osteopetrosis is a rare genetic disease with abnormal bone remodeling caused by defective osteoclast-mediated bone resorption. There are three clinically distinct phenotypes of osteopetrosis: the infantile malignant autosomal recessive form, the intermediate autosomal recessive form, and the adult benign autosomal dominant form (1). To date, mutations have been identified in carbonic anhydrase II (CAII), TCRG1 (a proton pump), CLCN7, and gl/gl genes. Genetic defects causing the autosomal dominant form are usually due to mutations in the CLCN7 gene, which encodes a chloride channel (2).

The infantile malignant form of osteopetrosis presents during infancy with symptoms related to malformed mastoid and paranasal sinuses. Small cranial foramina may compress cranial nerves, causing blindness, deafness, and oculomotor paresis. Failure to thrive and fractures are characteristic findings. Due to reduction of the bone marrow cavity, patients usually have anemia and thrombocytopenia with extramedullary erythropoiesis. Untreated children usually die during the first decade of life due to hemorrhage, infections, and severe anemia. About 40% of patients present with fractures related to brittle osteopetrotic bones, or with osteomyelitis. There is usually sufficient marrow cavity for normal hematopoiesis. Patients have generalized osteosclerosis, and radiological features are usually diagnostic. Radiography is a useful modality for diagnosis of osteopetrosis, in which bones are uniformly sclerotic. The entire skull is thickened and dense, especially at the base. Sinuses are small and underpneumatized. Vertebrae are extremely radiodense on radiographs (1,3,4).

Case report

A 42-year-old female patient presented with numbness in her hands, and belt-like paresthesia in her chest in the T2 dermatome, which lasted for one week. Additional review of systems was unrevealing. She was diagnosed with osteopetrosis at the age of 18 after she had sustained a pathologic fracture of her right femur. Her family history was remarkable for 14 adult relatives (2 aunts and 12 cousins) with osteopetrosis. The patient also had other 2nd degree adult relatives with nonsyndromic deafness without other neurologic manifestations. She was not on any medications for osteopetrosis. Cranial and wrist radiographs showed diffuse hyperostosis. Bones were uniformly sclerotic and, typically, appeared as a bone within a bone. The entire skull was thickened and dense, especially at the base. Vertebrae were extremely radiodense, and showed extramedullary hematopoiesis (Fig. 1).

The patient's physical examination was unremarkable, with stable vital signs. Her neurological exam revealed diminished superficial sensation below C4, and diminished vibration sense and increased deep tendon reflexes in her lower extremities bilaterally without pathological reflexes.
Her complete blood count showed anemia (hemoglobin, 8 g/dL; hematocrit, 24%), normal platelet count (282,000/mm³) with normal blood chemistry values. Magnetic resonance imaging (MRI) with a 3 T unit (Siemens, Erlangen, Germany) showed multiple periventricular demyelinating lesions and an enhancing lesion in the cervical spinal cord at the level of C4 (Fig. 2a–d). Her visual and sensory evoked potentials were within normal limits. A lumbar puncture was performed. While cerebrospinal fluid (CSF) cell count, protein, and glucose levels were within normal range, CSF had increased IgG index (0.75) and oligoclonal bands. Other laboratory findings were normal (CRP, vitamin B₁₂, Treponema pallidum hemaglutination antibody, anticyclophilin IgM-IgG, antinuclear antibody, anti-dsDNA, and lupus anticoagulant). The patient was treated with intravenous high-dose methylprednisolone (1 g once a day) for five days with an oral taper in one week. Her complaints resolved completely one month after steroid administration.

Three years after her first episode, the patient had another relapse of right optic neuritis and numbness in her left groin. Her neurological exam revealed decreased vision in her right eye (6/10) and diminished superficial sensation below T10. Her MRI showed two enhancing lesions; one in the right optic nerve, and one in the thoracic spinal cord at the level of T10 along with three new enhancing lesions in the frontal white matter and right brachium pontis (Fig. 2e-h). After the second relapse, the patient was diagnosed with multiple sclerosis, and her relapse was treated with a five-day course of intravenous high-dose methylprednisolone (1 g once a day).

Three months after her second relapse, the patient presented with acute left hemiplegia. Computed tomography (CT) (16-slice row CT scanner, Siemens) showed a 5.5 x 3.5 x 4.5 cm right temporal lobe hematoma. This hematoma was evacuated. Because the patient was normotensive, in order to exclude any vascular abnormalities or aneurysm, CT angiography was performed pre-operatively, and no pathological findings were observed (Fig. 3). Except for her platelet count (118,000/mm³), her routine lab values were normal. The brain biopsy performed during the operation to exclude vasculitis or amyloid angiopathy was normal. The postoperative course was uneventful, and the patient was discharged from the hospital with left hemiparesis.

Discussion

The infantile malignant autosomal recessive form of osteopetrosis can often present with hemorrhage in various tissues, as well as fatal infections due to low granulocyte levels (4–8). In contrast, the adult benign autosomal dominant form is not associated with hemorrhage, but usually presents with orthopaedic and neurological problems (e.g., cranial nerve compression, hydrocephalus, seizures, or ischemic stroke). Although rare, cerebral calcification and neuronal accumulation of
Figure 2. a–h. MRI images of the patient’s central nervous system. Axial FLAIR cranial image (a) shows a hyperintense lesion (arrow) in the left centrum semiovale. Postcontrast axial SE T1-weighted cranial image (b) demonstrates contrast enhancement in the lesion (arrow). All cranial images reveal prominent thickening of the calvarium with medullary hypointensity compatible with sclerosis. Sagittal TSE T2- and TSE T1-weighted spinal images (c, d) show a cervical intramedullary demyelinating lesion at the level of C4 with contrast enhancement, and diffuse sclerosis of the cervical vertebrae. Sagittal TSE T2- and SE T1-weighted cranial images (e, f) disclose a new enhancing periventricular punctate lesion (arrows). Sagittal TSE T2- and postcontrast TSE T1-weighted spinal images (g, h) demonstrate an intramedullary enhancing lesion (arrows) at the level of T10, and sclerosis of the thoracic vertebrae.

Figure 3. a–c. Axial CT image without contrast (a) revealed a hyperdense heterogenous mass compatible with right basal ganglia hemorrhage. Coronal subsegmental MIP of cranial CT angiography (b) shows normal vascular structures. Early postoperative axial CT image (c) demonstrates residual changes.
ceroid lipofuscin may cause neurono-
pathic osteopetrosis (8). In all forms
of osteopetrosis, the main features are
pathologic alteration of osteoclastic
bone resorption, and thickening of
bones. Our patient had typical radio-
logic findings for osteopetrosis, as well
as a history of pathologic fracture. To
our knowledge, this is the first report
of a case of a cerebral hemorrhagic
complication associated with the adult
form of osteopetrosis.

In contrast to the infantile form, the
adult form is not expected to confer
bone marrow deficiency and resultant
low platelet counts. Accordingly, our
patient initially had normal platelet
counts, although they decreased dur-
ing follow-up at the same time as the
formation of a temporal hematoma.
Anemia and thrombocytopenia might
thus have been caused by decades of
intense extramedullary hematopoiesis
(depicted in Fig. 1c), over-consuming
and exhausting the hematopoietic re-
sources, ultimately resulting in intrac-
erebral bleeding.

An association between osteopetrosis
and multiple sclerosis is more enigmat-
ic, and is open to speculation. While
the coexistence of these disorders
might be purely coincidental, a muta-
tion in the CLCN7 gene might have
played a pathogenic role. Because there
are many asymptomatic adult family
members, we suspect that the CLCN7
gene might be involved. The chloride
channel exists as a dimer of CLCN7
proteins on the cell membrane. A het-
erozygous mutation in one allele is be-
lieved to interfere with the function of
the chloride channel despite the pres-
ence of normal protein expressed by
the other allele (9); however, there are
no data to suggest a possible relation-
ship between the membrane channel
proteins and multiple sclerosis or cer-
ebonal hemorrhage. Further research on
chloride channel proteins may disclose
an etiologic link between these two dif-
ferent diseases.

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