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RECEIVED 14 June 2022

ACCEPTED 25 October 2022

PUBLISHED 07 December 2022

CITATION

Zhang B, Zhang Y, Li Q, Jiang Q, Chu W,
Gong H, Li R and Ji H (2022), Case
report: Chronic lymphocytic leukemia/
small lymphocytic lymphoma and
monomorphic epitheliotropic intestinal
T-cell lymphoma: A
composite lymphoma.
Pathol. Oncol. Res. 28:1610653.
doi: 10.3389/pore.2022.1610653

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Case report: Chronic lymphocytic leukemia/small lymphocytic lymphoma and monomorphic epitheliotropic intestinal T-cell lymphoma: A composite lymphoma

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Background: Composite lymphomas involving B-cell and T-cell lymphomas is very rare.

Case presentation: We reported a 63-year-old gentleman with composite chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL). The patient was admitted to our hospital due to abdominal pain, and was diagnosed with CLL/SLL after bone marrow (BM) biopsy, BM aspiration, and flow cytometry. Two weeks later, he was diagnosed with MEITL based on pathological analysis after intestine excision. Next gene sequencing (NGS) findings identified two hotspot mutation sites (*STAT5B* and *DNMT3A*) closely related with the pathogenesis of CLL/SLL and MEITL. Additionally, *BCOR* mutation was only detected in the CLL/SLL area. The likely pathogenic mutations of CLL were *SETD2*, *NOTCH1*, *SF3B1*, and *PTPN11*, while the likely pathogenic mutations related with the MEITL were *TET2* and *ZRSR2*. Mutations of *GATA3*, *PLCG2*, and *FAT1* were identified in both CLL/SLL and MEITL areas, but the clinical significance was unknown. Finally, the patient died in the 12-month follow-up after surgery.

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; BM, bone marrow; BTK, Bruton tyrosine kinase; CHIP, clonal hematopoiesis of indeterminate potential; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; EATL, enteropathy-associated T-cell lymphoma; FR, fludarabine refractoriness; HL, Hodgkin lymphoma; IHC, immunohistochemistry; MCH, corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; NGS, next-generation sequencing; NHL, non-Hodgkin lymphoma; PLCG2, phospholipase C γ 2; PTCL, peripheral T cell lymphoma.

Conclusion: We report a rare case of composite CLL/SLL and MEITL that highlights the importance of careful inspection of hematologic neoplasms. We also present the results of NGS of different gene mutations in CLL and MEITL tissues.

KEYWORDS

case report, chronic lymphocytic leukemia, composite lymphoma, small lymphocytic lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma

Introduction

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a typical indolent non-Hodgkin lymphoma (NHL) characterized by accumulation of malignant B cells in bone marrow (BM), peripheral blood and lymph nodes. Richter's syndrome refers to high-grade NHL or Hodgkin lymphoma (HL) in patients with CLL/SLL. Approximately 2%–8% of patients with CLL/SLL would develop diffuse large B cell lymphoma (DLBCL), and less than 1% would present classic HL (1). In rare cases, CLL/SLL patients present T-cell malignancies with an incidence of approximately 1%, which is usually in the anaplastic large cell type or with a cytotoxic phenotype (2). Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) is a rare primary intestinal T-cell lymphoma formerly known as type 2 enteropathy-associated T-cell lymphoma (EATL), resulting in very poor prognosis. In this study, we reported an extremely rare case presenting simultaneous CLL/SLL and MEITL.

Case presentation

A 63-year-old gentleman was referred to our hospital due to needle-like pain in the upper abdomen for at least 15 days on November 18, 2020. The pain was transient and was relieved shortly, but he showed serious pain and vomiting occasionally. Gastroscopy showed reflux esophagitis and chronic atrophic gastritis. Doppler ultrasonography of the abdomen showed no abnormalities. Routine blood examination results were as follows: white blood cell, $17.9 \times 10^9/L$ (normal range: $4\text{--}10 \times 10^9/L$); lymphocyte ratio, 62.5% (normal range: 20%–40%); lymphocyte, $11.0 \times 10^9/L$ (normal range: $1\text{--}3 \times 10^9/L$); erythrocyte, $4.7 \times 10^{12}/L$ (normal range: $3.5\text{--}5.5 \times 10^{12}/L$); hemoglobin, 87 g/L (normal range: 110–160 g/L); mean corpuscular volume (MCV), 67 fL (normal range: 82–92 fL); corpuscular hemoglobin (MCH), 19 pg (normal range: 27–31 pg); mean corpuscular hemoglobin concentration (MCHC), 284 g/L (normal range: 320–360 g/L); and ferritin, 8.21 ng/ml (normal range: ≥ 20 ng/ml). Upon physical examination, the patient showed bilateral inguinal lymphadenectasis. A smoking history was reported by himself with a duration of about 20 years (50 cigarettes per day). Nowadays, the patient does not smoke for 20 years. He had a history of drinking alcohol (about 150 g per day) for 40 years.

BM biopsy showed a markedly hypercellular marrow (85%), which was diffusely involved by a small lymphocytic infiltration (80%) (Figure 1A). The infiltration consisted of numerous small

lymphocytes and scattered paraimmunoblasts (Figure 1B). The tumor cells were positive for CD20, CD5, and CD23, and were negative for CD3, CD10, TdT, and cyclin D1 (Figures 1C–E). For the aspirate smear, the majority (80%) were small lymphocytes with coarse chromatin. Peripheral blood smear showed scattered, small to medium sized lymphoma cells with irregular nuclear contour. Flow cytometry on BM aspirate demonstrated the presence of kappa restricted B cells, together with positive staining for CD19, CD20, CD22, CD5, and CD23. No *CCND1* gene break or *P53* gene deletion was identified by FISH, while no mutation was identified in *MYD 88* gene after Sanger sequencing.

The patient was then diagnosed with CLL/SLL and microcytic hypochromic anemia simultaneously. Thoracic and abdominal CT showed lymphadenopathy in mediastinum, bilateral neck, axillary area, enterocolia, retroperitoneal and pelvic cavity, as well as splenomegaly. CT scan indicated partial thickening in the small intestine. Thus, low-stage CLL/SLL was considered, and the patient merely received iron supplement for the treatment. However, the patient still reported persistent needle-like pain in the upper abdomen after treatment. CT enterography showed thickening in the small intestinal wall (Figures 2A–C), together with multiple lymphadenopathies in the abdominal cavity and retroperitoneum. Colonoscopy indicated three polyps with a size of 0.8 cm, 0.7 cm, and 0.4 cm, respectively. Pathological analysis indicated tubular adenoma with low-grade dysplasia. Finally, the patient was discharged with attenuation in the abdominal pain without treatment.

The patient showed recurrence of abdominal pain lasting for 2 weeks after discharge. Abdominal CT showed increase in the diameter and number of lymph nodes. Enteroscopic examination indicated multiple ulcers in the distal jejunum, which were deeper in site with an irregular margin covering them with white pus moss (Figures 2D,E). Based on the biopsy, inflammatory disease was considered by a general pathologist. Then he received laparoscopic exploration and partial enterectomy after endotracheal intubation and combined intravenous-inhalation anesthesia, which indicated multiple ulcers and narrowing in the small intestine. The intestinal wall was narrow and there was a mass at the position that was about 100 cm from the Treitz. Then a part of the intestine including the narrow lesion and the mass ($2.5 \text{ cm} \times 1.0 \text{ cm} \times 0.5 \text{ cm}$) was excised. A narrowing site in the intestinal wall was observed at a distance of 2.5 cm from the mass. There was an ulcer in the lesion with a length and a diameter of 2.0 cm and 0.5 cm, respectively. Intestinal edema was noticed between the mass and the narrowed intestinal wall. The villous architecture was distorted in the

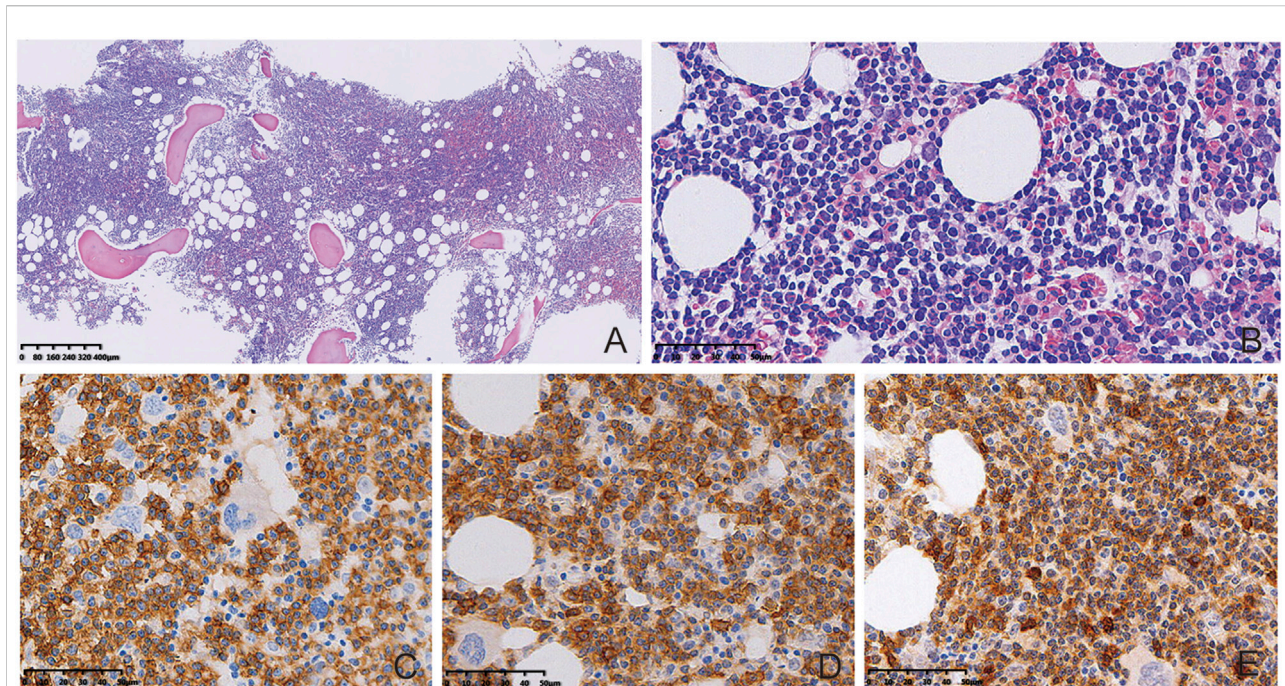


FIGURE 1

BM biopsy results. BM biopsy showed diffuse involvement by a small lymphocytic infiltration ((A), HE, 40x). Presence of numerous small lymphocytes and scattered paraimmunoblasts in the infiltrated tissues ((B), HE, 400x). The tumor cells were positive for CD20 ((C), Enlvision, 400x), CD23 ((D), Enlvision, 400x), and CD5 ((E), Enlvision, 400x).

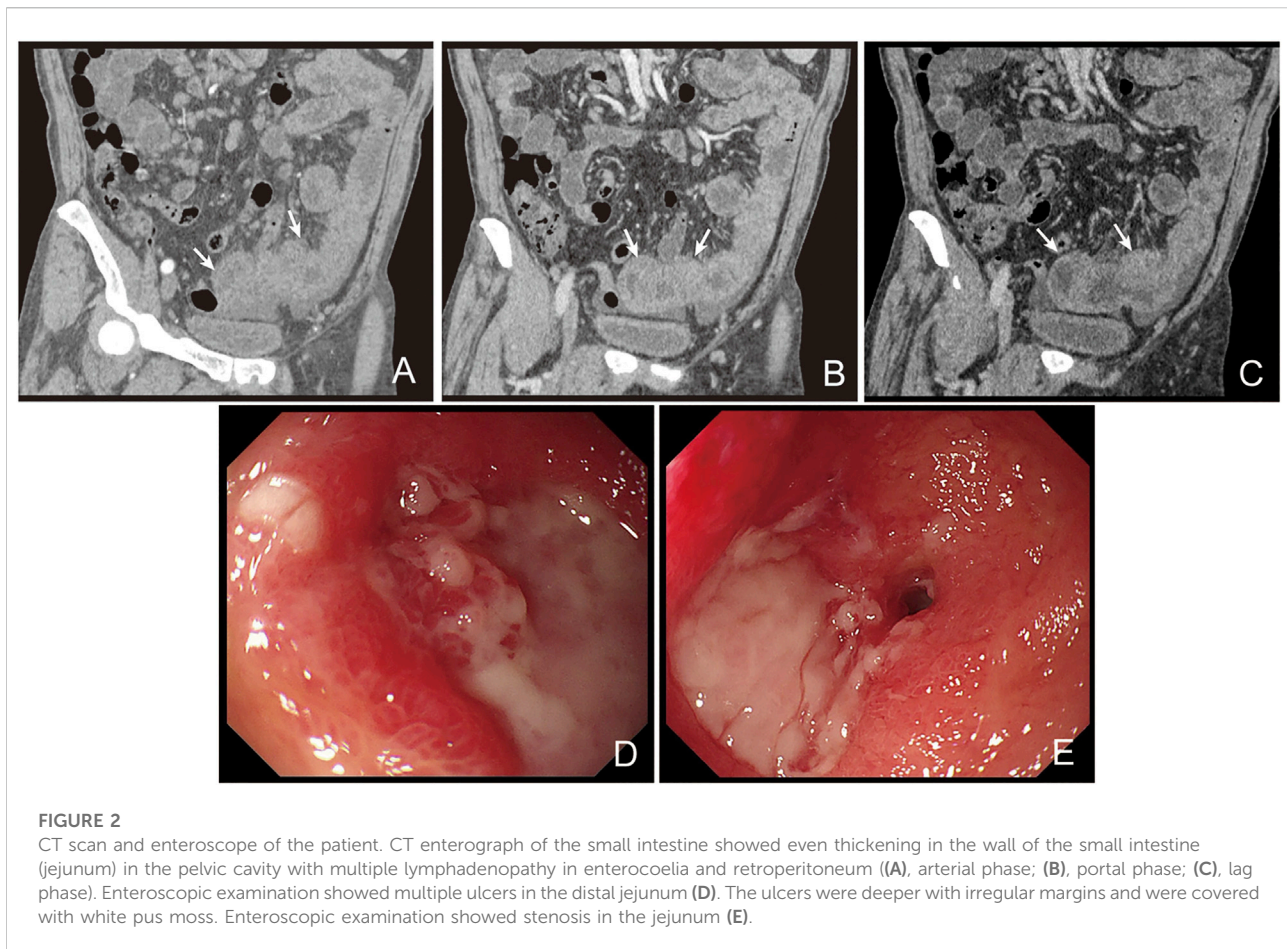
mass and the whole layer was diffusely infiltrated by neoplastic lymphocytes. The villi were broadly expanded and infiltrated by the tumor cells, presenting prominent epitheliotropism in the peripheral intestine (Figures 3A–C). The cells were moderate in size with a generous rim of the pale cytoplasm. The nuclei were irregular, and most of them showed finely dispersed chromatin and inconspicuous nucleoli. Partial nuclei showed nuclear fold, prominent nucleoli, and dense chromatin. There was no inflammatory background or necrosis. Additionally, small lymphoid cells were seen around the blood vessels in the intestinal wall (Figure 3D).

The tumor cells were positive for CD3, CD7, CD8, CD43, CD56, TIA1, Granzyme B, and Bcl-2. In addition, the tumor cells were negative for CD20, CD79a, CD10, Bcl-6, MUM-1, CD23, cyclin D1, CD2, CD4, CD5, and CD30. The Ki-67 index was in a range of 70%–80% (Figures 3E–L). Tumor cells near the blood vessels were positive for CD20, CD79a, CD5, CD23, CD43, and Bcl-2. The Ki-67 index was in a range of 5%–10% (Figures 3M–P). The results were summarized in Table 1. At the focal edge area of the mass, there was mixed immunophenotype expression. The expression of EBV was negative in the tumor mass and the cells in the peripheral vessels. Finally, the patient was diagnosed with composite lymphoma with MEITL and CLL/SLL simultaneously. The peripheral blood and BM were not invaded by MEILT tumor cells based on the aspiration and the BM biopsy, which was confirmed by flow cytometry to the BM and peripheral blood.

There was clonal rearrangement for the IG detection using specific BIOMED-2 primers based on peripheral blood sample. Sanger sequence confirmed that it was IGHV3-33_06. The homologous degree was 100% compared with the germline sequence. PCR-based TCR assay revealed a small monoclonal T-cell population in a background of oligoclonal T-cells.

For the next-generation sequencing (NGS), B- and T-neoplastic cell content was estimated based on morphology, immunohistochemistry (IHC) and *IG/TCR* gene rearrangement. Two different paraffin blocks, with about 20% neoplastic cells in the HE sections, were selected for *IG* and *TCR* gene rearrangements and targeted sequencing. IHC indicated CLL/SLL harboring *IG* gene rearrangement, and MEILT harboring *TCR* gene rearrangement. Enrichment for areas of interest was scraped manually when comparing with the HE staining. High-throughput sequencing analysis was performed using haematopoietic and lymphoid specific panels covering the coding sequence (CDS) of 143 Hematological Disease genes through Illumina NextSeq 550 with a mean sequencing depth of 1000× (SINO-US Diagnostics Lab, Tianjin, China) (Supplementary Table S1). Data were analyzed using the bioinformatics pipeline in-house.

According to the NGS results, the pathogenic hotspot mutations of CLL/SLL and MEILT were *STAT5B* (c.1924A>C, p.N642H) and *DNMT3A* (c.2678G>A, p.W893*). Additionally, gene mutation on *BCOR* (c.1005dupC, p.S336Lfs*45) was only



detected in the CLL/SLL area. The likely pathogenic mutations of CLL were *SETD2* (c.4688delG, p.G1563Afs*2), *NOTCH1* (c.7541_7542del, p.P2514Rfs*4), *SF3B1* (c.2902-2A>T), and *PTPN11* (c.1492C>T, p.R498W). The *TET2* (c.4094G>T, p.G1365V) and *ZRSR2* (c.1237A>G, p.K413E) mutations were likely pathogenic for the MEILT. Furthermore, mutations on *GATA3* (c.124C>T), *PLCG2* (c.1311T>G), and *FAT1* (c.7130C>T) were detected in both CLL/SLL and MEITL areas, which were classified as variants of uncertain clinical significance (UVS) (Table 2).

For the follow-up, the patients did not receive additional treatment and passed away on January 6, 2022. This study was performed according to the convention of the Declaration of Helsinki, and the study protocols were approved by the Ethics Committee of Qilu Hospital (Qingdao). Written informed consent was obtained from the patient and his guardians.

Discussion

Composite lymphoma is defined as coexistence of two distinct types of NHL or a rare combination of HL and NHL

in a single organ or tissue (3), comprising 1%–4% of malignant lymphomas (4). Discordant lymphoma is defined as two distant sites involving two different lymphomas. In cases of sequential occurrence of two different lymphomas, it is known as a secondary lymphoma. Our patient was first diagnosed with CLL/SLL, and then was diagnosed with MEITL 1 month afterwards. The abdominal symptoms were presented at the first visit and the two NHLs were presented in the intestinal wall simultaneously. Therefore, the patient was diagnosed with composite lymphoma with CLL/SLL and MEITL.

In 1992, Strickler et al firstly reported 2 cases with nodal peripheral T cell lymphoma (PTCL) concurrent with CLL/SLL (5). Since then, 36 additional cases had been reported, among which 21 cases showed composite lesions involving both PTCL and CLL/SLL in the same biopsy (6). Among these 38 cases, 22 cases (57.9%) were qualified as PTCL or PTCL nos, including 12 with a cytotoxic phenotype, while 12 cases (31.6%) were ALCLs including 6 ALK-positive, 5 ALK-negative, and 1 ALK status unknown. The other 4 cases (10.5%) showed aggressive EBV-negative natural killer (NK)-cell leukemia ($n = 1$), EBV-positive nasal NK/T-cell lymphoma ($n = 1$), T-large granular lymphocyte leukemia ($n = 1$), and nodal lymphoma with a TFH cell phenotype ($n = 1$) (6). MEITL is a cytotoxic CD8⁺ T cell

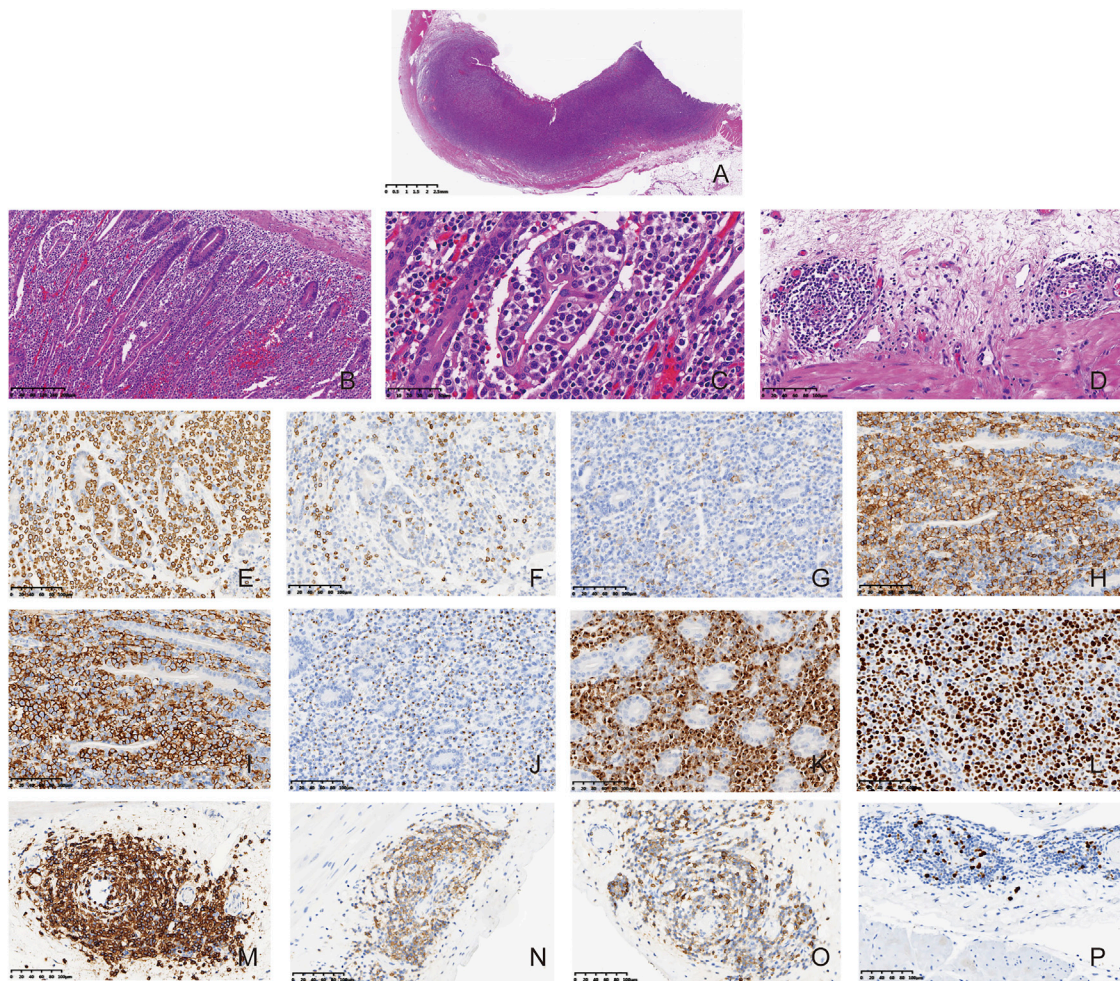


FIGURE 3

Composite CLL/SLL and MEITL. Microscopically, the intestinal wall was diffusely infiltrated by the neoplastic lymphocytes ((A), HE, 8x). The villous architecture was distorted and the neoplastic cells showed prominent epitheliotropism ((B,C), HE, 100x). The cells were generally medium in size with a generous rim of the pale cytoplasm. The nuclei were irregular, and most of them had finely dispersed chromatin and inconspicuous nucleoli. ((C), HE, 400x) CLL/SLL tumor cells were found around the blood vessels in the intestinal wall at the periphery of the tumor ((D), HE, 200x). The MEITL tumor cells in the mass were positive for CD3 ((E), Enlvision, 200x), negative for CD5 (F), Enlvision, 200x) and CD4 ((G), Enlvision, 200x), positive for CD8 ((H), Enlvision, 200x), CD56 ((I), Enlvision, 200x), TIA-1 ((J), Enlvision, 200x) and Granzyme B ((K), Enlvision, 200x). The Ki-67 index of MEITL was in a range of approximately 70%–80% ((L), Enlvision, 200x). The CLL/SLL tumor cells in the mass were positive for CD20 ((M), Enlvision, 200x), CD23 ((N), Enlvision, 200x), and CD5 ((O), Enlvision, 200x). The Ki-67 index of CLL/SLL were about 5%–10% ((P), Enlvision, 200x).

lymphoma, which accounts for the vast majority of primary intestinal T-cell lymphoma in Asia. Most MEITL cases show jejunal and ileal involvement. The neoplastic cells are featured by medium-sized round nuclei with a rim of pale cytoplasm, which usually infiltrate the intestinal epithelium. Our patient presented abdominal pain, and the medium-sized tumor cells infiltrated the intestinal wall with prominent epitheliotropism. Finally, the patient was confirmed with CLL and MEITL based on the immunophenotype analysis.

The patient was misdiagnosed as Inflammatory disease at first based on biopsy by a general pathologist. After reviewing the biopsy slides, we noticed atypical lymphoid cells in the background of necrosis and inflammatory

exudation. Some tissues were crashed and the morphology was indistinguishable. Besides, there was no epitheliotropism in the biopsy. These may lead to misdiagnosis based on the biopsy. Furthermore, attention should be given to the morphology of the tissues, in order to avoid misdiagnosis.

In our patient, *STAT5B*, *DNMT3A*, *GATA3*, *PLCG2* and *FAT1* mutations were identified in both CLL/SLL and MEITL tumor cells. Activating mutations in *STAT5B* have been identified in a high proportion of MEITL cases (7-9). In a previous study, Diamantopoulos et al showed that the expression of *STAT5B* was correlated with the presence of EBV and LMP1, which was negatively correlated with the

TABLE 1 Clinical and pathological features of CLL/SLL and MEITL in the patient.

Antibody	Clone	MEITL	CLL	Antibody	Clone	MEITL	CLL
CD20	L26	–	+	CD2	AB75	–	–
CD79a	SP18	–	+	CD3	SP7	+	–
CD10	UMAB235	–	–	CD5	SP19	–	+
Bcl-2	SP66	+	+	CD7	EP132	+	–
Bcl-6	LN22	–	–	CD4	SP35	–	–
MUM-1	EP190	–	–	CD8	SP16	+	–
CD23	SP23	–	+	CD43	DF-T1	+	+
Cyclin D1	SA38-08	–	–	CD56	MX059	+	–
TIA-1	2G9A10F5	+	–	CD30	UMAB256	–	–
GranzymeB	EP230	+	–	Ki-67	30-9	70%–80%	5%–10%

overall survival of the CLL patients (10). Somatic *DNMT3A* mutations were rarely identified in CLL and MEITL patients, however, low *DNMT3A* expression was associated with the pathogenesis of more aggressive diseases (11, 12). Trimech et al reported a small series of patients with composite lymphomas consisting of CLL/SLL and angioimmunoblastic T-cell lymphoma (AITL), in which the AITL comprised prominent clear cells with similar mutations consisting of TET2 or DNMT3A alterations (6). *DNMT3A* mutation was identified in both CLL/SLL and MEITL tissues in our case. As the expression of VAF was low, *DNMT3A* might be a manifestation of clonal hematopoiesis of indeterminate potential (CHIP) in case of the patient. In addition, *TET2* mutation was found in MEITL area rather than the CLL area, which was not frequent in

MEITL patients (12). As the expression of VAF was 8.4%, we think *TET2* mutation might be a passenger mutation or a manifestation of CHIP in these patients. Mutational analyses suggested that CLL progression on ibrutinib was closely related to the mutations of *BTK* and/or *PLCG2* genes (13). Monica et al reported that 10.3% of fludarabine refractoriness (FR)-CLL cases showed mutations of *FAT1* gene that encoded a cadherin-like protein involving in the negative regulation of Wnt signaling. On this basis, *FAT1* mutation may play important roles in the development of a high-risk phenotype (14). In our case, *PLCG2* and *FAT1* mutations were also detected in MEITL areas, and *GATA3* mutations were identified in CLL and MEITL. *GATA3*, *PLCG*, and *FAT* mutations showed similar VAFs in CLL and MEITL tissues,

TABLE 2 The results of the NGS in CLL and MEITL areas.

Lymphoma	Mutated gene	Transcript ID	Mutated site	Nucleic change	Amino acid change	dbSNP	VAF (%)
The pathogenic mutation							
CLL	STAT5B	NM_012448	Exon 16	c.1924A>C	p.N642H	rs938448224	1.1
CLL	DNMT3A	NM_022552	Exon 23	c.2678G>A	p.W893*	rs750515748	2
CLL	BCOR	NM_017745	Exon 4	c.1005dupC	p.S336Lfs*45	—	23.1
MEITL	STAT5B	NM_012448	Exon 16	c.1924A>C	p.N642H	rs938448224	20.7
MEITL	DNMT3A	NM_022552	Exon 23	c.2678G>A	p.W893*	rs750515748	1.4
The likely pathogenic mutation							
CLL	SETD2	NM_014159	Exon 5	c.4688delG	p.G1563Afs*2	—	16.9
CLL	NOTCH1	NM_017617	Exon 4	c.7541_7542del	p.P2514Rfs*4	rs763016003	18
CLL	SF3B1	NM_012433	Intron 19	c.2902-2A>T	—	—	1
CLL	PTPN11	NM_002834	Exon 13	c.1492C>T	p.R498W	rs397507541	1
MEITL	TET2	NM_001127208	Exon 9	c.4094G>T	p.G1365V	—	8.4
MEITL	ZRSR2	NM_005089	Exon 11	c.1237A>G	p.K413E	RS766869777	1.6
Variants of uncertain clinical significance							
CLL	GATA3	NM_001002295	Exon 2	c.124C>T	p.P42S	rs774975933	41.3
CLL	PLCG2	NM_002661	Exon 14	c.1311T>G	p.S437R	—	47.2
CLL	FAT1	NM_005245	Exon 10	c.7130C>T	p.T2377M	rs201363601	45.9
MEITL	GATA3	NM_001002295	Exon 2	c.124C>T	p.P42S	rs774975933	49.5
MEITL	PLCG2	NM_002661	Exon 14	c.1311T>G	p.S437R	—	55.7
MEITL	FAT1	NM_005245	Exon 10	c.7130C>T	p.T2377M	rs201363601	42

which indicated that the mutations in this patient were germline variants.

Mutations of *SETD2*, *NOTCH1*, *SF3B1*, *BCOR*, and *PTPN11* were identified in the CLL/SLL area of our patients. In a previous study, Parker et al. identified recurrent deletions of the *SETD2* locus in 3% (8/261) of CLL patients, and they detected mutations of *SETD2* in an additional 3.8% of patients (23/602) based on NGS results (15). Their data highlighted *SETD2* aberration as a recurrent, early loss-of-function event in CLL pathobiology linked to aggressive diseases (15). However, the alterations in *SETD2* gene were more frequent in MEITL as recorded in 93% of Western European cases (16), and in 70% of cases from North America (17). In contrast, Chen et al. only reported two cases with *SETD2* mutation in Chinese MEITL patients (8). In our case, *SETD2* mutation was found in the CLL/SLL area, not the MEITL area. Mutations in *NOTCH1* and *SF3B1* were associated with a poor prognosis in CLL/SLL cases (1, 18). The *SF3B1* variant showed a very low allele burden and loss of function, which was not likely to be an oncologically relevant variant in this patient. Previously, Richter's transformation had been considered to be associated with *NOTCH1* mutations (1, 19), and *BCOR* mutation was detected in 6.25% of CLL patients (20). This was the first report on *PTPN11* mutation in CLL and *ZRSR2* mutation in MEITL. However, the VAF of *PTPN11* and *ZRSR2* is very low, and further studies are required to investigate the unknown significance.

The following aspects may help to explain the pathology of composite lymphomas. Firstly, there was an underlying chronic immune dysregulation and T-cell stimulation in CLL patients. Certain factors secreted by CLL cells (e.g. inflammatory cytokines), may chronically stimulate normal lymphocytes, which then could lead to neoplastic transformation (21). In addition, studies on cellular immunity in patients with CLL/SLL reported reduced T-cell function with a paradoxical clonal expansion of CD8⁺ T cells and increased circulating CD8⁺ T-cell counts (22). This might explain the fact that the majority of T-cell lymphomas in CLL/SLL patients may have a cytotoxic phenotype, which expressed CD8 and/or cytotoxic granule proteins, in contrast to T-cell lymphomas in the general population (2, 6, 23-25). Secondly, composite lymphomas may be transformed from a stem cell with the possibility of developing into B-cell or T-cell lineages under different stimulations. Thirdly, the composited malignancies may not be directly related but may represent a shared genetic predisposition or step-by-step oncogenic potential. In cases with simultaneous diagnosis of CLL/SLL and T-cell lymphoma, it is not possible to determine which is primary. Nevertheless, in the present case, no specific treatment regimen was given to the CLL prior to diagnosis of MEITL. Additionally, both CLL and MEITL harbored *STAT5B*, *DNMT3A*, *GATA3*, *PLCG2*, and *FAT1* mutations. All these suggested that these two lymphomas may be derived from the same progenitor cells, while the different gene mutations might

indicate that the progenitor cells received different environmental stimulation.

Conclusion

In summary, we report a rare case of composite CLL/SLL and MEITL that highlights the importance of careful histopathologic inspection and immunophenotypic features of hematologic neoplasms. We also highlight the utilization of NGS in screening different gene mutations in CLL and MEITL tissues.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Qilu Hospital (Qingdao). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant for the publication of this case report.

Author contributions

BZ: Writing, original draft preparation. QL, QJ, and RL: Collected the data. YZ, WC, and HG: Analyzed the data, reviewing, and editing. All authors read the final manuscript and approved the submitted version.

Funding

This work was supported by Natural Science Foundation of Shandong Province (No. ZR2020MC068 to HJ).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

We sincerely appreciate Professor Xiaoqiu Li (Department of Pathology, Fudan University Shanghai Cancer Center) for

the help in the diagnosis of the case. We sincerely appreciate the technician Long Chen (SINO-US Diagnostics Lab, Tianjin, China) and Professor Yuan Tang (Department of Pathology, West China Hospital) for the help in the interpretation of the NGS results.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.por-journal.com/articles/10.3389/pore.2022.1610653/full#supplementary-material>