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A rare case of multiple sclerosis and cerebral hemorrhage associated with osteopetrosis

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ABSTRACT
Osteopetrosis, or Albers-Schönberg disease, is a rare hereditary disease characterized by osteoclast dysfunction and consequent diminished bone resorption and disturbed bone building and remodeling, resulting in abnormally dense and brittle bones. Bone marrow failure, pathologic fractures, and neurologic deficits are common. Osteopetrosis is diagnosed on radiographs. Patients have generalized osteosclerosis, and radiographs may show evidence of fractures. We report a case of cerebral hemorrhage and multiple sclerosis associated with the benign adult form of osteopetrosis.

Key words: • *osteopetrosis* • *cerebral hemorrhage* • *multiple sclerosis*

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.

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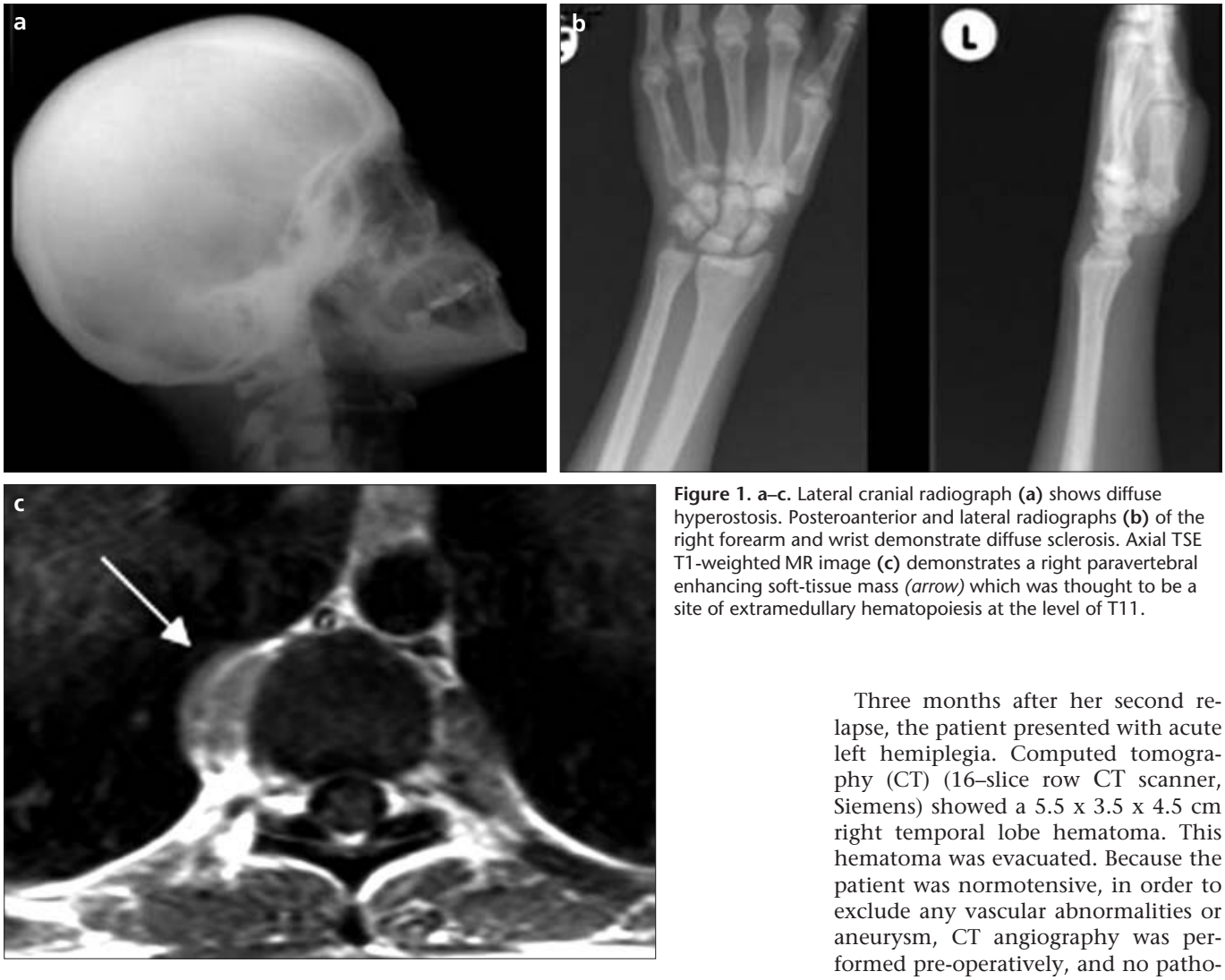

Figure 1. a–c. Lateral cranial radiograph **(a)** shows diffuse hyperostosis. Posteroanterior and lateral radiographs **(b)** of the right forearm and wrist demonstrate diffuse sclerosis. Axial TSE T1-weighted MR image **(c)** demonstrates a right paravertebral enhancing soft-tissue mass *(arrow)* which was thought to be a site of extramedullary hematopoiesis at the level of T11.

Her complete blood count showed anemia (hemoglobin, 8 g/dL; hematocrit, 24%), normal platelet count (282,000/mm^3) 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 B_{12}, *Treponema pallidum* hemaglutination antibody, anticardiolipin 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/mm^3), 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

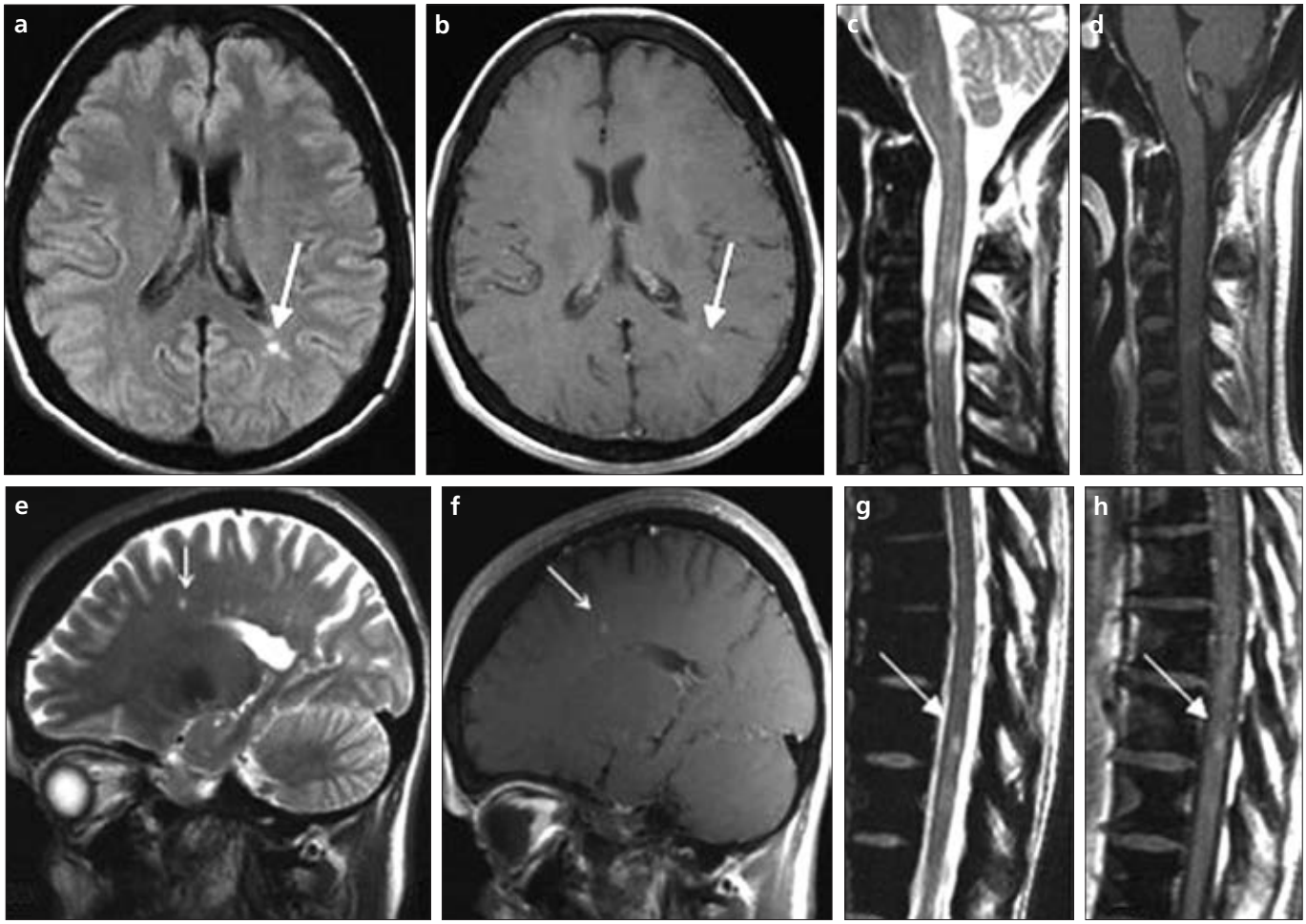

Figure 2. a–h. MRI images of the patient's central nervous system. Axial FLAIR cranial image **(a)** shows a hyperintense lesion *(arrow)* in the left centrum semiovale. Postcontrast axial SE T1-weighted cranial image **(b)** demonstrates contrast enhancement in the lesion *(arrow)*. All cranial images 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 vertabrae.

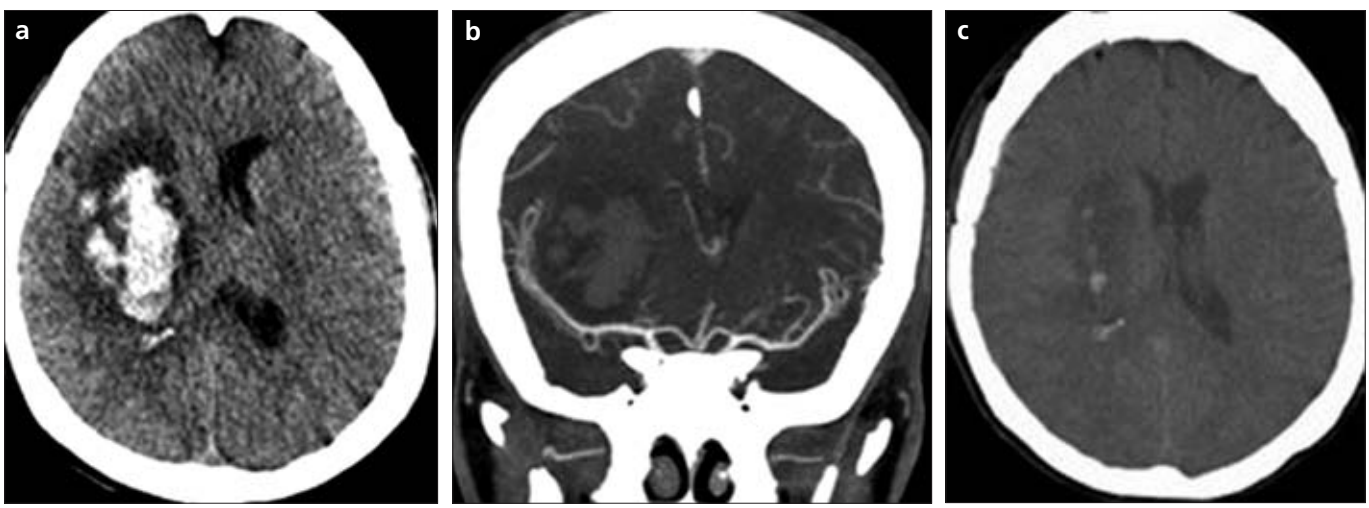

Figure 3. a–c. Axial CT image without contrast **(a)** revealed a hyperdense heterogenous mass compatible with right basal ganglia hemorrhage. Coronal subsegmental MIP of cranial CT angiography **(b)** shows normal vascular structures. Early postoperative axial CT image **(c)** demonstrates residual changes.

ceroid lipofuscin may cause neuronopathic 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 radiologic findings for osteopetrosis, as well as a history of pathological 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 during 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 resources, ultimately resulting in intracerebral bleeding.

An association between osteopetrosis and multiple sclerosis is more enigmatic, and is open to speculation. While the coexistence of these disorders might be purely coincidental, a mutation 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 heterozygous mutation in one allele is believed to interfere with the function of the chloride channel despite the presence of normal protein expressed by the other allele (9); however, there are no data to suggest a possible relationship between the membrane channel proteins and multiple sclerosis or cerebral hemorrhage. Further research on chloride channel proteins may disclose an etiologic link between these two different diseases.

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