

## Case Report

# An unusual case of intertrigo in an adult caused by purely cutaneous Langerhans cell histiocytosis

Godfrey Baldacchino, Michael J. Boffa, Alexandra Betts, Alex Gatt

## Abstract

We report a case of persistent intertrigo in an adult, eventually diagnosed as cutaneous Langerhans cell histiocytosis (LCH). It is known that LCH has a predilection for intertriginous areas, however purely cutaneous disease as in our case, is uncommon and usually other systems are affected. Following the report, literature of similar cases is reviewed to determine possible outcomes and to decide on the best possible treatment options.

## Keywords

Intertrigo, Langerhans cell histiocytosis

## Case report

A 29-year old obese Maltese man was referred to the Dermatology Department in March 2012, with a one month history of worsening burning sensation in both axillae and groins, not responding to topical antifungal creams. A similar episode had apparently occurred a few months earlier and settled after application of a topical steroid/antifungal cream. He had a history of schizoaffective disorder and was on fluphenazine 25mg depot injection every 5 weeks but had no previous history of skin or other medical problems. No positive symptoms were elicited on systemic enquiry.

On examination there were striking, symmetrical, well-circumscribed, non-scaly erythematous-violaceous areas of induration in both axillae extending towards the proximal medial aspect of the arms (fig 1a). The affected areas were warm to touch and slightly tender. There were similar changes beneath the abdominal apron and in the groins extending towards the anterolateral thighs (fig 1b), and over the lateral right foot and ankle (fig 1c). There was no palpable lymphadenopathy, no hepatosplenomegaly and no visible abnormality in the scalp, external ears, mouth and nails.

An incisional biopsy from the right axilla was taken at presentation and empirical treatment with clarithromycin for 2 weeks for possible cellulitis was prescribed, with only minimal reduction in erythema at review 3 weeks later. Histology showed papillary dermal and deep dermal perivascular clusters and sheets of large ovoid cells with abundant pale cytoplasm and irregular, grooved reniform nuclei. These cells were accompanied by a variably dense inflammatory infiltrate composed of lymphocytes, eosinophils, and occasional plasma cells. Immunohistochemistry showed diffuse expression of S100 and CD1a by the large ovoid cells (fig 2). These features were consistent with

**Godfrey Baldacchino\*** MD, SCE (Derm)

Department of Dermatology,  
Sir Paul Boffa Hospital,  
Floriana, Malta  
godfrey.baldacchino@gov.mt

**Michael J. Boffa** MD, FRCP (Lond)

Department of Dermatology,  
Floriana, Malta  
Sir Paul Boffa Hospital

**Alexandra Betts** B.Ch.D, FRCPath

Pathology Department,  
Msida, Malta  
Mater Dei Hospital

**Alex Gatt** MD, FRCPath

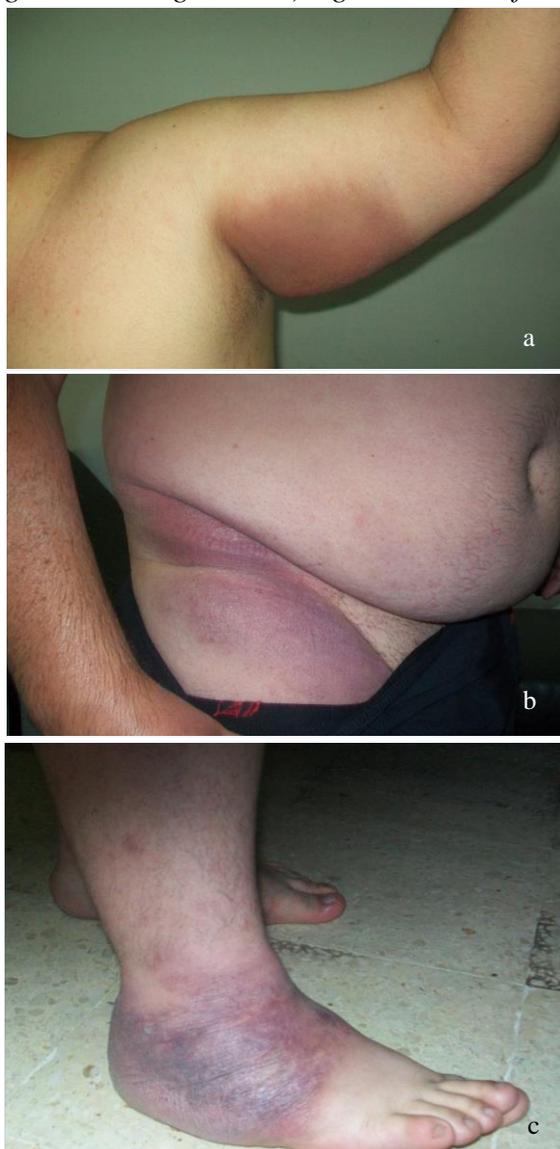
Haematology-Oncology Department,  
Mater Dei Hospital  
Msida, Malta

\*Corresponding Author

## Case Report

*Langerhans cell histiocytosis (LCH).*

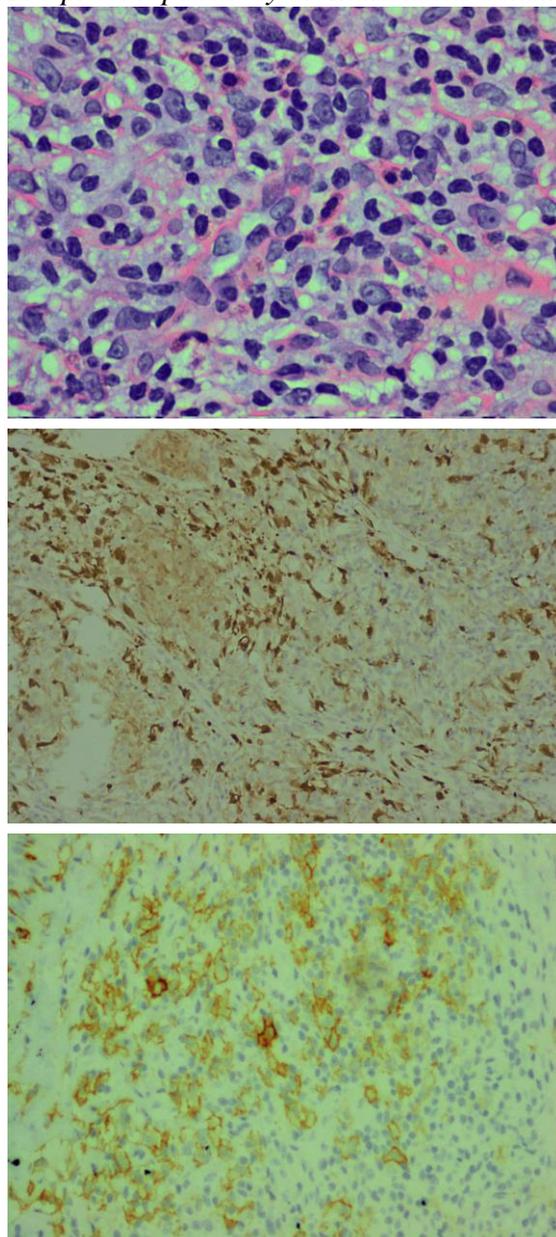
**Figure 1:** Indurated warm erythematous-violaceous plaques of LCH affecting the a) left axilla, b) right groin and thigh, and c) right ankle and foot



During follow up, topical hydrocortisone butyrate cream twice daily gave some symptomatic relief. However the skin lesions persisted. Another infiltrated area was noticed on the right temple in May 2014, and this was also confirmed to be LCH on biopsy. General physical examination never showed any other abnormalities. Routine blood tests showed a mildly elevated erythrocyte sedimentation rate ranging between 33 and 19 mm/hr (normal <15mm/hr), raised blood glucose, slightly deranged liver function tests, and combined hyperlipidaemia. Abdominal ultrasound showed a fatty liver and left renal pelviureteric dilatation

with a small stone.

**Figure 2:** Histology of a biopsy taken from the right axilla A) H&E showing clusters and sheets of large ovoid cells with abundant pale cytoplasm and irregular, grooved reniform nuclei. B) CD1a and C) S100 protein positivity on Immunohistochemistry



The patient was referred to a haematologist for further investigation of the LCH and to a diabetologist for better glycaemic and lipaemic control.

Hormone profile showed an elevated prolactin level attributable to fluphenazine. Complete blood count (CBC), serum protein electrophoresis, and specific gravity, remained

normal throughout. Skeletal survey, computerized tomography scans of brain, thorax, abdomen and pelvis, and magnetic resonance imaging of the pituitary, failed to detect any other foci of LCH other than in the skin.

In view of previous reports of cutaneous LCH responding to phototherapy, the patient was started on twice weekly narrow band ultraviolet B treatment (NB-UVB-TL01) in June 2014. Over the first 9 months of treatment, the lesions of LCH softened and faded slightly. However, no further improvement was observed by March 2015. The patient was subsequently offered psoralen combined with ultraviolet -A treatment (PUVA), but refused further treatment except topical hydrocortisone butyrate. He remains well apart from his persistent skin lesions and is being followed up regularly by dermatologists and a haematologists.

PET scan performed in June 2015, confirmed disease was still limited to the affected areas of skin.

### Discussion

Intertrigo is a dermatosis involving the skin folds. Epithelial loss caused by friction of moist apposing skin is the commonest cause of intertrigo. Secondary growth of opportunistic organisms such as yeasts, bacteria, and dermatophytes at such sites, account for most other causes. Seborrhoeic dermatitis, contact dermatitis, atopic dermatitis and psoriasis are also fairly common causes.<sup>1</sup> This case adds LCH as another cause to be considered in cases of refractory intertrigo.

LCH is an enigmatic condition characterized by tissue invasion and damage by Langerhans cells (LHs). These cells are large, with abundant pale cytoplasm and a reniform nucleus. They immunohistochemically stain for langerin (CD207), CD1a and S100, and ultrastructurally contain Birbeck granules. The aetiology is unclear. Debate whether LCH is a neoplastic process, an immune disorder or a genetic condition is ongoing.

Recent literature favours the theory that LCH is a neoplasm with monoclonal proliferation of bone-marrow-derived monocytes exhibiting CD1a+ and langerin on immunohistochemistry (langerin denoting the presence of Birbeck granules where electron microscopy is not available). This particular pattern of immunohistochemistry staining

correlates with consistent X chromosomal mutations on human androgen receptor genes (HUMARA) of lesional LC.<sup>2-4</sup> Further support that LCH is a neoplastic condition is the presence of BRAF V600E mutations in 57% of subjects with LCH.<sup>4</sup> The detection of chromosomal fragility on chromosomes 1, 4, 6, 7, 9, 16, 17 and 22 together with telomere shortening in lesional Langerhans cells further supports a neoplastic origin.<sup>6</sup>

A reactive immune process is suggested by the presence of multiple inflammatory markers such as TNF- $\alpha$  and others in lesional tissue in response to an unidentified stimulus.<sup>7</sup> However, LCs remain immature both morphologically and functionally, with non-dendritic roundish cells which fail to stimulate an effective T-cell immune response. Such LCs express CD83 and CD40 which denote immaturity. Cytokines enhancing maturation such as TNF- $\alpha$  and IL-1 $\beta$ , and others preventing maturation like TGF $\beta$ 1 and IL-10 are detected but lesions tend to contain immature LCs.<sup>6-8</sup> These cells can be transformed to functional maturity by the addition of CD40+ ligand but their morphology is not altered.<sup>7</sup>

Some evidence advocating that LCH is a genetic condition is obtained from studies that demonstrated an 86% concordance in monozygotic twins with LCH and that LCH occurs more often in families where there is one affected member.<sup>9</sup> However it is not clear which mechanisms are involved.

Chu postulates the involvement of D-retrovirus in the pathogenesis.<sup>10</sup> Again no definite proof is currently available.<sup>3</sup>

Adult LCH is uncommon with an estimated yearly incidence of 1-2 per million.<sup>11</sup> It usually, but not exclusively affects Caucasians, is commonest between 30-50 years of age, and becomes rarer with advancing age.<sup>12</sup> LCH can affect one or more organ systems and in any combination. The nomenclature of specific LCH syndromes such as Letterer-Siwe disease, eosinophilic granuloma, and Hand-Schuller-Christian disease has been abandoned because of inconsistency of the clinical pictures. Instead LCH is classified by the Histiocyte Society into three categories according to the organ systems affected: (i) single system disease, (ii) multisystem disease, and (iii) multisystem disease with organ failure.<sup>10</sup>

The clinical course of LCH is unpredictable.

Barres et al. suggested that BRAF-V600e mutations in bone marrow dendritic cells favour high risk for multisystem disease with organ failure, whereas if the mutation occurs only in lesional dendritic cells this would represent the low risk type of LCH.<sup>13</sup> Unfortunately, BRAF-V600e mutations are only detected in about half of the cases of LCH. Single system disease may remain confined to the respective system (low risk) or may progress to involve other organs (multisystem disease). Multisystem disease, with liver, spleen, bone marrow, lung and skeletal involvement, is considered as high risk with increased mortality.<sup>14</sup> In our patient, to date no extension to other organ systems has been noted. He is thus considered as a case of purely cutaneous LCH and classified as low risk for developing multisystem disease with organ failure.

Cutaneous lesions of LCH occur in at least 50% of adult cases of LCH and are usually associated with multisystem disease involving bone, lungs, pituitary gland and reticuloendothelial system. Purely cutaneous LCH occurs in only 7% of all patients with LCH.<sup>15</sup> This highlights the singularity of our case which occurred in Malta with a population of 440 000.

Cutaneous LCH has a predilection for intertriginous and seborrhoeic areas. Multiple reports of LCH affecting groins, perineum, perianal area, genitalia, axillae, inframammary folds, scalp and retro auricular areas have been published.<sup>10-11,14,16-18,20</sup> In spite of this, there is no published literature to explore why LCH preferentially affects such sites. We postulate that these sites may harbour low- grade non-specific inflammation, either due to friction of opposing skin surfaces or superficial infection which could induce the release of chemoattractants to LCs.

Cutaneous manifestations of LCH are diverse and often pose diagnostic difficulty during physical examination. The commonest types of lesions include yellow-brown scaly patches, papules and nodules with or without exudate. Rarer manifestations of cutaneous LCH include lesions clinically similar to pyoderma gangrenosum, bruising, amoebiasis, eruptive xanthomata, prurigo nodularis, arthropod bites, vesicles, pustules, cherry spots, plane warts, Darrier's disease, and pyogenic granuloma. Nail involvement with paronychia, nail grooving and onycholysis are also

documented.<sup>1,14,16</sup> Our patient had uniform, mildly infiltrated red-violaceous plaques without petechiae, scaling or ulceration in the intertriginous areas, scalp and ankle. Although these sites are commonly involved in LCH, this type of lesion appears rarely, if ever documented.

The possibility that single system LCH may progress to multisystem disease always needs to be considered. Diabetes insipidus due to pituitary invasion by LCH is one of the best-known complications.<sup>17</sup> Haematological malignancies such as chronic myelomonocytic leukaemia, acute lymphatic leukaemia and lymphomas are also possible complications.<sup>18</sup>

In our case, the condition so far appears to be progressing only as cutaneous LCH with new lesions on the right ankle and right temple developing over a period of two years. No other abnormality attributable to LCH or haematological malignancy has been found in other systems despite thorough investigation.

In our patient, NB-UVB had a noticeable but short-lived effect, thus further therapeutic modalities were considered to try to halt the condition. Such modalities would include PUVA, local radiotherapy, imiquimod, systemic isotretinoin, low dose methotrexate, cyclosporine, topical nitrogen mustard, thalidomide and intralesional interferon- $\alpha$  or interferon- $\beta$ .<sup>18-23,27</sup> This order of single-agent treatment offers successive options of treatment with the intention of limiting adverse effects. However, the efficacy of individual treatments was inconsistent with several reports of treatment failure and relapse.<sup>27</sup> Our patient refused PUVA and other treatments, despite his concern about the cosmetic appearance of the lesion on the scalp.

For resistant cases of LCH or multisystem disease affecting vital organs, chemotherapy regimens are often used. These include combinations of chlorodeoxyadenosine, vincristine, vinblastine, cytarabine, 6-mercaptopurine, cyclophosphamide, etoposide and systemic steroids.<sup>18,20,25-27</sup>

Our patient needs lifelong follow-up in order to monitor any extension of his condition, relapses and any other arising complications.

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## Case Report

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