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CLINICAL PATHOLOGY CONFERENCE CASE #6: MULTIPLE TUMORS OF THE SKULL IN A PEDIATRIC PATIENT

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Clinical Presentation: A 2-year-old female from Guatemala presented with multiple tumors affecting the skull, orbits, and the maxillary sinuses. Clinical examination revealed bilateral exophthalmos and marked periorbital swelling in the left eye that was displaced inferiorly. Additionally, the patient had slight hyperpigmentation associated with the periorbital swellings, and temporal swelling was also present. Bleeding from the right nostril, clear fluid dripping from the left nostril, and mouth breathing were present.

Axial and coronal slices of magnetic resonance imaging (MRI) showed multiple, hypointense, space-occupying masses in the right occipital lobe, right temporal lobe, right transverse sinus, left orbit, left temporal lobe, and cerebellum. Focal areas of cortical destruction were also noted. Non−contrast-enhanced, coronal computed tomography soft tissue window showed 2 masses in the orbits, both with internal calcifications seen encroaching on the superior surfaces of the right and left globes (Figure 1).

Differential Diagnosis: On the basis of the findings on clinical examination and radiographic imaging of the multiple masses in the skull, orbits, and maxillary sinuses, the differential diagnosis for this case included a range of common pediatric head and neck tumors with multifocal and/or metastatic presentation. The differential diagnoses included the following: lymphoma (Hodgkin and Non-Hodgkin), neuroblastoma, retinoblastoma, rhabdomyosarcoma, osteosarcoma, thyroid carcinoma, Langerhans cell histiocytosis, Ewing sarcoma, and salivary gland tumors.[1,2]

Lymphomas are the most common head and neck tumors in children, with Hodgkin lymphoma being more common than non-Hodgkin lymphoma.[1,2] On MRI, lymphomas in the head and neck region appear as homogeneous, hypointense masses with rare calcifications.[3]

Neural tumors are the next most common pediatric tumors in the head and neck region.[1,2] These include neuroblastomas and retinoblastomas, both occurring more commonly in children less than 2 years of age. Neuroblastoma, however, is more common than retinoblastoma in young children.[1,2] Retinoblastoma is a primary malignancy of the retina, whereas neuroblastoma is a malignancy of the immature cells that are found in several areas of the body. Neuroblastomas most often arise in the adrenal glands and may metastasize to other parts of the body, including the head and neck region. Hyperpigmentation of the eyes, or raccoon eyes, can be seen in neuroblastomas involving the eye.[4] On MRI, neuroblastomas present as heterogeneous, hypointense masses, and on computed tomography, internal calcifications can be demonstrated.[5]

Soft tissue sarcomas are the third most common head and neck tumors in the pediatric population, with rhabdomyosarcomas being the most common. Osteosarcomas are also seen in children but occur less frequently in infants and toddlers.[1,2] On imaging, osteosarcomas are seen within bone, whereas rhabdomyosarcomas are seen within soft tissue. About 10% to 20% of rhabdomyosarcomas can involve the orbit.[6] Clinically, hyperpigmentation of the eyes ("raccoon eyes") can be seen in rhabdomyosarcomas involving the eye. On MRI, rhabdomyosarcomas may present as intermediate to high signal intensities without internal calcifications. Bone destruction of the temporal bone and skull base and invasion of various structures in the head and neck region are also seen.[2]

Other less common head and neck tumors in children include thyroid cancers, Langerhans cell histiocytosis, Ewing sarcoma, and salivary gland carcinoma.[1,2] In older children, thyroid cancers, Ewing sarcoma, and salivary gland neoplasms are more commonly seen compared with Langerhans cell histiocytosis (LCH).[1,2] LCH is a disorder characterized by an excess of immune system cells, known as *Langerhans cells*. These excess immature Langerhans cells form tumors in the skull or the long bones. On imaging, these tumors are seen as masses within bone, rather than in soft tissues.

On the basis of the young age of this patient, the clinical presentation of bilateral periorbital swellings with slight hyperpigmentation, and imaging showing multiple hypointense, soft tissue masses with internal calcifications displacing, rather than destroying or infiltrating, adjacent structures, the following tumors were initially excluded from the differential diagnosis: lymphoma, retinoblastoma, rhabdomyosarcoma, osteosarcoma, thyroid carcinoma, LCH, Ewing sarcoma, and salivary gland tumors. A diagnosis of metastatic neuroblastoma with brain and eye involvement had to be excluded.

Diagnosis and Management: Incisional biopsy of a sinonasal lesion revealed several soft tissue fragments (Figure 2). Histopathologic analysis of these tissue fragments demonstrated diffuse sheets of mononuclear, medium-sized cells showing irregular cytoplasmic and nuclear contours with eosinophilic granular cytoplasm. Some of these tumor cells presented with a plasmacytoid disposition. Additionally, small eosinophilic, round cells resembling eosinophils were noted, and within these small round cell populations, large round cells with pale eosinophilic cytoplasm and folded or grooved nuclei resembling coffee beans were also seen. Intermingled macrophages and a subacute inflammatory infiltrate at the periphery of the tumor were also noted. Considering the histologic features observed, a diagnosis of LCH was hypothesized, and an immunohistochemical analysis was performed. LCH was ruled out, along with most of the above-mentioned differential diagnoses, because the tumor cells were negative for S-100, CD1a, CD207, leukocyte common antigen, terminal deoxyribonucleotide transferase, desmin, CD138, chromogranin, and neuron-specific enolase and were positive for vimentin. Given the immunohistochemistry (IHC) results, a differential diagnosis of myeloid sarcoma (MS) was considered, and additional IHC analyses were performed for confirmation. The tumor cells showed strong positivity for myeloperoxidase,

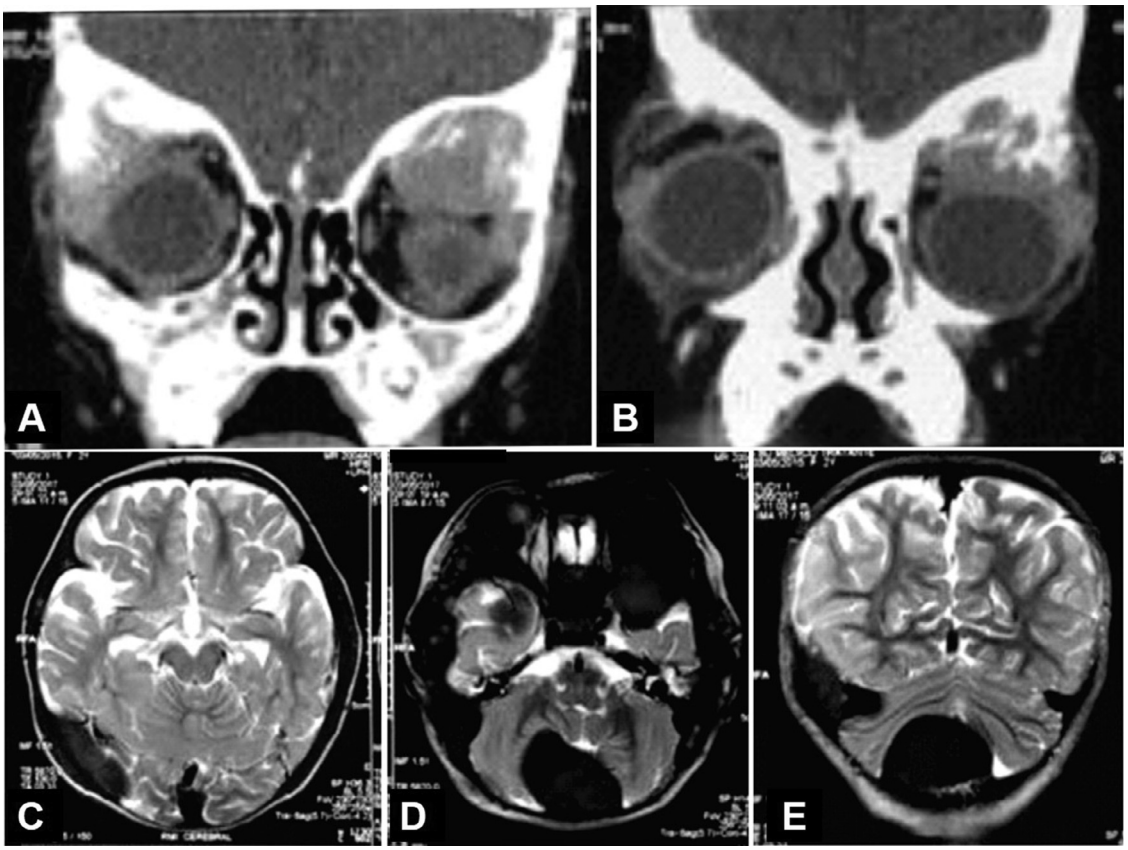

Fig. 1. Imaging features. Non−contrast-enhanced, coronal computed tomography (CT) soft tissue window shows 2 masses in the orbits. Focal areas of cortical destruction are observed **(A, B)**. Axial and coronal slices of magnetic resonance imaging (MRI) show multiple, hypointense, space-occupying masses in the right occipital lobe, right temporal lobe, right transverse sinus, left orbit, left temporal lobe, and cerebellum. No destruction of adjacent structures is noted **(C, D, & E)**.

CD68 (KP1), and CD99, and were negative for CD34 antibody. This immunophenotype is compatible with MS. The patient, as a result, was investigated for the possibility of medullary involvement with acute myeloid leukemia (AML) or myelodysplastic syndrome/myeloproliferative neoplasm. Negative findings of these conditions confirmed a diagnosis of extramedullary MS. Consequently, the patient underwent chemotherapy, and after 1 year, remains alive and is in complete remission. Long-term follow-up was encouraged because of the possibility of recurrence or the development of AML in the future.

Discussion: Myeloid sarcoma, also known as *granulocytic sarcoma* or *chloroma*, is a malignant tumor characterized by myeloid blast cells proliferation.[7] MS can precede, be concomitant with, or develop as a sign of relapse in patients with AML. It can also arise as a result of blast transformation of hematologic disorders, such as chronic myeloid leukemia, myelodysplastic syndrome, or myeloproliferative neoplasm, and in rare instances MS can appear de novo (normal bone marrow and hematologic findings).[7,8]

MS can affect any extramedullary site, such as the lymph nodes, skin, upper airways, gastrointestinal tract, peritoneum, and other soft tissues.[7,9,10] Head and neck region involvement is rare, and within this region, MS is most often seen in the oral cavity, mainly occurring in the gingiva.[11] MS can also manifest as multiple lesions, as seen in our case.[12] This entity arises in a wide age range (1−85 years; median age of 61 years).[7,11] Although some authors report that MS is more common in pediatric patients, with 60.1% of cases affecting patients younger than 15 years of age.[13,16,17] Pediatric patients with MS with head and neck involvement commonly present with orbital involvement and unilateral, or bilateral exophthalmos.[18-21]

According to the review by Shields et al., the main conditions that can cause bilateral orbital masses in children are idiopathic nongranulomatous orbital inflammation, metastatic neuroblastoma, and MS. Those authors also stated that approximately 60% of MS present with bilateral orbital involvement.[19] Patients with MS presenting with multiple cranial lesions, bilateral proptosis, and bitemporal swellings have been reported; however, this presentation is often seen in patients with leukemia.[22,23] As mentioned previously, MS can precede AML manifestations and, in some cases, can be an indicator of future development of AML. The mean time interval between development of MS and AML can be anywhere from 5 to 10 months. Nevertheless, in some cases, MS is present for up to 4 years before the development of AML.[13,15,18] For these reasons, long-term follow-up is advised. It is worth mentioning that in some cases, patients with oral MS did not present or develop associated leukemia or myeloproliferative neoplasms.[10]

Because of the nonspecific nature of the clinical presentation, biopsy with appropriate IHC is necessary for the correct diagnosis of MS.[11,12] Microscopically, the tumor is composed of diffuse sheets of immature mononuclear cells with irregular

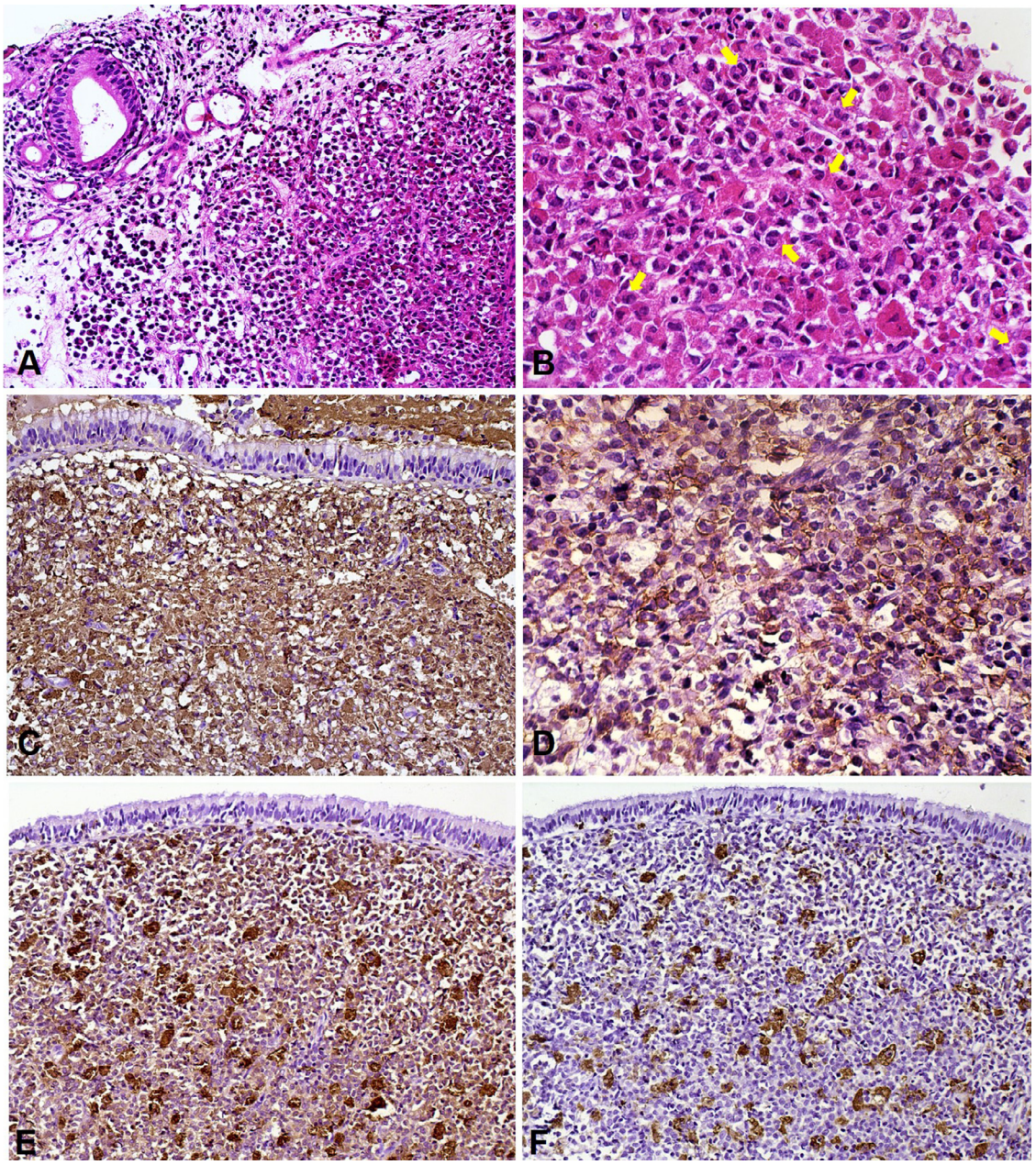

Fig. 2. Histopathologic and immunohistochemical features. The lesion was composed of abundant mononuclear, medium-sized cells intermingled with a subacute inflammatory infiltrate and foci of eosinophils **(A)**. Diffuse sheets of lesional cells showing irregular cytoplasmic and nuclear contours and eosinophilic granular cytoplasm, with some cells presenting with plasmacytoid disposition. In addition, large round cells with pale eosinophilic cytoplasm with folded or grooved nuclei were observed *(yellow arrows)* **(B)**. The tumor cells show strong positivity for myeloperoxidase **(C)**, CD99 **(D)**, CD68 KP1 **(E)**, and CD68 PGM marked the macrophages specifically **(F)**. (Hematoxylin and eosin [HE]: **A,** × 20; **B,** × 40) (Immunohistochemistry: **C, E, & F,** × 20; **D,** × 40).

nuclear contours that may show different stages of myeloid differentiation, including myeloblasts characterized by round to folded nuclei intermingled with eosinophilic myelocytes. The tumor cells are frequently intermixed with reactive inflammatory infiltrate, as observed in our case.[7,8,10] Therefore, IHC remains crucial to confirm this diagnosis, mainly with the use of myeloid or myelomonocytic markers, such as myeloperoxidase, CD68 (KP1), and lysozyme. Additionally, MS is generally positive for CD99, CD34, KIT/CD117, and CD163.[7,11,13] In our case, however, the tumor cells were negative for CD34. The literature contains reports of some cases where CD34 protein was not expressed.[9]

In the presence of existing signs and symptoms of, or a prior diagnosis of, AML, clinicians and pathologists are more likely to make a clinical diagnosis and perform the correct histopathologic and IHC analyses orientated to the diagnosis of MS.

Nevertheless, because the clinical presentation is nonspecific and the histopathology is variable, especially when there is no suspicion of AML, most cases of MS are initially misdiagnosed as malignant lymphoma or even inflammatory conditions.[12-15] As in our case, the clinical presentation and some histopathologic features superimposed with other entities, such as LCH, make a definitive diagnosis of MS very challenging.[11,12,16]

The recommended treatment for MS is similar to the chemotherapy regimens for AML, even without evidence of hematologic disorders or medullary involvement. The prognosis of patients with AML with concomitant MS or relapsed MS is very poor. The survival rate is around 50%,[10,13] which is similar to that of patients with isolated MS because of the high rate of recurrence during the nonleukemic period and the risk of progression to AML. However, in patients who have achieved complete remission after chemotherapy, the overall survival rate is higher.[12,24,25]

In summary, in pediatric patients with orbital masses (particularly if they are bilateral) and multiple tumors affecting the skull, a diagnosis of MS should be strongly considered to avoid misdiagnoses and delay in treatment. After confirming the diagnosis with biopsy and IHC, prompt assessment for the possibility of underlying AML is necessary.

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