Case study

Case study on Langerhans cell histiocytosis of bone

ABSTRACT:

Aims: To precise, the epidemiological, clinical, para-clinical, therapeutic and prognostic characteristics ofskeletal involvement in Langerhans cell histiocytosis.

Materials and methods:A retrospective and descriptive study of patients with Langerhans cell histiocytosisadmitted in Internal Medicine Departments of HediChaker University Hospital ofSfax between 1996 and 2018. Cases of Langerhans cell histiocytois confirmed with histo- pathological examination were included.

Results: Four cases of LCH with bone involvement were noted. All patients enrolled were male and the mean age at diagnosis was 23.25 years. The bone lesions were unifocal in two cases and multifocal with multisystemic LCH in the others. The treatment consisted of curettage in two cases and two patients received systemic therapy with corticosteroids and vinblastine respectively. The outcome was favorable in two patients with eosinophilicganuloma and systemic replaces were noted with novel bone lesions in two patients presenting the systemic form of the disease.

Conclusion: LCH is a rare disease in children and young adult males. In the presentseries, bone was the most frequently involved site.The circumstances of discovery of bone localization were the pain swelling lesion in different sites. Biopsy is necessary to obtain diagnosis confirmation. The prognosis of this pathology depends largely on early diagnosis,on other organs affected and the response to treatment.The new class of BRAF inhibitors may be a promising therapeutic option in LCH which needs to be assessed in prospective studies mainly in bone lesions.

Key-words: *Langerhans cell histiocytois, bone involvement, adult.*

1.INTRODUCTION:

Langerhans cell histiocytosis (LCH) represents a spectrum of Disorders that share in common a tissue infiltration by dendritic Langerhans cells organized in granulomas. The Langerhans nature is confirmed in immuno- histochemistry by expressing CD1a or langerin / CD207 and in electron microscopy by the presence of Birbeck granules [1,2] . Although severaletiopathogenichypotheses have been advanced (infectious, immunological, genetic or neoplastic), theetiology remains unknown [3,4,5]. LCH can occur at any age, but it affects preferentially the child and the young adult [1].It covers a series of entities with a widely varied clinical presentation and prognosis from singleorgan to multisystem

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involvement. Any organ or system of the human body can be involved. Bone is the most frequent site noted in about 80% of cases, nonetheless few studies have been conducted (LCH) to precise its characteristics[6]. The aim of the presentstudy is to precise the epidemiological, clinical, para-clinical, therapeutic and prognostic characteristics ofskeletal involvement in Langerhans cell histiocytosis.

2. MATERAILS AND METHODS:

A retrospective study of patients with Langerhans cell histiocytosis admitted in Internal Medicine Departments of HediChaker University Hospital of Sfax between 1996 and 2018. Cases of Langerhans cell histiocytois confirmed with histo-pathological examination were included.

3.RESULTS:

Case 1:

A 22-year- old patient was admitted in January 2005 to internal medicine department for disseminated LCH. At the age of 14years the patient presented a diffuse alveolysis with general bone pain. The patient was referred first tothe maxillofacial and Orthodontics department.To explore these unexplainedsymptoms,a skeletalscintigraphyshowed diffuse hyperfixation at the base and the cranial vault, the jaws, the upper extremity of the left femur, the diaphysis and theleft femoral condyle, the left iliac wing, the lower extremityof the left tibia and the head of the right fibulaThe body scan revealed multiple lytic and blowers lesionsaffecting the whole skeleton. Inthe skull,theselesions interested the frontal, temporal and mastoid bone, the sphenoid bone, the occipital bone, the two rocks complicated with otitis media, the left malar boneand the mandible. The bone involvement concerned also the spine and costal arcs.The lesionsaffected even the left iliac bone and the acetabular region(figure n°1).In upper limbs, there were bilateral lesions in carpal bones.In the lower limbs, the bone lesions were extendedin the leftfemur and in tarsal bones. The thoracic and abdominal tomography showed a multiple micro-nodular, reticular,cystic lung lesionsand homogeneoushepato-splenomegaly.The association of diffuse osteolytic lesions, lung and liver involvements evoked the diagnosis of systemic LCH confirmed bythe presence of increased numbers of Langerhans' cells in the bronchoalveolar-lavage fluid and identified by staining with antibodies against CD1a.The patient was treated with 8 weekly pulses of vinblastine (5 mg / m2) with a favorable outcome particularly of bone lesions at the control scintigraphy.Three years later, the patient presented with a mandibular pain. The dental panoramic showed multi-compartmental extended osteolytic lesions affecting the hemi mandible, especially on the right (figure n°2). Maxillofacial CT scan revealed aggressive lytic lesions affecting the mandibular branches**.** The thoraco-abdominal CT showed the extension of nodular and cystic pulmonary lesions**.** The patient was treated with 6 weekly pulses of vinblastine (5mg/m^2), steroidsat high doses and methotrexate 15mg per week with good clinical therapeutic response. The combination of methotrexate and steroid was interrupted after 3 years of sustained remission.

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Case 2:

A 21-year-old patient was admittedin September 2011 to otolaryngology department with a history of lower right maxillary pain since4 months. A facial CT tomography revealed a right maxillary lytic lesion extending to the floor of the ipsilateral orbit associated with a lamellar periosteal reaction without reactioninfiltration of the adjacent tissues.The surgical exploration confirmed the presence of atumor process in the right sinus. Histopathological examination of the biopsied tumor showed a cluster of histiocytic cells with a polymorphic infiltrate particularly rich in eosinophilicpoly-nuclear cells and rare giant multinucleated cells without associated necrosis. In immunohistochemistry, histiocytic cells were labeled by anti-CD1a, anti-PS100 and anti-CD68 antibodies.Then the patient was referredto internal medicine department. The physical examination was normal. The sinus radiograph revealed an osteolytic lesion next tothe right maxillary sinus (figure n°3). All other investigations including complete blood count, chemistries, liver function,skeletalscintigraphy and the thoracic tomography were within normal. The diagnosis of eosinophilic bone granuloma inright maxillary was retained. The treatment consisted ofcurettage of the lesion already done at the same time of the diagnostic biopsy.

Case 3:

A 38-year-old patient was admitted in 2004 in endocrinology departmentwith progressivepolydipsia with concomitant polyuria and nocturia.Diagnosis of diabetes insipiduswas established after a water deprivation test. Cerebral MRI showed maxillomandibular multifocal osteolytic lesions, thickening of the pituitary stalk and disappearance of the T1 post- pituitary hyper signal. Histopathological examination of the bonelesion revealed a granulomatous infiltrate rich in histiocytes and eosinophilic polynuclear cells with positive immunostaining of the CD1a +, PS100 + and CD68 + type. The diagnosis of LCHwas made. The patient received high-dose corticosteroid therapy with substitutive treatment with DDAVP. Three years later, the patient experienced bilateral mixed deafness related to bilateral bone lysis of the petrous apex confirmed with the rock tomography.Then, the patient was referredto the internal medicine department. The thoracic tomography showed a diffuse micro-cystic lesion of the lung. The patient was treated with 8 courses of vinblastine combined with high dose corticosteroid therapy. Three years following treatment, the disease was considered in remission with persistent irreversible bilateral deafness and sequellar lung lesions.

Case 4:

A 12-year-old patient was referred to neurosurgery departementin January 2013 with a one month history of pain and swelling of thetempal area. The brain tomography showed a left temporal osteolytic lesion (figure n°4). Cerebral MRI concluded with a left fronto-temporal lytic lesion. The anatomopathologicalexamination of biopsied lesionrevealed a polymorphic granulation tissue consisting of atypical nucleus histiocytes, multinucleate giant cells like osteoclastic type, numerous foam cells associated with lymphocytes and plasma cells with some poly-nuclear cells. In immunohistochemistry, the cells were strongly positive for CD68 and PS100, and they were irregularly

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positive for CD1a. The patient was addressed to internal medicine department. Physical examination, biological and radiological assessments were normal. The diagnosis of eosinophilic bone granuloma in the temporal bone was retained. Five years post-surgery, there are no signs of recurrence of the lesion.

Table1: Clinical characteristics, treatment and outcome of our patients

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Patient N°	Location of bone lesion	Systemic involvements	Type of disease	Treatment and outcome
1	-The skull: the frontal, temporal,mastoidian, sphenoid and occipital bone, the two rocks, the left malar boneand the mandible. -The spine and costal arcs. -The left iliac bone and the acetabular region. -The leftfemur. -The tarsal and carpal bones.	Lung, spleen and liver involvements.	Systemic LCH with riskorgans involvement.	**Initial treatment:** 8 weekly pulses of vinblastine with a favorable outcome. **Treatment ofsystemic relapse after three years:** The vinblastine in combination of steroids and méthotrexatewith good therapeutic response
2	-The right maxillary bone	-	Eosinophilic bone granuloma	The treatment consisted of curettage of the lesion with no relapses
3	-The maxillomandibular bone -The bilateral petrous apex	Bone, lung and post-pituitary endocrine involvements	Systemic LCH	**Initial treatment:** high-dose corticosteroid therapy with substitutive treatment with DDAVP **Treatment of systemic relapse after three years:** Vinblastine combined with high dose of corticosteroid therapy with persistent irreversible bilateral deafness and sequellar lung lesions.
4	-The left fronto-temporal bone.	-	Eosinophilic bone granuloma	The treatment consisted of surgical excision of the lesion with favourable outcome

3. DISCUSSION:

Bone is the most frequent involvement in LCH noted in about 80% of cases and represents approximately 50% of the localizations in the adult [6,7]. There is a predilection of location for the flat bone (skull, ribs, sternum, iliac bones and scapula), the vertebrae and also the long bones (femur, humerus and tibia). The small bones of the hands or feet are rarely affected [8,9,10].Bone lesions may be asymptomatic and revealed in radiological findings or cause localized painful swelling of the soft tissues or pathological fracture [11]. Some bone lesions can be discovered during complications [12].In the cranial vault, the lesion is manifested by the appearance of soft swelling as reported in our fourth case report [13].The involvement of the temporal bone can be manifested by otorrhea,hypoacusis or repeated otitisand even a sequential deafness [14]. These clinical symptoms were observed in our third patient. The maxillary and mandibular localization is frequent and its symptoms are nonspecific as in 3 of our patients and the most common clinical signs are intraoral mass, pain, gingivitis, dental exfoliation and mucous ulceration [15]. Spinal involvement accounts for 15 to 30% of localizationsin systemic LCH and about 10 to 15% ineosinophilic granulomas [16]. The level of vertebral involvement varies with age. In adults, 47% of reported cases involve the cervical spine, 33% the thoracic spine, and 20% the lumbar spine [17].Some authors emphasize the exceptional nature of neurological disorders [18]. The iliac bone is most often reached with a very evocative localization to the cookie cutter [19]. The involvement of the peripheral skeleton is rare and classically localized in the long bones (femur, humerus).In the presentseries, vertebral and iliac bone involvement was detected in our first patient with no neurological disorders. On standard radiography, single or multiple bone lesions are typically lytic known as "geography maps" or "punch" with or without peripheral sclerosis. In the skull, the typical appearance of a LCH lesion is a well-defined lytic lesion, with non-sclerotic margins, involving both inner and outer table, resulting in a double-contour appearance, sometimes associated with an adjacent soft tissue mass [13].In the long bones, the lesions are essentially diaphyseal producing images of oval osteolysis with periosteal and often lamellar, appositions [12, 20]. In all cases of the base of the skull and the facial mass, computed tomography(CT)allows to better analyze the osteolysis, and especially the invasion of the soft parts[21]. In the spine, the involvement predominates in the vertebral body. The typical aspect corresponds to the vertebra plana described by Calvé in 1924[22]. The MRI is the most effective examination to analyze the expansion of the tumor in the marrow and the nerve roots and to check the integrity of the intervertebral disc [12, 20]. Skeletalscintigraphy allows evaluation of bone lesion extension and follow-up of lesions after treatment.The presentseries is particular by the richness of the radiological signs. A bone biopsy is crucial to confirm LCH and it was performed in all our patients allowing the diagnosis of LCH in 3 cases[18]. Therapeutic strategy of skeletal involvement in Langerhans cell histiocytosis depends on clinical form. The unifocal bone lesionresponds well to local therapy such as curettage, excision or possibly intra-tumoral steroid injections [8]. Persistence symptoms of disease, or expansion of the lesion aftersurgical intervention, may respond to the subsequent radiotherapy [23]. The use of bisphosphonates in monthly treatment has been successfully reported in some patients [24,25,26,27].In the presentseries, complete excision of the bone lesion (curettage) waseffective in two cases.In the multifocal bone lesions or associated with multisystem lesions of LCH, the systemic reference treatment is based on the combination of

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vinblastine and corticosteroids.In a retrospective multicenter study, vinblastine was shown to have good response in adults as a first line treatment; however, many patients experienced reactivation in long-term follow-up [28]. The first-line systemic treatment of our patients was based on high-dose corticosteroid therapy which was proposed in multifocal LCH bone withpost-pituitary involvement in the third case. Eight courses of vinblastine were indicated in disseminated LCH with pulmonary and liver involvement in the first case. In both casesrelapses were noted affecting the maxillofacial bone, the lung and the liverin the first case and the auricular bone as well as the lung in the second case. Induction therapy with vinblastine has been indicated in combination with corticosteroid therapy in two cases. Methotrexate was also introduced in the case with organ risk involvement.

LCH is also a source of late sequelae. Prevalence of squelae is as follow:orthopaedic related 27%, diabetes insipidus 19%, growth retardation 13%, cosmetic 10%, neurological 7%, hearing 7%, anterior pituitary hormone deficiency 7%, hepatobiliary 4% and ophthalmological 3%[29]. Orthopedic sequelae are common in plurifocalform: vertebra plana, kyphoscoliosesandbone deformities ranging from aesthetic impact to functional disorders, tooth loss, dental articular disorder [30].In the presentseries, the subsequent evolution was favorable in 3 cases. LCH was responsible for mixed bilateral sequelal deafness and diabetes insipidus in one case.

In this,study researcherstried to highlight clinicalpara-clinical and therapeutic features of bone involvements in LCH that is characterized by its recurrence and multifocal localizations in disseminated form of the disease. However, its main limitations are the small size of our population and it is also aretrospective study.Vemurafenib, a BRAF inhibitor was effecticve in an open-label, non- randomized study in cases of LCH with BRAF- V600E mutation. Dabrafenib is another BRAF inhibitor that was efficacious in refractory cases of LCH with more safety. This new therapeutic option stills not well documented (31, 32,33, 34). Therefore,further experiences need to be gained especially in the treatment with prospective trials targeting the genetic pathogenesis pathways which are the mutation of BRAF-V600E and MAPK genes [35, 36, 37, 38, 39,40, 41].

4. CONCLUSION

LCH is a rare disease in children and young adult males. Bone is the most frequently involved site. The circumstances of discovery of bone localization were the pain swelling lesion in different sites. It is characterized by lytic lesions of variable aggression. CT and/or MRI may complement radiography. Biopsy is necessary to obtain diagnosis confirmation. The prognosis of this pathology depends largely on early diagnosis, other organs affected and the response to treatment.

LISTS OF FIGURES:

Figure n°1: vertebral and iliac bone Langerhans cell Histiocytosis

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Figure n°2: osteolytic lesions of Langerhans cell Histiocytosis affecting the hemi mandibleand the scalp

Figure n°3:osteolytic lesion of Langerhans cell Histiocytosis next to the right maxillary sinus.

Figure n°4: temporal osteolytic lesion of Langerhans cell Histiocytosis on the brain tomography

COMPETING INTEREST: Authors have declared that no competing interests exist.

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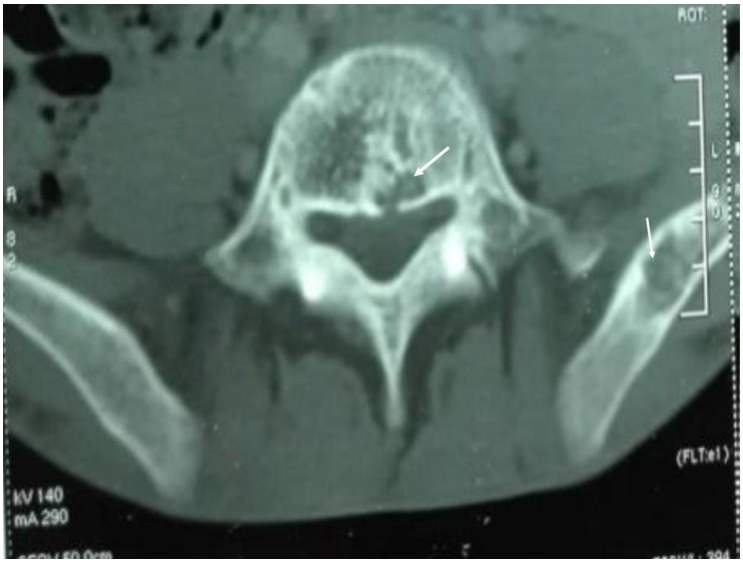

Figure n°1 : vertebral and iliac bone Langerhans cell Histiocytosis

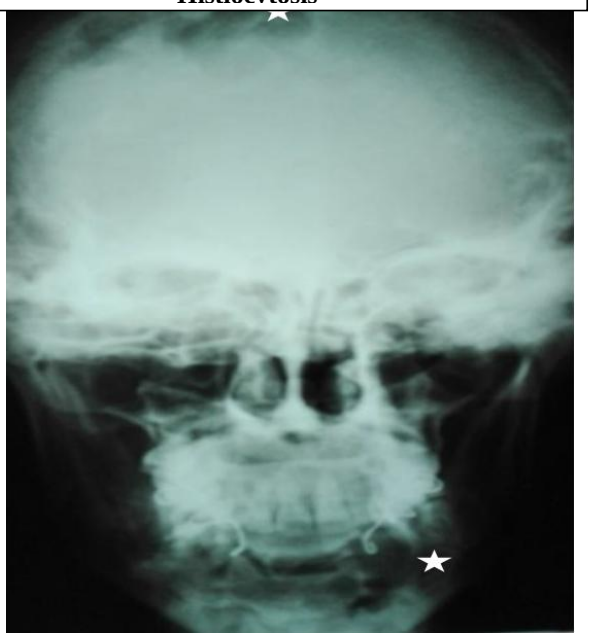

Figure n°2: osteolytic lesions of Langerhans cell Histiocytosis affecting the hemi mandibleand the

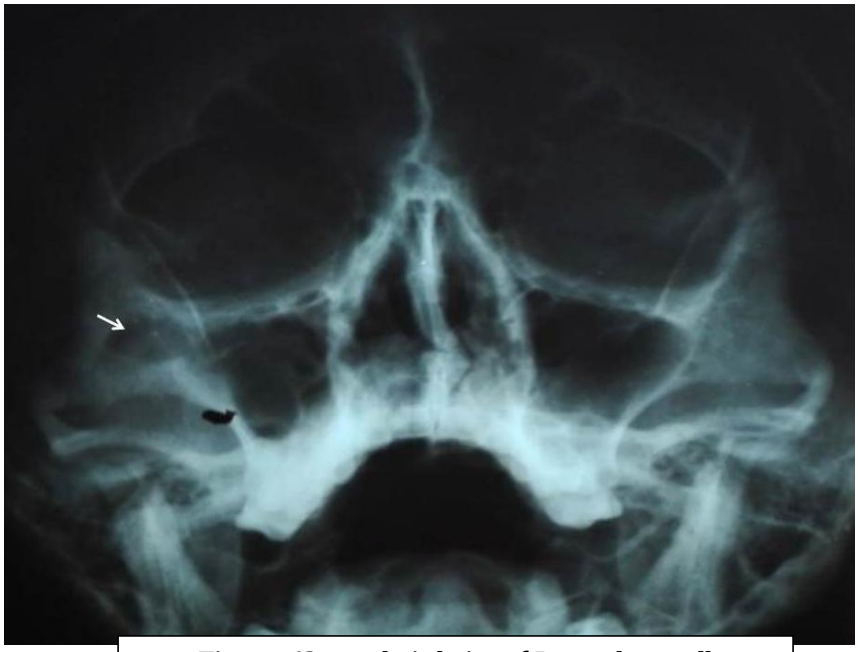

Figure n°3:osteolytic lesion of Langerhans cell Histiocytosis next to the right maxillary sinus.

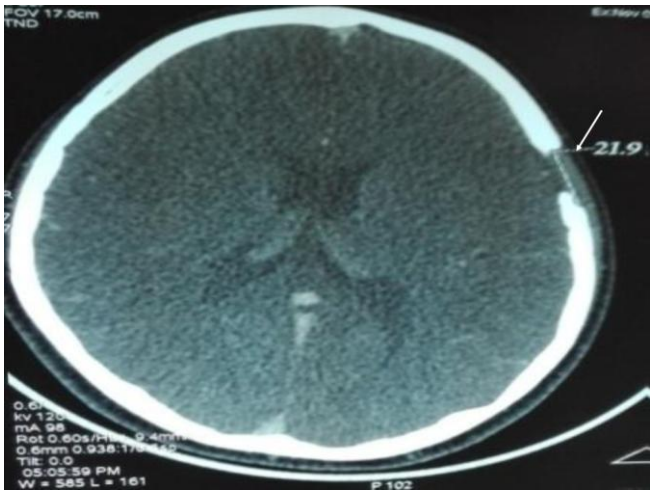

Figure n°4: temporal osteolytic lesion of Langerhans cell Histiocytosis on the brain tomography