Case study

Case study on Langerhans cell histiocytosis of bone

ABSTRACT:

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

Materials and methods: A retrospective and descriptive study of patients with Langerhans cell histiocytosis admitted in Internal Medicine Departments of Hedi Chaker University Hospital of Sfax 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 eosinophilic ganuloma 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 present series, 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 several etiopathogenic hypotheses have been advanced (infectious, immunological, genetic or neoplastic), the etiology 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 single organ to

Comment [VS1]: para-clinical

Comment [VS2]: Space ????

Comment [VS3]: eosinophilic

Comment [VS4]: granuloma

Comment [VS5]: Future suggestion ?

multisystem 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 present study is to precise the epidemiological, clinical, para-clinical, therapeutic and prognostic characteristics of skeletal involvement in Langerhans cell histiocytosis.

2. MATERAILS AND METHODS:

A retrospective study of patients with Langerhans cell histiocytosis admitted in Internal Medicine Departments of Hedi Chaker 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 14 years the patient presented a diffuse alveolysis with general bone pain. The patient was referred first to the maxillofacial and Orthodontics department. To explore these unexplained symptoms, a skeletal scintigraphy showed diffuse hyper fixation at the base and the cranial vault, the jaws, the upper extremity of the left femur, the diaphysis and the left femoral condyle, the left iliac wing, the lower extremity of the left tibia and the head of the right fibula The body scan revealed multiple lytic and blowers lesions affecting the whole skeleton. In the skull, these lesions interested the frontal, temporal and mastoid bone, the sphenoid bone, the occipital bone, the two rocks complicated with otitis media, the left malar bone and the mandible. The bone involvement concerned also the spine and costal arcs. The lesions affected 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 extended in the left femur and in tarsal bones. The thoracic and abdominal tomography showed a multiple micro-nodular, reticular, cystic lung lesions and homogeneous hepato-splenomegaly. The association of diffuse osteolytic lesions, lung and liver involvements evoked the diagnosis of systemic LCH confirmed by the 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), steroids at high doses and methotrexate 15 mg per week with good

Comment [VS6]: para-clinical,

Comment [VS7]: Bold ??

Comment [VS8]: Skeletal scintigraphy

Comment [VS9]: Hyper fixation

Comment [VS10]: mastoid bone

Comment [VS11]: micro-nodular,

Comment [VS12]: particularly

clinical therapeutic response. The combination of methotrexate and steroid was interrupted after 3 years of sustained remission.

Case 2:

A 21-year-old patient was admitted in September 2011 to otolaryngology department with a history of lower right maxillary pain since 4 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 reaction infiltration of the adjacent tissues. The surgical exploration confirmed the presence of a tumor process in the right sinus. Histopathological examination of the biopsied tumor showed a cluster of histiocytic cells with a polymorphic infiltrate particularly rich in eosinophilic poly-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 referred to internal medicine department. The physical examination was normal. The sinus radiograph revealed an osteolytic lesion next to the right maxillary sinus (figure n°3). All other investigations including complete blood count, chemistries, liver function, skeletal scintigraphy and the thoracic tomography were within normal. The diagnosis of eosinophilic bone granuloma in right maxillary was retained. The treatment consisted of curettage 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 department with progressive polydipsia with concomitant polyuria and nocturia. Diagnosis of diabetes insipidus was 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 bone lesion revealed a granulomatous infiltrate rich in histiocytes and eosinophilic poly nuclear cells with positive immunostaining of the CD1a +, PS100 + and CD68 + type. The diagnosis of LCH was 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 referred to 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 departement in January 2013 with a one month history of pain and swelling of the tempal area. The brain tomography showed a left temporal osteolytic lesion (figure n°4). Cerebral MRI concluded with a left fronto-temporal lytic lesion. The

Comment [VS13]: Bold ??

Comment [VS14]: September

Comment [VS15]: poly-nuclear

Comment [VS16]: referred

Comment [VS17]: Bold ??

Comment [VS18]: Bold ????

Comment [VS19]: departement

anatomopathological examination of biopsied lesion revealed 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 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.

Comment [VS20]: poly nuclear

Table1: Clinical characteristics, treatment and outcome of our patients

Comment [VS21]: Bold

Comment [VS22]: Bold

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 bone and the mandible. -The spine and costal arcs. -The left iliac bone and the acetabular region. -The left femur. -The tarsal and carpal bones.	Lung, spleen and liver involvements.	Systemic LCH with risk organs involvement.	**Initial treatment:** 8 weekly pulses of vinblastine with a favorable outcome. **Treatment of systemic relapse after three years:** The vinblastine in combination of steroids and méthotrexate with 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	The treatment consisted of surgical excision of the

			granuloma	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 otitis and 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 localizations in systemic LCH and about 10 to 15% in eosinophilic 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 present series, 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]. Skeletal scintigraphy allows evaluation of bone lesion extension and follow-up of lesions after treatment. The present series 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 lesion responds well to local therapy such as curettage, excision or possibly intra-tumoral steroid injections [8]. Persistence symptoms of disease, or expansion of the lesion after surgical intervention, may respond to the subsequent radiotherapy [23].

Comment [VS23]: present

Comment [VS24]: non -sclerotic

Comment [VS25]: (CT)

The use of bisphosphonates in monthly treatment has been successfully reported in some patients [24,25,26,27].In the present series, complete excision of the bone lesion (curettage) was effective 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 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 with post-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 cases relapses were noted affecting the maxillofacial bone, the lung and the liver in 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 plurifocal form: vertebra plana, kyphoscolioses and bone deformities ranging from aesthetic impact to functional disorders, tooth loss, dental articular disorder [30]. In the present series, 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 researchers tried to highlight clinical para-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 a retrospective 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.

Comment [VS26]: and bone

Comment [VS27]: present

Comment [VS28]: para-clinical

Comment [VS29]: ,

Comment [VS30]: What is the meaning ?

LISTS OF FIGURES:

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

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.

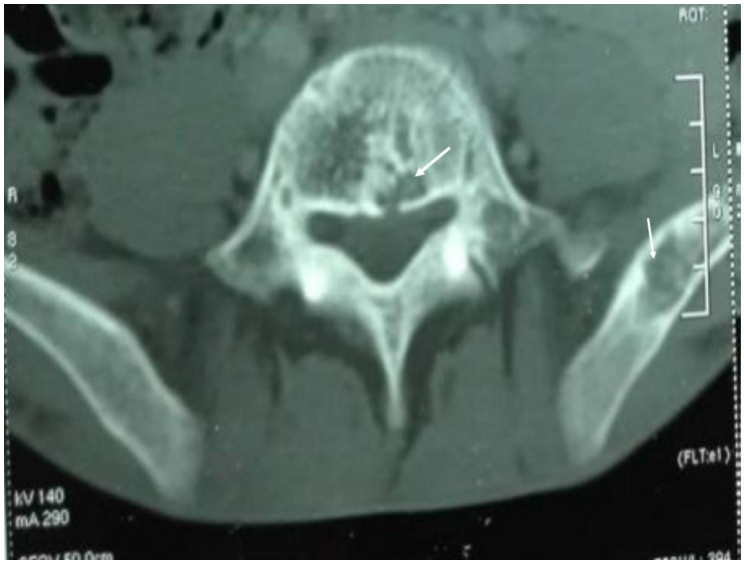
Figure n°4: temporal osteolytic lesion of Langerhans cell Histiocytosis on the brain tomography

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

REFERENCES:

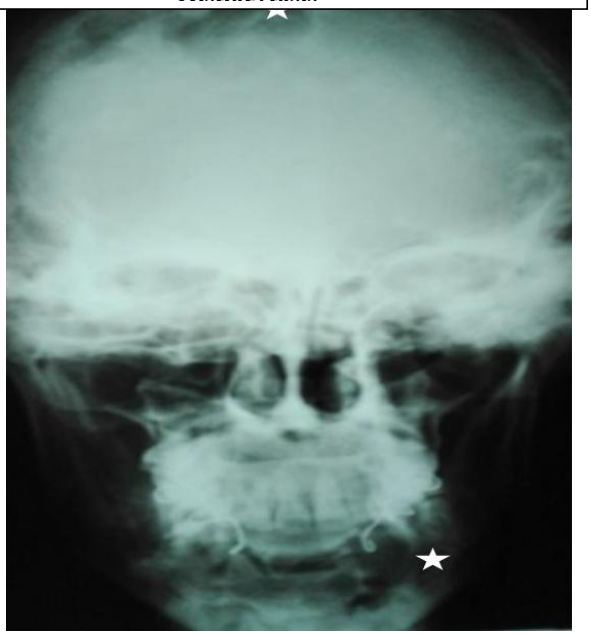
1. Stephan jl. Histiocytoses langerhansiennes et non langerhansiennes. Arch Pediatr, 2002. 9:934–41.
2. Lieberman Ph, Jones Cr, Steiman Rm, et al. Langerhans cell (éosiniphilic) granulomatosis. A clinicopathologic study encompassing 50 years. Am J Surg Pathol. 1996; 20 :519-52.
3. Arico M, Egeler RM. Clinical aspects of Langerhans cell histiocytosis. Hematol Oncol Clin North Am. 1998; 2:247-58.
4. Badalian-Very G, Vergilio JA, Degar BA, MacConaill LE, Brandner B, Calicchio ML, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood 2010;116:1919–23
5. B. Ng-cheng-hin, c. O'hanlon-brown, c. Alifrangis and j. Waxman. Langerhans cell histiocytosis: old disease new treatment. Q J Med 2011; 104:89–96
6. F. Geismann, J. F. emile, J. Donadieu, P. Andry, C.Thomas et N. Brousse. Aspects cliniques et physiopathologiques de l'histiocytose Langerhansienne : une prolifération clonale de cellules dendritiques de Langerhans. John Libbey Euro text. Revue Hématologie. 1997; **3**, 1: 33-43.
7. Oehler E, Leogite J, l Hellal k, Feuillet B, Evenat F, Ghawche F. Bone lesions. Rev Med Interne. 2014;**35**:554–5.
8. Lahiani D, Hammami BK, Maaloul I, Frikha M, Baklouti S, Jlidi R et al. Histiocytose langerhansienne osseuse multifocale : révélation tardive chez une femme de 76 ans. Rev Med Interne. 2008;29:249–51.
9. Islinger RB, Kuklo TR, Owens BD, Horan PJ, Choma TJ, Murphey MD, et al. Langerhans' cell histiocytosis in patients older than 21 years. Clin Orthop Relat Res 2000;379:231–5
10. Kilpatrick SE, Wenger DE, Gilchrist GS, Shives TC, Wollan PC, Unni KK. Langerhans' cell histiocytosis (histiocytosis X) of bone. A clinicopathologic analysis of 263 pediatric and adult cases. Cancer 1995;76:2471–84
11. Suonita K , Jean Francois b , Elisa Ab, L, Gustavo S ,Anne C, and Nathaly B. Skeletal involvement in Langerhans cell histiocytosis. Insights Imaging. 2013 Oct; 4(5) : 569–579.
12. Bollini G, Jouve Jl, Launay F, Viehweger E. Manifestations orthopédiques des histiocytoses langerhansiennes. Arch Pediatr. 2008; 15:526–8.
13. Okamoto K, Ito J, Furusawa T, Sakai K, Tokiguchi S. Imaging of calvarial eosinophil granuloma. Neuroradiology. 1999 ; 41 : 723-8.
14. A. Matrane, A. Guensi, M. Kebbou. Histiocytose Langerhansienne osseuses multifocale : intérêt de la scintigraphie osseuse planaire. Médecine nucléaire. 2012 ;36 : 730-735.
15. Dhanu G R , Malay V T , Raghavendra H , And S P Shrutha. A rare and unusual case report of Langerhans cell histiocytosis**.** J Oral Maxillofac Pathol. 2017; **21(1)** : 140–144.
16. Floman Y[1], Baron E, Mosheiff R, Mirovsky Y, Robin Gc, Ramu N. Eosinophilic granuloma of the spine. J Pediatr Orthop B. 1997 ; **6** :260-5.
17. Garg B, Sharma V, Eachampati Kk, Malhortha R, Bhan S. An unusual presentation of eosinophilic granuloma in an adult: A case report. J Orthop Surg (Hong Kong) 2006. **14:81**-3.
18. Green Ne, Robeston Ww, Kilroy Aw. Eosinophilic Granuloma of the spine with associated neural deficit. J Bone Joint Surg Am, 1980; 62:1198–202.

19. Zachary Christopher Md, Odion Binitie Md, Evita Henderson Jackson Md,Joseph Perno Md, Rikesh J. Makanji Md. Langerhans cell histiocytosis of bone in an adult: A case report. Radiology Case Reports. 2018; 13:310–314
20. Azouz Em, Saigal G, Rodrigeuz Mm, Podda A. Langerhans' cell histiocytosis: pathology, imaging and treatment of skeletal involvement. Pediatr Radiol, 2005;35:103–15.
21. Hermans R, De Foer B, Smet Mh, Leysen J, Feenstra L, Fossien E et al. Eosinophile granuloma of the head and neck: CT and MRI features in three cases. Pediater Radiol 1994; 24: 33-6.
22. Weston Wj, Goodson Gm.*Vertebra plana (Calve).*J Bone Joint Surg Br, 1959; 41:477-85.
23. Pereslegin Ia, Ustinowa U. Radiotherapy of eosinophilic granuloma of bone. Int J Radiat Oncol Biol Phys 1981; **7:** 317-21.
24. Morimoto A, Shioda Y, Imamura T, Kangane H, Sato T, Kudo K, et al. Nationwide survey of bisphosphonate therapy for children with reactivated Langerhans cell histiocytosis in Japan. Pediatr Blood Cancer, 2011; 56:110–5.
25. Brown RE. Bisphosphonates as antialveolar macrophage therapy in pulmonary Langerhans cell histiocytosis? Med Pediatr Oncol 2001; 36:641–3
26. D'Souza MJ, Oettinger CW, Shah A, Tipping PG, Huang XR, Milton GV. Macrophage depletion by albumin microencapsulated clodronate: attenuation of cytokine release in macrophage-dependent glomerulonephritis. Drug Dev Ind Pharm 1999; 25:591–6
27. Montella L, Merola C, Merola G, Petillo L, Palmieri G. Zoledronic acid in treatment of bone lesions by Langerhans cell histiocytosis. J Bone Miner Metab 2009; 27: 110-113 [PMID: 19018458 DOI: 10.1007/s00774-008-0001-2
28. Abdellatif T, Gwneal L, Julien H, Antoine N, Stephane D, Achille A, Vinblastine chemotherapy in adult patients with langerhans cell histiocytosis: a multicenter retrospective study. Orphanet Journal of Rare Diseases, 2017; 12:95.
29. Tin Wai C, Wing K L, Frankie Wai Tsoi C, Shekhar Medhukar K, Winnie Chiu Wing C, Vincent Lee and al Late *outcomes in children with Langerhans cell histiocytosis*. Arch Dis Child. 2017 Sep; 102(9):830-835.
30. Bollini G, Jouve Jl, Gentet Jc, Jaquemier M, Bouyala Jm. Bone lesions in histiocytosis X. J Pediatr Orthop, 1994; 11:469-77.22.
31. Diamond EL, Subbiah V, Lockhart AC, et al. Histiocytosis: analysis of data from the histology-independent, phase 2, open- label VE- BASKET Study. JAMA Oncol. 2018;4:384-388
32. Bhatia A, Ulaner G, Rampal R, et al. Single- agent daBR AFenib for BRAFV600E- mutated histiocytosis. Haematologica. 2018;103: e177-e180
33. Papapanagiotou M, Griewank KG, Hillen U, et al. Trametinib- induced remission of an MEK1-mutated langerhans cell histiocyto-sis. JCO Precis Oncol.2017;1:1-5
34. Masayuki kobayashi,Arinobo Tojo.Langerhans cell Histiocytosis in adults.advances in physiopathology and treatment. Cancer Science. 2018;109:3707–3713.
35. Carl C E. A, Ladish S,. M C Clain Kl. How I treat Langerhans cell histiocytosis. Blood. 2015 Jul 2; 126(1): 26–35.
36. Carl E. Allen, M.D., Ph.D., Miriam Merad, M.D., Ph.D., and Kenneth L. McClain, M.D., Ph.D Langerhans-Cell Histiocytosis. N Engl J Med 2018; 379:856-868
37. Michaloglou C, Vredeveld LC, Mooi WJ, Peeper DS. BRAF(E600) in benign and malignant human tumours. Oncogene 2008;27:877-95
38. Cagnol S, Chambard JC. ERK and cell death: mechanisms of ERK-induced cell death — apoptosis, autophagy and senescence. FEBS J 2010;277:2-21
39. Poulikakos PI, Zhang C, Bollag G, et al. RAF inhibitors transactivate RAF dimers and ERK signalling in cells with wild-type BRAF. Nature. 2010;464:427-30
40. Haroche J, Cohen-Aubart F, Emile JF, et al. Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation. Blood. 2013;121:1495-500.
41. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med. 2015;373:726-36



299
300

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



301
302
303
304

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

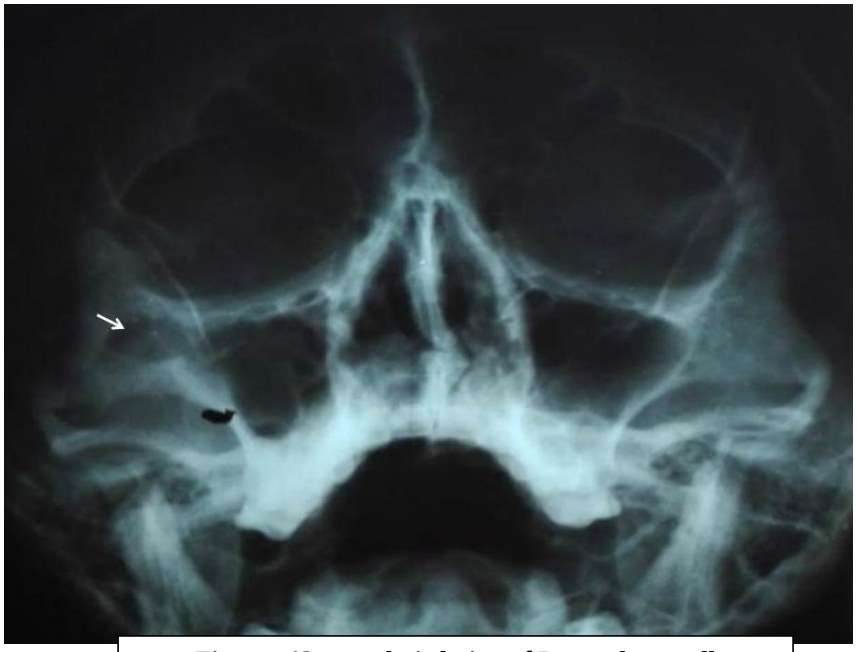


Figure n°3: osteolytic lesion of Langerhans cell Histiocytosis next to the right maxillary sinus.

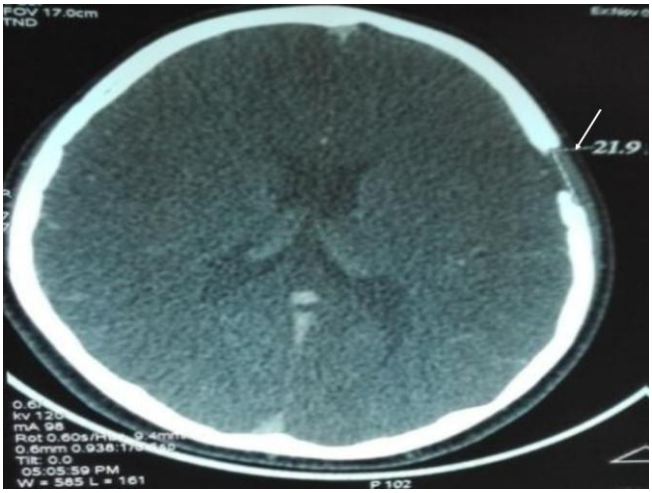


Figure n°4: temporal osteolytic lesion of Langerhans cell Histiocytosis on the brain tomography