymphoma, especially DLBCL, was the most common subtype, and PTC was the most frequent solid tumor. Clinicians should focus on these cases to improve diagnosis and treatment.

Keywords Lymphoma, Neoplasms, Multiple primary malignancies, Diagnosis, Clinical features

Introduction

Lymphoma complicated by malignant solid tumors is classified as multiple primary malignancies (MPMs) [1]. Currently, the diagnostic criteria for MPMs proposed by Warren et al. are widely accepted [2]. The International Classification of Diseases, 11th Revision continues to support and adopt the definition of MPMs, providing a detailed classification of various tumor types in its oncology section, including a clear definition and categorization of MPMs. Specifically, each tumor must be independently confirmed as malignant, exhibit distinct histological types, and exclude metastatic or recurrent tumors [3]. Based on the interval between the diagnosis of the first and second primary tumors, MPMs can

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be classified into synchronous and metachronous types. Synchronous carcinoma (SC) are defined as those with a diagnostic interval of six months or less, whereas metachronous carcinoma have a diagnostic interval of more than six months [2].

In recent years, the application of techniques such as immunohistochemistry (IHC), molecular detection, endoscopy, and positron emission tomography/computed tomography (PET/CT) has gradually improved the detection rate of MPMs. However, SC account for only 0.37–2.79% of patients with malignant tumors, with a low incidence [4, 5, 6, 7, 8, 9, 10].

Lymphoma is one of the most common malignant tumors in China. Its pathological types are complex and heterogeneous, and treatment strategies vary accordingly [11]. Lymphoma complicated by malignant solid tumors is rare, although some cases have been reported previously [12, 13, 14]. In a study involving 92 patients with non-Hodgkin's lymphoma (NHL), the incidence of synchronous tumors was only 0.8% [6]. Currently, the pathogenesis, incidence, clinical characteristics, and treatment of lymphoma complicated by malignant solid tumors remain unclear. To enhance understanding of such cases, we collected 35 cases of lymphoma complicated by malignant solid tumors, summarized their clinical features, and explored potential pathogenesis. These findings aim to provide valuable insights for clinical diagnosis and treatment strategies.

Materials and methods

Patients and diagnostic criteria

We conducted a retrospective analysis of lymphoma cases presented to Yantai Yuhuangding Hospital from January 2018 to March 2023, and screened for patients with malignant solid tumors. Specimens were obtained through surgical resection or needle biopsy to ensure accurate pathological diagnoses, which included routine morphological examination and IHC staining. Each case was independently diagnosed by two pathologists and subsequently reviewed and confirmed by two senior specialists with subspecialty expertise in hematopathology at the associate chief physician level or higher. The diagnosis and classification of lymphoma were based on the 2017 WHO classification of lymphoid neoplasms, while those of solid tumors adhered to the WHO classification of tumors. In all cases, both tumors were confirmed to be primary malignancies, occurring either simultaneously or within an interval of less than six months. This study was approved by the Medical Ethics Committee of Yantai Yuhuangding Hospital Affiliated with Qingdao University, and the requirement for patient informed consent was waived.

Follow-up

Detailed follow-up data were obtained from telephone interviews, and causes of death were extracted from clinical records or obtained from patients' families. As of March 8, 2023, the follow-up time ranged from 0 to 68 months. Follow-up time was defined as the time from the patient's initial diagnosis to the final follow-up date or the date of death.

Results

Patient characteristics

A total of 1726 cases of lymphoma were diagnosed between January 2018 and March 2023, of which 35 cases were also complicated with malignant solid tumors, with an incidence of approximately 2.03%. Among the 35 patients, there were 22 males and 13 females, with the median age of 67 (49–83) years.

Lymphoma pathological subtypes

All 35 cases of lymphoma complicated by malignant solid tumors were NHL, of which 32 cases (91.43%) were B-cell NHL and 3 cases (8.57%) were T-cell NHL. The lymphoma cases comprised 14 cases of diffuse large B-cell lymphoma (DLBCL, 40.00%), 8 cases of small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL, 22.86%), 7 cases of marginal zone lymphoma (MZL, 20.00%), 3 cases of peripheral T-cell lymphoma (PTCL, 8.57%), 2 cases of follicular lymphoma (FL, 5.71%), and 1 case of Waldenström macroglobulinemia (WM, 2.86%) (Fig. 1A).

Solid tumors subtypes

There were 9 cases of papillary thyroid carcinoma (PTC, 25.71%), 8 cases of colorectal cancer (CRC, 22.86%), 7 cases of lung cancer (LC, 20.00%), 5 cases of gastric cancer (GC, 14.29%), 2 cases of prostate cancer (PCa, 5.71%), 1 case of breast cancer (BC, 2.86%), 1 case of clear cell renal cell carcinoma (ccRCC, 2.86%), 1 case of pharyngeal squamous cell carcinoma (PSCC, 2.86%), and 1 case of bladder cancer (BLCA, 2.86%) (Fig. 1B).

Treatment and prognosis

Of the 34 patients receiving treatment, 8 cases received treatment for lymphoma only, 8 cases received treatment for solid tumors only, and 18 cases received treatment for both types of tumors. The treatment modalities for lymphoma included chemotherapy in 18 cases, radiotherapy in 1 case, a combination of chemotherapy and radiotherapy in 1 case, chemotherapy with autologous stem cell transplantation in 1 case, chemotherapy combined with targeted therapy in 2 cases, surgery in 3 cases, no treatment in 8 cases, and 1 case lost to follow-up. The treatment modalities for solid tumors included surgery in 17 cases, surgery combined with chemotherapy in 1

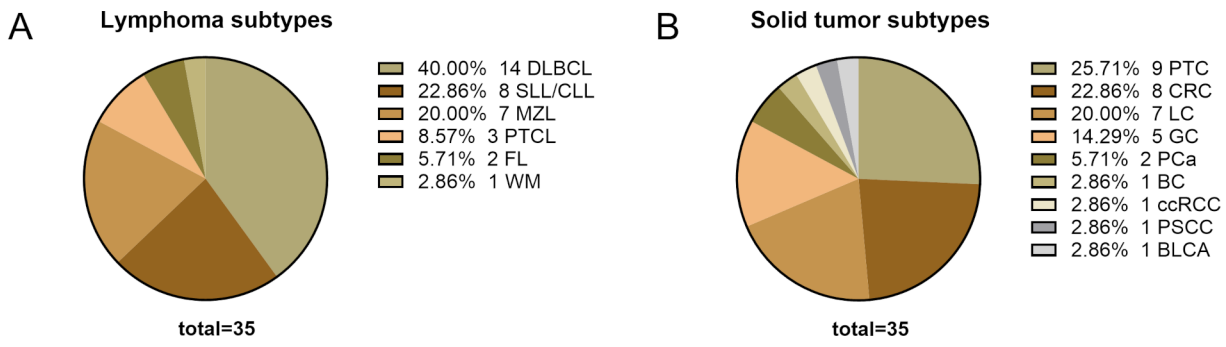

Fig. 1 Distribution of lymphoma and solid tumor subtypes among 35 cases. (**A**) Lymphoma subtypes. (**B**) Solid tumor subtypes

case, surgery combined with radiotherapy and chemotherapy in 2 cases, chemotherapy in 1 case, surgery combined with targeted therapy in 1 case, targeted therapy in 1 case, endocrine therapy in 3 cases, no treatment in 8 cases, and 1 case lost to follow-up. Among the 35 SC patients, 24 survived, 6 died, and 5 were lost to follow-up. The follow-up period ranged from 0 to 68 months, with a median follow-up time of 18 months (Table 1).

Discussion

The occurrence of SC is relatively rare. The reported incidence of SC ranges from 0.37 to 2.79%, which may be attributed to differences in the duration of retrospective analyses, sample sizes, and the inclusion of autopsy series or analyses of specific tumors associated with SC in certain studies [4, 5, 6, 7, 8, 9, 10]. We collected clinical and pathological data from 1,726 lymphoma patients and found that 35 patients had SC, with an incidence rate of 2.02%, which is within the range of the incidence rate reported above. During follow-up, six patients died, five of whom had DLBCL combined with gastrointestinal adenocarcinoma, and four of them died within six months. These findings suggest that patients with DLBCL combined with adenocarcinoma have a higher risk of death and worse prognosis. Furthermore, all CRC-related deaths occurred in elderly patients, who had poor chemotherapy tolerance and a higher risk of severe infections and multiple organ failure.

Among the 35 SC cases in our study, DLBCL was the most common lymphoma type, consistent with previous findings in non-MPM NHL patients [15, 16]. Although the digestive system was the most commonly affected site by solid tumors, the most common SC was DLBCL combined with PTC. This aligns with the findings of Jiang et al. [6], but differs from a systematic review of 308 SC cases, which identified MALT lymphoma with gastrointestinal tumors as the most frequent combination, with the discrepancy possibly related to the smaller sample size in our study [17]. The pathogenesis of lymphoma combined with PTC remains unclear. Recent studies have shown that BRAFV600E mutation can induce immunosuppression. BRAFV600E reactivates the developmental factor TBX3, which subsequently upregulates CXCR2 ligands in a TLR2-NFκB-dependent manner, facilitating the recruitment of myeloid-derived suppressor cells (MDSCs) into the tumor microenvironment. By increasing the infiltration of MDSCs, BRAFV600E promotes the progression of thyroid cancer [18, 19]. Karrethet al. found that the BRAF pseudogene (BRAFP1) is frequently overexpressed in DLBCL, potentially acting as an oncogene by enhancing BRAF activity and activating the MAPK signaling pathway, thus accelerating the development and progression of DLBCL [20]. Furthermore, the BRAFV600E mutation has also been identified in hairy cell leukemia, DLBCL, MZL, SLL/CLL, and multiple myeloma [21, 22, 23, 24, 25]. Therefore, BRAF mutations may serve as a key driver in the coexistence of lymphoma and PTC.

The etiology of synchronous lymphoma combined with carcinoma remains unclear. However, long-term smoking and alcohol consumption have been recognized as major pathogenic factors for MPMs in the respiratory and digestive systems [26, 27, 28]. Among the cases we collected, three patients with LC, one with PSCC, and one with PCa had a history of smoking for more than 30 years. Additionally, four patients with GC or CRC had a history of alcohol consumption for more than 20 years. Talamini et al. found that smoking is a significant risk factor for NHL, with heavy smokers having approximately twice the risk compared to non-smokers [29]. A pooled analysis conducted by the International Lymphoma Epidemiology Consortium, involving 15,486 participants from nine case-control studies, revealed a modest increase in risk across all NHL subtypes [30]. Furthermore, long-term exposure to radiation, industrial pollution, and other environmental factors also contribute to the development of MPMs [8, 31, 32, 33, 34].

Table 1 Clinical data of 35 patients with lymphoma complicated with primary solid tumor

No.	Sex/age	Lymphoma			Solid tumor			1st Tumor	Survival Status	Follow-up (month)
		Subtypes	site	Treatment	Subtypes	site	Treatment			
1	M/49	MALT	Parotid gland	RT	Papillary carcinoma	Thyroid	Surgery	Lymphoma	Survival	38
2	M/69	SLL/CLL	Lymph node	No treatment	Clear cell carcinoma	Kidney	Surgery and Axitinib	Lymphoma	Survival	34
3	F/59	DLBCL	Sinuses	RCDOP, RCHOP, RTX, MTX, and autoHSCT	Papillary carcinoma	Thyroid	Levothyroxine sodium	Lymphoma	Survival	33
4	M/76	DLBCL	Abdominal cavity	No treatment	Adenocarcinoma	rectum	No treatment	Solid tumor	Death	3
5	F/66	DLBCL	Pelvic cavity	RCHOP and RCDOP	Papillary carcinoma	Thyroid	NA	Lymphoma	NA	NA
6	F/55	DLBCL	Lymph node	RCHOP, RCDOP and RGDP	Papillary carcinoma	Thyroid	Surgery	Solid tumor	NA	NA
7	M/74	DLBCL	Small intestine	Refusal of treatment	Adenocarcinoma	Stomach	Surgery	Lymphoma	Death	6
8	F/81	DLBCL	Pharynx	RminiCHOP and RminiCDOP	Papillary carcinoma	Thyroid	No treatment	Lymphoma	Survival	28
9	F/70	MALT	Breast	Mammotome excision	Invasive ductal carcinoma	Breast	Surgery, EPI, CTX, DTX and RT	Lymphoma	Survival	27
10	M/80	PTCL	Skin	miniCVP and miniCHOP	Adenocarcinoma	Prostate	Endocrine therapy	Lymphoma	Survival	27
11	M/70	MZL	Lymph node	RCDOP, CVP and Obrutinib	Adenocarcinoma	Prostate	Endocrine therapy	Lymphoma	Survival	27
12	M/62	SLL/CLL	Appendix	Surgery and Ibrutinib	Adenocarcinoma	Lung	Surgery	Solid tumor	Survival	26
13	F/72	FL	tonsil	RCHOP	Adenocarcinoma	Lung	Surgery	Lymphoma	Survival	24
14	M/74	SLL/CLL	Abdominal cavity	No treatment	Adenocarcinoma	Colon	Surgery	Solid tumor	Survival	23
15	F/67	DLBCL	Stomach	RCDOP	Papillary carcinoma	Thyroid	No treatment	Lymphoma	Survival	19
16	F/83	DLBCL	Stomach	R-miniCDOP, R2-GemOx and BR	Adenocarcinoma	Rectum	No treatment	Lymphoma	Death	6
17	M/57	FL	Lymph node	RCHOP	Squamous cell carcinoma	Lung	Microwave ablation	Lymphoma	Survival	17
18	F/55	SLL/CLL	Lymph node	Ibrutinib and RTX	Micropapillary carcinoma	Thyroid	Surgery	Lymphoma	Survival	68
19	M/68	PTCL	Small intestine	CHOP	Papillary urothelial carcinoma	Bladder	Transurethral resection of bladder tumors	Solid tumor	NA	NA
20	M/75	DLBCL	Lymph node	R2-GemOx	Adenocarcinoma	Colon	No treatment	Solid tumor	Death	1
21	F/55	MALT	Stomach	RT and RCVP	Papillary carcinoma	Thyroid	Surgery	Lymphoma	Survival	56
22	M/65	DLBCL	Stomach	miniCHOP and RCHOP	Adenocarcinoma	appendix	Surgery	Solid tumor	Death	6
23	M/80	SLL/CLL	Lymph node	No treatment	Adenocarcinoma	Stomach	Surgery	Lymphoma	NA	NA
24	M/72	SLL/CLL	Lymph node	No treatment	Adenocarcinoma	Lung	Cisplatin and Pemetrexed	Lymphoma	Death	20
25	M/68	MZL	Lymph node	No treatment	Adenocarcinoma	Stomach	Surgery and SOX	Lymphoma	Survival	41
26	M/62	MZL	Lymph node	NA	Squamous cell carcinoma	Pharynx	Surgery, RT and chemotherapy	Lymphoma	NA	NA
27	M/71	DLBCL	Ileocecal	RCHOP	Adenocarcinoma	Colon	No treatment	Lymphoma	Survival	16
28	M/59	DLBCL	Lymph node	RCHOP and PD1 + RICE	Adenocarcinoma	Stomach	Surgery	Lymphoma	Survival	15
29	M/62	DLBCL	Tonsil	RCDOP	Adenocarcinoma	Stomach	Surgery	Solid tumor	Survival	14
30	M/79	SLL/CLL	Rectum	Surgery	Adenocarcinoma	Rectum	Surgery	lymphoma	Survival	14
31	F/66	SLL/CLL	Lymph node	No treatment	Adenocarcinoma	Lung	Targeted therapy	Solid tumor	Survival	7
32	M/59	PTCL	Lymph node	Chemotherapy	NA	Lung	Surgery	lymphoma	Survival	10

Table 1 (continued)

No.	Sex/ age	Lymphoma			Solid tumor			1st Tumor	Survival Status	Follow-up (month)
		Subtypes	site	Treatment	Subtypes	site	Treatment			
33	M/65	WM	bone marrow	Obrutinib	Adenocarcinoma	Colon	Surgery	Solid tumor	Survival	7
34	F/67	MZBL	Lymph node	BR	Papillary carcinoma	Thyroid	No treatment	Lymphoma	Survival	1
35	F /65	DLBCL	Lymph node	RCHOP	Adenocarcinoma	Lung	No treatment	lymphoma	Survival	0

Abbreviation: MALT: marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue; SLL/CLL: small lymphocytic lymphoma/chronic lymphocytic leukemia; DLBCL: diffuse large B-cell lymphoma; PTCL: peripheral T-cell lymphoma; MZL: marginal zone lymphoma; FL: follicular lymphoma; WM: Waldenström macroglobulinemia; RT: Radiotherapy; RCDOP: rituximab + cyclophosphamide + vincristine + liposomal doxorubicin + prednisone; RCHOP: rituximab + cyclophosphamide + vincristine + doxorubicin + prednisone; auto-HSCT: autologous hematopoietic stem cell transplantation; R2-GemOx: rituximab + lenalidomide + gemcitabine + oxaliplatin; BR: rituximab + bendamustine; RCVP: rituximab + cyclophosphamide + vindesine + dexamethasone; RGDP: rituximab + gemcitabine + cisplatin + dexamethasone; SOX: oxaliplatin + tegafur; MTX: methotrexate; RTX: rituximab; CTX: cyclophosphamide; DTX: docetaxel; EPI: epirubicin; RICE: rituximab + ifosfamide + carboplatin + etoposide; NA, not available

Conventional imaging (CI) techniques, including ultrasound, computed tomography, magnetic resonance imaging, and nuclear imaging, have limitations in detecting SC due to their localized imaging approach. In contrast, PET/CT offers more advantages in diagnosing SC compared to CI [35, 36]. For elderly men, we suggested that PET/CT and gastrointestinal endoscopy should be used as key methods for diagnosing colorectal tumors and confirming lymphoma. In our study cohort, a 79-year-old male patient had a rectal biopsy revealing adenocarcinoma. Post-surgical pathological examination showed moderately differentiated adenocarcinoma, and SLL/CLL was present within the full-thickness intestinal wall. A collision tumor refers to the coexistence of two independent primary malignancies occurring at the same anatomical site or organ, which come into contact or infiltrate each other to form a single mass. Among lymphomas involved in collision with solid tumors, DLBCL is the most commonly observed type [17]. The pathogenesis of collision tumors remains unclear, although several hypotheses have been proposed. The most widely accepted theory is neoplastic heterogeneity, which posits that collision tumors originate from two distinct clones of neoplastic cells that develop independently and coexist within the same anatomical site. This phenomenon may be facilitated by impaired immune surveillance associated with lymphoma, thereby creating a permissive microenvironment for the development of a secondary malignancy [37, 38, 39]. Another possible mechanism is the interaction theory, which suggests that one tumor induces changes in the epidermis or stroma through paracrine effects, with the altered microenvironment promoting the formation of a second tumor [40].

Currently, there is no unified treatment principle for lymphoma combined with malignant solid tumors. Our retrospective analysis included a 75-year-old male patient diagnosed with DLBCL and colon adenocarcinoma passed away less than a month after diagnosis. During rituximab treatment for DLBCL, the patient developed diarrhea, abdominal pain, liver and kidney failure, and an IL-6 level exceeding 5000 ng/ml, suggesting cytokine release syndrome (CRS) induced by rituximab. Rituximab-induced CRS has been reported, and we found that underlying conditions such as heart disease, diabetes, and advanced age increase the risk of fatal CRS [41, 42]. This can be achieved by reducing the injection dose, administering rituximab after CHOP chemotherapy, or using premedication to reduce adverse reactions [15, 43]. We analyzed whether the sequence of treatment for both types of tumors had an impact on prognosis in SC patients and found no statistically significant difference. This may be attributed to the small sample size of patients receiving treatment for both tumors simultaneously ($n = 18$). Furthermore, we observed no significant difference in prognosis between lymphoma patients with or without a background of solid tumors. These findings may be attributed to factors such as the patients' overall health status, the heterogeneity and staging of both lymphoma and solid tumors, and the limited sample size, as well as the significant differences in gene mutations, tumor cell proliferation and metastasis abilities, tumor microenvironment, and therapeutic responses, which largely determine tumor progression, prognosis, and sensitivity to treatment [44, 45, 46]. Therefore, we recommend that treatment plans for SC be individualized to improve patients' quality of life.

Conclusion

This study highlights the rare occurrence of synchronous lymphoma combined with malignant solid tumors and provides clinical insights into its presentation, treatment challenges, and prognosis. Our findings indicate that DLBCL is commonly associated with solid tumors, with PTC being the most frequent concomitant malignancy. Despite the complexity of managing these cases, we observed no significant difference in prognosis between lymphoma patients with concomitant solid tumors and those with lymphoma alone. This may be attributed to the heterogeneity of both lymphoma and solid tumors, differences in patients' overall health status, and the

limited sample size. As the pathogenesis and optimal treatment strategies remain unclear, we recommend an individualized treatment plan based on the type and stage of both lymphoma and solid tumors, as well as the patient's overall condition, with the aim of improving outcomes. In the future, we plan to further validate the effectiveness of treatment strategies through larger sample sizes and multi-center collaborations, providing more clinical evidence for the development of individualized treatment plans.

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Author contributions
Guohua Yu designed and conceived the study. Yuan Gao and Ning Zhu drafted the manuscript. Ning Zhu and Yunjun Wang critically revised the manuscript. Yuan Gao, Yu Pan and Shishou Wu performed literature research. Yan Yang, Ying Yin and Liyan Zhang drafted tables and create images. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval
The study was exempted from review by the Institutional Review Board at the Yantai Yuhuangding Hospital.

Patient consent for publication
The authors confirm that written informed consent for publication was obtained from the patients involved in this study. The patients provided consent for the use of their medical information, including images and other relevant data.

Conflict of interest
The authors declare that they have no conflict of interest.

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