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Case Report

Mantle cell lymphoma concurrent with T-large granular lymphocytic leukemia: report of a case and review of literature

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Abstract: Mantle cell lymphoma is one of the B-cell lymphomas. The concurrent presentation of mantle cell lymphoma with large granular lymphocytic leukemia simultaneously has never been reported. In this case we present an old man with concomitant mantle cell lymphoma and large granular lymphocytic leukemia diagnosed by the morphology of the bone marrow aspiration, immunophenotyping of the peripheral blood by flow cytometry detecting the increased CD3+CD4-CD8+ cells, immunohistochemical studies of lymph node showed cyclinD1+, chromosome analysis by fluorescence in situ hybridization (FISH) showed t(11,14), positive results of IGH and TCR rearrangement studies. The patient discharged from the hospital voluntarily and lost the follow-up. A brief discussion is also presented.

Keywords: Mantle cell lymphoma, large granular lymphocytic leukemia, concurrent

Introduction

Mantle cell lymphoma (MCL) is a B-cell neoplasm which accounts for around 3%-10% of non-Hodgkin lymphoma [1]. The diagnosis of MCL can be made by immunohistological stains detecting the presence of cyclin D1 expression, presence of rearrangement of the immunoglobulin (Ig) genes as well as the cytogenetic abnormalities with t(11,14) [2, 3]. Large granular lymphocytic (LGL) leukemia is a kind of lymphoproliferative disorders involving the clonal proliferation of Natural Killer (NK) or T cells. The 2008 World Health Organization (WHO) classification distinguishes 3 entities among the LGL leukemia: T-LGL leukemia, aggressive Natural Killer (NK) cell leukemia, and chronic NK lymphoproliferative disorders (LPD), the later considered as a provisional entity. As we all know, the abnormal cell types in MCL and LGL leukemia are quite different, originated from B and T lymphocyte cell lineages, respectively. Some cases of MCL coexistence with other B-cell neoplasm have been reported, but the concomitant presentation of MCL and LGL leukemia is extremely rare and all the reported cases are for the secondary LGL proliferation induced by the therapy of MCL [4, 5].

We describe a patient suffering from MCL concurrent with T-LGL leukemia, and the clinicopathology characteristics of this disease were also reported, as well as the clonal cytogenetic and molecular abnormalities. To our best knowledge, no concomitant of MCL and LGL which are diagnosed at the same time has been reported.

Case report

A 66 years old Chinese male, Han ethnic, presented to the hematology department of the First Affiliated Hospital of Nanjing Medical University with diffused lymphadenopathy in October 2013. He found the enlargement of his lymph nodes around the neck, axilla and groin several months before. No fever, sweating, weight loss, fatigue or dizziness could be found during this period of time. His physical examination revealed his vital signs are in the normal range, normal skin color without pale or icterus. Diffused enlarged lymph nodes around the

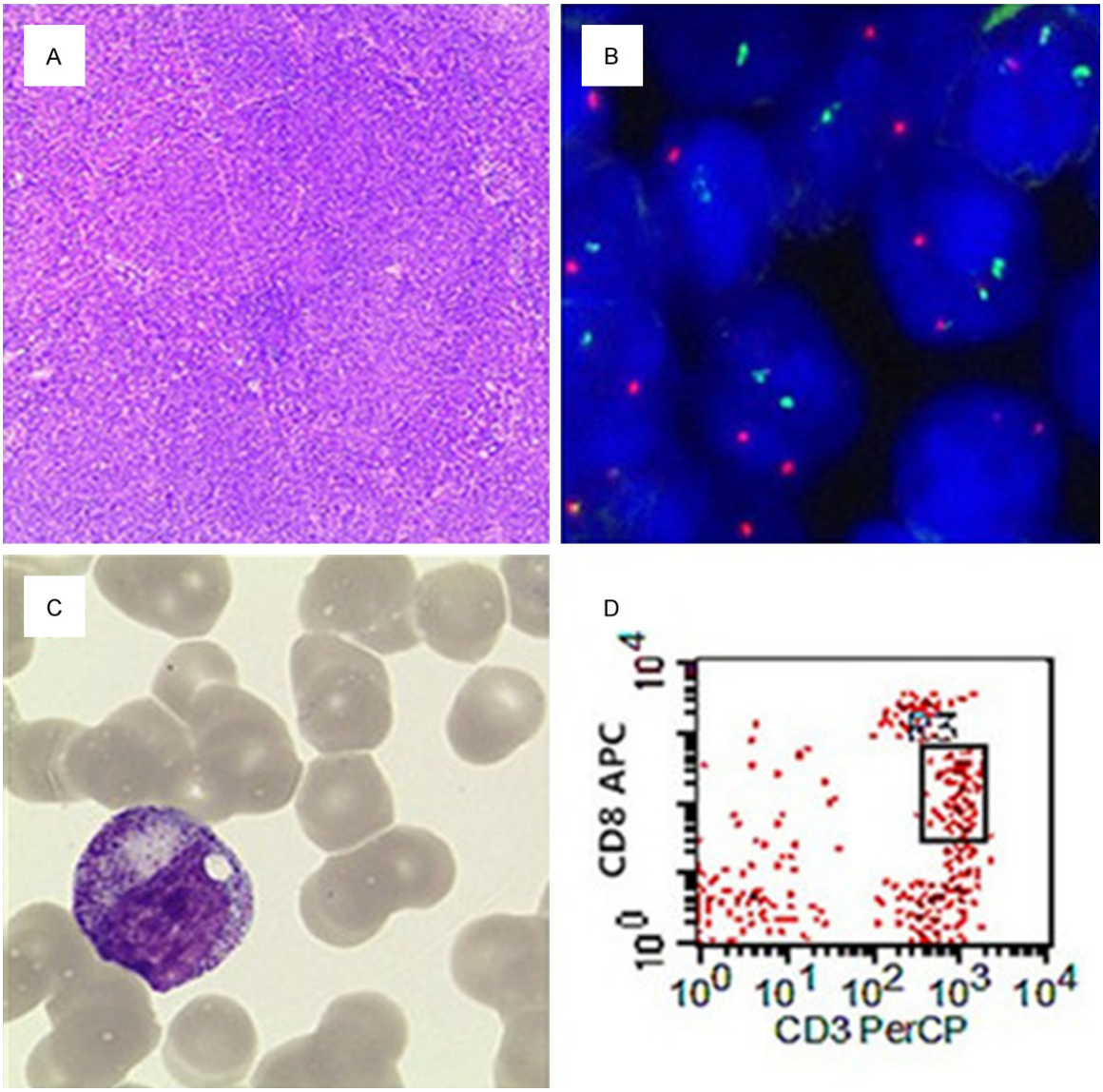

Figure 1. A serial of the examinations confirmed the diagnosis according to 2008 WHO classification for tumors of haematopoietic and lymphoid tissues scheme. A. Biopsy of the lymph node next to the neck revealed lymphoma. B. Fluorescence in situ hybridization (FISH) showed overlap of the probe suggesting the chromosomal t (11, 14). C. Bone marrow aspirate showed frequent large granular lymphocytes. D. Lymphocytes subtype analysis by flow cytometry revealed increased CD3+CD4-CD8+ cells.

bilateral mandible, upper part of his neck, axilla, groin without tenderness could be touched, and the biggest one is in size of about 3 cm × 3 cm. The abdomen was soft to palpate without hepatosplenomegaly. Complete blood cell count analysis showed a leukocyte count is 9500/uL with 23% lymphocytes, hemoglobin of 13.4 g/dL, and a platelet count of 175,000/uL. The liver function, renal function, coagulation test, tumor markers, lactate dehydrogenase (LDH) and autoimmune markers were all in the normal range. The EBV-DNA and CMV-DNA examined by polymerase chain reaction (PCR) were both negative. PET-CT showed diffused lymphadenopathy with abnormal increased uptake of FDG next to the both sides of the neck, in the supraclavicular fossa, axilla, mediastina, at the anterior part of the trachea, subcarina, both hilar, mall omentum sac, in the retroperitoneal, bilateral pelvis and groin.

Peripheral blood smear test showed granular lymphocytes account for approximately 50% of the lymphocytes, with the absolute count is

1100/uL. Peripheral lymphocyte subtype analysis by flow cytometry showed normal ratio of the total lympocytes with 26.6% (normal range: 20%-40%), and slightly increased number of CD3+ cells with 76.4% (normal range: 65%-75%), prominently exceptional elevated of CD3+CD4-CD8+ cells with 39.1% (normal range: 21%-29%). Bone marrow aspirate and biopsy showed myeloid hyperplasia and hypoplasia of erythroid and megakaryocytes along with frequent large granular lymphocytes. Immunophenotyping of the bone marrow cells by flow cytometry demonstrated normal lymphocytes count and slightly increased the ratio of NK-T cells. The immunohistochemical result of the lymph node at the right neck revealed CD20+, PAX-5+, CD5 dim+, Bcl-2+, CyclinD1+, Ki-67 50%, CD3-, CD10-, Bcl-6- and Mum-1-. Further PCR studies of the peripheral blood were positive for clonal T-cell receptor (TCR) and IGH genes rearrangement simultaneously. The chromosome analysis of the lymph node next to the neck by fluorescence in situ hybridization (FISH) showed t(11,14) (**Figure 1**). The diagnosis of mantle cell lymphoma with large granular lympocytic leukemia was confirmed according to 2008 WHO classification for tumors of haematopoietic and lymphoid tissues scheme [2]. The patient refused to take any further intervention and discharged from our hospital voluntarily for economic reasons.

Discussion

MCL is one of the B cell lymphomas with the worse prognosis (median survival 3-5 years) as it has an aggressive evolution, characterized by the t(11;14)(q13;q32) translocation leading to overexpression of cyclin D1 [6]. It is reported that MCL could be seen in the concurrence with other B-cell neoplasm, such as chronic lymphocytic leukemia and follicular lymphoma [2, 7-9]. There are also some case reports about mantle cell lymphoma coexistence with some solid tumor, just like the prostate cancer and intestinal adenocarcinoma [10, 11]. T-LGL leukemia is an indolent leukemia that represents 2%-3% of all small lymphocytic leukemias, even less rare than MCL [2, 12]. The disease of MCL coexisted with T-LGL is a unique neoplasm, that need us to master the clinical feature and explore the biological characteristics deeply.

In this patient, diffused lymphadenopathy is the main clinical demonstration, with typical laboratory test for MCL and T-LGL, including t(11,14), LGL cells in blood film, elevated T cells phenotype by immunotyping, clonal IgH and TCR gene rearrangement. The review of cases failed to report the simultaneous composition of mantle cell lymphoma and LGL leukemia. The molecular pathogenesis has been described a lot by many studies in LGL leukemia; it is believed that various deregulated signaling pathways, including NF-kB, JAK/STAT3, PI3K/AKT are playing an important part in the proliferation and apoptosis in the lympocytes which will finally precipitate the happening of LGL leukemia [11]. The constitutive activation of PI3K/AKT/NF-kB signaling pathway promote T cells proliferation and prolong the survival time of T cells by inhibiting apoptosis, and the down regulation of PI3K/AKT pathway could lead the spontaneous apoptosis of LGL leukemia [12, 13]. The pathogenesis of MCL is complicated and still remains unclear, but the activation of NF-kB signaling pathway is observed in the cells of MCL in the previous study [14] and several medications which are in the use of the treatment of mantle cell lymphoma have been reported by affecting the PI3K/AKT/mTOR and PI3K/AKT/NF-kB signaling pathways to induce the apoptosis and cell death [15-18]. For instance, the usage of fenofibrate, an agonist for peroxisome proliferator-activated receptor-alpha will induce apoptosis in treating MCL by decreasing the translocation of NF-kB-p65 and inhibiting the DNA binding of NF-kB [15]. Concurrent use of PI3K inhibitor and mTOR antagonist will induce cell apoptosis and reduce the drug resistence in mantle cell lymphoma [16]. These findings could imply that the composition of MCL and LGL leukemia may not be found coincidentally; the common signaling pathway may not only demonstrate the pathogenesis of the two malignancies but also provide a hint in the further treatment.

In this case, we made diagnosis of the mantle cell lymphoma composition with T-large granular lymphocytic leukemia by the morphology, flow cytometry, immunohistochemistry, IGH and TCR rearrangement studies and fluorescence in situ hybridization (FISH). The hypothetic pathogenesis of the concurrency is presented by this paper but additional studies for more cases are still needed for a better understanding of the concomitant occurrence of simultaneous mantle cell lymphoma and T-large granular lymphocytic leukemia.

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Disclosure of conflict of interest

None.

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