

Extramedullary hematopoiesis in the facial sinus in a patient homozygous for Hemoglobin Lepore: the first case in literature

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Abstract. – Extramedullary hematopoiesis (EMH) is a proliferation of hematopoietic tissue outside the bone marrow. The most affected areas are paravertebral ones. We report the case of a patient with homozygous Hb Lepore, not regularly transfused since the age of four years until the age of 29 years, when paravertebral heterotopic masses were first observed. After about 10 years she started reporting clinical signs suggestive of sinusitis. Computed tomography (CT) and Magnetic Resonance Imaging (MRI) showed heterotopic masses in the ethmoid and in the frontal sinuses.

Involvement of the sinuses of the large facial area represents a rare localization of EMH. Various cases have been reported in patients with thalassemia intermedia, but no case has been reported with HbLepore. The diagnostic gold standard is MRI, which provides highly accurate and clear images. The treatment is based on hydroxyurea and/or an intensive transfusional regime and sometimes on surgery.

Key Words:

Extramedullary hematopoiesis, Sinuses, Thalassemia.

Introduction

Thalassemia intermedia (TI) represents a clinical entity with a wide spectrum of genotypes and phenotypes that is more severe than β -thalassemia minor but milder than β -thalassemia major. Patients usually come to medical attention in late childhood or even adulthood. They show mild to moderate anemia with a hemoglobin level ranging between 7 and 10 g/dL, which is sustainable without the need for regular transfusion management¹. The Hemoglobin Lepore (HbLepore) is a rare he-

moglobinopathy that arises from a crossing over of genes controlling the δ and β chain synthesis that produce a new $\delta\beta$ chain². The homozygous state is associated with thalassemic-like pictures ranging from a transfusion dependent disease to a TI. The production of tumor masses composed of extramedullary hematopoiesis (EMH) is well documented in TI with an incidence that may reach up to 20%¹. EMH can involve virtually any organ or tissue; the most frequent location is paraspinal that occurs in 11% to 15% of cases. It is thought that more than 80% of cases may remain asymptomatic, and the lesions are usually discovered incidentally by radiological techniques³⁻⁵. Instead, the occurrence in the paranasal sinuses is an exceedingly rare phenomenon⁶⁻¹⁰. We present a case of a homozygous HbLepore patient presenting as a TI with EMH localized in paranasal sinuses.

Case report

A female patient with homozygous HbLepore clinically presenting as a TI has been irregularly transfused since the age of four years until the age of 29 years, when paravertebral heterotopic masses were first observed. She started a treatment with hydroxyurea but it was discontinued for hematological toxicity (neutropenia). Then, a regular transfusion regimen with iron chelation was prescribed in order to maintain the concentration of hemoglobin at a level of 7 to 8 g/dL. At the age of 39 years the patient was referred for the first time to our department for a progressive bilateral nasal obstruction, frontal headache, facial pain and clear rhinorrhea. Computed tomography (CT) demonstrated a total soft-tissue filling of the sphenoid sinus with initial extrinsication in

the left posterior ethmoid cell. The diameters of this mass were: transversal axis 30 mm x 24 mm; longitudinal axis 26 mm; CT-density was about 85 HU (average value). The cortical appeared thinner, without evidence of bone erosions. The lesion partly wrapped the cavernous sinus and the orbital apex. There was not an involvement of the pituitary gland, optic nerve and other cranial nerves. There were considerable intrasinus calcifications. The picture was consistent with the diagnosis of the solid mass. The differential diagnosis included EMH, atypical mucocele and sarcoma. Therefore, the patient underwent a Magnetic Resonance Imaging (MRI) with pre-contrast and post-contrast media sequences that showed an intermediate-signal intensity of an expanded sphenoid sinus on T1-weighted image (Figure 1a). The lesion was isointense with medium-low signal in T2 STIR, confirming the solid nature of the lesion, without fluid component (Figure 1b). Axial T1 MRI post gadolinium injection showed a tissue process occupying the sinus with heterogeneous enhancement. The lesion did not involve the pituitary gland, from which it was separated by a hypo-signal border (Figure 2a,b). Diffusional

study and the respective ADC map demonstrated the absence of restriction in Diffusion MRI, with a high b-value ($b = 800$), and ADC value was $0.3 \times 10^{-3}/\text{sec.}$, guiding the diagnosis of a non-malignant lesion. The trans-nasal needle biopsy of the mass showed: highly cellulated zones with trilinear immature and mature cells, mainly erythroid hyperplasia and myeloid precursors; presence of hemosiderophage macrophages and dilated sinusoids containing erythroblasts. In some areas there were fragments of fibroid tissue, fat and pigmented elements, caused by a degradation of hemoglobin. Imaging workup and histopathological findings account for the diagnosis of EMH of the facial sinus. Considering the previous toxicity to hydroxyurea and the low hemoglobin levels maintained by the patient, a hypertransfusional regiment would increase hemoglobin concentration to 13-14 g/dl after transfusion and never allow the levels to fall below 9,5-10 g/L at all times and helps to decrease the compensatory hemopoietic tissue expansion, was planned. Two years after the start of treatment, the MRI picture resulted unchanged but further dimensional progressions were averted.

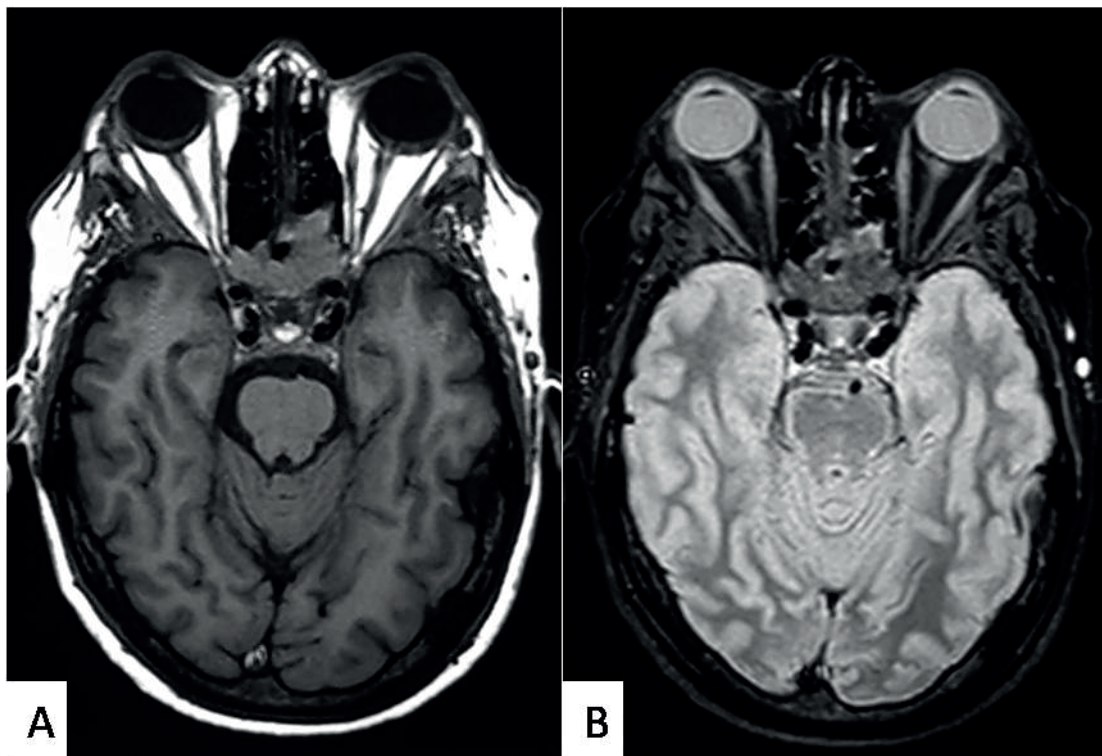


Figure 1. T1-weighted (a) and FLAIR (b) MR images, axial plane, demonstrated intermediate signal intensity in T1 and medium-low signal in FLAIR, confirming the solid nature of the lesion, without contextual fluid component.

Discussion

EMH has been documented in a variety of blood disorders characterized by a long-time lasting ineffective erythropoiesis, resulting from either increased red cell consumption (chronic hemolytic anemia such as thalassemias, congenital hemoglobinopathies and spherocytosis) or, more rarely, insufficient production (myelofibrosis, leukemias, lymphomas, bone metastases of solid tumors and Gaucher's disease)². Location of EMH in the head and neck is rare and it has been described in the subglottis, middle ear, orbit, lacrimal pathway and thyroid. Few cases of sinus involvement have been reported¹⁰. EMH in the paranasal sinuses has been hypothesized to arise as a result of herniation of medullary tissue into the paranasal cavity due to underline bone marrow hyperplasia (paraosseous development)⁶. To the best of our knowledge this is the first patient homozygous for HbLepore with EMH, and particularly localized in facial sinus.

A detailed radiology study is essential for diagnosis and management of EMH^{1,11,12}. CT scan shows a heterogeneous and hypo vascular soft-tissue mass with interspersed areas of fat attenuation and homogeneous contrast enhancement⁶. Involving the paranasal sinuses, the calcification in a trabecular pattern may be observed, as represented in our patient. On MRI, which is the imaging of choice, the soft-tissue mass demonstrates signal intensity and enhancement similar to that of red marrow and intramedullary hematopoiesis¹³. In our case, the sagittal T1 MRI – post gadolinium injection – showed predominantly homogeneous enhancement that was more prominent to that of the bone marrow; the un-enhanced T1 and T2 images of the same region had similar intensity to bone marrow¹³. The Diffusion MRI study did not show a restrictive signal in diffusion with a high b-value (800); it signaled a benign lesion¹⁴.

Tissue biopsy is usually not needed for diagnosis in paravertebral EMH, given characteristic appearance on MRI^{1,7,9}. When the mass involves the paranasal sinuses, a biopsy is required to rule out a neoplastic etiology or chronic inflammatory reaction⁶. Histopathological findings of EMH show trilinear hematopoiesis with erythroblastic hyperplasia and megakaryocytes. The presence of myeloid precursors and rich vasculature are typical of active recent EMH lesions, while a lot of fatty tissue and iron deposits are typical of inactive older lesions^{3,6}.

Therapy usually depends on the severity of symptoms, size of the mass, the clinical condition

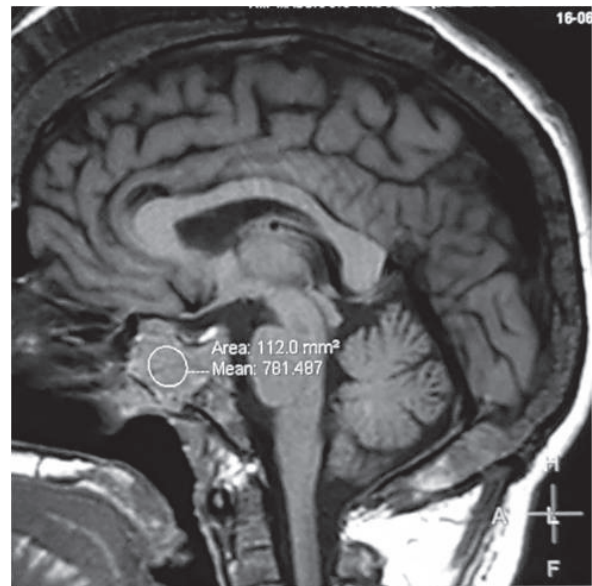


Figure 2. T1 -weighted MR images, sagittal plane, pre-contrast (a) and post-contrast (b). Contrast-enhanced T1-weighted MR image showed a tissue process occupying the sinus with heterogeneous enhancement. The tissue process respected pituitary gland, which is separated by a hypo-signal border (arrow).

of the patients and previous treatment. If the lesion is asymptomatic and it is not localized in a risk anatomic site, a *wait-and-see* strategy may be indicated^{1,10}. Treatment of EMH may include red blood cell hypertransfusional regimen, surgical intervention, radiotherapy, hydroxyurea and, more rarely, thalidomide administration^{1,10,14,15}. Transfusions usually represent the first attempt to reduce the mass size. Hydroxyurea is commonly administrated in combination with transfusions or alone in patients who cannot be transfused for religious reasons or clinical condition, such as previous alloimmunisation. Radiation therapy has proven to be a very effective treatment for the high radiosensitivity of this condition^{1,10,16,17}.

In our patient, surgical intervention was not considered as the first line of treatment, considering the location. Radiotherapy was not recommended due to the critical neurovascular structures that are next to the paranasal sinuses^{6,18}. Hydroxyurea was not considered as an option, as previously the drug induced bone marrow toxicity. Then, we proposed a hypertransfusional regimen, considering that the previous transfusional treatment, with lower hemoglobin levels, resulted ineffective in preventing the development of EMH. The results were only partially encouraging, since after two years from the start of the

treatment the mass resulted unchanged although further dimensional progressions was prevented.

Conclusions

We have described a rare case of EMH evolved in the paranasal sinuses, in a patient homozygous Hb Lepore presenting as a TI. This observation underlines how EMH must be considered in the differential diagnosis of paranasal sinus masses in patients affected by a chronic haemolytic anaemia. The diagnostic process can be enigmatic and it requires an appropriate history, a characteristic appearance on CT and MRI, and sometimes a biopsy that clearly shows a hematopoietic tissue. Finally, the partial response to hypertransfusional regimen confirms how the best treatment of EMH remains an open question and underlines how it must be tailored on the site of the mass, as well as on the medical history of the patient.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgments

All authors meet the ICMJE authorship criteria.

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