Abstract  Osteopetrosis is a rare genetic disorder in which the function of osteoclasts is defective, resulting in impaired bone resorption. This disease is usually accompanied by myelosuppression due to decreased marrow space and by osteomyelitis, especially in the sub-mandibular bone. We report the case of a 72-year-old woman with an autosomal dominant form of osteopetrosis who suffered from peripheral T-cell lymphoma. Accurate clinical and pathological diagnoses and staging were difficult due to nonspecific reactive hyperplasia of the lymph nodes, even though we used several scintigraphic techniques and [18 F]fluorodeoxyglucose positron emission tomography. We also paid special attention to myelosuppression and exacerbation of osteomyelitis after combination chemotherapy. Severe infectious complications were avoided by early administration of G-CSF for leukocytopenia and by continuous oral administration of antibiotics. The patient achieved complete remission after four courses of chemotherapy and this status has been maintained for 6 months.

Keywords  Chemotherapy · Osteopetrosis · Peripheral T-cell lymphoma

Introduction

Non-Hodgkin’s lymphoma (NHL) is a common hematological malignancy that appears in every generation, and its treatment modalities have been advanced markedly in recent decades. Although the etiologies of some NHLs (Epstein–Barr virus related lymphoproliferative disorders, human T-cell leukemia virus type I related leukemia/lymphomas, and Helicobacter pylori induced mucosa-associated lymphoid tissue lymphomas) have been elucidated, there are still many NHLs of unknown pathophysiology. Some authors have reported that cytokines, including IL-4, IL-5, IL-6, IL-7, TNF-α, and TGF-β, are key effectors of the pathogenesis for several NHLs [3, 6].

Osteopetrosis is an uncommon disorder in which bone trabeculae are remarkably thickened, resulting in decreased marrow space with reduced hematopoiesis. In an animal model, the underlying defect was reported to be dysfunction of osteoclasts with mutation of the M-CSF gene [10]. Although cytokine dysregulation has not yet been established in humans, it may occur in some patients.

In this paper, we present a case report of peripheral T-cell lymphoma in a patient with osteopetrosis and discuss the possible relationship between the lymphoma and osteopetrosis. We also discuss the clinical problems in the diagnosis and treatment of NHL complicated by osteopetrosis.

Case report

A 72-year-old woman visited Hokkaido University Hospital in November 1999 with bilateral cervical and axillary lymph node swelling. Physical examination revealed enlarged surface lymph nodes in bilateral cervical, supraclavicular, axillary, and inguinal areas. Computed tomography and ultrasonography revealed enlarged lymph nodes in the abdominal para-aortic areas and mild hepatosplenomegaly. 68Ga scintigraphy showed increased uptake in the right submandibular area, and [18F]fluorodeoxyglucose positron emission tomography (FDG-PET) showed increased uptake in the bilateral neck, right lateral chest wall and bilateral inguinal areas (Fig. 1). After the first biopsy of the lymph node from the right cervical area, histological examination revealed nonspecific reactive change without malignancy. A second excisional biopsy from the left axillary lymph node demonstrated peripheral T-cell non-Hodgkin’s lymphoma (unspecified) by the REAL classification and the new WHO classification. Immunophenotype analysis of the lymphoma cells showed CD3(+), CD43(MT-1) (+), CD45RO(UCHL-1) (+), CD20(L26) (−) and CD79a(MB-1) (−), indicating T-cell origin. Although bone scintigraphy using 99mTc indicated increased uptake in the extremities, there was no increased uptake in a pathologic fracture that was detected in her...
right femur. Posterior iliac bone biopsy showed marked thickening of the bone trabeculae with severe reduction of the medullary marrow space, and chest X-ray showed increased bone density, findings consistent with osteopetrosis. Bone marrow scintigraphy using $^{111}$In showed decreased uptake in the central bone marrow and increased peripheral extension. Laboratory data showed mild anemia (Hb 9.2 g/dl), leukocytopenia (3100/µl; neutrophils 54%, lymphocytes 32%, monocytes 5%, eosinophils 8%, basophils 1%, and abnormal lymphoid cells 0%), increased serum LDH (488 IU/l) and markedly increased soluble IL-2 receptor (1591 U/ml). The HTLV-1 antibody tested negative.

The patient was diagnosed as having stage III NHL and was treated with combination chemotherapy of CHOP, the dose of which was reduced to 80% because of her age and suppressed myelopoiesis. Since she suffered from bilateral submandibular osteomyelitis before the chemotherapy, oral administration of antibiotics was continued after the chemotherapy, and the infection was not exacerbated by the treatment. Leukocytopenia was not so severe because of the early administration of G-CSF, starting just after the chemotherapy, and her clinical condition was uneventful after four courses of CHOP therapy. The size of all palpable surface lymph nodes were found to be remarkably decreased after treatment. A new bone fracture of the left femur was found during the course of the treatment, and the patient required supportive equipment for her bilateral lower extremities. The patient achieved complete remission after four courses of the chemotherapy and this status has been maintained for the six months until now. The diagnosed cytopenias and LDH elevation have persisted even after the four courses of effective chemotherapy; this indicates that the findings were related to the osteopetrosis alone, not to the lymphoma.

Discussion

There has been only one reported case of NHL with osteopetrosis [9]. This may be because of the extremely rare frequency of the onset of NHL in patients with osteopetrosis, because the recessive form is usually accompanied by early death. The death rate in the autosomal recessive form of osteopetrosis, which is observed in infants and young children, is very high in the first 10 years of life, due to hemorrhage from thrombocytopenia and fatal infection from leukocytopenia [5, 8]. Our patient's case is compatible with the autosomal dominant form of osteopetrosis, a form that sometimes remains clinically asymptomatic throughout life and is only diagnosed incidentally. Although circulating M-CSF, which is decreased in animal models, was reported to be not reduced in patients with malignant osteopetrosis [7], Lajeunesse et al. reported that the production of M-CSF from osteoclasts was normalized after allogeneic bone marrow transplantation [4]. Therefore, some kind of cytokine dysregulation may play an important role in the pathogenesis of NHL in patients with osteopetrosis. In this patient, the serum M-CSF level was normal at diagnosis.

The major clinical problems in diagnosis of NHL in patients with osteopetrosis are difficulties in accurate staging and accurate pathological evaluation because patients with osteopetrosis sometimes show lymph node swelling due to infectious complications in later life. Actually, the first biopsy in our patient showed nonspecific reactive hyperplasia of the lymph node due to chronic submandibular osteomyelitis. Moreover, unspecific lymphadenitis around the lymphoma is common. Therefore, repeated biopsies and a combination of several imaging techniques, such as $^{67}$Ga-scintigraphy and FDG-PET were very useful for accurate diagnosis and clinical staging in our patient. Recently, FDG-PET has been shown to be a sensitive and specific imaging technique for predicting lymphomatous involvement, as was seen in our patient [1].

Usually, pancytopenia due to decreased marrow space and submandibular osteomyelitis are observed in later life in patients with osteopetrosis. Therefore, we should pay special attention to infectious complications in patients with osteopetrosis. Although our patient had been suffering from submandibular osteomyelitis and was given antibiotics before chemotherapy, there was no exacerbation of the infection, even during the leukocytopenic period after the chemotherapy. The early administration of G-CSF and continuous oral administration of antibiotics might have been effective in our patient.

Although the autosomal recessive form of osteopetrosis is potentially reversible by allogeneic bone marrow transplantation with engraftment of normal functioning osteoclasts, it is likely that our patient would not have been a candidate for this treatment owing to her advanced age and the delayed manifestation [2]. Therefore, the final goal in our patient is complete remission of not osteopetrosis but NHL; however, administration of

![Fig. 1 Whole-body FDG-PET findings on admission](image-url)