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Bone Marrow Scintigraphy with Technetium-99m Anti-NCA-95 to Monitor Therapy in Malignant Osteopetrosis

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We report a case of a 2-mo-old girl with malignant osteopetrosis. Conventional radiological investigations of the skull and left hand showed the characteristic pattern of generalized sclerosis. Bone marrow immunoscintigraphy with ^{99m}Tc-labeled antibodies against nonspecific cross-reactive antigen (NCA) 95 was performed before and after bone marrow transplantation. Before transplantation, whole-body images showed bone marrow stores exclusively in the base of the skull. The rest of the skeleton did not reveal any hematopoietic activity. The liver and spleen showed increased antibody uptake as expected in extramedullary hematopoiesis. Repeat scintigraphy after bone marrow transplantation from her haploidentical father demonstrated an almost completely normalized tracer distribution corresponding to her clinical and hematological improvement. Bone marrow immunoscintigraphy appears to be an ideal complement to radiograph diagnostics in malignant osteopetrosis. In primary diagnosis, scintigraphy demonstrates the quantitative extent of bone marrow displacement. It also proves an ideal tool in monitoring the effectiveness of therapy after bone marrow transplantation.

Key Words: osteopetrosis; bone marrow immunoscintigraphy; anti-NCA-95 antibody; bone marrow transplantation

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Osteopetrosis is a hereditary disorder of the skeleton, which is also known as Albers-Schönberg disease, osteosclerosis, osteopetrosis generalisata or marble bone disease. A relatively benign form transmitted autosomal dominantly can be distinguished from the autosomal recessive form also called malignant or infantile osteopetrosis (*1*). The disease is thought to result from a deficiency of osteoclasts, causing abnormally increased bone density as well as impaired bone remodeling and reabsorption of the calcified substantia spongiosa (*2,3*). During the course of the disease, the marrow spaces become obliterated leading to pancytopenia, which is complicated by infections, bleeding or death in severe cases. The adult form is characterized by less severe clinical presentations. Patients are often asymptomatic until osteosclerosis is discovered on radiographs obtained for pathologic fractures or cranial nerve palsy (*1*). Characteristic findings of conventional radiographs comprise increased bone density and poorly remodeled bones (*4*).

Bone scintigraphy in osteopetrosis demonstrates a diffuse increase in tracer uptake often combined with focal accumulation in fracture sites or areas of osteomyelitis.

For patient management, the grade of bone marrow displacement and the resulting hematopoietic dysfunction need to be known. Established methods for visualization of bone marrow alterations are MRI and bone marrow scintigraphy. We report on the value of bone marrow immunoscintigraphy with ^{99m}Tc-labeled monoclonal anti-NCA-95 antibodies (MAbs) in a case of malignant osteopetrosis before and after bone marrow transplantation (BMT).

CASE REPORT

A 2-mo-old girl was referred to the department of pediatrics in our hospital due to a discrete macrocephaly. She was the first child of related parents from Turkey. The pregnancy was normal, but birth was accomplished by cesarean section. The postpartum clinical course was complicated by findings of a tense fontanel, big skull and protrusion of the forehead. At the time of the third health care examination, the size of skull was above the 97th percentile. Except for an increased lactate dehydrogenase (LDH), all blood values and investigations were normal. A few weeks later, a rotavirus gastroenteritis occurred. At that time, hemoglobin and thrombocytes were decreased, which was considered to be a postinfectious alteration. At the age of 8 wk, the family pediatrician found a decreased blood count, a clear hepatosplenomegaly and increased size of the skull. During a second stay in hospital, physical examination revealed good general condition, but poor nutrition, a macrocephalus and a massive hepatosplenomegaly. Laboratory findings demonstrated a hemoglobin of 7.7 g/dl. White blood cell count was 21,740/ml (normal range 3000–15,000/ml) and thrombocytes 93,000/ml (100,000–400,000/ml). LDH was elevated to 2000 U/l (160–520 U/l) and triglycerides to 465 mg/dl (10–130 mg/dl). Repeated bone marrow aspiration was very difficult and demonstrated 26% atypical cells but no blasts.

Radiographic examinations of the skull and left hand showed a generalized sclerosis, which led to the diagnosis of osteopetrosis (Fig. 1).

The patient was referred to the department of nuclear medicine for bone marrow scintigraphy. We intravenously injected 15 μg anti-NCA-95 antibodies (MAb BW 250/183, Behring Marburg, recently distributed by CIS International, Dreirich, Germany) labeled with 30 MBq (0.8 mCi) ^{99m}Tc. Whole-body scans were obtained 4 hr after injection using a double-head gamma camera system equipped with low-energy, high-resolution collimators

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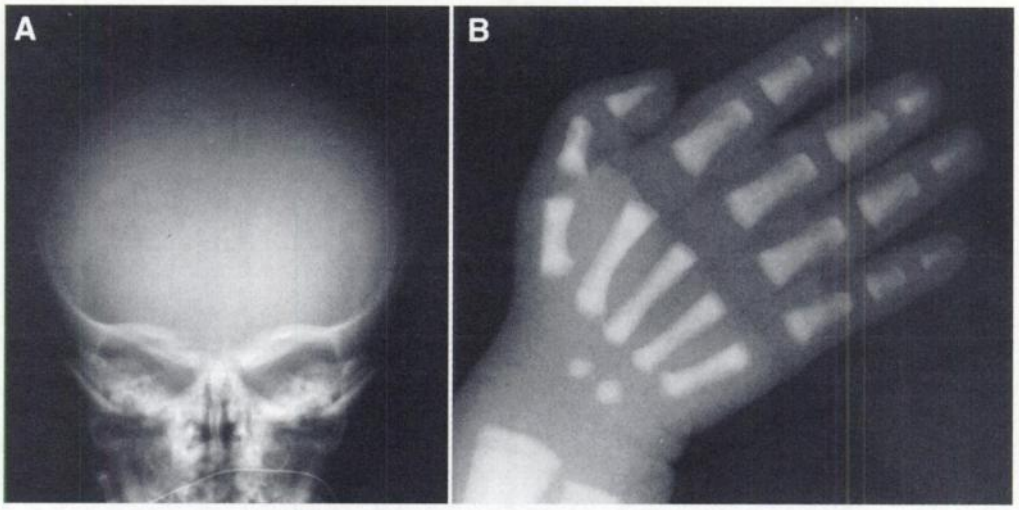

FIGURE 1. Radiograph images of (A) head and (B) right hand demonstrate typical bone sclerosis.

(Bodyscan, Siemens, Erlangen, Germany). Granulopoietic bone marrow was only detectable at the skull base and to a lesser extent in the calvarium (Fig. 2). The rest of the skeleton did not show any antibody accumulation, but uptake in the liver and spleen was increased as in the case of extramedullary hematopoiesis.

The first therapeutic approach with corticosteroids resulted in normalized hemoglobin and thrombocytes. However, decreased blood counts occurred after the medication was stopped. At 5 mo of age, BMT was performed from her human leukocyte antigen-haploidentical father. Before BMT, hemoglobin was 7.2 g/dl, thrombocytes decreased to 45,000/ml (100,000–400,000) and white blood cells to 2220/ml (normal range 3000–15,000/ml).

Four months after BMT, the patient had improved clinically and laboratory findings demonstrated normal values. Hemoglobin had increased to 11.0 g/dl. White blood cell count was 4920/ml (normal 3000–15,000/ml) and thrombocytes were 295,000/ml (100,000–400,000/ml). Bone marrow imaging at this time (Fig. 3) revealed normal distribution of hematopoietic bone marrow. Compared with the first study, uptake in the calvarium was still increased, and tracer accumulation in the liver and spleen had normalized.

DISCUSSION

Malignant osteopetrosis is a very rare hereditary disease of autosomal-recessive transmission that causes osteoclastic malfunction and subsequent general osteosclerosis. It is more frequently seen in countries where inbreeding is common such as Costa Rica or Saudi Arabia (*5*). Whereas the dominant or benign form usually shows no clinical symptoms, the infantile or malignant form can be fatal within the first decade without treatment. Symptoms of infantile osteopetrosis are anemia, granulocytopenia and thrombocytopenia, which may cause death by infection or bleeding. Neurological sequelae such as cranial nerve compression with blindness, deafness or facial nerve paresis are also seen. Occasionally, these are accompanied by hydrocephalus, convulsions and mental retardation (*1*). The sooner patients become symptomatic, the more severe is the clinical course (*2*). The radiological diagnosis is easily made by characteristic features such as generalized bone sclerosis (especially skull base, distant radius and ulna and proximal humerus) without corticomedullary demarcation and, sometimes, bone within a bone or endobone phenomena (*6*).

Current therapeutic approaches are based on different pathogenetic considerations. The assumed failure of osteoclasts causing diminished resorption of calcified cartilage is treated with high doses of calcitriol, which was found experimentally effective in stimulating osteoclast formation and function (*7*).

Recently, BMT for treatment of malignant osteopetrosis was

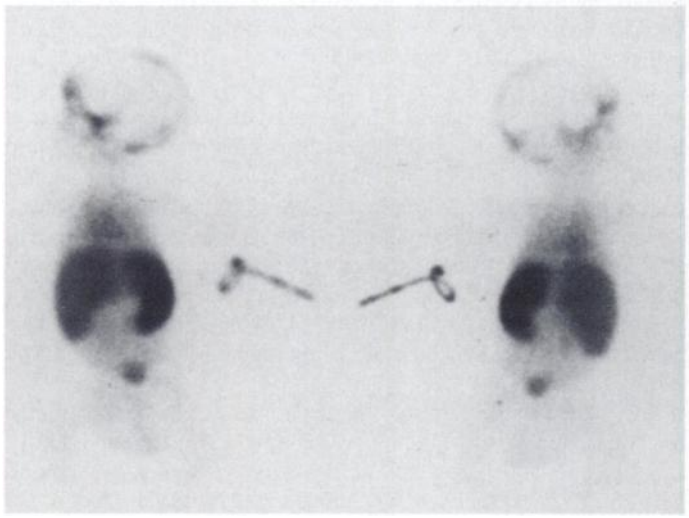

FIGURE 2. Bone marrow immunoscintigraphy with ^{99m}Tc-labeled anti-NCA 95 antibodies 4 hr postinjection shows hematopoietic bone marrow in skull base and areas of extramedullary hematopoiesis in liver and spleen.

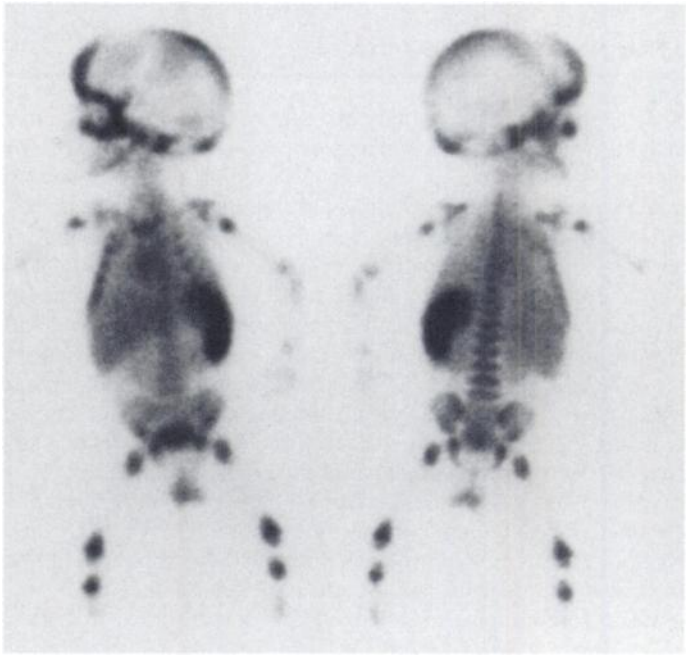

FIGURE 3. Whole-body bone marrow immunoscintigraphy shows tracer accumulation in large part of skeleton demonstrating good therapy outcome after BMT.

introduced by Coccia et al. (*8*). Until now, this method appeared to be the only curative therapy of osteopetrosis with a success rate of 13%–78% (*5,9*) depending on the histocompatibility between donor and patient. By providing large numbers of osteoclast precursors, BMT induces normal bone resorption and reversal of the osteopetrotic state (*10*).

For planning therapy and evaluating success of BMT, the individual bone marrow stores should be known. There are currently two established methods for visualizing bone marrow, MRI and bone marrow scintigraphy. In most of the previously reported cases, bone marrow scintigraphy was performed using ^{99m}Tc-sulfur colloid or ^{111}In-labeled white blood cells (*11,12*). We applied ^{99m}Tc-labeled anti-NCA-95 antibodies. The advantage of our method is the selective MAb binding to granulocytes and their precursor cells, whereas ^{99m}Tc-sulfur colloid delineates only the reticuloendothelial system. Limitations of the conventional technique are caused by high tracer uptake in the liver and spleen, which hampers evaluation of neighboring skeletal areas (e.g., ribs, spine).

In our case, the only visible marrow store was localized at the base of the skull. Increased extramedullary hematopoiesis was found in the liver and spleen. The remaining skeleton did not show any hematopoietic activity. This corresponds to results from a study by Elster et al. (*2*), who described three stages of bone marrow distribution in infantile osteopetrosis depending on the age of the patient. During the first year of life, bone marrow stores are found in the skull base as we demonstrated in this case. The marrow activity of the skull base, in these cases, is significantly higher than in the calvarium. In later development, the marrow stores are evenly distributed between skull base and calvarium (Stage II). Stage III is characterized by extensive bone marrow storage in the calvarium. We suggest this is the normal course of the disease although the findings of Elster et al. (*2*) were made during several therapeutic efforts. The second bone marrow immunoscintigraphy of our case demonstrated redistribution of bone marrow after BMT. The shift of bone marrow to the physiological sites was made possible by the transplanted osteoclasts, which induced normal bone resorption.

CONCLUSION

This case demonstrates the usefulness of BMT to treat infantile or malignant osteopetrosis. Bone marrow scintigraphy with ^{99m}Tc-labeled anti-NCA-95 antibodies proved suitable for demonstrating the extent of disease as well as patient response to treatment.

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