

Synchronous mantle cell lymphoma bone marrow involvement complicated with extensive-stage small cell lung cancer: A case report and literature review

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Abstract. Mantle cell lymphoma (MCL) is a B-cell non-Hodgkin lymphoma with an advanced stage; it occurs frequently and affects the lymph nodes, spleen, blood and bone marrow. The synchronous occurrence of MCL bone marrow involvement (MCLBMI) and malignant tumors is extremely rare. To the best of our knowledge, synchronous extensive-stage small cell lung cancer (ES-SCLC) and MCLBMI have not been previously reported. In the present study, a rare case of ES-SCLC with synchronous MCLBMI is reported in a 59-year-old man. The patient received cisplatin, etoposide, dexamethasone and rituximab chemotherapy for the treatment of both malignancies. The follow-up computed tomography scan disclosed regression of the left upper lobe mass and the routine blood test indicated that the platelet count was gradually increasing to normal levels. Following therapy, the patient achieved a partial response. The experience in this case report indicated that the treatment of synchronous SCLC and MCLBMI requires consideration of the respective patient clinical features, biological behavior and cumulative toxicity of the treatment regimens administered for both malignant tumors. The present study demonstrated that thrombocytopenia was not a chemotherapy contraindication, thus providing a new treatment option for this type of patient.

Introduction

Multiple primary malignant neoplasms (MPMNs) are multiple tumors with different pathogenetic origins that manifest in one or more organs and tissues of the same patient; they may be synchronous or metachronous (1). The synchronous occurrence of MPMNs is very rare. It is usually difficult to assess the staging of each neoplasm, and to determine the optimal

treatment according to the individual tumor risk (2). Mantle cell lymphoma (MCL) is an aggressive B-cell non-Hodgkin's lymphoma (NHL) with a characteristic chromosomal translocation, t(11;14)(q13;q32), that can lead to cyclin D1 over-expression (3). Small cell lung cancer (SCLC) is an aggressive cancer type of neuroendocrine origin with a poor prognosis, which is strongly associated with cigarette smoking (4). Synchronous MCL bone marrow involvement (MCLBMI) complicated with extensive-stage SCLC (ES-SCLC) is extremely rare. The diagnosis of this condition and its treatment requires a multidisciplinary medical team to ensure an optimal clinical outcome. In the current study, a case report of a male patient affected by primary synchronous tumors, including MCLBMI and ES-SCLC, is presented. The reported information aims to improve the awareness for the diagnosis of MCLBMI complicated with ES-SCLC and provide a reference for appropriate diagnosis and treatment.

Case report

Patient. A 59-year-old man was admitted to the Department of Spinal Surgery of the College of Medicine, Lishui Hospital, Zhejiang University (Lishui, China) in September 2020 due to lumbar disc herniation. The patient had not presented with serious illnesses in the past and was a heavy smoker. A physical examination indicated an axillar lymph node (diameter, 2 cm), which was hard and fixed. The blood cell count indicated thrombocytopenia (platelet count, $52 \times 10^9/L$; reference range, $125-350 \times 10^9/L$). The whole-body positron emission tomography (PET)/computed tomography (CT) scan, which was performed on 7 days post-presentation, indicated radiotracer uptake in the lymph nodes and systemic lymphadenopathy, including the presence of cervical, submandibular, axillar, paraaortic, intrapelvic and inguinal lymph nodes. Splenomegaly was also noted in the patient (Fig. 1). A lymph node biopsy was recommended; however, this was refused by the patient. In March 2021, the patient visited the hospital again due to the enlargement of the right axillary lymph nodes. A right axillary lymph node biopsy was performed, which revealed lymphoproliferative lesions, and lymphoma was suspected. A bone marrow biopsy revealed a low number of atypical lymphoid cells in small clusters, with scattered infiltration in the bone marrow hematopoietic tissue. Therefore, chronic lymphocytic leukemia or lymphoma was suspected. The patient refused to

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Key words: mantle cell lymphoma, bone marrow involvement, small cell lung cancer, synchronous, treatment

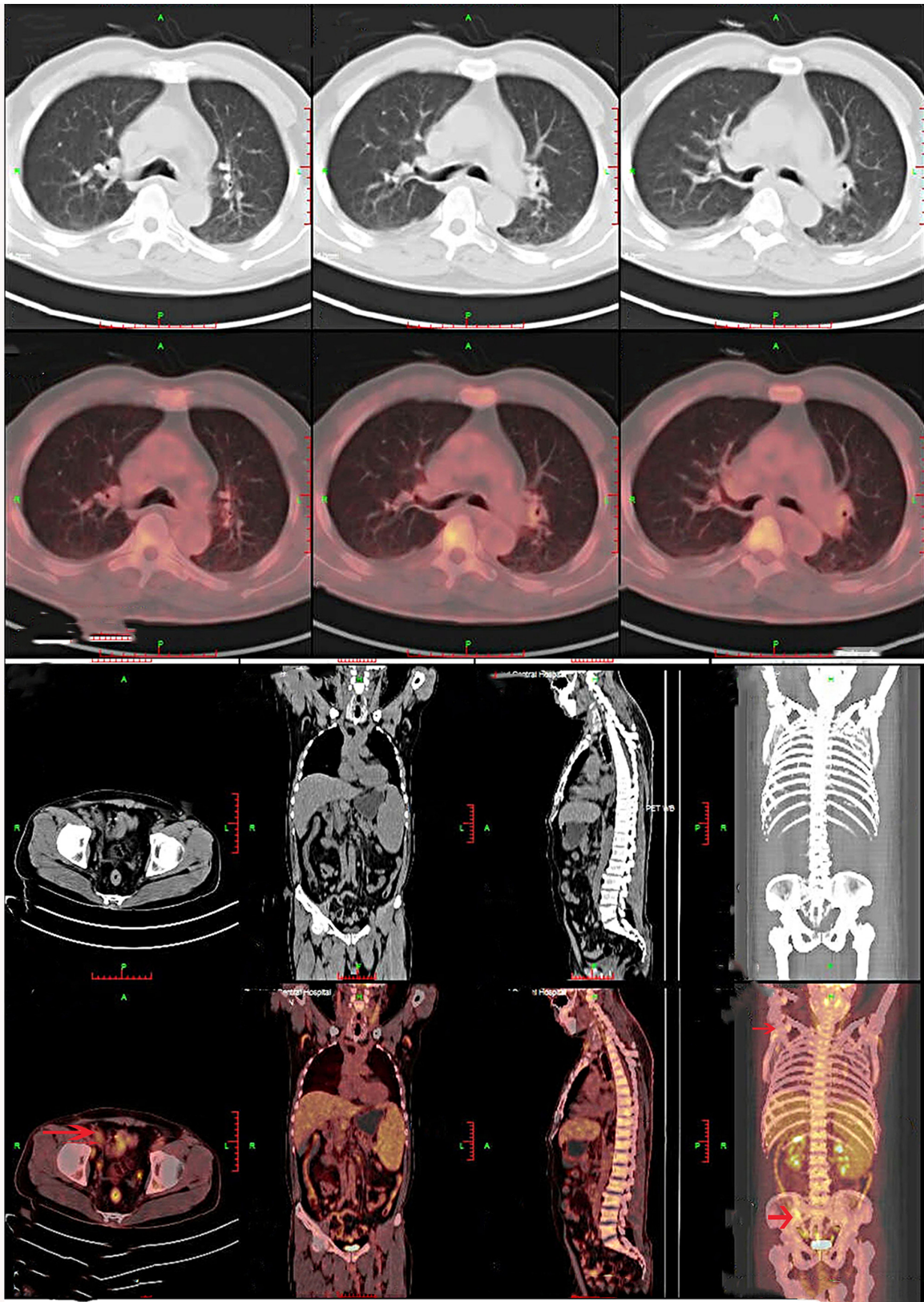


Figure 1. Whole body positron emission tomography-computed tomography scan performed at 7 days post-presentation. PET-CT revealed radiotracer uptake in the lymph nodes and systemic lymphadenopathy, including the presence of cervical, submandibular, axillar, paraaortic, intrapelvic and inguinal lymph nodes.

undergo a further immunohistochemical examination of the bone marrow and a lymph node biopsy for personal reasons. In July 2021, the patient visited a local hospital due to chest pain. Chest CT revealed a solid lesion in the left upper lobe of

the lung (~3 cm in diameter). Subsequently, the patient visited another hospital (Shanghai Zhongshan Hospital; Shanghai, China) and underwent a whole-body PET/CT scan. The scan revealed several soft-tissue masses in the left lung near

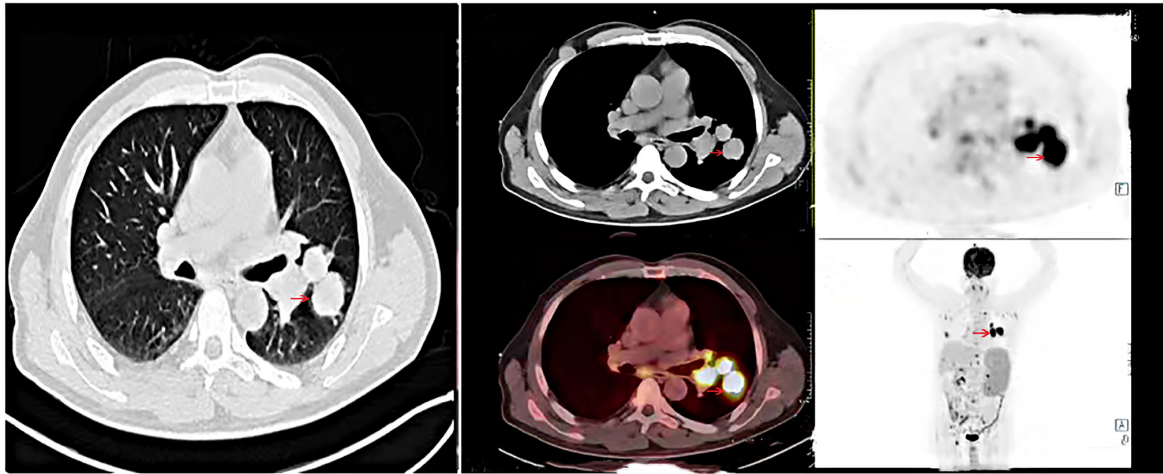


Figure 2. Whole body positron emission tomography-computed tomography scan performed in July 2021. PET-CT revealed several soft-tissue masses in the left lung near the hilum and posterior segment of the left upper lobe, with maximum dimensions of 3.6x2.6 cm.

the hilum and posterior segment of the left upper lobe, with maximum dimensions of 3.6x2.6 cm [maximum standardized uptake value (SUVmax), 10.9]. Based on this evidence, a malignant tumor was suspected. Systemic enlarged lymph nodes (~1.2 cm in diameter; SUVmax, 3.0), splenomegaly (SUVmax, 3.6) and bone metastases were also observed (Fig. 2). The patient was referred to the Department of Thoracic Surgery of The Second Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, China). A CT-guided biopsy of the left lobe mass was performed and histological analysis revealed diffuse sheets of small, round, fusiform cells, with scant cytoplasm, and inconspicuous or absent nucleoli with finely granular nuclear chromatin. The patient was therefore diagnosed with SCLC (Fig. 3A). The immunohistochemical stains were positive for thyroid transcription factor-1 (Fig. 3B), synaptophysin (Fig. 3C), glycoprotein hormones α -polypeptide (CgA) (Fig. 3D) and cluster of differentiation (CD)56 (Fig. 3E), the proliferation fraction (Ki-67) (Fig. 3F) was ~50%, and the staining was also positive for neuron-specific enolase (Fig. 3G), whereas staining was negative for cytokeratin 7 (Fig. 3H). The patient did not receive chemotherapy due to thrombocytopenia. In August 2021, the patient visited the College of Medicine, Lishui Hospital, Zhejiang University (Lishui, China) again due to thrombocytopenia and was admitted to the Department of Hematology.

The patient underwent laboratory tests, including a complete blood count, an assessment of tumor markers and an evaluation of lactate dehydrogenase activity (Table I). Monoclonal immunoglobulin gene rearrangements were detected. The bone marrow smear indicated an increased proportion of mature small lymphocytes, accounting for 28% of the total lymphocyte count, with occasional lymphoid cells. Bone marrow immunophenotyping indicated that the small B lymphocytes accounted for 19.83% of nuclear cells (60.91% of lymphocytes), which mainly expressed CD19, human leukocyte antigen DR isotype, immunoglobulin (Ig) M, CD79b and CD20, and weakly expressed CD5 (Fig. 4). The nuclear cells did not express CD10, CD23, FMC7 or CD200, and CD19/CD20 double-positive cells were negative for the κ -light chain and positive for the λ -light chain (Fig. 4).

Ig variable heavy chain somatic hypermutation testing was not performed. The detection of exons 2-11 of the TP53 gene was negative.

Histopathological examination of the right axillary lymph node revealed the presence of mature small lymphocytes (Fig. 5A), which were positive for CD20 (Fig. 5B), cyclin D1 (Fig. 5C), SRY-box transcription factor 11 (Fig. 5D), Bcl-2 (Fig. 5E), paired box 5 (Fig. 5F) and Oct2 (Fig. 5G), the Ki-67 index was low (10-30%) (Fig. 5H), and negative for CD3 (Fig. 5I), CD5 (Fig. 5J), Bcl6 (Fig. 5K), CD10 (Fig. 5L), CD21 (Fig. 5M), CD23 (Fig. 5N), CD30 (Fig. 5O), CD15 (Fig. 5P), CD43 (Fig. 5Q), multiple myeloma oncogene 1 (Fig. 5R), CD163 (Fig. 5S), epithelial membrane antigen (Fig. 5T), cytokeratin AE1/AE3 (Fig. 5U) and Epstein-Barr virus non-coding RNA (Fig. 5V), as determined by immunohistochemical analysis. A bone marrow biopsy was performed and the data indicated the presence of MCL characterized by the infiltration of intermediate sized B-cells into the mantle zones (Fig. 6A). Immunohistochemical staining was positive for CD20 (Fig. 6B), PAX5 and cyclin D1 (Fig. 6C), whereas it was negative for CD3, CD5 and CD23. The patient was diagnosed with stage IV MCL (symptom status A) according to the Lugano 2014 Classification (5). A brain magnetic resonance imaging scan demonstrated the absence of abnormal lesions. The patient was finally diagnosed with MCLBMI complicated with ES-SCLC. A total of six cycles (3 weeks per cycle) of chemotherapy were administered, consisting of rituximab (600 mg on day 0), cisplatin (30 mg on days 1-3), etoposide (100 mg on days 1-3) and dexamethasone (10 mg on days 1-5) (R-DEP) for both primary tumors at the College of Medicine, Lishui Hospital, Zhejiang University (Lishui, China). In August 2021, chest CT indicated a left lung mass with maximum dimensions of 5.5x2.3 cm. Following the six aforementioned treatment cycles, CT indicated that the left pulmonary masses were reduced to maximum dimensions of 1.2x1.1 cm (Fig. 7A), and routine blood tests indicated that the blood platelet count was gradually increasing (Fig. 7B). Whole body PET-CT scans in December 2021 indicated that, following therapy, fluorodeoxyglucose (FDG) uptake was slightly increased in the slightly larger lymph node noted under

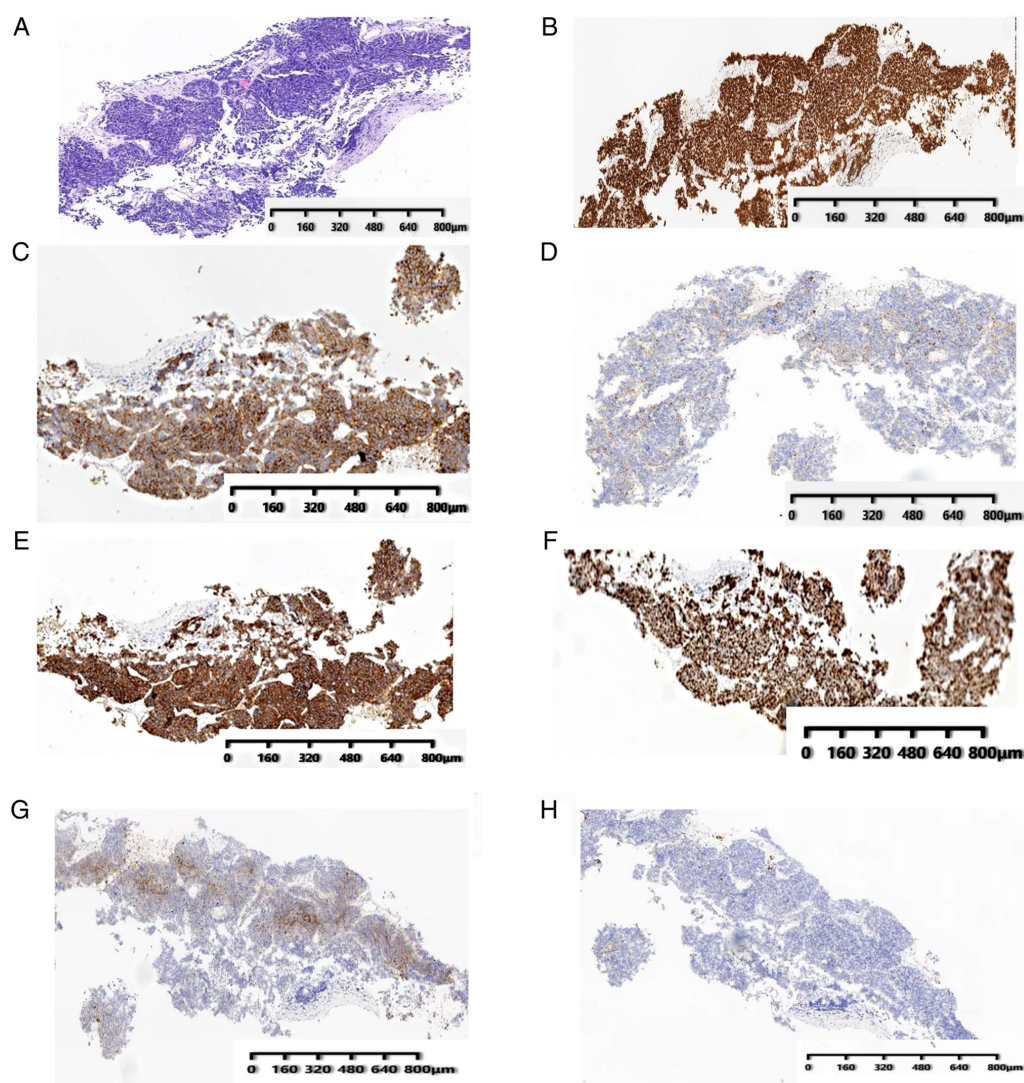


Figure 3. Computed tomography-guided biopsy of the left lobe mass assessed by histological and immunohistological analysis. (A) Hematoxylin and eosin staining patterns. (B) thyroid transcription factor-1 staining (positive). (C) Synaptophysin staining (positive). (D) Glycoprotein hormones α -polypeptide staining (negative). (E) Cluster of differentiation 56 staining (positive). (F) Ki-67 index, 50%. (G) Neuron-specific enolase (positive). (H) cytokeratin 7 (negative) (scale bars, 800 μ m).

the right armpit. This suggested that the lesion was still active, although the remaining systemic lymph nodes and spleen lesions were reduced in size and inactivated. FDG uptake was slightly increased locally in the left upper lobe mass, and multiple bone metastases were noted throughout the body (Fig. 7C). The patient experienced a stable disease status in the 9-month follow-up period. Follow-up was conducted once per month. The patient will be followed up every 3 months for 2 years. This case achieved a partial response according to the International Working Group response criteria (Cheson classification) (6). The patient has a poor prognosis due to ES-SCLC with synchronous MCLBML.

Imaging examinations. PET/CT imaging (Biograph mCT; Siemens AG) was performed 60 min after intravenous injection of ^{18}F -FDG imaging agent (Shanghai Atomic Kexing Pharmaceutical Co., Ltd.). Before the examination, the patient fasted for >4 h, and the fasting blood glucose level was controlled to within 10.0 mmol/l (reference range, 3.90-6.10 mmol/l). ^{18}F -FDG was injected through the

Table I. Laboratory tests, including reference ranges.

| Factor assessed | Test results (reference range) |
|--|-----------------------------------|
| White blood cell count, $\times 10^9/\text{l}$ | 5.6 (3.5-9.5) |
| Hemoglobin level, g/l | 118 (115-150) |
| Platelet count, $\times 10^9/\text{l}$ | 51 (125-350) |
| Serum tumor markers | |
| CEA, ng/ml | 23.5 (<5.0) |
| CA19-9, U/ml | 357 (<43) |
| CA72-4, U/ml | 32.6 (<6.9) |
| NSE, ng/ml | 157.9 (<16.3) |
| ProGRP, pg/ml | >5,000 (<63) |
| Lactate dehydrogenase level, U/l | 222 (109-245) |
| Cytogenetic abnormalities | None |

CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen; NSE, neuron-specific enolase; ProGRP, progastrin-releasing peptide.

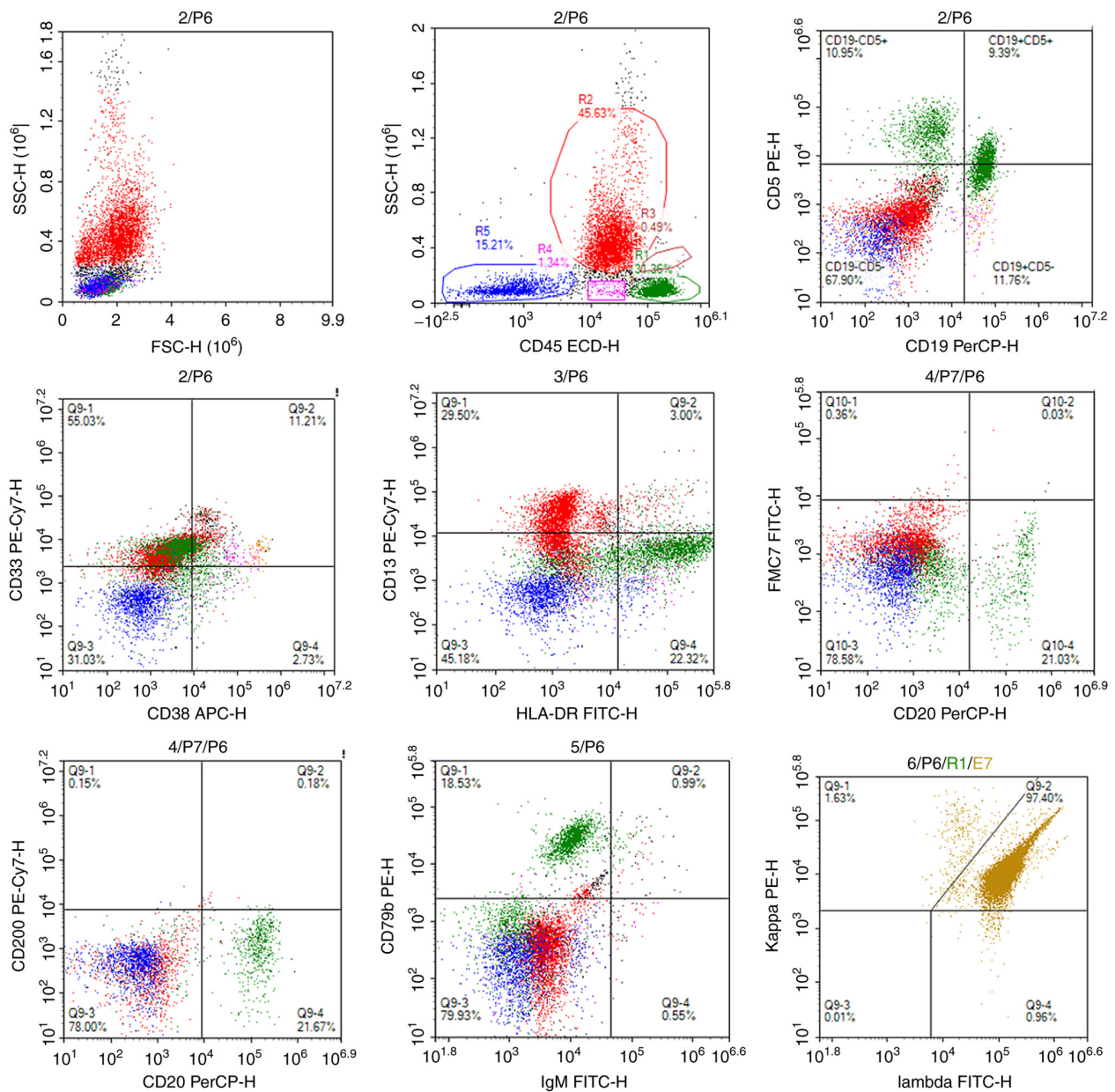


Figure 4. Bone marrow flow cytometry immunophenotyping performed in August 2021. CD, cluster of differentiation.

superficial forearm vein. The scanning range was from the base of the skull to the middle of the femur. The current was 120 mA, the voltage was 120 kV and the scanning time was 21-30 sec. The thickness of the scanning slice was 5 mm. Body PET collection was performed afterward, generally using 6 to 7 beds, with 2.0 to 3.0 min/bed. The head scanning method was performed with the same values as the whole-body PET/CT, and 1 bed was collected. CT data was automatically used by the CT machine to perform attenuation correction on the PET images for image reconstruction and fusion.

Flow cytometry (FCM) immunophenotyping. The FCM immunophenotyping analysis was performed in the Hangzhou Adicon Clinical laboratory (Hangzhou, China). Bone marrow aspiration specimens were collected. Next, the sample was incubated at 4°C for 5 min in the dark. Samples (1.5 ml) were added into a conical centrifuge tube

with 10 ml erythrocyte-lysing solution (cat. no. 348202; BD Biosciences). The cells were preserved after lysis procession. The cells were counted after filtration in PBS with 0.1% BSA (cat. no. PM22316; Perfemiker) with a 200-mesh nylon membrane filter (cat. no. QN3029; Beijing Biolab Technology Co., Ltd.). Cell suspension (100 μ l; adjusted to a concentration of 5×10^6 /ml) was added to each tube, and then the antibodies were added for incubation at 4°C for 30 min. Finally, the cells were preserved with incubation in the dark at 4°C to acquire data after cell washing. The antibodies used were as follows: Anti-CD5 (PE; 1:2; cat. no. 347307; BD Biosciences), anti-CD19 (PC5; 1:2; cat. no. A07771; Beckman Coulter, Inc.), anti-HLA-DR (FITC; 1:4; cat. no. 347363; BD Biosciences), anti-IgM (APC; 1:2; cat. no. 750365; BD Biosciences), anti-CD79b (PE; 1:4; cat. no. 557931; BD Biosciences), anti-CD20 (PC5; 1:2; cat. no. IM2644U; Beckman Coulter, Inc.), anti-CD10 (FITC; 1:4; cat. no. 347503; BD Biosciences),

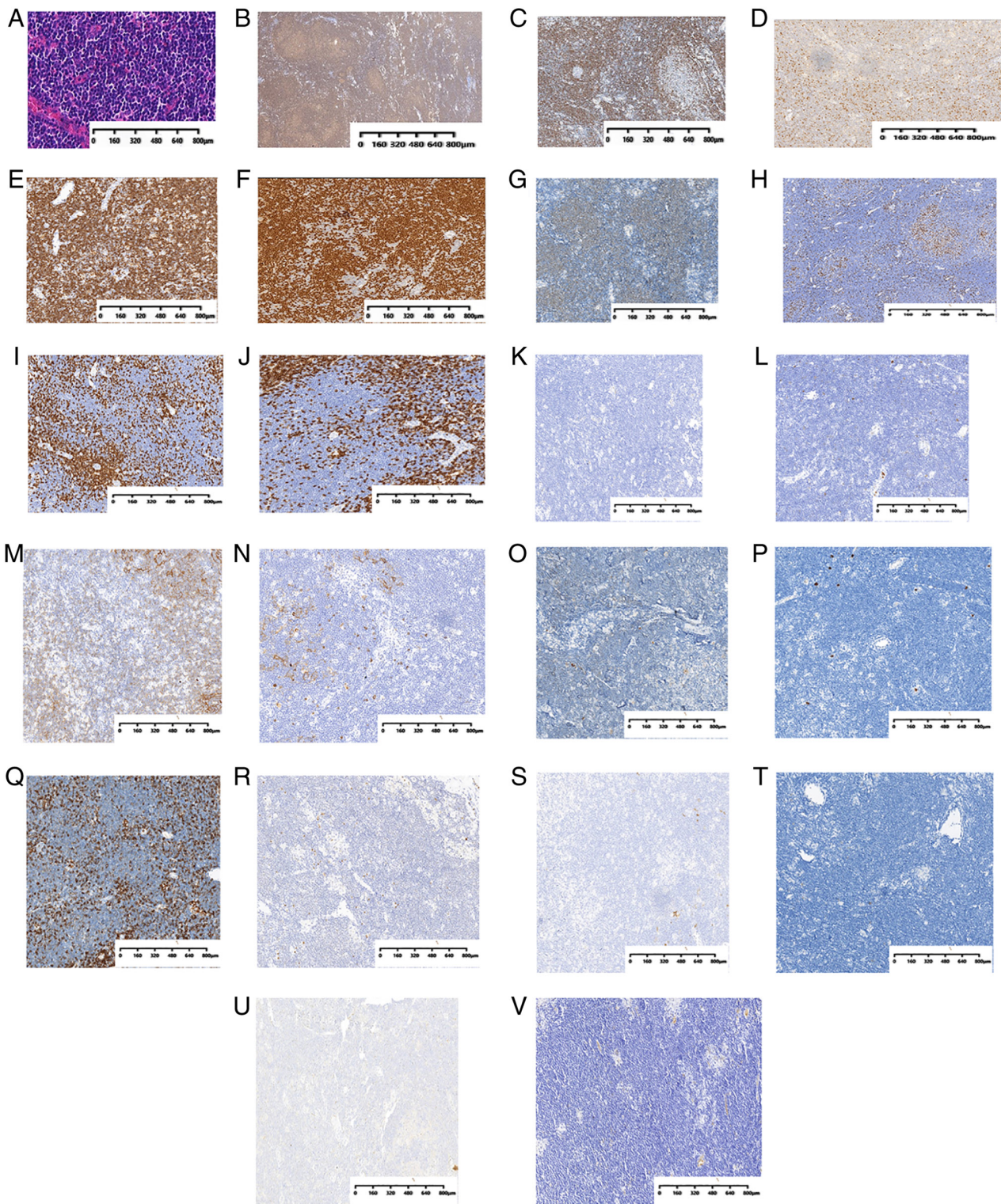


Figure 5. Histopathological examination of the right axillary lymph node biopsy. (A) Hematoxylin and eosin staining patterns. (B) Cluster of differentiation 20 staining (positive). (C) Cyclin D1 staining (positive). (D) SRY-box transcription factor 11 (positive). (E) Bcl-2 (positive). (F) Paired box 5 (positive). (G) Oct2 (positive). (H) Ki-67 index, 10-30%. (I) CD3 (negative). (J) CD5 (negative). (K) Bcl6 (negative). (L) CD10 (negative). (M) CD21 (negative). (N) CD23 (negative). (O) CD30 (negative). (P) CD15 (negative). (Q) CD43 (negative). (R) Multiple myeloma oncogene 1 (negative). (S) CD163 (negative). (T) Epithelial membrane antigen (negative). (U) Cytokeratin AE1/AE3 (negative). (V) Epstein-Barr virus non-coding RNA (negative). Scale bars, 800 μ m.

anti-CD23 (PE; 1:4; cat. no. 341007; BD Biosciences), anti-CD200 (PE-CY7; 1:2; 655735; BD Biosciences), anti-FMC7 (FITC; 1:4; cat. no. 340919; BD Biosciences), anti- κ (FITC; 1:4; cat. no. C15623; Beckman Coulter, Inc.) and anti- λ (PE; 1:4; cat. no. C15189; Beckman Coulter, Inc.). All

of the fluorochromes and antibodies were acquired from BD Biosciences or Beckman Coulter, Inc. FCM was performed using a NovoCyte D3000 (ACEA Bioscience, Inc.) and data were analyzed with NovoExpress™ software (V1.2.5; ACEA Bioscience, Inc.).

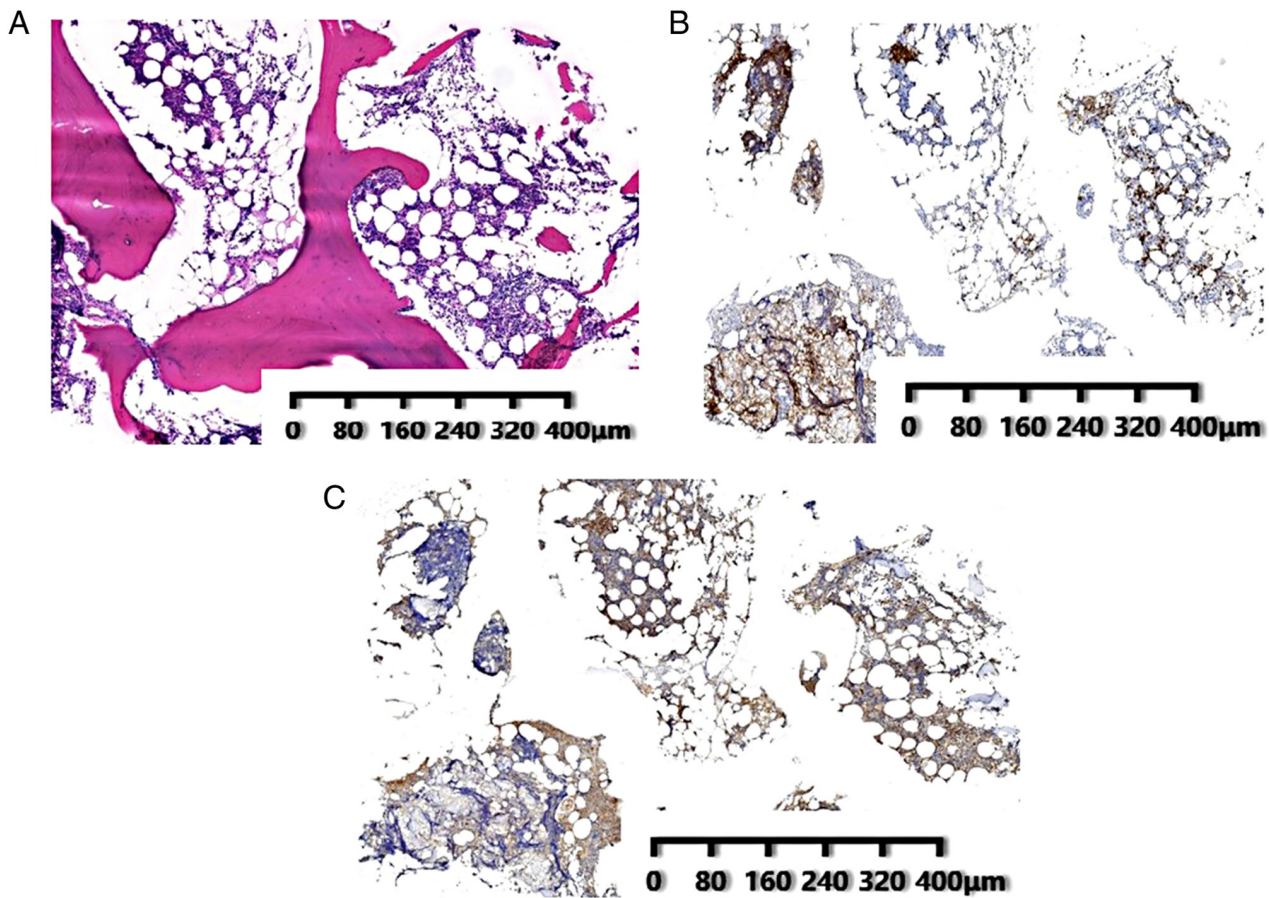


Figure 6. Bone marrow biopsy specimens of the right posterior superior iliac spine. (A) Hematoxylin and eosin staining patterns. (B) Cluster of differentiation 20 staining (positive). (C) Cyclin D1 staining (positive) (scale bars, 400 μ m).

Biochemical examinations. The complete blood count was analyzed by a Coulter LH750 Automatic Blood Cell Analyzer (Beckman Coulter, Inc.). The biochemical tests, including those for lactate dehydrogenase and tumor markers, were performed on a HITA CHI 7600 Automatic Biochemical Analyzer (Hitachi, Ltd.) and a Tellgen Super Multiplex Immunoassay System TESMI-F4000 (Tellgen Corporation), respectively. All of the examinations were conducted and analyzed by the Clinical Laboratory of Lishui Hospital, Zhejiang University.

Histopathological staining. The tissue was fixed with 4% neutral formalin at room temperature for 12 h and embedded in paraffin after dehydration, before 4- μ m thick serial sections were prepared for hematoxylin and eosin staining at room temperature for 90 min. The pathological tissue slice was observed under an optical microscope (Olympus BX45; Olympus Corporation).

Immunohistochemistry (IHC). The formalin-fixed (4%) tissue specimens were used for further pathological and immunohistochemical examinations by the Department of Pathology of Lishui Hospital, Zhejiang University. Immunohistochemical staining was performed with antibodies from EnVision Systems (Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd. and Hangzhou HealthSky Biotechnology Co., Ltd.). The paraffin sections were deparaffinized in three changes of xylene, 5 min each at 60°C, rehydrated with 100% ethanol (two changes; 5 min each) and 95% ethanol (three changes; 2 min

each), and then immersed in distilled water. Afterwards, the paraffin sections were rinsed (3 time for 5 min each) in PBS-T (0.01 M PBS pH 7.4; 0.02% KH_2PO_4 , 0.29% N_2HPO_4 , 0.02% KCl, 0.8% NaCl, 0.05% BSA, 0.05% Tween-20 and 0.0015% TritonX-100), and then blocked with 3% peroxide-methanol at room temperature for 10 min for endogenous peroxidase ablation. The duration and temperature of incubation with primary antibodies were overnight at 4°C and those of secondary antibodies were 30 min at 37°C. The paraffin sections were coloured with 3,3-diaminobenzidin, and kept at room temperature without light for 10 min. Finally the sections were stained with hematoxylin at room temperature for 90 min, dehydrated, cleared and mounted with neutral gum, and then images were captured under a light microscope (Olympus BX45; Olympus Corporation). The negative control group was assessed using the same steps as the positive control, where the negative control sample used PBS instead of primary antibody. The antibodies were as follows: CD20 (1:100; cat. no. ZM-0039), cyclin D1 (1:200; cat. no. ZA-0101), SRY-Box transcription factor 11 (1:200; cat. no. ZM-0366), Bcl-2 (1:100; cat. no. ZA-0536), paired box 5 (1:100; cat. no. ZA-0566), Oct2 (1:100; cat. no. ZA-0560), CD3 (1:100; cat. no. ZA-0503), CD5 (1:100; cat. no. ZA-0510), Bcl-6 (1:100; cat. no. ZA-0691), CD10 (1:100; cat. no. ZM-0283), CD21 (1:100; cat. no. ZM-0525), CD23 (1:100; cat. no. ZA-0516), CD30 (1:100; cat. no. ZA-0591), CD15 (1:100; cat. no. ZM0037), CD43 (1:100; cat. no. ZM-0048), multiple myeloma oncogene

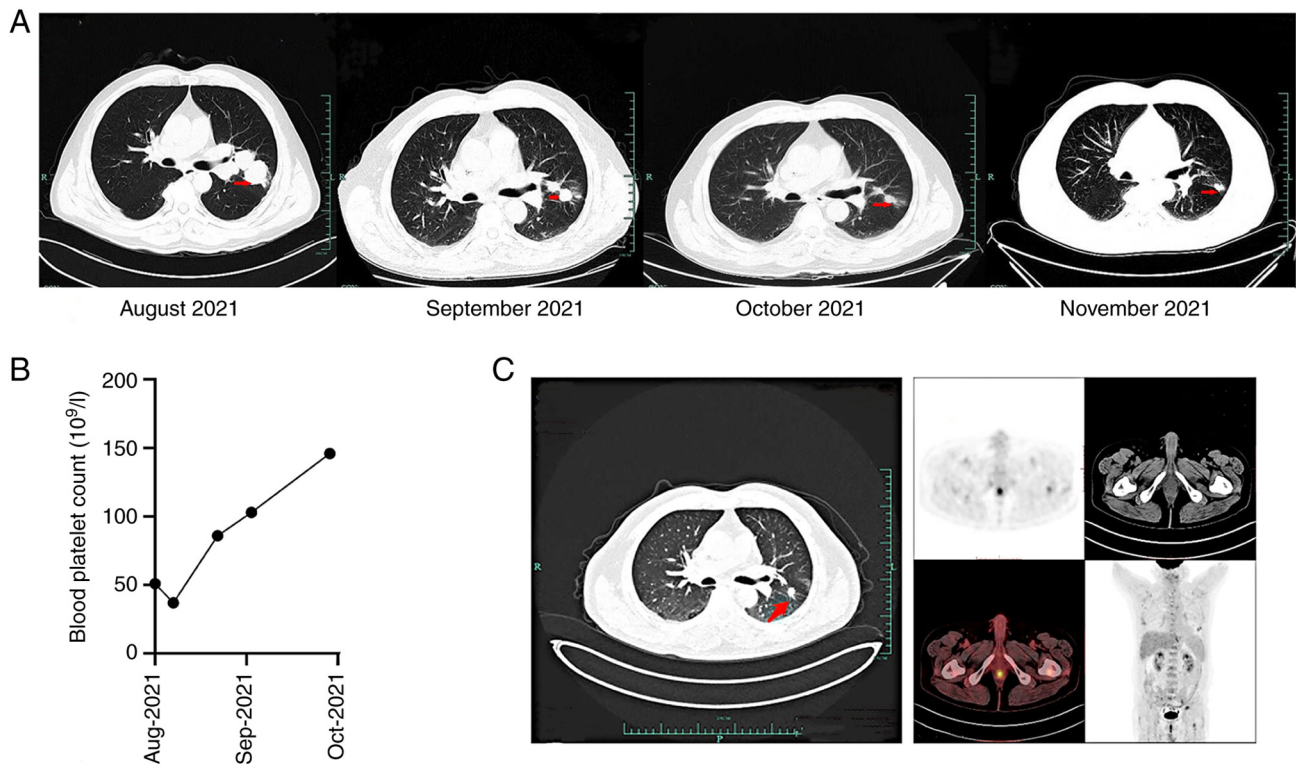


Figure 7. Serial CT images and blood platelet count changes during the treatment. (A) Serial CT images indicating changes in the left upper lobe mass of the lung during the treatment course. (B) The changes in the blood platelet count following therapy. (C) Whole body positron emission tomography-CT scan performed. CT, computed tomography.

1 (1:100; cat. no. ZA-0583), CD163 (1:100; cat. no. ZM-0428), epithelial membrane antigen (1:100; cat. no. ZM-0095), cytokeratin AE1/AE3 (1:100; cat. no. ZM-0069) and Epstein-Barr virus non-coding RNA (1:100; cat. no. ZM-0105) (all Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd.), and thyroid transcription factor-1 (1:100; cat. no. BFM-0379), CD56 (1:200; cat. no. BFM-0232), CgA (1:100; cat. no. BFM-0102), Syn (1:100; cat. no. BFM-0147), neuron-specific enolase (1:100; cat. no. BFM-0120), CK7 (1:100; cat. no. BFM-0373) and Ki-67 (1:100; cat. no. BFM-0310) (all Hangzhou HealthSky Biotechnology Co., Ltd.). The secondary antibody was from the Histostain-SP Kit (1:200; cat. no. SPN-9001; Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd.).

Literature review

Search strategy. A comprehensive literature search was performed using the PubMed (<https://pubmed.ncbi.nlm.nih.gov>), Web of Science (<http://webofscience.com>) and Cochrane Library (<https://www.cochranelibrary.com/>) databases between January 2000 and May 2022, with the following terms: 'Mantle cell lymphoma and lung cancer' OR 'MCL and lung carcinoma' OR 'synchronous and lymphoma' OR 'lymphoma and small cell lung cancer' OR 'multiple primary malignant neoplasms and lymphoma'.

Study identification. Studies were included if they met the following criteria: i) Referring to lymphoma and lung cancer; ii) concerning patients with a diagnosis of histologically confirmed lymphoma and lung cancer; iii) containing relevant

information on clinical course, treatments and outcomes; iv) written in English; and v) containing one or multiple clinical case reports or letters. Other recognized solid malignant tumors and haematological malignancies were excluded. Reviewers resolved all discrepancies by discussion during the study identification process.

Discussion

MPMNs are defined as two or more primary malignant tumors in the same patient at the same time or during different time periods, which can occur in the same organ or other organs. Multiple primary cancers occur at the same time and are synchronized tumors (diagnosed within a 6-month period), while those occurring at different time periods are called metachronous (diagnosed at >6-month intervals) (7,8). MCL is a rare and distinct type of B-cell NHL, which presents at an advanced stage and frequently involves multiple extranodal sites, such as the bone marrow, spleen and peripheral blood (9). SCLC is a high-grade malignancy with the worst prognosis of all the pulmonary epithelial tumors. A large quantity of epidemiological data has reported the risk factors of the occurrence of two primary malignant tumors, including cancer treatment strategies, common pathogenic factors of two types of cancer (such as smoking and viral infection), and genetic susceptibility (single nucleotide polymorphisms) (10,11). A variety of second primary cancers may develop in patients with lymphoma. Chien *et al* (12) demonstrated that the probability of developing a second malignant tumor in patients with NHL was 1.5-fold higher than that noted in the general population; the second

Table II. Key characteristics of patients with synchronous MCL and lung carcinoma.

| First author, year | Age, years | Sex | Symptoms | Smoking status | Carcinoma site/type | Lymphoma site/type | Treatment regimen | Follow-up time, months, and status (Refs.) |
|----------------------------------|------------|-----|--|-------------------|----------------------------|---------------------------|---|--|
| Kampalath <i>et al</i> , 2004 | 58 | F | Cervical lymphadenopathy | Moderate to heavy | LUL/SCC | Right neck lymph node/MCL | 6 cycles of cisplatin and etoposide, and weekly cycles of rituximab for 8 weeks | 36, relapsed (18) |
| Aqeel <i>et al</i> , 2018 | 55 | F | Severe lower flank pain radiating to the lower abdomen and chest | 30 pack/year | RUL/lepidic-predominant AC | RUL/MCL | 6 cycles of chemotherapy (meprednisone, gencitabine and cisplatin) | 12, survived (32) |
| Hatzibougias <i>et al</i> , 2008 | 73 | M | Dyspnea and fever | Heavy | RUL/papillary AC | RUL pleura/MCL | 6 cycles of chemotherapy (Endoxan, Farnorubicin and vincristine) | 14, survived (33) |
| Kai <i>et al</i> , 2018 | 71 | F | Abdominal distension | Not available | PE/AC | PE and BM/MCL | DVCP and then rituximab and bendamustine | 3, died (34) |
| Samuel <i>et al</i> , 2018 | 61 | M | Not available | Former smoker | RUL and LRPLN/AC | LRPLN/MCL | NA | NA (35) |
| Braham <i>et al</i> , 2017 | 45 | M | Inguinal mass | Heavy | RUL/AC | Inguinal/MCL | 6 cycles of alternating RCHOP and RDHAP regimens followed by ASCT | 36, died (36) |

AC, adenocarcinoma; ASCT, autologous stem cell transplant; BM, bone marrow; CHOP, cyclophosphamide, Adriamycin, vincristine and prednisone; DVCP, cyclophosphamide, doxorubicin, vincristine and prednisone; MCL, mantle cell lymphoma; LRPLN, lower right paratracheal lymph node; LUL, left upper lobe; RUL, right upper lobe; SCC, squamous cell carcinoma; F, female; M, male; PE, pleural effusion; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; RDHAP, dexamethasone, high-dose Ara C and cisplatin.

primary malignant tumor included leukemia, multiple myeloma, bone or soft tissue tumors, and lung cancer. The literature of MPMNs with regard to lymphoma and lung cancer includes mainly case reports (13-15). Previous studies have shown that lung cancer is the most common second primary malignant tumor in patients with lymphoma. Lorenzo Bermejo *et al* (16) retrospectively analyzed the medical records of 60,901 patients with NHL and demonstrated that 6,815 developed a second primary malignant tumor, of which lung cancer was one of the most common tumor types. An additional meta-analysis of 74,831 patients with Hodgkin lymphoma indicated that 793 patients developed a second primary lung cancer; the relative risk of lung cancer was higher with time. The peak incidence of lung cancer was noted in 10-14 years of follow-up (17).

With regard to the differential diagnosis, lymphoma and other primary malignant tumors can occur at the same site or at different sites, which makes the diagnosis of the disease more complicated (2,18). It is difficult to distinguish synchronous primary malignant tumors from metastatic malignant tumors (2). MCLBMI can be misdiagnosed as SCLC involvement, since BM involvement has been frequently reported in SCLC (19-21). BM immunophenotyping and histopathological analysis can be used for the differential diagnosis. Synchronous primary cancers can be diagnosed if pathological examinations of the tumors in different body regions favor the characteristics of independent primary cancers (7). In the present case, the diagnosis was straightforward, since the histological tumor types between the MCL and SCLC were distinct. However, the reports on MCL complicated with primary SCLC are very rare. Kampalath *et al* (18) reported a rare case of SCLC with synchronous MCL in a 58-year-old female. The patient was treated with rituximab, cisplatin and etoposide, complete remission was maintained for ~2.5 years, while partial remission was achieved in the present case treated with rituximab, cisplatin, etoposide and dexamethasone. In case a single tumor is not fully characterized by its clinical manifestations, attention should be paid to the possibility of multiple tumors occurring at the same time. In the present case report, the patient exhibited symptoms of chest pain and had a long history of heavy smoking. The CT scan indicated a soft-tissue mass in the chest, which was localized in the upper lobe of the left lung, with a maximum diameter of 2 cm. In order to identify whether it was primary lung cancer, the patient underwent a lung biopsy and immunohistochemical analysis to confirm the diagnosis. The histological diagnosis of the soft-tissue lesion was SCLC.

Although the association between solid tumors and NHL is currently inconclusive, a correlation may exist between the two tumor types. In the 2005 multicenter clinical study (13 centers, with 109,000 cases of NHL) by Brennan *et al* (22), the incidence of NHL secondary to other primary malignancies was considerably higher than that of the normal population. However, the association between the NHL subtypes and the pathological types of primary lung malignancies is not clear when reviewing the existing literature reports; diffuse large B-cell lymphoma combined with lung squamous cell carcinoma is reported more frequently, followed by SCLC, adenocarcinoma and large cell lung cancer (2,23-25).

Little is known regarding the risk factors of the simultaneous occurrence of lymphoma combined with other primary malignant tumors. The current clinical observational studies

have shown that it may be associated with smoking, age, the chemotherapy used for the lymphoma and autologous stem cell transplantation (22,26,27). The current patient was >45 years old, a smoker and had a high risk for developing lung cancer. The occurrence of primary lung cancer may be related to smoking; however, it is not clear whether other risk factors are involved. The occurrence of multiple primary tumors may be associated with the following factors: Ethnicity, environmental exposure (nuclear radiation), medical factors (chemotherapy and radiotherapy) and genetic mutations (28,29). The currently known single gene mutations in patients with multiple primary tumors are as follows: PTEN, BRCA1/BRCA2, TP53, retinoblastoma 1 and nth-like DNA glycosylase 1 (29,30). In patients with multiple primary tumors with lung adenocarcinoma, the EGFR mutation rate, especially that of exon 19 deletions, was higher than that in patients without multiple primary tumors (31).

The evidence found in the literature regarding concurrent SCLC and MCL is scarce. Therefore, no standard guideline is available for the treatment and prognosis of this disease. Upon routine examination, the current patient presented with thrombocytopenia (platelet count, $52 \times 10^9/l$) and systemic lymphadenopathy in September 2020; however, the patient did not initially realize the severity of the condition. The patient was finally diagnosed with synchronous MCLBMI and ES-SCLC. In the current case report, the treatment required consideration of the respective clinical features and a treatment plan that would cover both malignancies. Therefore, a multidisciplinary team meeting was organized to discuss the optimal strategy. The combination of cisplatin and etoposide was used as a standard therapy for the treatment of SCLC. It is also the standard second-line chemotherapy for NHL. Rituximab, a humanized anti-CD20 monoclonal antibody has shown considerable activity in MCL. Therefore, the patient underwent treatment with R-DEP. However, a lower dose of chemotherapy than the standard dose was administered due to the thrombocytopenia. The therapy was effective and the patient achieved a partial response.

In the literature, a total of 6 cases with synchronous MCL and lung carcinoma were reported, and all of them received chemotherapy (18,32-36) (Table II). Specifically, Kampalath *et al* (18) reported that a rare case of synchronous MCLBMI and ES-SCLC was treated with cisplatin, etoposide and rituximab, and remained in complete remission for ~2.5 years following the initial diagnosis. No thrombocytopenia was reported in this case, unlike in the current case.

MCL is characterized by CD5 and cyclin D1 expression. However, weak CD5 expression was observed in the bone marrow but no CD5 expression was observed in all biopsies in the present case. Both FCM and IHC can be used to determine differences in CD5 protein expression individually. FCM analysis could be used for the quantitative detection of CD5-positive cells. It would be quite hard to quantify the CD5 protein expression levels with IHC staining. As for the reasons for different CD5 expression in bone marrow species and all biopsies, on the one hand, FCM is more sensitive than IHC in detecting CD5 expression, while on the other hand, the antibody for the immunohistochemical detection was different from that of FCM. Immunohistochemical examination is the standard method of diagnosing lymphoma. It is important to recognize the limitations of FCM and IHC for the detection

of CD5 expression. If FCM could not have been performed in the present case, it may have led to a different diagnosis of CD5-negative MCLBML. Finally, histopathological staining and IHC examination are the standard methods to subclassify lymphoma, while FCM is probably the most effective method that can be used to determine the clonality and antigen expression of lymphoid cell populations (37). Therefore, there are two major limitations in the present study that could be addressed in future research. First, FCM was applied to only bone marrow immunophenotyping detection, but not to right axillary lymph node immunophenotyping detection. Second, this study was based on a single sample.

In conclusion, the present study described a case of synchronous MCLBML complicated with ES-SCLC. The patient underwent treatment with R-DEP and achieved a partial response. Although the patient did not achieve complete remission, the experience of this case provides a new option for the treatment plan of synchronous MCLBML complicated with ES-SCLC. However, the treatment experience in this case also shows that R-DEP therapy seems to be inadequate. Therefore, more effective combination therapy options are required to improve the effect of the treatment. Synchronous development of these two malignant tumors is one of the most challenging problems in cancer diagnosis and treatment. The treatment plan requires comprehensive consideration and multidisciplinary cooperation regarding both tumors. The incidence of synchronous MCLBML and ES-SCLC is extremely low; therefore, further studies are required with a larger sample size. The present case report highlights the importance of the detailed analysis of lymphoma lung involvement and primary lung cancer. In similar cases, in which suspicion is raised over the presence of MCLBML and malignant tumors, the application of immunohistochemical analysis is crucial to provide an accurate diagnosis. Therefore, we propose a diagnostic workflow to more accurately diagnose MCLBML and ES-SCLC in the future as follows: If the clinical manifestations of the patient included unexplained lymphadenopathy, a lung mass and cytopenias, such as thrombocytopenia, neutropenia, and anemia, a lymph node biopsy, bone marrow biopsy and CT-guided biopsy of the lung mass should first be performed. If the results of further IHC detection indicate mantle cell lymphoma in combination with small cell lung cancer, then an accurate diagnosis can be made.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

NX contributed to the analysis and interpretation of the data and wrote the paper. LL conceived and designed the paper. ZF and WL obtained medical images (e.g., PET-CT and CT scans) and analyzed the data. CZ and JZ performed the bone marrow examination, advised on patient treatment and collected the data. NX, LL, ZF, WL, CZ and JZ performed the original draft preparation. LL and NX confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

All procedures were approved by the Ethics Committee of College of Medicine, Lishui Hospital, Zhejiang University (Lishui, China; approval no. 2022100).

Patient consent for publication

Written informed consent was obtained from the patient for the publication of the present study.

Competing interests

The authors declare that they have no competing interests.

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