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Review Article

Risks in Histiocytic Syndromes

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Abstract

Histiocytosis is a heterogeneous group of diseases of unknown cause that are characterized by the proliferation of cells of the mononuclear phagocytic system (MFS) (monocytes, macrophages, dendritic cells) in different organs and systems. Therefore, a bibliographic review was carried out on the lesions and risks in histocytic syndromes.

Keywords: Histiocytosis; Bone Resorption; Oral Manifestation; Syndrome

Introduction

We decided to make a section on this topic, due to its complexity, so that readers can understand it better and internalize the magnitude of this disease and its impact on society. As a historical account, it is known that in 1913 the word histiocyte was used for the first time, and its cellular system has received different nomenclatures. It is currently known that it is a very complex cellular system that actively intervenes in the body's defense, both in an immunologically specific and non-specific way. There are experimental studies that point to the probability that environmental factors influence differentiation towards one or the other branch of histiocytic cells. The etiology is unknown.

A supposedly viral infectious cause has not been demonstrated. It is also not known whether Langerhans cell histiocytosis (LCH) is a reactive or neoplastic process. The fact that in the majority of cases of LCH it has been demonstrated that the proliferation of Langerhans cells is clonal would favor malignancy. On the other hand, the varied clinical spectrum of LCH, with cases of spontaneous regression of the lesions, would indicate that it is a reactive process. It is possible that the origin of the proliferation, clonal or not, of Langerhans cells lies in an abnormal stimulation of the immune system, with alteration of suppressor T lymphocytes. This proliferation would be enhanced by the production of cytokines (IL-1, IL-4, IL-8, GM-CSF and tumor necrosis factor, among others).

This influence can affect both precursor cells and fairly differentiated cells. Therefore, it should not be surprising to detect, in parallel, histiocytosis or proliferations of histiocytes made up of cells that present mixed characteristics between different types of cells of histiocytic origin. The main cells of the cutaneous histiocytic system are epidermal Langerhans Cells (LC), dermal macrophages and factor XIIIa+ dermal dendrocytes. Histiocytosis X has frequently been studied as a cancer-like disease. Current research raises the suspicion that this is actually an autoimmune phenomenon, in which abnormal immune cells attack the body, rather than fighting infections.

- **Objective:** to describe the main complications and risks of diseases and injuries of histiocytic syndromes.
- **Reference search methods:** scientific information was collected through a search using the following descriptors in English: The Medical Subject Headings (MeSH): "histiocyte, histioid, osteopathy, hematopathy.
- **Analysis strategy:** the search was based solely on histiocytic syndromes of the oromaxillofacial complex.

Developing

These cells can form tumors, which can affect various parts of the body, including the complex bones of the skull, face, jaw and other areas. Genetic variants are found among the presentation forms. This condition is said to affect approximately 1 in 200,000 people a year.

The highest incidence is evident in children aged 1 to 15 years, with a rate that reaches its maximum among children aged 5 to 10 years. Those affected may present with localized lesions (injury clearly affecting the skin or a single bone lesion) or generalized, affecting several organs or systems [1,2].

They are rare diseases, predominantly in childhood, with very diverse severity and with biological characteristics bordering on the field of Hematology, Immunology, Oncology and Dermatology. But sometimes its first signs may appear in the oral cavity, and the stomatologist, whether a maxillofacial surgeon or any other specialty of the career, must be oriented and suspect these injuries when the case is presented. In this term of histiocytosis, diseases in which histiocytic proliferation occurs secondarily are excluded, such as the granulomatous reaction in chronic infections, graft-versus-host disease, X-linked lymphoproliferative syndrome or hereditary lipoidoses, etc. Whenever we talk about Histiocytosis, unknowns and questions arise that make it a topic of great interest, since the unification of criteria, its debate and constant updating contribute to the enrichment of knowledge about this topic, so interesting, and at the same time necessary that stomatology professionals master it [1,3].

Classification The great clinical diversity leads to dissimilar presentations, mostly with early cutaneous expression, which allows directing the diagnosis. In practice, it is often necessary to discuss as a team with the dermatology specialist to make an accurate diagnosis. In infants, the pediatrician can direct therapy, particularly in cases of systemic involvement, always relying on the relevant specialties, depending on the patient's clinical condition. Classically, the International Histiocyte Society classifies them into three large groups [4].

Systemic (invasive) Langerhans cell histiocytosis It appears mainly in infants or children under three years of age who present a systemic clinical picture (hyperthermia, asthenia, anorexia, weight loss), associated with signs of diffuse infiltration: lymphadenopathy, hepatosplenomegaly, bone marrow infiltration (pancytopenia, anemia, infections)., hemorrhages). Essential aspects to take into account given the great risk they pose for individuals. The existence of multiple lytic bone lesions with involvement of adjacent soft tissues is common, which in the calvaria gives rise to the geographical skull, in the bones of the cranial base to exophthalmos and diabetes insipidus, in mastoids to exudation and otorrhea, in vertebrae to vertebral crushing [4,5].

Histiocytosis type I (Langerhans cell histiocytosis)	Disease formerly known as histiocytosis X, and which has received various eponyms: Abt-Letterer-Siwe disease, Hand-Schuller-Christian disease, Hashimoto-Pritzker disease, which reflect the variability of its presentation. However, currently the name Langerhans cell histiocytosis and its classification into localized or systemic forms is preferred.
Histiocytosis type II (non-Langerhans cell histiocytosis)	They include a very varied group of histiocyte proliferation diseases whose phenotype is different from that of the Langerhans cell. Clinically they are divided into 3 groups: With predominant skin involvement (juvenile xanthogranuloma). With predominant systemic and skin involvement. Mainly extracutaneous diseases (hemophagocytic lymphohistiocytosis).
Histiocytosis type III or malignant.	They are classified according to the cells that produce it.

Table a

Lung involvement and signs of immunodeficiency with repeated infections are also common. On the skin it debuts with minimal papular, pseudovesicular lesions (at first they can simulate sweating), which in a few days will acquire a purpuric appearance. Predilection to affect seborrheic areas (scalp, skin folds). Tendency to erode in the folds and in some cases to xanthotomize. The cutaneous condition may precede the systemic one [5,6].

It may be the case that one or multiple osteolytic lesions appear in the jaws or facial bones. Localized Langerhans cell histiocytosis (non-invasive) In this case we will emphasize the exclusive or autoinvolutional forms of cutaneous presentation

Illig-Fanconi's disease: it manifests itself only with skin lesions, similar to invasive forms in its first phase, although not very extensive and that do not progress, but show involutive behavior in several weeks. As a result that this variant of auto -involutive histiocytosis usually affects infants, a close monitoring is necessary to confirm their regression and rule out that injuries do not progress or are associated with an invasive form in their evolution. Always maintaining close communication with the parents, explaining in

Papular form nodular form	Illig-Fanconi disease
Located or disseminated	Hashimoto-Pritzker disease
Bone exclusive affectation in a single location	Eosinophilic granuloma (osteolithic lesion, usually located in long bones)

Table b

detail every step and therapeutic decision that is taken. Xantohistiocytosis: It is characterized by the presence of multiple xanthomas tuberos (papular and xantagranuloma youth) normoliphemic, not family or xanthomas of various types, especially in extensive plaques in the large folds and especially in the facial region, in the Xantoma Disseminatum [5-7].

The latter usually sees with tasteless diabetes and mucous affectation, especially oral and tracheolangea. Patients with type I neurofibromatosis who have a youthful xantharanuloma have a greater risk of developing monocytic leukemia, so the presence of coffee spots with milk associated with xantrogranuloma should make think of this diagnosis and forces hematological evolutionary follow -up. Unique localized forms of juvenile xantagranuloma and forms of systemic commitment (ocular, lung, pericardium, testicle) are very rare. The presence of flat Xantoma disseminated in childhood is also exceptional, which can be indicative of paramemia, myeloma or lymphoproliferative process [8,9].

Benign cephalic histiocytosis and generalized eruptive histiocytoma are two almost identical ways of presentation, so we present their differential diagnosis

Benign cephalic histiocytosis	Generalized eruptive histiocytoma
Benign cephalic histiocytosis Yellowish maculopular papular lesions in the cephalic pole or multiple chronic generalized histiocytomas.	In this way the injuries are asymptomatic.
No systemic commitment	No systemic commitment
Autoinvolutive behavior	Autoinvolutive behavior

Table c

The xantomized variant of them is the papular xantoma that is presented in adults and in children. Exceptional in children is hereditary mucinous histiocytosis, of which family cases have been described and that today is considered a form with mucoid degeneration of the progressive nodular histiocytoma of the adult. Xantogranuloma Youth Micronodular Disseminated. The presence of multiple xanthomas normoliphemic tuberos is characteristic. When a patient with these diagnoses is presented to our consultation, we must be very cautious and conservative with the proceeding that is required to do, always assess the risk of benefit with the head doctor, to clearly explain to the patient and/or family [9,10].

In general, we can say that these diseases can vary from the asymptomatic commitment and auto-resolutive commitment of a single organ or systems, to the commitment, chronic and progressive or acute and fatal. Eosinophilic granuloma: it is the most benign, it has only unique bone lithic lesions that are especially located in the bones of the skull 50 % of unifocal cases appear in children over 5 years Bone lesions are in order of frequency in the skull, femur, pelvis, ribs and vertebrae. The unique cranial condition is usually manifested as a mass associated with pain or even asymptomatic, however, in extreme cases it can cause chronic and deafbet otorrhea if it affects mastoid region. Due to lithic nature, injuries originate a radiological defect in scratch. There are cases that start Mor the jaw observing the same radiological pattern, this is compromised between 20 and 40 %. There are generally well -defined osteolytic images or on other occasions of irregular limits. At the beginning of the process, lesions can resemble periodontitis or a necrotizing gingivitis process, later the alveolar sheet and teeth are destroyed, especially the posterior mandibular are left without bone support and gives the image of being in the air (“ Floating image”) [11].

Spontaneous dental exfoliation is possible and also spontaneous fracture in advanced cases. Dental mobility can be accompanied in the first moments for pain and discomfort. Many times due to oversized infection of opportunistic microorganisms (actinomycosis, candida, etc.) The commitment of the jaws is always after that of the jaw. The variant that was previously known as Letterer-Siwe’s disease, which some authors still recognize it, is the acute, disseminated form, with multisystemic commitment, highly lethal, usually appears in children under 2 years and can manifest from birth from birth. The family incidence is less than 2% [12].

Infants with a worse prognosis often have affected the lungs, liver or bone marrow. Lymphadenopathies are manifest that can be massive, with characteristics of granulomatous processes. In many patients there is bone shot with lesions of a lithic nature in skull and protosis by orbital commitment. Bone marrow is accompanied by anemia, neutropenia and platelet. The same goes for Hand-Schüller-Christian disease the chronic form, with the classic triad of cranial lesions, exophthalmos and diabetes and diabetes and the eosinophilic granuloma or localized form in the bone and/

or lung. It affects children between 2 and 5 years of age. The oral manifestations of these two variants are initially similar to those indicated in reactive Langerhans cell disease but is the company of granulomatous nodular lesions in the gum and vestibular groove. These proliferative masses can be painful [13].

In histiocytosis, the most affected organs and systems, in decreasing order are: cortical bone tissue, bone marrow, skin, central nervous system, oral mucosa, lymph nodes, spleen, liver, lung, intestine and thymus. Cutanene lesions are presented in more than 30 % of infants, are often the first sign of disease, and is characterized by eritematous or yellowish, desamative pardo, located in trunk, scalp, lumbosacra region and intertriginous areas that can converge and form xanthomatous appearance plates or can ulcerate leaving hypocromic scars. Hence the importance of doing a detailed physical examination, and in the case of pediatric patients, we must always analyze the status of the skin, since it can guide and/or notify us of any nosological process that is being established [13,14].

The scalp is affected in a large percentage, so it can be confused with the diagnoses of seborrheic dermatitis and the chapter tune and can be complicated with dermatophyte or bacteria infections due to the alteration of the cellular immune response and the use of topical steroids.

As explained above, it is a complex and uncommon disease, difficult to diagnose, because it can be asymptomatic, it has been the case of patients who have suffered a mild trauma and in the study process, it is that the injury has been diagnosed. It is essential to corroborate if there is a commitment from other regions other than the head and neck, for which dissimilar imageological studies must be carried out throughout the skeleton and soft tissues. Within these image methods, the most sophisticated are computerized tomography or magnetic resonance, which today constitute a necessary and irreplasable complement. Since they show more quality, the anatomy of the lesion, the degree of intraóseo extension, and the commitment of the soft parts. This is especially valid in lesions that compromise the base of the skull and the spine [15].

With respect to treatment depends on the extension of the disease. If it is restricted to a single system, it is generally benign with a high possibility of spontaneous remission, so the treatment will be aimed at stopping the progression of those injuries that can lead to permanent damage It is also beneficial to follow up on any lonely and asymptomatic bone lesion, especially because it can disappear spontaneously. Painful lesions can be treated by bounded at the time of diagnostic biopsy. Multisystemic disease, on the contrary, must be treated with systemic chemotherapy, where favorable results have been obtained. In epidemiological studies, a higher risk of suffering HCL has been associated in children with infections in the neonatal period, exposure to solvents and thyroid diseases. On the other hand, in several studies an unexpectedly high HCl association with neoplasms has been demonstrated, especially acute leukemias, which can precede, diagnose concomitantly or after the HCl [16].

It is necessary to make clear to relatives that the forecast is very variable, and oscillates from cases with spontaneous remission, especially when there are localized bone lesions, to disseminated shapes with severe organic dysfunction and fatal course. Between both groups, patients with bone condition or multiple soft tissues would be located, without organ dysfunction. It is important to emphasize that the HCL forecast is given mainly by the degree of dysfunction of the affection. Therefore, it is important to carry out a deep and systematic study, of the most commonly affected organs and systems, such as skeleton, skin, lung, liver, spleen, lymph nodes, central nervous system and bone marrow. It is difficult to systematize, by the presentation and clinical course so variable and by the low frequency of the HCl, which makes it difficult to carry out rigorous clinical trials. For therapeutic purposes, the localized disease is distinguished from the generalized. Located disease usually affects bone, skin or lymph node. Bone lesions can be treated with low dose radiotherapy, intralesional glucocorticoids or excisional biopsy. If there is no risk of deformity or fractures, expectant behavior can be chosen, since sometimes spontaneous resolution occurs. Cutaneous lesions can also be resolved spontaneously or with local treatment with photochemotherapy, etc [17].

The treatment of disseminated disease consists of chemotherapy, with alkaloids of the Vinca (vinblastin), antimetabolites (metretrexate) or etoposide, isolated or in combination and associated with glucocorticoids or not. The stomatologist must be a participant in the evolution of these patients, since, regardless of their benign or malignant characteristics, oral tissues may be affected. That according to their location they are classified as

In the mouth, cases have been reported with involvement exclusively of the oral mucosa, but the greatest number corresponds to the maxillary bones with one or more lesions distributed in one or both jaws, with the lower jaw being the most affected, where the lesions are generally located at level of premolars, molars and mandibular angle.

Type I or alveolar	The lesions are confined to the alveolar bone. The patient presents pain and tooth mobility, associated with symptoms of periodontal disease such as bleeding, swelling and ulceration of the gums. Radiographically, destruction of the alveolar bone is observed in a manner similar to the bone resorption of periodontitis. In severe injury, the bone supporting the teeth is lost, causing displacement of the teeth involved, giving a radiographic image of a floating tooth.
Type II or intraosseous	The lesions are located inside the bone, outside the alveolar area. The most common symptom is swelling with or without pain of the affected bone area. Radiographically, a destructive central lesion with an aggressive appearance is observed, with expansion of bone tables, periosteal reaction, and diffuse osteolysis that suggests malignant tumor or osteomyelitis. In some cases, cystic and multicystic images can be observed.
Type III or mixed	The lesions involve the interior and alveolar area of bone. A mixture of symptoms and radiographic changes noted for Type I and II injury are observed. Radiographically it cannot be established which type of injury originated.

Table d

In a few cases, injuries have been reported at the level of the mandibular condyle. Lesions of the jaws may correspond to a unifocal disease or may be part of a multifocal involvement, where there are also lesions in other bones of the body. In the jaws, the most frequent symptoms are the presence of one or several soft palpable masses arising from the bone with or without pain, deformation and displacement of the cortical bone tables, loosening of teeth, post-extraction sockets that do not heal, gingival hyperplasia with sacred and ulceration [19,20].

Occasionally the evolution of the bone lesion leads to a pathological fracture. Radiographic alterations are not pathognomonic and can be confused with bone tumors, osteomyelitis, odontogenic tumors, giant cell granulomas and ossifying fibromas. There are multiple histocytic diseases, below we present a box with a summary of several of these conditions. Taken from the book by Dr. Santana Garay [21,22].

There are other classifications and ways of organizing them, but in our opinion these are quite complete. In general, the professional must understand that these diseases pose a great surgical risk, since they are generally accompanied by hematological, dermatological, autoimmunological and oncological disorders, separately or together. Therefore, before carrying out the slightest procedure, the risk-benefit must be carefully analyzed, because these patients are at risk of hemorrhage, infection, pathological fractures, dehiscences, and healing disorders. Many have neoplasms in certain locations that make them prone to frequent seizures. Others have affected motor functions, making it almost impossible for them to carry out personal and oral hygiene properly, which makes them dependent on family members. Emphasis must be placed on the elimination of different toxic habits and how it positively influences the prognosis [23-25].

Macrophage diseases	Reagents Hoarding disease Benign macrophage proliferation disease Non-malignant hemophagocytic diseases of macrophages Malignant Acute monocytic leukemia Myelomonocytic leukemia 5q35 histiocytic leukemia
Langerhans cell diseases	Reagents Eosinophilic granuloma of bones Hand-Shuller-Christian disease Langerhans cell histiocytosis With frequent relapses Spontaneously curable histiocytosis Hashimoto-Pitzker syndrome Malignant Progressive histiocytosis: o Enf. De Letterer-Siwe (allegedly) Langerhans cell lymphoma

Table e

In addition, it should be added that sometimes these patients suffer from diabetes insipidus, a disorder that will influence the electrolyte balance and hydration of the patient. All these risk factors and others must be studied and analyzed calmly and responsibly, so as not to cause more harm to the individual than the disease itself causes [26].

Conclusion

The main complications and risks of histiocytic syndromes in the oromaxillofacial complex, as well as their sequelae, were described. Based on an exhaustive review of the literature, as well as the author's previous experience. These injuries have a high international morbidity rate and cause multiple physical, mental and social conditions. Thanks To my wife for all her unconditional professional and personal support.

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