Cancer Treatment Reviews 41 (2015) 320–331

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Tumour Review

Langerhans cell sarcoma: A systematic review

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ARTICLE INFO

Article history:
Received 10 February 2015
Accepted 27 February 2015

Keywords:
Langerhans cell sarcoma
Langerhans cell histiocytosis
Malignant histiocytosis X
Human

ABSTRACT

Langerhans cell sarcoma (LCS) is a rare malignant tumour of Langerhans cells with a poor outcome. Given its rarity, there is a lack of evidence regarding the most appropriate treatment for this condition. Therefore the aim of this work was to review, compile, analyse and present clinical details and to determine the optimal treatment regimen.

A search of PubMed, CINAHL, EMBASE, Cochrane, CENTRAL, clinicaltrials.gov and Google Scholar was supplemented by hand searching. Data extracted included demographics, treatment, type of LCS and clinical outcome. Of 510 citations identified by a systematic literature search, 46 case series including 66 subjects with LCS met criteria for analysis.

The most common treatment modality was chemotherapy, used alone or in combination in 47 cases (71%) followed by surgery in 31 cases (47%). Overall mean (S.E.) disease specific survival and disease free survival were 27.2 (3.9) and 18.3 (3.8) months respectively. There was a significant difference in both disease specific and disease free survival between the local, loco-regional and disseminated disease cohorts (DSS $p = 0.014$; DFS $p < 0.001$).

More localised disease confers a survival advantage. Multi-modality therapy appears to be most effective, with the addition of radiotherapy to chemotherapy appearing beneficial. Complete surgical excision with clear margins being most effective for local disease control. Any adjuvant therapy should not be delayed. Bone marrow transplant appears to be the most reliable treatment in terms of outcome especially in disseminated disease however has well known patient selection and toxicity/tolerance issues. The role of cell surface markers for prognostication remains unclear.

Introduction

Langerhans cells function as antigen presenting cells within the histiocyte system. These are found in the supra-basal region of mucous membranes and the dermis, lymph nodes and the thymus gland and play a role in the immune response. The histiocyte system is divided into two cellular subsets: phagocytic cells (antigen processing cells) and dendritic cells (antigen presenting cells). Dendritic cells comprise the follicular dendritic cells found in the germinal centre of a lymph node, inter-digitating dendritic cells found in the periphery of a lymph node, and Langerhans cells found in the epithelia [1]. Langerhans cell sarcoma (LCS) is a rare malignant tumour of langerhans cells.

Langerhans cell tumours are classified by the World Health Organisation (WHO) into Langerhans cell sarcoma (LCS) and Langerhans cell histiocytosis (LCH) [2]. LCH is a clinically benign disease, however rarely can transform into LCS [3]. LCS displays features typical of malignant tumours i.e. rapid growth, local invasion, the ability to recur and metastasise. Langerhans cells can be distinguished by their morphology (characteristic longitudinally grooved nuclei and with the presence of Birbeck granules) and immunohistochemical profile CD1a+ve, S100+ve, CD21−ve, CD35−ve and CD68−ve [4]. The differentiation between the two is based on characteristic cytological findings; LCS is characterised by malignant cytological features eg. atypia, and number of mitoses present. A positive immunohistochemical staining for CD1a, CD207 (Langerin) and S-100 protein are confirmatory of LCS [5,6].

Given its rarity, it is unsurprising that there is a lack of evidence regarding the most appropriate treatment for this condition. Also, since the pathophysiology of LCS is poorly understood, most of the treatment protocols remain empirical and combination of surgery and chemoradiotherapy produce an unpredictable response.

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http://dx.doi.org/10.1016/j.ctrv.2015.02.011
0305-7372/

Further difficulty is encountered in searching for historical data as the nomenclature for both histiocytic and dendritic cell neoplasms has changed through time: LCS was previously named malignant histiocytosis X, which should be differentiated from malignant histiocytosis (a syndrome of systemic proliferation of atypical histiocytes). Therefore the aim of this work was to review, compile, analyse and present clinical details including the management and outcomes of this challenging disease entity.

Materials and methods

We conducted a systematic literature search on 21st September 2014 of MEDLINE (1966 to September 2014), CINAHL, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Clinical Trials, without language restriction for studies including combined key terms and exploded Medical Subject Headings of the terms: (“langerhans cell sarcoma”[MeSH Terms] OR (“langerhans”[All Fields] AND “cell”[All Fields] AND “sarcoma”[All Fields]) OR “langerhans cell sarcoma”[All Fields]) OR ((“histiocytic sarcoma”[MeSH Terms] OR (“histiocytic”[All Fields] AND “sarcoma”[All Fields]) OR “histiocytic sarcoma”[All Fields] OR (“malignant”[All Fields] AND “histiocytosis”[All Fields]) OR “malignant histiocytosis”[All Fields]) AND X[All Fields]). We also scanned the references in the retrieved articles. Institutional review board approval was not necessary because all data were retrieved from previous published sources.

For article selection three authors (JH/RCD/LM) independently screened the titles and abstracts of the search results and identified articles eligible for full-text review. Inclusion criteria for obtaining the full-text article included original studies, case reports, and case series on Langerhans cell sarcoma. Exclusion criteria at this stage included general reviews, editorials and other studies not specific for this condition. Abstracts in all languages were reviewed however non-English articles with insufficient detail in the abstract were excluded.

For subject data extraction, inclusion criteria included articles that identified subjects with primary Langerhans cell sarcoma – data for outcome (death or recurrence of disease), and follow-up period from presentation to outcome; and the treatment modality of choice [7]. In cases of identified Langerhans cell sarcoma with incomplete information, all available treatment, outcome and follow-up data were extracted. Data also were extracted on demographics, disease characteristics, and diagnostic criteria. Exclusion criteria for pooled analysis included insufficient data to perform survival analysis or overlapping data between studies. We resolved any disagreement between reviewers by consensus.

Disease extent was classified by both site (organ or system involvement) and into local, loco-regional and disseminated cohorts with local equating to single site disease, loco-regional equating to single site with involvement of the regional/draining lymph node groups, and more extensive disease classified as a disseminated disease.

All statistical calculations were performed using SPSS Version 21 (Chicago, IL, USA). Rates of overall, disease-specific and disease free survival were estimated by means of the Kaplan–Meier method and were compared by the log-rank test. A univariable model was developed using Cox regression to investigate presence of local versus locoregional versus disseminated disease as prognostic indicators. Time dependent co-variants were investigated to identify concordance with the proportional hazards assumption.

Results

The abstracts for 510 articles were reviewed. Of these 459 were excluded, including 5 whose full text was not in English with insufficient data in the abstract for inclusion, leaving 51 articles. Accessing the references of these yielded 7 more articles. Fifty-eight papers underwent full text review of which a further 12 were excluded (Fig. 1). In total 46 studies were included in the final analysis yielding 66 cases presented in Table 1. Lucas et al. [8] was found to be an update on a previously published case by Diaz-Sarrio et al. [9], therefore the updated data was used. The detailed search strategy can be found in Fig. 1.

The median age at presentation was 50 years (Inter-quartile range: 30–65 years). The cases ranged from congenital to 88 years at diagnosis. LCS appears to be a disease primarily of the adult population given 86.4% of cases presented after the age of 20. Within the cohort of patients under the age of 20, 66% had multi-organ disease, and 66% of cases were female. The overall male to female ratio was 1.3:1 without any apparent clustering in any specific age group.

Presentation

The most commonly affected sites at diagnosis were lymph nodes (49 cases – 74.2%) followed by the skin (32 cases – 48.5%), lung (19 cases – 28.8%), liver (11 cases – 16.7%) and spleen (10 cases – 15.2%).

Single site involvement was seen in 33.3% of cases, loco-regional involvement was seen in 25.8% and 40.9% of cases had disseminated disease. Within the single-site cohort, the skin was involved in 10 cases (45.5%), lymph nodes in 8 cases (36.4%) and bone in 3 cases (13.6%). Within the loco-regional cohort with the exception of nodal disease (present in all 17 cases by definition) the most common sites were again mucosal with the skin in 11 cases (64.7%) and 1 case (6%) each of disease from the nasopharynx, pyriform sinus and right tonsil. The exceptions were 2 cases involving the liver and gallbladder respectively. In patients with disseminated disease the commonest site involved was again

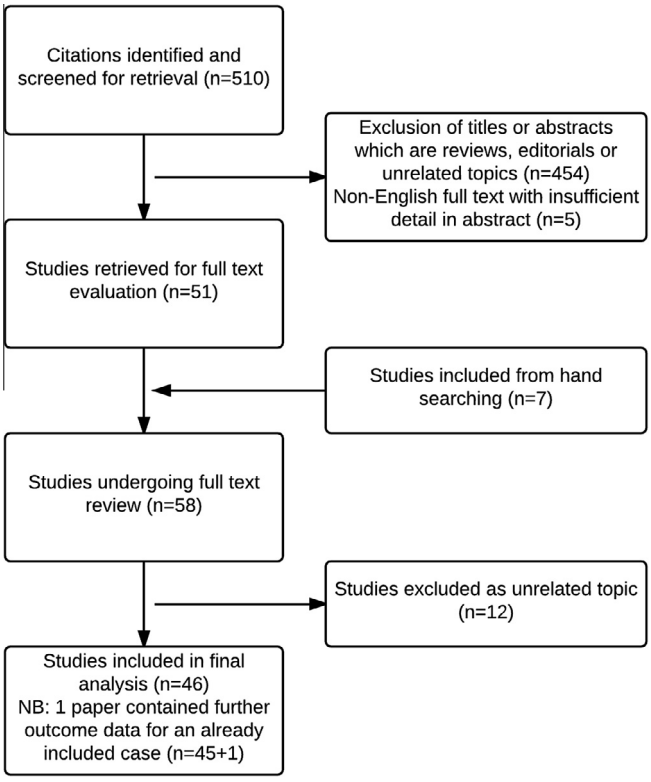

Fig. 1. Flowchart of article retrieval.