Malignancy-Associated Hypercalcemia Related with Receptor Activator of NF- κ B Ligand (RANKL) Expression in T-Cell Acute Lymphoblastic Leukemia

Kenichi Tahara^a Hiromi Koiso^a Yo-hei Osaki^a Tomomi Sekigami^a Akihiko Yokohama^a
Takayuki Saitoh^b Norifumi Tsukamoto^a Hirokazu Murakami^b Masahiro Abe^c
Hiroshi Handa^a

^aDepartment of Hematology, Graduate School of Medicine, Gunma University, Maebashi, Japan;

^bDepartment of Health Science, Graduate School of Health Sciences, Gunma University, Maebashi, Japan;

^cDepartment of Medicine, Tokushima University, Tokushima, Japan

Malignancy-associated hypercalcemia (MAH) is a common paraneoplastic syndrome [1]; however, MAH is relatively rare in acute lymphoblastic leukemia (ALL) with an incidence of only 2.5–4.8% [2, 3]. There are 2 main categories of MAH, namely, humoral hypercalcemia of malignancy (HHM), which is the most common cause of MAH and accounts for 80% of occurrences, and local osteolytic hypercalcemia (LOH) [4]. Humoral factors such as the parathyroid hormone-related protein (PTHrP) produced by tumor cells promote systemic bone resorption and causes HHM [5]. Meanwhile, inflammatory cytokines such as interleukin (IL)-1 β , IL-6, tumor necrosis factor (TNF)- α , macrophage inflammatory protein (MIP)-1 α , and MIP-1 β produced by tumor cells cause LOH [6–9]. PTHrP can also cause LOH [4, 10]. The receptor activator of NF- κ B ligand (RANKL), which is expressed on the surface of bone marrow stromal cells such as osteoblasts, binds to the receptor activator of NF- κ B (RANK) on the osteoclast precursors, induces differentiation and activation of osteoclasts [11], and is also one of the factors causing LOH [12]. The mechanism of

MAH in ALL has not been fully clarified because of its rarity. Herein, we report a case of precursor T-ALL complicated with hypercalcemia and investigate the factors triggering MAH.

An 18-year-old man suffering from cervical lymph node swelling and night sweats was referred to our hospital. Physical examination revealed substantial swelling of the bilateral palatine tonsils and generalized lymphadenopathy. A complete blood cell count showed normal levels (hemoglobin concentration, 14.0 g/dL; white blood cell count, 6.8×10^9 /L with no leukemic cells; platelet count, 156×10^9 /L). Human T-cell leukemia virus type-1 antibody was negative. Bone marrow aspiration biopsy showed hypercellular marrow with 40.7% leukemic cells. The leukemic cells were positive for cytoplasmic CD3, CD2, CD7, CD8, CD13, CD19, and CD79a, while negative for CD34, TdT, CD1, CD3, CD4, and MPO by flow-cytometric analysis. Immunohistochemical study revealed that the leukemic cells were positive for CD3 and TdT. Based on these data, he was diagnosed with T-ALL. The serum calcium level was normal at 9.5 mg/dL at the time of admis-

sion but increased to 13.8 mg/dL with the increase of lactate dehydrogenase (LDH) before chemotherapy. Serum intact PTH and 1,25(OH) $_2$ vitamin D $_3$ levels were below normal ranges, and PTHrP was undetectable. Serum type I collagen cross-linked N-telopeptides and urinary deoxypyridinoline were elevated, suggesting hypercalcemia induced by bone resorption. Therefore, inflammatory cytokines associated with bone metabolism were analyzed. The TNF- α level was within normal ranges, and IL-1 β was undetectable. Immunohistochemical analysis revealed that the leukemic cells were positive for RANKL and MIP-1 β , weakly positive for MIP-1 α , but negative for IL-1 β (Fig. 1). Chemotherapy combined with bisphosphonate and calcitonin administration promptly reduced the serum calcium level to normal (Fig. 2). Swelling of the palatine tonsils and generalized lymphadenopathy were reduced with the improvement in hypercalcemia during induction chemotherapy. However, they reappeared concomitantly with the recurrence of hypercalcemia. Although he received re-induction chemotherapy, he did not achieve complete remission. He was

Fig. 1. Immunohistochemical staining for RANKL, MIP-1 β , MIP-1 α , and IL-1 β in the bone marrow. The leukemic cells were positive for RANKL (a) and MIP-1 β (b), weakly positive for MIP-1 α (c), but negative for IL-1 β (d). $\times 1,000$.

Fig. 2. Clinical course and laboratory data: levels of serum Ca, lactate dehydrogenase (LDH), serum type I collagen cross-linked N-telopeptides (S-NTx), and urinary deoxypyridinoline (U-DPD). BCE, bone collagen equivalent; BM, bone marrow.

transferred to another hospital for allogeneic hematopoietic stem cell transplantation.

The findings in this case suggested that MAH was induced by LOH, which was in turn triggered by RANKL, MIP-1 α , and

MIP-1 β produced by leukemic cells. The hypercalcemia developed just before the elevation in LDH, which is associated with leukemic cell proliferation, and serum calcium promptly decreased during chemotherapy. These data supported the hypoth-

esis described above. However, computed tomography and 18-fluorodeoxyglucose positron emission tomography did not show any bone disease; thus, the contribution of HHM to hypercalcemia could not be ruled out. We also cannot rule out the

possibility that the leukemic cells produced PTHrP and caused LOH, a mechanism which has been reported previously [13]. Measuring soluble RANKL in the serum and immunohistochemical analysis for PTHrP might be helpful to solve each question because PTHrP was undetectable in the serum.

In conclusion, this is the first case of T-ALL in which the possible mechanism of MAH occurrence, which occurs through direct interaction between leukemic cells and osteoclasts, is proposed. Further biological studies are needed to validate this mechanism.

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Disclosure Statement

The authors have no conflict of interest.

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