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ORIGINAL ARTICLE

Incidental lymphoma in lymph node dissection for carcinoma in the abdominopelvic cavity: a single-institution experience

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Abstract

Incidental detection of lymphoma in lymph node (LN) dissection for carcinoma is extremely rare. The occurrence and clinicopathological features of this rare condition have not been characterised. The medical records of 11,889 consecutive patients who underwent LN dissection for carcinoma in the abdominopelvic cavity were retrospectively reviewed. Among these patients, 11 had lymphomas detected in LN dissections and 7 had no previous history of lymphoma, representing an incidental detection rate of 0.06% (7/11889). The patients had a median age of 63 years (range, 48–69 years), and the male-to-female ratio was 1:2.5. The sites and histological types of the carcinoma were as follows: adenocarcinoma of the sigmoid colon (2 cases), endometrioid adenocarcinoma of the endometrium (2 cases), squamous carcinoma of the uterine cervix (1 case), adenocarcinoma of the stomach (1 case), and adenocarcinoma of the rectum (1 case). All incidental lymphoma cases (100%, 7/7) were low-grade B cell non-Hodgkin lymphoma (B-NHL), including 5 cases of follicular lymphoma (grades 1–2) and 2 cases of small lymphocytic lymphoma. The median follow-up interval was 39 months (5–65 months). All the patients were alive at the end of the follow-up period. Low-grade B-NHL can be incidentally detected during LN dissection for carcinoma in the abdominopelvic cavity. The subtype of incidental lymphoma is likely related to the epidemiology of lymphoma classes in the corresponding area. We should be aware of simultaneous occurrence of incidental lymphoma during lymphadenectomy for carcinoma.

Keywords Incidental lymphoma · Lymph node dissection · Carcinoma · Clinicopathological feature

Introduction

The coexistence of lymphoma and carcinoma in the same patient is unusual. Lymphoma can occur previously, synchronously, or subsequently to the primary carcinoma [1–3]. An increasing number of subsequent lymphomas have been observed in cancer patients in recent years, and a considerable amount of data has accumulated in the literature [4, 5]. However, synchronous lymphoma in the lymph nodes (LNs) in patients with carcinoma is a rare condition, and only a few cases have been reported worldwide; these instances are mostly documented as case reports rather than as study series [1–3, 6–9].

The main purpose of LN assessment during LN dissection for carcinoma is detection of metastatic carcinoma. However, under extremely rare conditions, lymphoma can be discovered incidentally during this process. Although several cases of non-Hodgkin lymphoma (NHL) have been incidentally discovered in LN dissections for prostate and renal cell carcinoma [3, 9, 10], the incidental occurrence and clinicopathological features of lymphoma during LN dissection for carcinoma in the abdominopelvic cavity have not been well characterised. To clarify this issue, we retrospectively reviewed data of 11,889 consecutive patients who underwent LN dissection for carcinoma over approximately 5 years at our institution. We analysed the occurrence and clinicopathological features of this rare condition, and based on our findings, we recommend that pathologists should be aware of the existence of incidental lymphoma in LN dissections for carcinoma.

Yuhua Huang, Shumei Yan and Lili Liu contributed equally to this work.

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Materials and methods

Patients, clinical data, and tissue samples

A total of 11,889 patients underwent LN dissection for carcinoma in the abdominopelvic cavity at the Sun Yat-sen University Cancer Center from January 2013 to August 2017. All LN dissections were performed in the context of primary surgical treatment for carcinoma in patients who did not receive neoadjuvant radiotherapy or chemotherapy. These 11,889 cases included cases of gastric carcinoma (2290 cases), colorectal carcinoma (3972 cases), pancreatic carcinoma (33 cases), liver carcinoma (338 cases), renal carcinoma (602 cases), bladder carcinoma (277 cases), prostate carcinoma (339 cases), and carcinoma of the female reproductive system (4038 cases). Among these patients, lymphomas were diagnosed in LN dissections in 11 cases. The medical records of these 11 patients were reviewed. Diagnostic criteria were established according to the revised 4th edition (2017) of the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues [11]. An additional cohort was utilised only to validate the accuracy of the primary diagnoses. This group included 500 random cases during the study period. The morphology of these 500 cases was retrospectively reviewed independently by two experienced haematopathologists, and a basic panel of immunostains (CD20, CD3, CD21, Ki67, BCL2, CD10, and cyclin D1) was used to detect possible missed cases.

Immunohistochemical analysis and Epstein-Barr virus–encoded RNAs in situ hybridisation

The Dako REAL™EnVision™ kit (Dako, Glostrup, Denmark) was used to detect all antigens. The pre-treatment methods, primary antibodies, and working dilutions used in this study are listed in the supplementary materials (Table S1).

The EBV Probe In Situ Hybridization Kit (ISH-6021, Zhongshan Golenbridge Biotechnology Co., Ltd., Beijing, China) was used to detect Epstein-Barr virus (EBV)–encoded RNAs (EBERs) according to the manufacturer's instructions. The main protocols were published in our previous study [12].

Fluorescence in situ hybridisation

Fluorescence in situ hybridisation (FISH) studies were performed for case #1 using 4-μm-thick unstained sections prepared from formalin-fixed and paraffin-embedded (FFPE) tissue blocks. The *IGH*/*BCL2* fusion probe (Vysis LSI IGH/BCL2 Dual Color, Dual Fusion Translocation Probe, Abbott Laboratories, Chicago, IL, USA) was used to interrogate the loci of interest. Before hybridisation, the slides were pretreated using an automated VP 2000 processor with standard protocols. After pre-treatment, the cells and *IGH*/*BCL2* fusion probe were codenatured at 80 °C for 5 min and then hybridised overnight at 37 °C using the ThermoBrite system (Abbott Laboratories). Nuclei were counterstained with 4,6-di-amidino-2-phenylindole (DAPI), and the FISH signals were analysed using an Olympus BX51 TRF microscope (Olympus, Tokyo, Japan) equipped with a triple-pass filter (DAPI/Green/Orange, Vysis). Hybridisation signals were assessed from 200 interphase nuclei with an established cut-off of 15% for rearrangement of the *BCL2* locus. Images were acquired and archived using the CytoVision Image Analysis System (Genetix, San Jose, CA, USA).

Molecular assays for gene rearrangements

Genomic DNA was extracted from FFPE tissues using the QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany). A commercial BIOMED-2 multiplex PCR system (Invivoscribe Technologies, San Diego, CA, USA) was used to detect the gene rearrangements of immunoglobulin (IG) in case #1. Eight sets of fluorogenically labelled primers (frameworks FR1-JH, FR2-JH, FR3-JH, DH-JH, DH7-JH, Vk-JkΓ, Vk-Kde+intron-Kde, and Vλ-Jλ) specific for the variable and joining regions of the IG gene were used. The PCR cycling conditions included denaturation at 95 °C for 7 min and 35 cycles of denaturation at 95 °C for 45 s, annealing at 60 °C for 45 s, and extension at 72 °C for 90 s. Gene scanning was conducted using an ABI 3500Xl Genetic Analyzer with GeneMapper Software (version 4.1; Life Technologies Corporation, Carlsbad, CA, USA) with appropriate positive and negative controls. Interpretation of clonal peaks was conducted following the Euroclonality guideline and the manufacturer's protocol [13].

Results

Occurrence and clinical features

Among the 11 patients with lymphoma detected in LN dissection, 4 had a history of lymphoma before surgery and 7 had incidentally identified lymphomas among the 11,889 patients, representing an incidental detection rate of 0.06%.The main clinical data of these 7 patients with incidental lymphoma are summarised in Table 1. The patients had a median age of 63 years (range, 48–69 years), and the male-to-female ratio was 1:2.5. Four patients presented with digestive tract symptoms, including haematemesis, melena, altered bowel habits, abdominal pain, and haematochezia, whereas the other 3 patients presented with irregular vaginal bleeding. Multiple enlarged regional LNs were revealed by preoperative computed tomography in case #5 and case #7, which were suspected to be metastatic carcinoma. The main clinicopathologic features of the 4 patients with a history of lymphoma prior to surgery

Table 1 Clinicopathological characteristics of 7 patients with incidental lymphoma detected in lymph node dissection for carcinoma in the abdominopelvic cavity

Case no.	Age	Sex	Main symptoms	Carcinoma			Lymphoma			Treatment		Outcome
				Site	Type	Stage	Site	Type	Stage	Carcinoma	Lymphoma	
1	65	M	Hematemesis and melena	Stomach	Adenocarcinoma	pT1bN0M0, IA	Perigastric LN	FL (G1)	III AS	Partial gastrectomy + lymphadenectomy	Rituximab*6	22 months, AWD
2	57	F	Altered bowel habits	Sigmoid colon	Adenocarcinoma	pT3N2aM0, III B	Para sigmoid LN	SLL	III A	Dixon procedure + lymphadenectomy; Xelox*6	Untreated	39 months, AWD
3	68	M	Abdominal pain	Sigmoid colon	Adenocarcinoma	pT2N0M0, II A	Para sigmoid LN	FL (G2)	II EB	Sigmoidectomy + lymphadenectomy	NA	65 months, AWD
4	69	F	Hematochezia	Rectum	Adenocarcinoma	pT3N0M0, IIA	Parareta LN	FL (G1)	III A	Dixon procedure + lymphadenectomy	Untreated	65 months, AWD
5	48	F	Irregular vaginal bleeding	Endometrium	Endometrioid adenocarcinoma	I	Pelvic LN	FL (G1)	IIA	Total hysterectomy and bilateral appendectomy + lymphadenectomy	Untreated	44 months, AWD
6	50	F	Irregular vaginal bleeding and weight loss	Endometrium	Endometrioid adenocarcinoma	IA	Pelvic LN	FL (G2)	IIA	Total hysterectomy and bilateral appendectomy + lymphadenectomy	Untreated	12 months, AWD
7	63	F	Irregular vaginal bleeding	Uterine cervix	Squamous carcinoma	IB1	Pelvic LN	SLL	IIA	Total hysterectomy and bilateral appendectomy + lymphadenectomy	Untreated	26 months, AWD

F, female; *M*, male; *AWD*, alive with disease; *LN*, lymph node; *FL*, follicular lymphoma; *SLL*, small lymphocytic lymphoma;*G1*, grade 1; *G2*, grade 2; *NA*, not available

are summarised in Table 2. No missed overt lymphoma was identified in the LN dissections in the cohort of 500 cases used for validation.

Pathological findings

The sites and histological types of the carcinoma are listed in Table 1. All incidental lymphomas (100%, 7/7) were low-grade B cell NHL (B-NHL), including 5 cases of low-grade follicular lymphoma (FL) and 2 cases of small lymphocytic lymphoma (SLL) (Table 1). All 5 FLs had a predominantly follicular pattern with closely packed follicles that effaced the nodal architecture. Neoplastic follicles were poorly defined, mantle zones were absent, and a mixture of centrocytes and centroblasts was observed. All cases had a marked predominance of centrocytes and only a few centroblasts (0–15 centroblasts/hpf) (Fig. 1a–d). All 5 patients with FL underwent staging bone marrow biopsies, and all were negative at diagnosis. Both cases of incidental SLL showed effacement of the architecture, with a pseudo-follicular pattern of regularly distributed pale areas corresponding to proliferation centres containing larger cells in a dark background of small cells (Fig. 2a–c). Peripheral blood examination and bone marrow biopsy ruled out chronic lymphocytic leukaemia (CLL) at diagnosis. Second bone marrow biopsies after 2 years revealed SLL involvement in both patients.

Immunophenotype and EBV infection status

The results of immunohistochemistry and EBER ISH are summarised in Table S2. Staining for CD21 showed follicular dendritic cell meshwork in the follicles in FL; neoplastic cells were CD20 positive with non-immunoreactivity for CD3. All FLs (100%, 5/5) expressed CD10, BCL6, and BCL2. No immunoreactivity for CD5, CD23, or cyclinD1 was observed in neoplastic cells. The Ki67 proliferation index in the FL cases ranged from 10 to 25% (Fig. 1e–i). For the SLL cases, lymphoid cells were positive for CD20, CD5, and CD23 (Fig. 2d–f), with non-immunoreactivity for CD10 and cyclinD1 in both cases. EBV was not detected in any of the 7 incidental lymphoma cases.

Molecular findings

A clonal peak was identified as a 335-base pair *IGHA* fragment in case #1. The heights of the clonal peaks were twofold greater than the polyclonal background. This case also harboured an *IGH*/*BCL2* fusion (Fig. 3).

Table 2 Clinicopathological characteristics of 4 patients with a history of lymphoma prior to surgery

Case no.	Age	Sex	Lymphoma history				Interval between lymphoma and carcinoma (months)	Carcinoma		Lymphoma in LND	
			Site	Type	Stage	Treatment		Site	Type	Site	Type
1	47	M	Axillary and inguinal LN	FL (G3a)	III	CHOP*2 cycles	6	Rectum	Adenocarcinoma	Pararectal LN	FL (G3a)
2	57	F	Cervical LN	DLBCL	II	NA	48	Uterine cervix	Squamous carcinoma	Pelvic LN	DLBCL
3	75	M	Tonsil	MCL	II	CHOP*3 + RT	36	Kidney	Renal cell carcinoma	Hilar LN	MCL
4	62	F	Cervical and axillary LN	SLL	II	Untreated	25	Colon	Adenocarcinoma	Mesenteric LN	SLL

F, female; *M*, male; *LN*, lymph node; *FL (G3a)*, follicular lymphoma (grade 3a); *DLBCL*, diffuse large B cell lymphoma; *MCL*, mantle cell lymphoma; *SLL*, small lymphocytic lymphoma; *NA*, not available; *CHOP*, cyclophosphamide, doxorubicin, vincristine, and prednisone; *RT*, radiotherapy

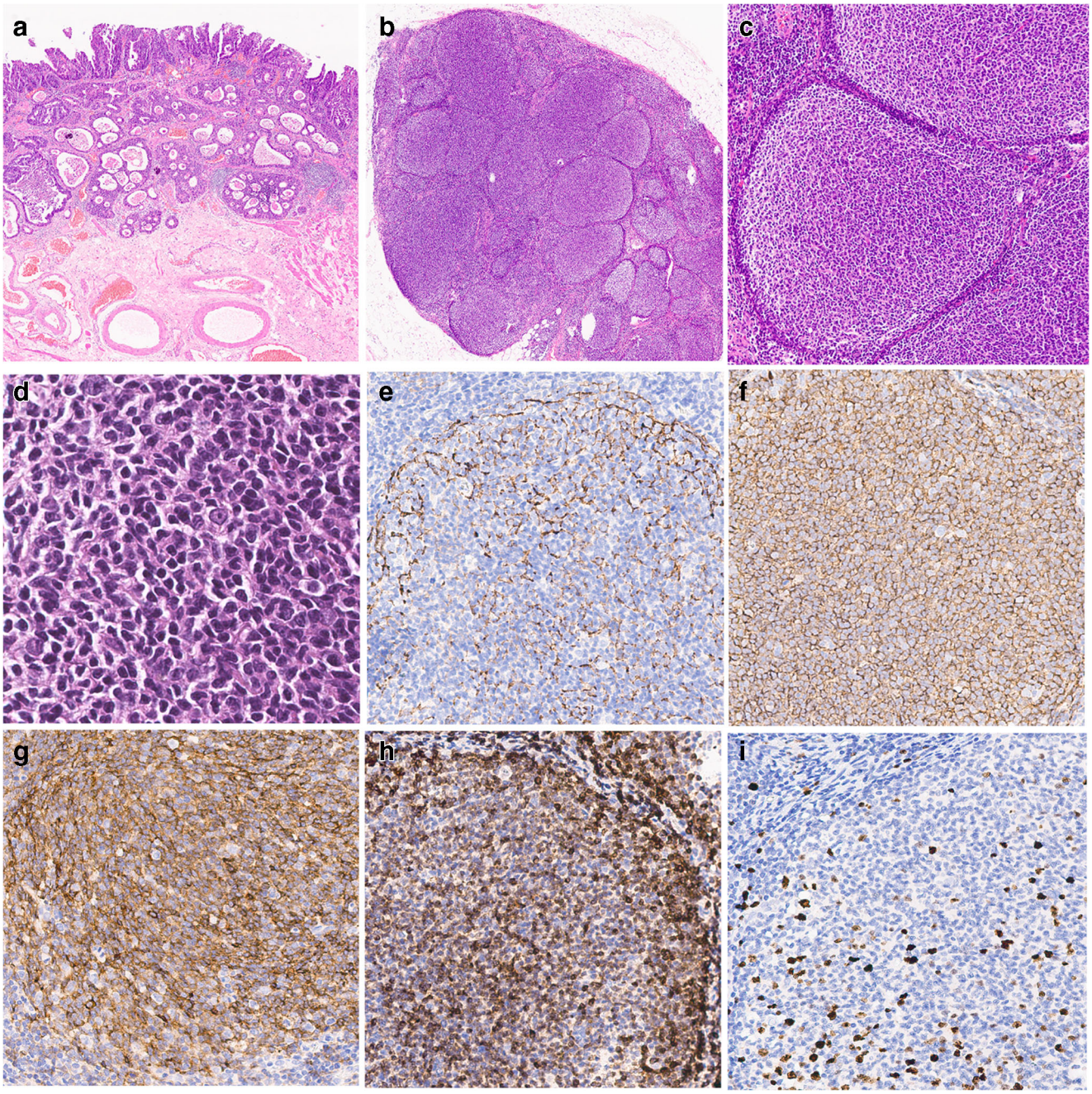

Fig. 1 Incidental lymphoma discovered in the lymph node dissection for gastric adenocarcinoma (case #1). **a** Moderately differentiated adenocarcinoma of the stomach (HE; ×20); **b** The neoplastic follicles in the perigastric lymph node were closely packed (HE; ×20); **c** The follicles lacked mantle zones and tangible body macrophages (HE; ×100); **d** The neoplastic follicles showed a marked predominance of centrocytes and only a few centroblasts (HE; ×400); **e** Staining for CD21 showed FDC meshwork in the follicles (IHC; ×200); **f** Follicles and interfollicular regions contained CD20+ B cells (IHC; ×200); **g** CD10 was expressed by the follicles and to a lesser degree the interfollicular neoplastic cells (IHC; ×200); **h** Follicles were BCL2+ (IHC; ×200); **i** Tumour cells showed a low proliferation fraction (IHC; ×200)

Treatment and follow-up

The treatment regimens are listed in Table 1. The median follow-up interval was 39 months (12–65 months). All the patients were alive at the end of the follow-up period.

Discussion

The incidental discovery of lymphoma in LN dissection for carcinoma is extremely rare, and the incidence remains unknown [1, 3, 8, 9, 14, 15]. In the present study, we retrospectively reviewed 11,889 consecutive patients who underwent

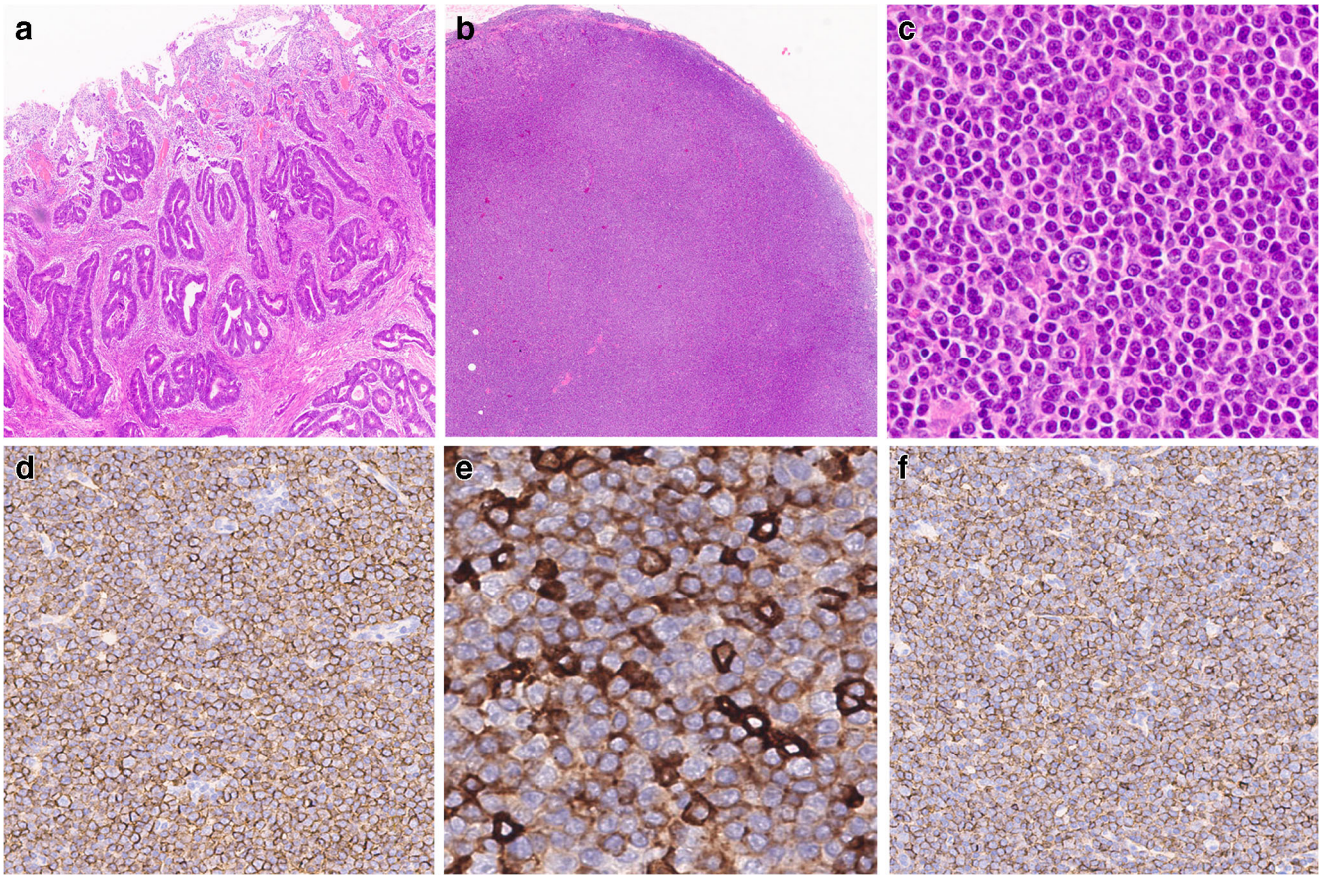

Fig. 2 Incidental small lymphocytic lymphoma discovered in the lymph node dissection for sigmoid carcinoma (case #2). **a** Moderately differentiated adenocarcinoma of the sigmoid (HE; ×40); **b** The lymph node showed effacement of the architecture, with a pseudo-follicular pattern of regularly distributed pale areas (HE; ×20); **c** The proliferation centre contained larger cells in a dark background of small cells (HE; ×400); **d** Lymphoid cells were diffusely positive for CD20 (IHC; ×200); **e** CD5 was weakly expressed by neoplastic cells (IHC; ×400); **f** Neoplastic cells diffusely expressed CD23 (IHC; ×200)

LN dissection for carcinoma in the abdominopelvic cavity over nearly 5 years in our institution. Our results revealed an incidental lymphoma detection rate of 0.06% (7/11,889), suggesting that pathologists should be aware of the simultaneous occurrence of incidental lymphoma in lymphadenectomy for carcinoma in the abdominopelvic LNs. The diagnosis of incidental lymphoma requires careful morphological assessment and immunostaining analysis. Some studies revealed an

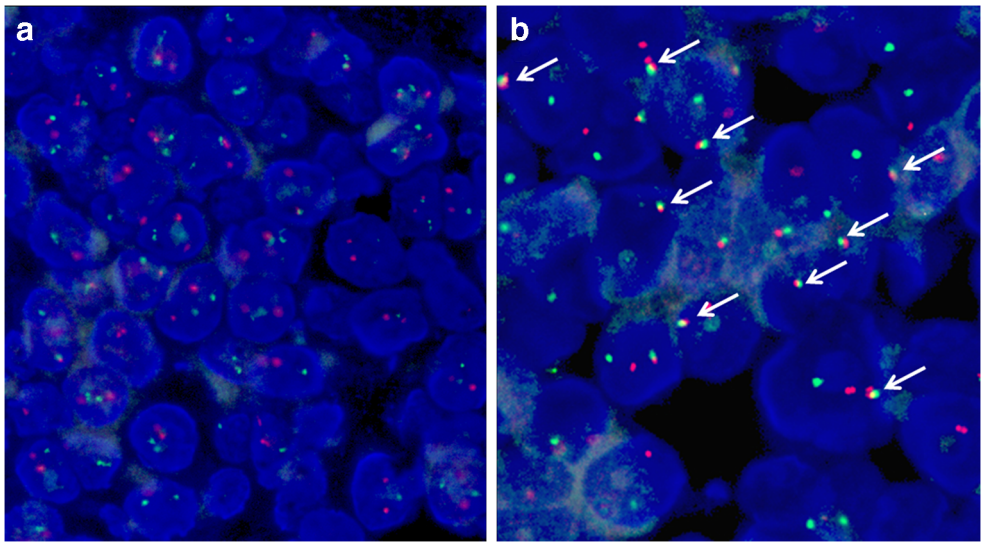

Fig. 3 Fluorescence in situ hybridisation (FISH) analysis for *t* (14;18) (q32; q21) *IgH*/*BCL2* translocation (case #1). **a** Two green signals and two red signals were observed in cases without *t* (14;18) (q32; q21) *IgH*/*BCL2* translocation (negative control) (FISH, ×400); **b** *IgH*/*BCL2* gene fusions were detected as yellow signals, indicating *t* (14;18) (q32; q21) translocation (arrows) (FISH, ×1000)

increased incidence of secondary lymphoma cancer patients in the long-term post-treatment period, which may have been greatly affected by chemotherapy and radiation [16, 17]. The association of lymphoma in the post-transplant setting is well recognised and associated with immune suppression, and a similar role is hypothesised for immune suppression in the context of multi-chemotherapy. Genetic predisposition does not play a role. Hence, the coexistence of carcinoma and secondary lymphoma may have a causal relationship. However, the aetiopathological mechanism underlying the coexistence of synchronous lymphoma and carcinoma has not yet been thoroughly examined. Interestingly, lymphomas were incidentally identified in 0.16% (18/10,659) of participants in a cancer surveillance program using [18F] fluorodeoxyglucose positron emission tomography/computed tomography [18]. However, it should be noted that only 5 lymphomas (0.05%, 5/10,659) were present in the LNs, and the other 13 lymphomas occurred in extra-nodal sites in that study. Accordingly, the detection rate of lymphomas in the LNs was 0.05% (5/10,659) [18], which was very close to our finding (0.06%). The minor differences in the results of these two studies may be because of different methodologies, location of the lymphoma, different populations, and sampling bias. Moreover, according to a study in Chinese patients [19], FL and CLL/SLL are the two most common asymptomatic lymphomas occurring in the LNs in middle-aged and elderly people. Furthermore, in this study, LN dissection was performed in the context of primary surgical treatment of immunocompetent patients with carcinoma. Therefore, the 7 patients showed coexistence of tumours that could not be explained by chemotherapy or radiotherapy effects. These results suggest that the coexistence of synchronous lymphoma and carcinoma is a coincidental occurrence rather than a causal relationship.

The clinicopathological features of lymphoma incidentally detected in LN dissection for carcinoma have not been well characterised. Our results showed that the median age of patients was 63 years (range, 48–69 years), and the male-to-female ratio was 1:2.5. It seems that the sex prevalence is biased towards women compared with the overall incidence of lymphoma. In fact, 34.0% (4038/11,889) of cases in the present series were patients with female reproductive carcinomas. Among the 7 incidental lymphomas, 3 cases were identified in patients with female reproductive carcinoma; the male-to-female ratio for the other 4 cases was 1:1. Therefore, selection bias of the patient population with abdominopelvic carcinoma suggests that the sex prevalence will be biased towards women.

All patients with incidental lymphoma presented with local symptoms of carcinoma and had an uneventful course of radical resection. Multiple enlarged regional LNs were revealed by preoperative computed tomography in only 2 of 7 patients, and the lesions were suspected to be metastatic carcinoma. Of note, all coincidental lymphomas in the present study were low-grade B-NHL, including FL and SLL. This is likely related to the epidemiology of lymphoma classes in Asia. Most patients with these lymphomas were asymptomatic, which may explain why these lymphomas were not detected prior to surgery. Because of the rarity of this condition, optimised therapeutic strategies have not been established. Because few patients with low-grade NHL can be cured and long-term survival without therapy is common [20], patients who are asymptomatic at the time of diagnosis are followed closely by an oncologist to identify and treat early sites of disease progression that can lead to serious and avoidable complications [9]. Further studies are needed to improve the understanding of this extremely rare condition.

The current study had some limitations. Although all cases were diagnosed by experienced pathologists and slides of 500 of 11,889 cases were re-reviewed by two experienced haematopathologists and no missed overt lymphoma was identified, we did not exhaustively re-review all slides from the 11,889 cases. It is possible that a few incidental lymphomas were missed. Additionally, incidental and isolated FL in situ is present in 2.3–3.23% in LN resection specimens, whereas incidental mantle cell lymphoma in situ is found in 0.59% of European patients [21, 22]. However, we did not find any in situ lesions in the subset of 500 cases in the parallel validation study. The main possible reason for this discrepancy is the methodology for the IHC detection of in situ lesions. To detect in situ lesions in previous studies, all LNs or LNs > 0.5 cm in size were immunohistochemically assessed [21, 22]. However, because the main purpose of the present study was detection of overt lymphoma, not in situ lesions with uncertain clinical significance, the LNs were immunohistochemically assessed only when malignant lymphoma was suspected morphologically. Therefore, an exhaustive retrospective immunohistochemistry screening for in situ lesions was not performed, and in situ lesions would not be easily detected in the present study. Furthermore, the prevalence of in situ lesions may differ in different populations and regions [23].

In summary, we retrospectively analysed 11,889 consecutive patients who underwent LN dissection for carcinoma in the abdominopelvic cavity in a single institution and found that the incidental detection rate was 0.06%. All cases of incidental lymphoma were low-grade B-NHL and tended to occur in middle-aged and elderly patients. We should be aware of the simultaneous occurrence of incidental lymphoma during lymphadenectomy for carcinoma in the abdominopelvic cavity.

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Compliance with ethical standards The study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center, and all patients provided written informed consent for the collection and publication of their medical information during the first visit to our centre (the RDD number is RDDA2018000601).

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

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