

Bulky primary tibia mantle cell lymphoma achieved complete remission with CHOP and DHAP plus rituximab: A case report

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Abstract. Mantle cell lymphoma (MCL) is a subtype of B-cell non-Hodgkin lymphoma. Heterogeneous and extensive lymphadenopathy is the most common clinical manifestation. Although skeletal involvement is not uncommon in other types of non-Hodgkin lymphoma, primary bone MCL is rare. The present study reported a case of primary tibia MCL in a 50-year-old male presenting with left tibia pain and a rapidly growing lump. Computed tomography and magnetic resonance imaging scans revealed a progressive lesion in the cortical bone and surrounding soft tissue mass. A positron emission computed tomography scan demonstrated increased glucose metabolism in the middle tibia without involvement of regional lymph nodes. An aspiration biopsy was performed, and pathological examination revealed small-medium sized cells strongly positive for cluster of differentiation (CD)5, CD20 and cyclin D1. Fluorescent *in situ* hybridization analysis confirmed the presence of immunoglobulin heavy chain/cyclin D1 gene fusion formed by t(11;14) translocation. As a result, primary bone MCL was diagnosed and rituximab-containing chemotherapy was administered. Following complete remission, autologous hemopoietic stem cell transplantation and rituximab maintenance therapy were performed. During the 2-year follow-up period, the patient remained in a good condition without signs of relapse.

Introduction

Mantle cell lymphoma (MCL) is a distinct entity of B-cell non-Hodgkin lymphoma, accounting for 6-9% of malignant lymphoma cases (1). MCL has a male predominance and the majority of patients with MCL are >50 years old (1). Due

to the lack of specific clinical manifestations, the majority of patients present with the advanced stage at diagnosis. A diagnosis of MCL depends on the pathological examination results. Biologically, MCL cells are characterized by cluster of differentiation (CD)5+, CD20+, CD10- and cyclin D1+. Although bone marrow, and the circulatory and the gastrointestinal systems are often involved, primary bone MCL is rare. To the best of our knowledge, only one case of primary spinal MCL has been reported in the literature to date (2). The present study discussed a case of bulky primary tibia MCL, for which complete remission was achieved with R (rituximab)-CHOP (rituximab 600 mg on day 1, cyclophosphamide 1.2 g on day 2, vindesine 4 mg on day 2, epirubicin 96 mg on day 2, prednisone 50 mg every 12 h on days 2-6) and R-DHAP (rituximab 600 mg on day 1, cisplatin 168 mg on day 2, cytarabine 3.3 g/q12h on day 3, dexamethasone 40 mg on days 2-5).

Case report

A 50-year-old male presented with left tibia pain with no apparent cause, at Fenghua District People's Hospital (Ningbo, China) in September, 2014. An X-ray revealed that local bone density was decreased. Computed tomography (CT) revealed local cortical bone rupture with abnormal density in the medullary cavity and surrounding soft tissue (Fig. 1A). Infectious etiology was considered and cefaclor (250 mg, every 8 h) was administered. After 1 month, the patient was transferred to the Affiliated Hospital of Ningbo University due to increased pain and presentation of a growing mass adjacent to the left tibia. No B symptoms, including unexplained fever of >38°C, drenching night sweats and loss of >10% body weight within 6 months, were reported except night sweats. There was no medical history of any previous disease or pathology. On physical examination, a 5x6-cm mass with a smooth surface was detected in the right lower extremity.

Initial blood tests identified a lactate dehydrogenase level of 646 U/l, β_2 -microglobulin level of 2388 ng/ml, C-reactive protein level of 4.7 mg/l, white cell count of 5,200 cells/ μ l, hemoglobin content of 15.0 g/l and a platelet count of 169,000 platelets/ μ l. Screening tests for human immunodeficiency virus, cytomegalovirus, EB virus, and hepatitis B and C were negative.

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Key words: mantle cell lymphoma, bone, rituximab, autologous hemopoietic stem cell transplantation

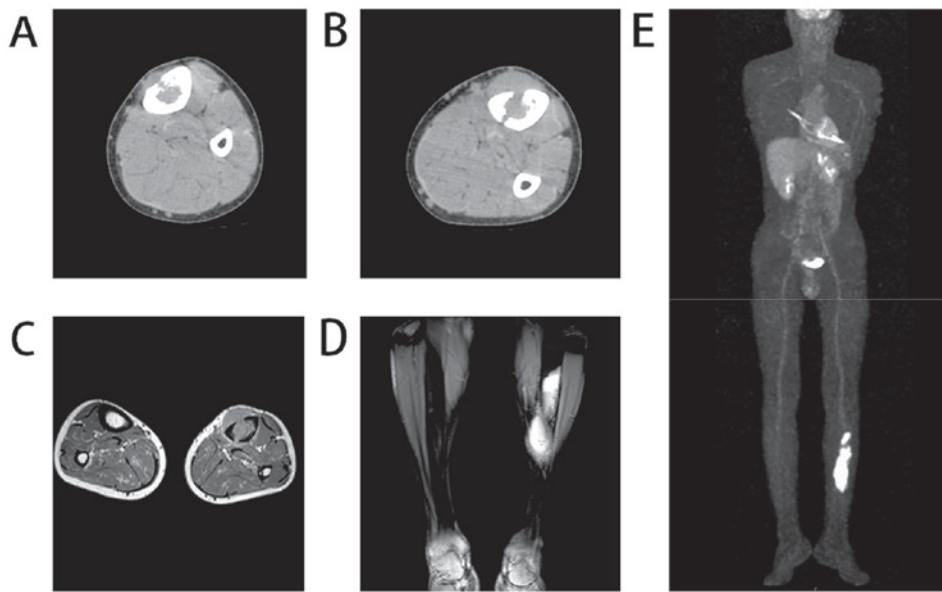


Figure 1. Radiological data prior to treatment. (A) CT demonstrated a small cortical bone defect with abnormal density shadows inside the medullary cavity with surrounding soft tissue swelling in September 2014. (B) At 1 month later, the bone lesion and soft tissue mass were visibly aggravated. Magnetic resonance imaging scans of the (C) horizontal and (D) coronal axes revealed long T1 and T2 signal intensities within bony marrow and mass around the left tibia in September 2014. (E) At the time of admission, positron emission tomography-CT demonstrated increased glucose metabolism in the middle of the left tibia (max SUV, 17) and left adrenal gland (max SUV, 7.6). CT, computed tomography; SUV, standardized uptake value.

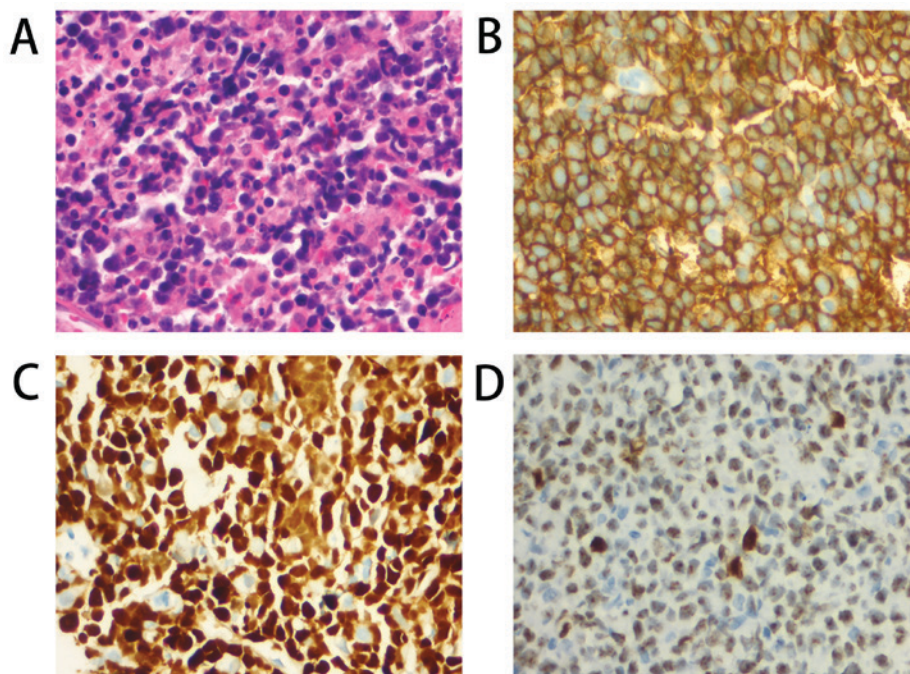


Figure 2. Histological and immunohistochemical staining (magnification, x400). (A) Hematoxylin and eosin staining demonstrated abnormal, diffuse, atypical, small-sized, slightly irregular cells. Immunohistochemical staining revealed that tumor cells were positive for (B) cluster of differentiation 20 and (C) cyclin D1. (D) Ki-67 was expressed in 80-90% of the cells.

CT (Fig. 1B) and magnetic resonance imaging (MRI) (Fig. 1C and D) scans demonstrated that the surrounding soft tissue mass originated from the medullary cavity through the more severe region of bone destruction. Positron emission tomography (PET)-CT demonstrated increased glucose metabolism and standardized uptake values in the left tibia and the left adrenal gland (Fig. 1E). No abnormal enlarged lymph nodes were identified through ultrasonography or

other examinations. An aspiration biopsy was performed on September 30, 2014. Histological and immunohistochemical staining revealed typical characteristics of MCL. Biopsy samples were fixed in formalin at 20°C for one night and decalcified with 20% ethylenediamine tetra-acetic acid for 5 h. Then the samples were dehydrated at 20°C using 100, 100, 95 and 75% graded ethanol series for 2 minutes each. Tumor tissue sections (3 μ m thick) were sliced, deparaffinized in

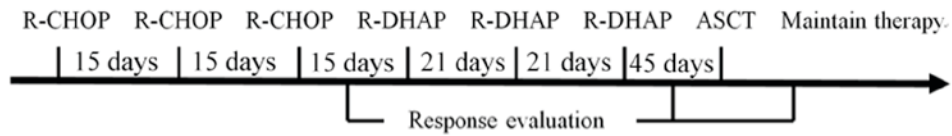


Figure 3. Initial treatment schedule. Three cycles of R-CHOP (rituximab 375 mg/m² mg on day 1, cyclophosphamide 700 mg/m² on day 2, vindesine 250 mg/m² on day 2, epirubicin 60 mg/m² on day 2, prednisone 50 mg every 12 h on days 2-6) every 15 days and three cycles of R-DHAP (375 mg/m² on day 1, cisplatin 100 mg/m² on day 2, cytarabine 200 mg/m² every 12 h on day 3, dexamethasone 40 mg on days 2-5) every 21 days were followed by ASCT. Then, rituximab at a dose of 375 mg/m² was administered every 3 months for maintenance therapy. ASCT, autologous stem cell transplantation.

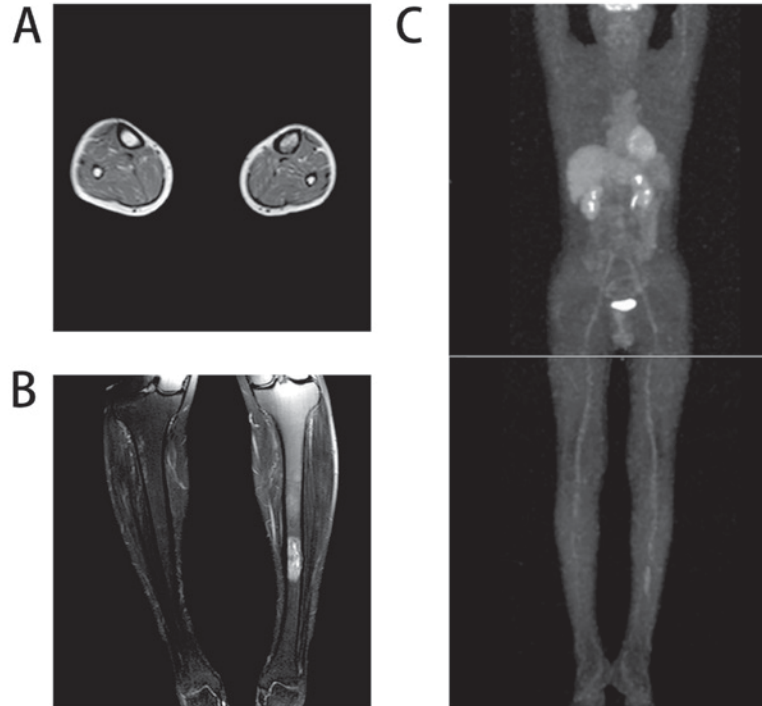


Figure 4. Radiological findings after treatment. (A) Horizontal and (B) coronal magnetic resonance imaging revealed that the range of abnormal signaling was notably reduced in April 2015. (C) positron emission tomography-CT demonstrated a slightly high-density shadow in the tibia with normal glucose metabolism following chemotherapy (max SUV, 4.8). SUV, standardized uptake value.

xylene and stained with hematoxylin and eosin for 3 minutes at 20°C. The tissue sections were visualized by a microscopy (TS100; magnification, x400; Nikon Corporation, Tokyo, Japan) and photographed by microscope camera (DS-Ri2; Nikon Corporation, Tokyo, Japan). Immunohistochemical staining was performed using the EnVision two-step staining method (2). Mouse anti-CD5 (cat. no. ZM-0280), anti-CD10 (cat. no. ZM-0283), anti-Ki-67 nuclear antigen monoclonal antibody (cat. no. ZM-0165) and rabbit anti-CD 20 (cat. no. ZA-0549), anti-Cyclin D1 (cat. no. ZA-0101) monoclonal antibodies were purchased from ZSQB-BIO corporation (Beijing, China). A pathological exam revealed diffuse, small-to-medium sized cells (Fig. 2A). Immunohistochemical staining performed as previously described (3) revealed that the cells were positive for CD5, CD20 (Fig. 2B), CD99, B cell CLL/lymphoma 6 (Bcl6), multiple myeloma oncogene, BCL2 apoptosis regulator (Bcl2) and cyclin D1 (Fig. 2C), but not for terminal deoxynucleotidyl transferase or CD10. Ki-67 was expressed in 80-90% of the cells (Fig. 2D). Cyclin D1 (CCND1)/immunoglobulin heavy chain (IGH) kit (F01019-00) was purchased from Beijing GP Medical Technologie, Ltd. (Beijing, China). Fluorescent *in situ* hybridization (FISH) analysis (4) was positive for

the rearrangement of IGH/CCND1 and Bcl6 fragmentation. IGH/BCL2 fusion gene, C-MYC breakage or P53 deletion were not detected. A bone marrow biopsy revealed no bone marrow infiltration (data not shown).

Following a thorough examination, bulky stage I_E was diagnosed according to the Ann Arbor staging system (5). Sequential induction therapy with three cycles of R-CHOP followed by three cycles of R-DHAP followed by autologous stem cell transplantation (ASCT) was adopted (Fig. 3). The first cycle of R-CHOP began on October 17, 2014. The left lower limb mass was reduced to 2x2 cm when the patient was re-assessed on October 31. The second cycle of R-CHOP chemotherapy began on November 3. The mass was almost gone by November 17. However, the third course of chemotherapy, which was originally scheduled to begin on November 20, was cancelled due to severe lung infection occurred on November 18. Ceftazidime (800 mg, every 8 h) was administered for 3 days and the patient still had high fever. Then biapenem (300 mg, every 12 h) and voriconazole (200 mg, every 12 h) was administered for 4 days. *Pneumocystis carinii* pneumonia was diagnosed on November 25. Sulfamethoxazole (400 mg, every 8 h), Kosice (50 mg,

every 24 h), methylprednisolone (40 mg every 12 h) was administered. Chest CT scans presented decreased shadow area on November 28 and the dose of methylprednisolone was reduced (40 mg, every day). The treatment for pneumonia ended on December 13. During the treatment of the lung infection, the mass grew gradually to 1x1 cm. The third course of R-CHOP began on December 20. Considering the gradual enlargement of the mass and the long interval between the second and third cycle of R-CHOP, another two cycles of R-CHOP were administered on January 7 and January 22, 2015. The first course of the following R-DHAP (rituximab 600 mg on day 1, cisplatin 168 mg on day 2, cytarabine 3.3 g/q12h on day 3, dexamethasone 40 mg on days 2-5) began on February 15. Complete remission was achieved following another two cycles of R-DHAP, which respectively began on March 9 and 31, 2015. MRI revealed that the range of abnormal signaling was notably reduced (Fig. 4A and B). PET-CT revealed a slight high-density shadow in the tibia with normal glucose metabolism (Fig. 4C). Peripheral blood stem cell collection began in April 13 and ASCT was conducted on May 12, 2015. For the past 2 years, rituximab at a dose of 600 mg was administered every 3 months for maintenance therapy. To date, no recurrence has been found by regular radiological follow-ups.

Discussion

Generally, primary bone lymphoma is considered to consist of a single bone lesion with or without regional lymphadenopathies (6). Although skeletal involvement is not uncommon in other types of non-Hodgkin lymphoma, the available literature on this in primary bone MCL is limited (7). To the best of our knowledge, only one case of primary spinal MCL has been previously reported (2). In the present case report, the imaging data provided evidence that MCL may have a clear bone origin without involvement of lymph nodes.

Diagnosis of MCL should be based on pathological examination of surgical specimens, preferably lymph nodes. The most characteristic morphological feature is small- or medium-sized lymphocytes with irregular nuclei. In addition, immunohistochemistry for the detection of typical patterns of an immunophenotype is mandatory. In the current case, the cells were positive for cyclin D1, CD5 and CD20, but negative for CD10. Additionally, FISH analysis detected IGH/CCND1 gene fusion and consequently MCL was diagnosed.

MIPI, Ki-67 index and bulky mass are effective markers in evaluating patient prognosis in MCL (8). In the current case, the patient was classified to have a low-risk prognosis according to the MIPI. Instead of local radiotherapy, systemic chemotherapy was adopted due to the following: i) The large tumor burden and high rate of proliferation, which was indicated by the rapidly enlarging leg lump, increasing size of the tibia lesion and high Ki-67 index; and ii) the possibility of increased glucose metabolism in the left adrenal gland was caused by MCL metastasis could not be excluded.

To date, the initial regimen for younger patients with MCL remains controversial. A phase II study from the Groupe d'Etudes des Lymphomes de l'Adulte suggested that CHOP and DHAP plus rituximab were safe and effective (9). According to the last European Society for Medical Oncology guideline,

a rituximab containing induction of CHOP and cytarabine followed by ASCT and consolidation is recommended (7). ASCT consolidation is potentially curative and has become a standard approach for patients with MCL (10). Despite the high rate of complete response following systemic chemotherapy followed by ASCT, patients do relapse. Rituximab maintenance therapy following transplantation was demonstrated to prolong event-free, progression-free and overall survival times in patients with MCL (11).

Generally, MCL is an incurable disease; nonetheless, early detection and treatment is essential to improve its management. The present case report confirmed the possibility of primary bone MCL with comprehensive and detailed clinical data. Nevertheless, the level of evidence supporting definitive methods of diagnosis and treatment of MCL remains low, and further studies are required to confirm the appropriate methods of detection and management, and to improve prognosis.

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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

SC collected the data and wrote the manuscript. MY contributed to the conception of the study, revised the manuscript and helped perform the analysis with constructive discussions.

Ethics approval and consent to participate

This case report was approved by The Ethics Committee of Ningbo University. Consent for publication was obtained from the patient.

Patient consent for publication

Consent was obtained from all participants in the present study.

Competing interests

All authors declare that they have no competing interests.

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