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VERSITA

GIANT CAVERNOMA OF THE SKULL AND SKELETAL-EXTRASKELETAL ANGIOMATOSIS ASSOCIATED WITH PARAPROTEINEMIA

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Abstract

Skeletal-extraskeletal angiomatosis is defined as a benign vascular proliferation affecting the medullar cavity of the bone and at least one other type of tissue, including skin, subcutaneous tissue, viscera, muscle, or synovium, and which does not spread to avascular tissue such as cartilage. Primary hemangiomas/ cavernous hemangiomas (cavernomas) are exceedingly rare in the skull, accounting for 0.2% of all osseous neoplasms and are usually located in frontal and parietal bones. The authors present the case of a 66-year-old man who was admitted with right-side hemiparesis. MRI revealed a destructive bone lesion of the left frontal bone. Digital subtraction angiography of the brain did not reveal pathological vascularization, but a minor submucous hemangioma was seen in the nasal airway. Urine test for Bence-Jones proteins was positive for IgG λ light chain. Bone marrow aspiration and CSF analysis revealed no evidence of systemic myelomatosis suggesting a monoclonal gammopathy of undetermined significance. A highly vascular tumor was surgically removed. The histopathology verified cavernous hemangioma of the skull and the nasal submucous hemangioma. We discuss the diagnostic procedure, possible pathophysiological mechanisms and treatment implementation. It is possible that immunoglobulins from monoclonal gammopathies have an etiologic role in the development of the bone and skin changes in older patients, as an acquired condition, by producing a vascular injury that could lead to the multiple hemangiomas in skeletal-extraskeletal angiomatosis. To prevent misdiagnosis with lesions of other origins, multiple lesions of the head must be resected and histopathologically verified. In conclusion, to the best of our knowledge, this is the first case of giant cavernous hemangioma of the skull associated with paraproteinemia and skeletal-extraskeletal angiomatosis limited to the head.

Keywords

• Skull • Cavernoma • Hemangioma • Monoclonal Gammopathy • Skeletal-extraskeletal angiomatosis • Paraproteinemia

Introduction

Skeletal-extraskeletal angiomatosis is defined as a benign vascular proliferation affecting the medullar cavity of the bone and at least one other type of tissue, including skin, subcutaneous tissue, viscera, muscle, synovium, or bone, and which does not spread to avascular tissue such as cartilage [1]. Primary hemangiomas / cavernous hemangiomas (cavernomas) are exceedingly rarely found in the skull, accounting for 0.2% of all osseous neoplasms [2] and are usually located in frontal and parietal bones [3-5]. Although commonest in the fourth decade of life (25% of all described cases), hemangiomatosis has been reported to occur from the third week of life to 77 years of age [4,6]. These tumors grow slowly before causing various symptoms such as headaches, swelling, erythema, facial deformity, focal neurological signs, or extremely rarely hemorrhages [1]. Massive enlargement across tissue planes is very uncommon [6]. The etiology of hemangiomatosis is still unknown, and is thought to be related to excess vascularization of the bone and other tissues. Salama *et al.* 1999 first proposed that immunoglobulin deposits from a monoclonal gammopathy producing vascular injury leads to the angiomatosis [7]. Reviews and case reports on skeletal-extraskeletal angiomatosis are few. Here we describe the first case of giant cavernous hemangioma of the skull as part of a skeletal-extraskeletal angiomatosis limited to the head in association with monoclonal gammopathy of undetermined significance (MGUS) and paraproteinemia.

Case Report

History and presentation. A 66-year-old man with positive familial history to calvarian rarefaction

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was admitted to the University Hospital Zagreb Neurology Department in 2005 after three months of unstable walking, paresthesias, and right-side weakness (suggesting supranuclear involvement). Neurological examination of the patient showed right-sided hemiparesis. A comprehensive work-up, including a head non-contrast multislice computed tomography (MSCT), magnetic resonance imaging (MRI) with and without Gadolinium-based contrast, digital subtraction angiography (DSA) of the brain, bone scintigraphy, total radiographical body skeleton survey, determination of urine Bence-Jones proteins and serum myeloma protein, total blood count and urine analysis were carried out to rule-out multiple myeloma. Total serum protein, gammaglobulin, erythropoietin, serum calcium, urine calcium, other serum electrolytes, prothrombine time, partial thromboplastine time, and international normalized ratio were all within the normal ranges. Serum protein electrophoresis revealed slightly increased levels of IgA (7.8 g/l) and low levels of IgG (5.8 g/l) and IgM (0.4 g/l) immunoglobulins. Laboratory investigation of the serum excluded hyperglobulinemia, anemia, trombocytopenia, neutropenia and hypercalcemia. A urine test for Bence-Jones proteins was positive to IgG λ light chain and measured between 50-150 mg/day. A bone-marrow biopsy demonstrated 10% plasmocytosis. Non-contrast MSCT revealed numerous inhomogenous left-sided frontoparietal osteolytic lesions, with a prominent one in the area of the bone's tabula interna measuring 3.5 cm in diameter. The patient was therefore suspected for having a plasmacytoma of the skull. A brain MRI protocol included: a) T1-weighted axial image (750/12, field of view 19.5x22 cm, imaging matrix 226x256, section thickness 5 mm) and b) T2 axial image (5600/90, field of view 20x23 cm, imaging matrix 250x296, section thickness 4 mm). MR images were interpreted by the neuroradiologist for the hyperintensities on axial and sagittal T1 and T2 weighted sequences and for enhancement after administration of Gadolinium-based contrast. The process was located in front of the coronal suture and spread along the thickened leptomeninges and dura mater.

Regular and Gadolinium-enhanced contrast MRI (Siemens, 1.5 T) scans in T1- and T2-weighted sequences showed hyperintensities that confirmed a presence of a diffuse, giant, expansive mass destroying diploic sutures and tabula interna of the left frontal bone and crossing over the midline toward the dorsal part of right frontal bone (Figure 1). The central part of the lesion was located in front of the coronal suture and spreaded along the thickened leptomeninges and dura mater. Coronal slices revealed the skull to be populated with numerous punctiform zones of bone rarefaction in the frontoparietal region (Figure 2). X-ray processing of the skeleton along with densitometry did not detected lytic lesions nor additional marrow abnormalities consistent with multiple myeloma. DSA of the brain excluded patological vascularization of the lesion, as well as an arteriovenous malformation (Figure 3). During the middle and late artery phase of the selective imagery of the right external carotid, one minor submucous hemangioma has been discovered in the anterior lateral part of the upper nasal airway (Figure 3). A bone scintigraphy revealed accumulation of the radioisotope in the right parietal bone (not shown). All of these

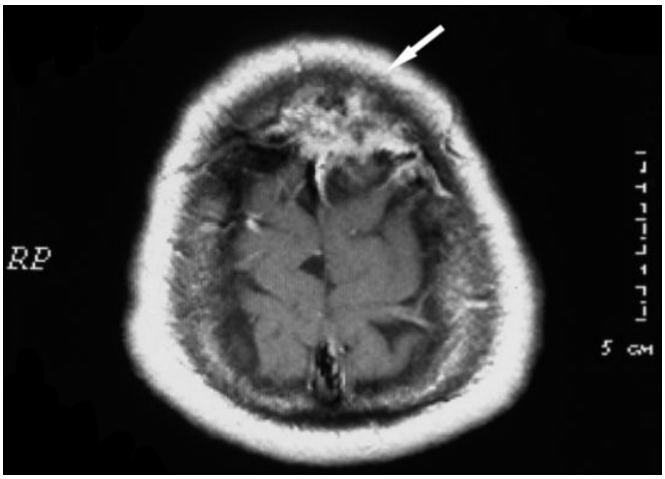

Figure 1. Cavernous hemangioma of the skull. Axial MRI in T1 sequence showing a large expansive and destructive hyperintense lesion within diploic suture and tabula interna of the left frontal bone (white arrow).

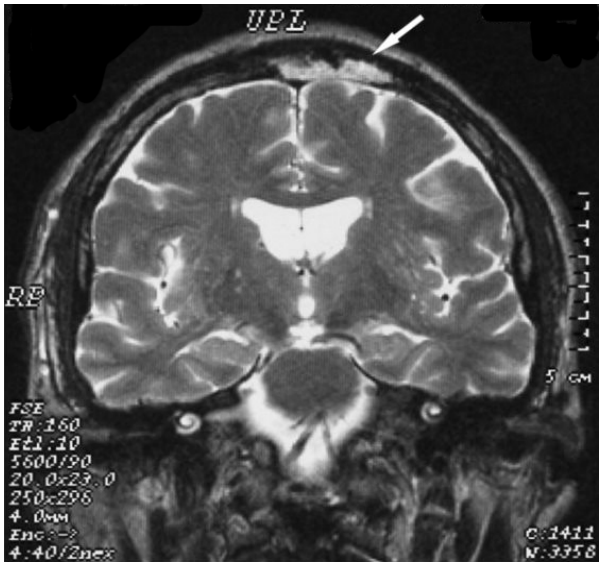

Figure 2. Coronal MRI in T2 sequence demonstrating a hyperintense lesion of the left frontal bone crossing the midline toward the dorsal part of the frontal bone (white arrow).

investigations were unremarkable in terms of a systemic myelomatosis (the patient was suspicious for having solitary plasmacytoma of the skull).

Surgery and Postoperative Course. The patient underwent neurosurgical treatment. The tumor was approached by the left side parietal osteoclastic craniotomy with additional removal of the osseous mass without dural destruction. Cranioplasty with Palakos® was achieved and a subdural drain left in place for 24 hours. During this procedure the macroscopically oval collection of tissue (measuring 5.0 x 4.0 cm in diameter and about 0.8 cm thick, containing superficially and centrally a smaller brownish mass measuring 2.5 cm in diameter) was exposed and excised. Intraoperative histopathology suggested that the tumor was not malignant (Figure 4). Histologic examination of paraffin-embedded tumor specimens revealed a highly vascularized mass that was composed of numerous vascular spaces covered with endothelial cells (Figure 4). Based on these histopathological results, a diagnosis of a giant cavernoma of the skull was made.

The postoperative course of the patient was uneventful. As the neurological symptoms were due to a directly expansive non-infiltrating superficial growth of the lesion, postoperatively the patient noted relief of the symptoms with complete recovery from sensorimotor disturbances. The patient has not exhibited any additional neurological deficits. After discharge from the hospital the patient did not undergo additional therapy. Follow-up MR imaging every two years confirmed full tumor removal and no recurrence. At 5 years postoperatively the patient has recovered completely, and MR images continued to be unremarkable for tumor recurrence. At the most recent visit in January 2011, the bone was unremarkable and the marrow disease had not progressed.

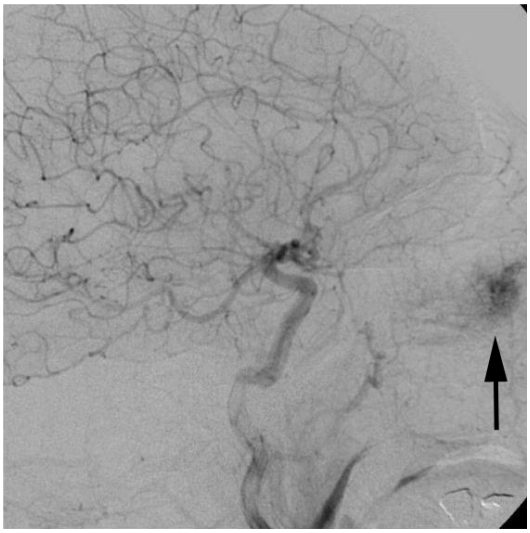

Figure 3. Digital subtraction angiography (DSA) shows no arteriovenous malformation or pathological vascularization of the lesion. Middle and late arterial phase of the selective imaging of the right external carotid shows a minor submucous hemangioma in the anterior lateral part of upper nasal airway (black arrow).

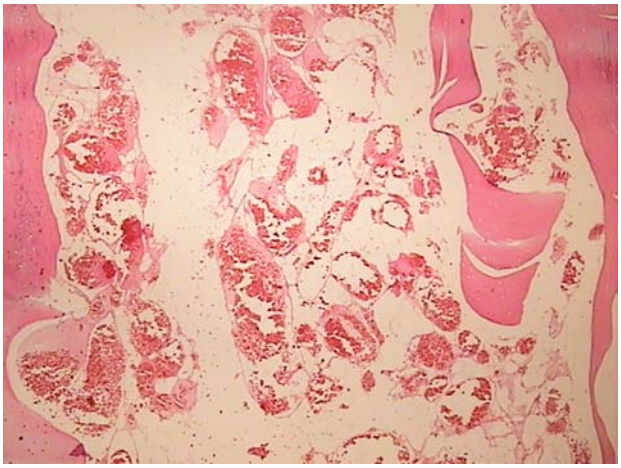

Figure 4. Cavernous hemangioma (cavernoma) of the skull (hematoxylin-eosin stain, magnification 40x).

Discussion

Hemangiomas represent an abnormal proliferation of blood vessels that may occur in any vascularized tissue [8-10]. It is still debatable whether these lesions are neoplasms, hamartomas, or vascular malformations. Hemangiomas occur most often in the skin or subcutaneous tissue, while a hemangioma of bone is much rarer condition. Most commonly, hemangiomas are localized in a single area, but multiple hemangiomas may occur in an individual by a process known as hemangiomatosis, such as in the case of skeletal-extraskeletal angiomatosis [1]. In the patient we describe here, we detected two cavernous hemangiomas, a giant one in the skull and minor one in the extraskeletal tissue (nasal submucosa).

A single case of cutaneous angiomatosis in association with monoclonal gammopathy has been described long time ago [11]. Another, more recent, case of skeletal angiomatosis in association with gastrointestinal angiodysplasia and paraproteinemia has been reported [12], but simultaneous presence of skeletal and extraskeletal angiomatosis associated with monoclonal gammopathy has not been described before. Therefore, this is probably the first case of skeletal-extraskeletal angiomatosis limited to the head and associated with MGUS and urinary Bence-Jones proteins of the IgG λ (light chain) type described.

Devaney *et al.* 1994 reported 14 cases of angiomatosis, three of them older than 60 years.

One of these 14 cases developed malignant lymphoma. Therefore, it is conceivable that immunoglobulin deposits may have an etiologic role in the development of the bony changes in elderly patients (angiomatosis being an acquired condition in this case). Furthermore, it has been hypothesized that cystic skeletal angiomatosis could develop either as a metastasing angioma or a vascular hamartoma, a congenital malformation of multicentric origin [7]. As angiomatosis of skin has been reported in association with intravascular immunoglobulin deposits from a monoclonal gammopathy, it also seems plausible that imunoglobulin deposits could have first produced vascular injury leading to the angiomatosis [7]. Although M protein usually remain stable over time, MGUS can evolve to multiple myeloma, Waldenström macroglobulinemia, chronic lymphocytic leukemia, plasmacytoma, amyloidosis, or lymphoma. In patients with MGUS or asymptomatic multiple myeloma, systemic treatment should be deffered until there is evidence of disease progression [13].

Hemangioma of the skull usually require surgery when symptoms are substantial enough or to prevent hemorrhages. It is important to confirm the diagnosis, as more agressive neoplasms such as solitary skull plasmacytoma or metastatic carcinoma may mimick hemangioma. Radiation may be used for the treatment of symptomatic hemangiomas that are surgically untreated. Chemotherapy has been used in the treatment of extensive vascular proliferation in extensive hemangiomatosis. Rarely, hemangiomas may be associated with other pathologic processes, such as coagulopathies and tumor-induced osteomalacia.

Our patient underwent neurosurgical treatment that led to full remission of the symptoms. Resection of the tumor revealed a highly vascularised lesion measured 3.5 cm in diameter and was classified histopatologically by the predominant cavernous type of vascular origin. In agreement with previous studies showing that most hemangiomas of bone are cavernous, and rarely capillary or mixed [14], we confirmed that in our case the hemangioma of the skull was of the cavernous type.

As histopathological findings excluded solitary skull plasmacytoma, the presence of Bence-Jones IgG λ light chain proteinuria remained unexplained. MGUS is the most common cause of laboratory-discovered monoclonal gammopathy. According to Durie and Salmon criteria for clinical staging system for multiple myeloma [11], in patients without lytic lesions, less than 5% of bone marrow plasma cells, a serum monoclonal protein levels below 20 g/l, and Bence-Jones urinary proteins value below 50 mg/day, are highly indicative of MGUS [2,15]. In the absence of malignant plasma cells and absence of osteolytic lesions, positive Bence-Jones proteins in urine, decreased residual IgA and low residual IgG requested a constant follow-up of our patient. In many patients with small amounts of monoclonal light chain in urine, the M-protein in the serum remains stable for many years. Disease progression from MGUS to multiple myeloma is likely to occur within 2-19 years in 19% of patients [15]. In the follow-up examination carried out 12 months after the operation our patient was doing well and without development of multiple myeloma.

The diagnosis of the cavernoma of the skull should be considered in the differential diagnosis of a solitary destructive mass of the calvaria because it can mimick solitary plasmacytoma or metastatic processes clinically or neuroradiologically. Such patients share a common radiologic picture of a osteolytic lesion, which can be interpreted as a solitary metastasis [1]. A case of an intradural hemorrhage from a cavernous hemangioma of the skull has also been reported [16]. To prevent misdiagnosis with lesions of other origins, an appropriate sequence of investigations is paramount to implement adequate treatment. Besides neuroimaging investigations and laboratory tests, all skull neoplasms need to be resected and histopathologically identified.

Angiomatosis shows no tendency toward malignant degeneration. Malignant de-differentiation may occur following radiation treatment for this condition [8,17]. Treatment of the cavernoma of the skull in our patient was surgical, with no additional therapy. There was no sign of malignant degeneration of the bone 5 years after diagnosis in this case. This patient's medical history clearly indicates a need for future investigations in order to determine key mechanisms in the pathogenesis of multiple hemangiomas.

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