Orbital Sclerosing Extramedullary Hematopoietic Tumor

Extradural hematopoiesis can occur in myeloproliferative disorder, including myelofibrosis,^1^ chronic myeloid leukemia,^2^ and, rarely, polycythemia vera.^3^ When fibroblastic proliferation accompanies a solid mass appearance, such lesions have been termed sclerosing extramedullary hematopoietic tumors (SEMHTs).^4^ We describe, to our knowledge, the first case of myelofibrosis with bilateral multiple SEMHTs in the orbitae.

Report of a Case. A 62-year-old woman sought medical treatment in April 2000 because of a slow-growing left lower-lid mass of 1 year’s duration. She had no associated pain, visual loss, or diplopia. Examination disclosed a left lower-lid mass measuring about 3 × 2 × 2 cm. The mass was not tender and was mobile. It had a smooth surface and appeared to be arising from the orbita. The patient’s best-corrected visual acuity was 20/30 OU. Measurement with a Hertel exophthalmometer showed a 2-mm proptosis in the left eye. The intraocular pressure was normal in both eyes. We found no afferent pupillary defect or optic nerve dysfunction. Extraocular movement showed marked limitation of depression and moderate limitation of abduction in the left eye. Fundoscopic findings in both eyes were unremarkable, and the optic disc sizes were within normal limits. Multiple palpable cervical and submandibular lymph nodes were present. The patient had a medical history of myelofibrosis that had been followed up and treated with systemic hydroxyurea since 1997. Splenectomy had been performed in 1997 for massive splenomegaly. There was no evidence of acute myeloid leukemia.

Computed tomography (Figure 1A) confirmed that the left lower-lid mass was arising from the orbita. In addition, multiple bilateral orbital soft tissue densities were present and were more abundant on the left side (Figure 1A and B). These were located predominantly in the intraconal and extracranal compartments, occupying a large part of the retrobulbar space on the left side. The intraconal lesions extended almost to the level of the optic foramen of sphenoid bone on both sides. However, no intracranial extension was present. The extracranal lesions were adjacent to the lacrimal gland. These lesions had ill-defined margins and infiltrated the area around the optic nerves and the lateral rectus muscle. Only minimal contrast enhancement was present. No bony erosion or intraocular involvement or extension was present. No dilated vasculature could be seen.

We performed a left anterior orbitotomy by means of a transcutaneous approach. A rubbery, multinodular pinkish tumor adhering to the surrounding tissue was identified. An incisional biopsy of the tumor was performed, and the specimen was submitted for histopathologic evaluation.

Histopathologic examination showed a mass composed largely of fibrous tissues with whorls of myxoid to sclerotic stroma and thick collagen strands. Numerous megakaryocytes, granulocytes, and erythrocyte precursors were scattered throughout the stroma (Figure 2). Normal maturation of granulocytes and erythrocyte precursors was also identified. The megakaryocytes were highlighted by myeloperoxidase staining (Figure 3), whereas the megakaryocytes showed positive staining for factor VIII–related antigen (Figure 4). No blast cells were present. The diagnosis was SEMHT.^4^

Results of a physical examination showed no evidence of extramedullary hematopoietic tumors elsewhere in the body. No further investigation was undertaken because of the presumed benign nature of the disease, although the patient was closely observed.
temic hydroxyurea was continued, but no additional chemotherapeutic agent or radiotherapy was administered. Follow-up computed tomography in 2001 and 2003 showed no significant change. The patient’s vision remained stable 3 years after her initial presentation.

Comment. Extramedullary myeloid tumors represent a form of extramedullary hematopoiesis and are considered benign. These can be seen as mass lesions and may occasionally arise in patients with chronic myeloproliferative disorders, such as myelofibrosis. Bone marrow exhaustion and fibrosis in myelofibrosis were previously believed to result in compensatory hyperplasia of extramedullary hematopoietic tissues, which has also been termed extramedullary hematopoiesis and tumor formation. The stroma of extramedullary myeloid tumors is usually composed of loose connective tissue with a variable degree of fibrosis. Fibrous hematopoietic tumors was the term used to describe extramedullary myeloid tumors with a predominantly fibrous component. Recently, SEMHT has been used to describe extramedullary myeloid tumor with prominent sclerosis. Remstein et al used this term to emphasize the extramedullary trilineage hematopoiesis and the predominantly sclerotic background. Although extramedullary hematopoiesis usually occurs in the liver, spleen, and lymph nodes, SEMHTs may occasionally manifest as mass lesions in the abdomen and on the serosal surface. Other sites include the skin, breast, and lung. Extramedullary myeloid tumors represent a form of extramedullary hematopoiesis and are considered benign. These can be seen as mass lesions and may occasionally arise in patients with chronic myeloproliferative disorders, such as myelofibrosis. Bone marrow exhaustion and fibrosis in myelofibrosis were previously believed to result in compensatory hyperplasia of extramedullary hematopoietic tissues, which has also been termed extramedullary hematopoiesis and tumor formation. The stroma of extramedullary myeloid tumors is usually composed of loose connective tissue with a variable degree of fibrosis. Fibrous hematopoietic tumors was the term used to describe extramedullary myeloid tumors with a predominantly fibrous component. Recently, SEMHT has been used to describe extramedullary myeloid tumor with prominent sclerosis. Remstein et al used this term to emphasize the extramedullary trilineage hematopoiesis and the predominantly sclerotic background. Although extramedullary hematopoiesis usually occurs in the liver, spleen, and lymph nodes, SEMHTs may occasionally manifest as mass lesions in the abdomen and on the serosal surface. Other sites include the skin, breast, and lung.

Morphologically, SEMHTs are characterized by fibromyxoid to sclerotic stroma with thick collagen strands containing megakaryocytes, granulocytes, and erythrocyte precursors. The fibromyxoid stroma may mimic various myxoid neoplasms, such as myxofibrosarcoma or myxoid liposarcoma. Moreover, the large, irregular, hyperchromatic nuclei of megakaryocytes may be misinterpreted as malignant tumors, such as Hodgkin disease, histiocytic lymphoma, and large cell lymphoma. However, careful examination will disclose cells with dark, round nuclei consistent with erythrocyte precursors, and oval cells with faint chromatin and a moderate amount of eosinophilic granular cytoplasm reminiscent of granulocytes. This raises the suspicion that the large cells may be megakaryocytes and that the histological results may indicate SEMHT. The megakaryocytes are scattered throughout the matrix and may be found singly or in clusters. No atypical lymphoid or myeloid blast population is present.

Immunohistochemical studies are necessary to demonstrate the trilineage of hematopoietic cells. Granulocytes are identified with myeloperoxidase stain. Erythrocyte precursors stain positively with glycophorin A. The expression of CD31 or factor VIII confirms the presence of megakaryocytes. The SEMHT is distinguished from the classic extramedullary myeloid tumors by the presence of a predominantly fibrous stroma. The stroma of extramedullary myeloid tumors is usually composed of loose connective tissue with a variable degree of fibrosis. Fibrous hematopoietic tumors was the term used to describe extramedullary myeloid tumors with a predominantly fibrous component. Recently, SEMHT has been used to describe extramedullary myeloid tumor with prominent sclerosis. Remstein et al used this term to emphasize the extramedullary trilineage hematopoiesis and the predominantly sclerotic background. Although extramedullary hematopoiesis usually occurs in the liver, spleen, and lymph nodes, SEMHTs may occasionally manifest as mass lesions in the abdomen and on the serosal surface. Other sites include the skin, breast, and lung.

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It is believed that myelofibrosis results from a proliferation of polyclonal fibroblasts that is secondary to cytokines released from clonal megakaryocytes or platelets. The orbita is not a typical site for extramedullary hematopoietic tumors. Splenectomy is not a typical site for hematopoiesis in either fetuses or adults, and the cause of SEMHT in the orbita is unknown. It has been postulated that circulating stem cells are increased in the peripheral blood of patients with myelofibrosis. These stem cells may deposit in peripheral organs via adhesion integrin molecules and may give rise to ectopic hematopoietic foci.

Although our patient developed orbital masses after splenectomy, it is not clear whether the formation of SEMHTs is related to splenectomy. Splenectomy may not be an important factor in the formation of SEMHTs. Moreover, splenectomy is commonly performed in patients with myelofibrosis, but the development of SEMHTs is relatively rare.

Although the initial imaging looks alarming, as of this writing, our patient’s disease has had a relatively benign course. The remaining orbital lesions have been more or less the same for the past 3 years, as serial computed tomography has shown no significant changes. In addition, the patient’s vision has remained stable. These findings suggest a benign disease.

In summary, this is the first reported case, to our knowledge, of SEMHT in the orbita. Sclerosing extramedullary hematopoietic tumors can histologically and radiologically mimic other soft tissue neoplasms. History of a myeloproliferative disorder and a high index of suspicion are important in making the diagnosis. The clinical course is relatively benign, and aggressive local therapy does not seem to be mandatory.

**Figure 4.** Immunostaining for factor VIII highlights megakaryocytes (original magnification ×600).

**Limbal Stem Cell Deficiency Associated With LADD Syndrome**

The lacrimo-auriculo-dento-digital (LADD) syndrome is an autosomal dominant hereditary disease with variable expression. It was first described in 1967 by Levy as an isolated case of bilateral absence of the tear system, cup-shaped ears, dry mouth, and dental, arm, and digital abnormalities. Subsequently, new clinical findings such as renal anomalies, absent salivary glands, congenital hip dislocation, congenital biahal and diaphragmatic hernias, sensory and conductive deafness, hypodontia, limb anomalies, xerostomia, and xerophthalmia were described associated with this syndrome.

Thirty-five cases of LADD syndrome are described in the literature and most of them include ocular involvement. In particular, 71% showed hypoplasia or aplasia of the tear glands, hypoplasia or aplasia of