Adulthood Langerhans Cell Histiocytosis: Experience of Two Portuguese Hospitals

Histiocitose de Langerhans no Adulto: Experiência de Dois Hospitais Portugueses

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Acta Med Port 2014 Nov-Dec;27(6):726-730

ABSTRACT

Introduction: Langerhans cell histiocytosis is a heterogeneous disease, more frequently diagnosed during childhood. Between 1/2001 and 12/2013, 20 adult patients were admitted at both Hospitals. This work aimed at characterizing this population.

Material and Methods: Retrospective study, review of clinical records.

Results: 16 patients were eligible to analysis. The median age at diagnosis was 34 years (15-48); 10 males and 6 females. The referral motive was: respiratory complaints – 37.5%; bone changes – 37.5%; dental complaints - 25%; constitutional symptoms - 19%; muco-cutaneous lesions – 6% and one patient (6%) was accidentally diagnosed after a thyroidectomy. The tissue of histological diagnosis was: bone - 50%; pulmonary tissue – 37.5%; liver, genital mucosa and thyroid - 6%, respectively. Staging was: single organ involvement (uni/multifocal) - 69% and multisystem disease in 31%. Clinical re-evaluation of these cases is being done at the moment. The median follow up was 5 years (1 month – 11 years) and the overall survival was 92%. Currently 19% are alive without signs of disease; 44% are alive with disease; 25% are under treatment and 12% died.

Discussion: These results agree with published literature. Considering the actual guidelines 56% patients were incompletely staged, which probably lead to suboptimal treatment. There is heterogeneity of clinical procedures aiming at staging and treatment of these patients.

Conclusion: The diagnosis of adulthood Langerhans cell histiocytosis is difficult considering the diversity of clinical behavior. Frequently this also leads to diagnosis delay. Prospective international clinical trials enrolling adult patients are important.

Keywords: Adult; Histiocytosis, Langerhans-Cell.

RESUMO

Introdução: A histiocitose de células de Langerhans é uma doença heterogénea e mais frequente em crianças. Entre 1/2001 e 12/2013 admitimos 20 doentes com HCL nas duas instituições. O objectivo deste trabalho foi caracterizar esta população, avaliando as formas de apresentação, o estadiamento e tratamento.

Material e Métodos: Estudo retrospectivo; consulta do processo clínico.

Resultados: Dos 16 doentes analisáveis verificamos uma mediana de idade 34 anos (15-48), 10 mulheres e 6 homens. Os motivos que determinaram a referenciação dos doentes foram: queixas respiratórias em 37,5%; alterações ósseas em 37,5%; queixas dentárias em 25%; sintomas constitucionais em 19%; lesões mucocutâneas em 6% e outro foi um achado histológico inesperado após tiroidectomia. O diagnóstico histológico foi obtido em: osso em 50%; pulmão em 37,5%; fígado, mucosa vulvar e peça de tiroidectomia em 6%, respectivamente. O estadiamento assumido na prática clínica foi: envolvimento de órgão único (uni/multifocal) em 69% e doença multissistémica em 31%. A mediana de seguimento foi cinco anos (dois meses-11 anos) e a sobrevivência global 92%. Actualmente: 19% estão vivos sem doença; 44% estão vivos com doença; 25% estão em tratamento e 12% morreram.

Discussão: Estes resultados estão de acordo com a literatura. No entanto, segundo as recomendações actuais consideramos que 56% doentes efectuaram estudo complementar incompleto condicionando subestadiamento e provavelmente subtratamento. Verifica-se heterogeneidade de procedimentos no estadiamento e tratamento.

Conclusão: Frequentemente há dificuldades e atraso no diagnóstico desta entidade clínica. São importantes estudos prospectivos internacionais na população adulta.

Palavras-chave: Adulto; Histiocitose de Células de Langerhans.

INTRODUCTION

Langerhans' cell histiocytosis (LCH) is a rare and heterogeneous disorder, partly explaining why its etiology, clinical outcome and therapy are so scarcely understood. It is still not determined whether it is mediated by an immunological or a neoplastic mechanism. It is however recognized as a clonal disorder and a mutation of the BRAF gene (BRAFV600E) has been recently identified, present in more than half of the patients, favouring the hypothesis of a neoplastic origin.[1-3]

These are cells of probable myeloid lineage and with a immunophenotype characterised by positive CD10, S-100 protein, CD207 and CD1a antigen.[1,2] They are presumably based in epidermal Langerhans's dendritic cells involved in antigen presentation, in a close relationship with T-lymphocytes. However, some authors describe these cells as originating from circulating plasmacytoid monocytes.[3,4]

LCH has an estimated incidence of 1-2 cases in adults and 3-5 in children/million/year. Due to a higher frequency in children many guidelines for adult patients are based on protocols developed for the therapeutic approach in children.[1,2]

It usually follows a heterogeneous clinical presentation,

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Recebido: 19 de Março de 2014 - Aceite: 07 de Julho de 2014

involving any organ or system. Bone involvement is the most common form of presentation both in adults and children. It usually presents with an osteolytic lesion and a pattern which is unifocal in the adult and multifocal in children. The sclerosis aspect is related to the beginning of the resolution process. It may affect, by frequency ranking, the bones of the skull, femur, orbit, rib, jaw, maxilla (Fig. 1) and vertebra.[1-4]

Central nervous system (CNS) involvement usually occurs by contiguity from cerebral lesions to the bones of the skull, with a predominance of the cerebellum, hypothalamic nuclei and pituitary gland, producing diabetes insipidus. The infiltration by the Langerhans' cells rarely produces a mass-effect and therefore is hardly ever identified by CT-scan.[1-4]

The lesions in the skin occur in 40% of the patients associated to a multi-system disorder and therefore their presence should prompt a search for internal organ involvement.[1]

Isolated LCH is considered as a distinct entity, related to tobacco addiction and usually affecting young patients. It presents with a typical micronodular radiological pattern, predominantly located in the upper lobes and in the perihilar regions, sparing the costophrenic angles (Fig. 2). The chest CT-scan shows a honeycomb pattern (Fig. 3). The pulmonary involvement is not frequent in disseminated disease.[1-4]

According to current guidelines, risk-organ involvement is defined by the involvement of the spleen, the liver, the bone marrow and the lung (excluding the isolated pulmonary involvement). Some authors consider a high risk category when the disease occurs in anatomical places with risk of disfigurement, organic dysfunction or when the CNS is involved.[1-4]

Different therapeutic approaches have been described, according to staging. In localized disease, namely in unifocal bone lesions, surgical curettage should be considered as first-line therapeutic option, as well as intralesional steroids or local radiotherapy. In multi-system disease or with risk-organ involvement, there is an indication for chemotherapy (vinblastine and prednisolone or cladribine, among others).[5-11]

Our work aimed to characterize a group of adult patients with LCH attending to two Hospital Centres – *Instituto Português de Oncologia* and *Hospital de São João* (IPO and HSJ), Porto, in order to assess their demographic and clinical characteristics, therapy, outcome, as well as overall survival.

MATERIAL AND METHODS

This was a longitudinal retrospective study involving a group of patients with LCH attending to the IPO and HSJ between January 2001 and June 2013. Data collection was based on patient's clinical records and retrospective clinical data collection. The statistical analysis used SPSS v13.0 software and Kaplan-Meier method was used in the survival analysis.

RESULTS

Our group of patients included 20 patients attending both institutions over a 12-year time period. Four patients were excluded from the overall analysis, three due to the absence of clinical data and one diagnosed in childhood. Among the 16 eligible patients, 10 were male. Median age was 34 years (15-48) and most patients were smokers (69% - 11 patients).

At the time of the initial examination, patients described: respiratory complaints (pneumothorax, persistent cough, imaging finding) - six patients (37.5%); bone complaints (pain, dysmorphia) - six patients (37.5%); dental complaints (odontalgia, mobility, spontaneous loss of teeth) - four patients (25%); constitutional symptoms - three patients (19%); mucocutaneous lesions were described by one patient, while in one patient the diagnosis was obtained unexpectedly within the histological examination of a thyroidectomy sample, with a concomitant thyroid papillary carcinoma (Table 1).

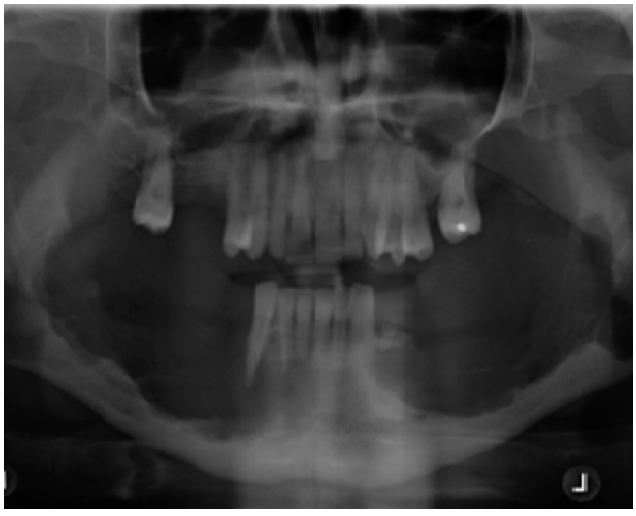

Figure 1 - Orthopantomography from a patient with LCH and jaw's bone involvement. A significant loss of bone mass and of multiple dental pieces may be observed..

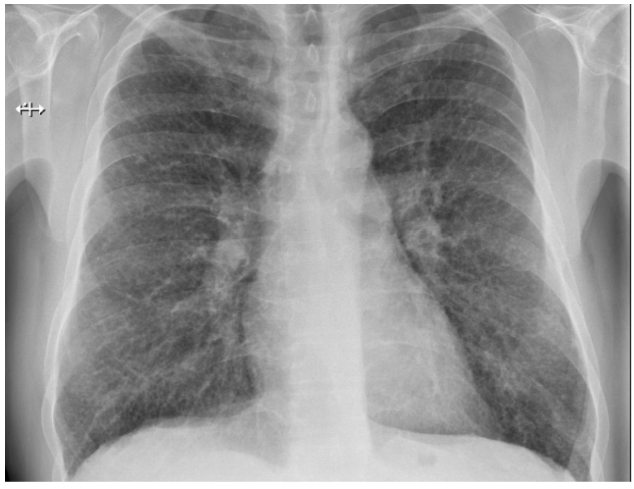

Figure 2 - Chest X-ray from a patient with LCH and lung involvement. A micronodular pattern, predominantly from the upper lobes and the perihilar region may be observed, sparing the costophrenic angles.

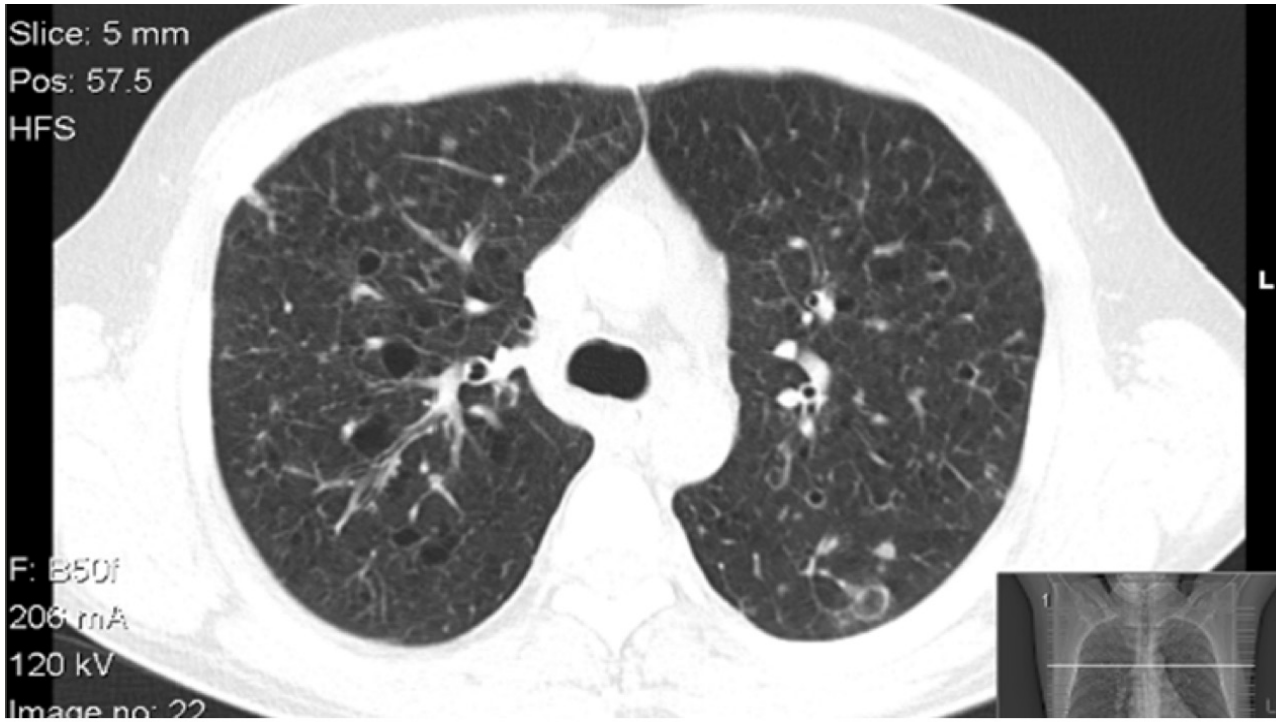

Figure 3 - CT-scan from a patient with LCH and lung involvement. The image shows a honeycomb pattern.

Nine of these patients (56%) were referred by Haematology, five (6%) by Chest Medicine, one (6%) by Endocrinology and one (6%) by Dermatology.

A five-month median time was found between the beginning of clinical complaints and diagnosis (two weeks – eight years). Three patients (19%) developed symptoms showing CNS involvement while the initial clinical presentation was under investigation.

A definite histological diagnosis was obtained in 15 patients; one patient started therapy based on a presumptive diagnosis (highly suggestive clinical signs and multiple inconclusive biopsies). Histological diagnosis was obtained from bone (eight patients; 50%), lung (two patients; 37.5%) and liver, vulvar mucosa and thyroidectomy samples (one patient, 6%, respectively). From the patients with lung involvement, five underwent bronchoalveolar lavage of which only one had diagnostic criteria and a lung biopsy was required in the remaining patients.

Staging established single-organ (uni or multifocal) involvement in 11 patients (69%) and multi-system disease in 5 patients (31%). Four patients (25%) presented with high risk-category organ involvement, 3 patients (19%) with lung concomitant with other organ's involvement and one patient (6%) with liver involvement. As previously described, three patients (19%) presented with CNS involvement with diabetes insipidus (one of these presented concomitantly with severe manifestations of organic psychosis) and 3 patients (19%) presented with bone involvement – vertebrae, jaw and bones of the skull.

Table 1 - Heterogeneity of clinical manifestations in patients with LCH

Reason for referral	Incidence (%)
Respiratory complaints	37.5%
Bone changes	37.5%
Dental complaints	25%
Constitutional symptoms	19%
Mucocutaneous lesions	6%
Histological incidental finding - thyroidectomy	6%

According to current guidelines, we considered that incomplete complementary investigation at the time of diagnosis was carried out in nine patients (56%), which probably induced understaging or undertreatment.

First-line therapy options are shown in Table 2.

A five-year median follow-up (two-months-11 years) and 92% overall survival (± 0.7%) were found. Currently, three patients (19%) are alive disease-free, seven patients (44%) are alive with active disease, four patients (25%) are on treatment and two patients (12%) died (due to decompensated diabetes insipidus and to peripheral T-cell non-Hodgkin lymphoma diagnosed after two therapeutic strategies for LCH).

We should note that one patient was referred for haematopoietic stem-cell transplantation and was excluded from the overall analysis, as diagnosis was obtained in childhood. This patient presented with multifocal bone disease and diabetes insipidus, with multiple relapses and several lines of therapy were carried out at the Paediatrics Department. Upon reaching adulthood, this patient was transferred to the Haematology Department and followed on chemotherapy with cladribine and allogenic haematopoietic stem-cell transplantation from an unrelated donor.

Table 2 - Therapeutic option according to staging

Therapeutic option	Uni-systemic %, (*n*)	Multi-systemic % (*n*)
Monitoring	19% (3)	6% (1)
Surgery +/- Radiotherapy	19% (3)	6% (1)
Corticotherapy	19% (3)	6% (1)
Vinblastine + Prednisolone	12.5% (2)	-
Vinblastine + Prednisolone + Etoposide	-	12.5% (2)

Table 3 - Guidelines for staging, adapted from Histiocyte Society's guidelines

Recommended staging tests	
Initially	Additional – specific clinical situations
Blood count	Bone marrow test and biopsy (unexplained persistent cytopenia)
Biochemistry including kidney function, electrolyte, liver function, total protein, albumin, ferritin levels.	Liver biopsy (with liver dysfunction and only if clinically relevant)
Blood clotting tests	Bronchoscopy with broncho-alveolar lavage (CT-scan showing lung involvement, although with no typical pattern, for differential diagnosis)
Urinary osmolarity/density	Brain MRI (with neurological or visual complaints, craniofacial bone lesions, to clarify invasion or extent)
Abdominal ultrasound	Spine MRI (to exclude compression with suspicious vertebral lesions)
Chest X-ray	ENT assessment/ high-resolution CT-scan/MRI (hearing changes, assessment of mastoid involvement)
Bone X-ray and/or bone scintigraphy study	Endoscopic study with biopsy (persistent and unexplained diarrhoea, malabsorption symptoms)

He is currently alive, with no evidence from the disease and with a 23-year clinical follow-up.

DISCUSSION

The results found are overall in line with what is described in international literature.

The wide range of referring hospital departments is related to the heterogeneity of initial clinical manifestations as well as with potential involvement of any organ or system.[1-3] Therefore, although it is a rare entity, medical specialties should be aware of this pathology in the adult patient, as it predominantly affects younger individuals. Diagnosis requires a high degree of suspicion and final diagnosis is based on the histological examination of the lesions and biopsies are not infrequently necessary in order to obtain a conclusive diagnosis.[1-3] The cytological examination of a sample obtained by bronchoalveolar lavage is described in literature (with a positive criteria of >5% CD1a+ cells in non-smokers); nevertheless, this examination was not very useful for the diagnosis in our group of patients as only one in five had positive criteria.[1]

As regards staging and according to current guidelines, we consider that a group of patients was understaged and subsequently undertreated.[1-4] Urinary osmolarity was not

assessed on most patients, nine patients did not undergo any bone staging nor any abdominal imaging evaluation and two patients presented with non-evaluated initial dental complaints. However, we should note that these are recent guidelines, unavailable at the time of the initial diagnosis in most of these patients. A clinical re-assessment of these patients is underway, including re-staging and considering the need for a therapeutic change. The recommended staging tests are shown in Table 3.[1,2]

Treatment options were in line with those described in literature and range from surgical curettage in unifocal bone lesion up to chemotherapy and haematopoietic stem-cell transplantation in relapsing or refractory multi-system disorder.[2-5,10,11] Nevertheless, randomized clinical trials supporting these or other therapeutic options for the adult population are still scarce. For this reason, we should refer the clinical trials carried out by the Histiocyte Society and we suggest following its recommendations for treatment of these patients.[2]

CONCLUSION

This retrospective analysis shows the wide range of clinical behaviour of this disorder, which makes its diagnosis more difficult and delayed. The heterogeneity of procedures in staging and treatment of these patients increase the need and importance of prospective, randomized and multicentric studies involving adult patients, due its low incidence in this age group.

OBSERVATIONS

Poster presentation at the annual meeting of the Portuguese Society of Haematology, Porto, 2013.

CONFLICT OF INTERESTS

The authors declare that there was no conflict of interests in writing this manuscript.

FINANCIAL SOURCES

The authors declare that there was no external financial source for writing this manuscript.

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Acta Med Port 2014:27:726-730

Publicado pela **Acta Médica Portuguesa**, a Revista Científica da Ordem dos Médicos

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1749-084 Lisboa, Portugal.
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E-mail: submissao@actamedicaportuguesa.com
www.actamedicaportuguesa.com
ISSN:0870-399X | e-ISSN: 1646-0758