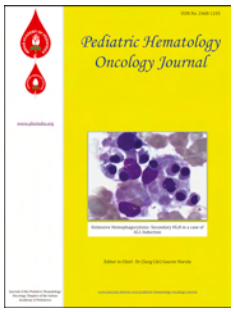

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Severe ocular involvement in a newborn with Langerhans Cell Histiocytosis

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Abstract

Langerhans Cell Histiocytosis (LCH) is a rare proliferative disease of the mononuclear phagocyte system, characterised by tissue infiltration of CD1a+ CD207+ histiocytes. The clinical presentation is variable, ranging from unifocal asymptomatic bone involvement to life-threatening multisystem disease, requiring aggressive therapeutic approaches. Intraocular involvement is uncommon and associated to poor visual and general prognosis.

We report a case of LCH in a newborn with severe ocular and multisystem risk-organ involvement, unresponsive to several lines of chemotherapy. Off-label administration of vemurafenib led to dramatic improvement at systemic level; however, chronic *sequelae* of ocular involvement resulted in poor visual prognosis.

Intraocular LCH involvement may be asymptomatic and clinical signs delayed, leading to severe complications, especially in newborns and young children. Screening for ocular involvement is essential for early treatment initiation, which can possibly improve the visual outcome. Vemurafenib is effective on systemic involvement, and its role in ocular LCH needs to be evaluated.

To the editor

Langerhans cell histiocytosis (LCH) is a rare disease characterized by tissue infiltration of CD1a+ CD207+ histiocytes, driven by mutations of the MAPK-pathway. The diagnosis, based upon clinical and radiological findings, requires biopsy confirmation.[1] The clinical presentation ranges from a self-limiting disease to a rapidly progressive one, potentially affecting any organ.[2] Intraocular involvement is rare and responsible for severe *sequalae*.[3]

We report the case of a newborn-onset LCH with cutaneous, skeletal (*Figure-A*), and risk-organ involvement, confirmed by skin biopsy (*Figure-E,F*) and $BRAF^{V600E}$ molecular detection.

During maintenance chemotherapy treatment, according to the LCH-IV protocol (clinical.gov-NCT02205762), at month 7 the patient presented a cutaneous reactivation (*Figure-C*) and developed bilateral cataract. Ophthalmologic evaluation revealed bilateral pupil seclusion, initial band keratopathy, and dense cataract; ocular fundus was not evaluable. Ultrasound B-scan showed choroidal thickening and a vitreal strand starting from the optic nerve head, initially interpreted as a persistent foetal vasculature syndrome. Initial conservative treatment with topical steroids and mydriatics was started, followed by cataract surgical removal without intraocular lens implant (*Figure-D*). Aqueous humour sampling and ocular fundus examination resulted inconclusive, and post-surgical visual acuity was very low.

Second-line regimen with 2-chlorodeoxyadenosine and cytosine arabinoside[4] was started, without clinical response, development of progressive nystagmus and visual acuity loss (without central nervous system involvement at magnetic resonance imaging, MRI). Off-label administration of the BRAF-inhibitor vemurafenib was started (at 120 mg *bid*, orally), based upon reported efficacy in a child,[5] leading to dramatic improvement of clinical condition, laboratory findings, cutaneous rash, and hepatosplenomegaly. Three months later, taking into account clinical remission and stability of ocular findings, vemurafenib was discontinued considering long-term safety concerns. Two months after vemurafenib discontinuation, a reactivation occurred at cutaneous and bone level, with

progression of ocular inflammatory process, resulting in band keratopathy, iris inflammatory infiltration, pupillary seclusion, and opacification of optic axes. Orbital MRI demonstrated the presence of fibrotic tissue in the vitreous chamber and thickening of the retinal-choroid layer (*Figure-B*). Surgical vitrectomy became mandatory to remove the fibrotic tissue and reopen the pupil. Aqueous humour evaluation was inconclusive, whereas histopathological examination of the iris and the vitreous specimens revealed an inflammatory infiltrate with large CD1a+/S100+ cells (*Figure-G,H*), confirming the suspicion of intraocular LCH. Post-surgical visual acuity remained very low. A complete radiological remission was obtained after 2 months of vemurafenib administration, and the drug was discontinued one year later. Considering the histology findings, the extension of ocular damage, and the local and systemic treatment inefficacy, any further ocular surgery was deemed vain.

At the age of five years, the patient presented persistent clinical remission, despite the persistence of pupil seclusion, severe band keratopathy, and complete visual loss.

Intraocular LCH is rare, with less than 15 cases reported. Intraocular infiltration may be asymptomatic and clinical signs delayed, especially in newborns and young children. Obtaining ophthalmological specimens is difficult, thus easily resulting in misdiagnosis, and therapeutic options are limited.

In our patient, ocular disease was recognized only secondary to cataract. Steroids and chemotherapy were ineffective on ocular disease, and clinical progression led to vemurafenib administration, with a dramatic systemic response. However, when vemurafenib was administrated, irreversible ocular lesions had already been documented. The effectiveness of targeted therapies in early phases of ocular disease remains an open question. In such instances, early recognition of ocular LCH involvement is essential to prevent ocular *sequelae*, especially in very young patients, considering their inability to complain on visual defects.

List of Abbreviations

LCH	Langerhans Cell Histiocytosis
MRI	Magnetic Resonance Imaging

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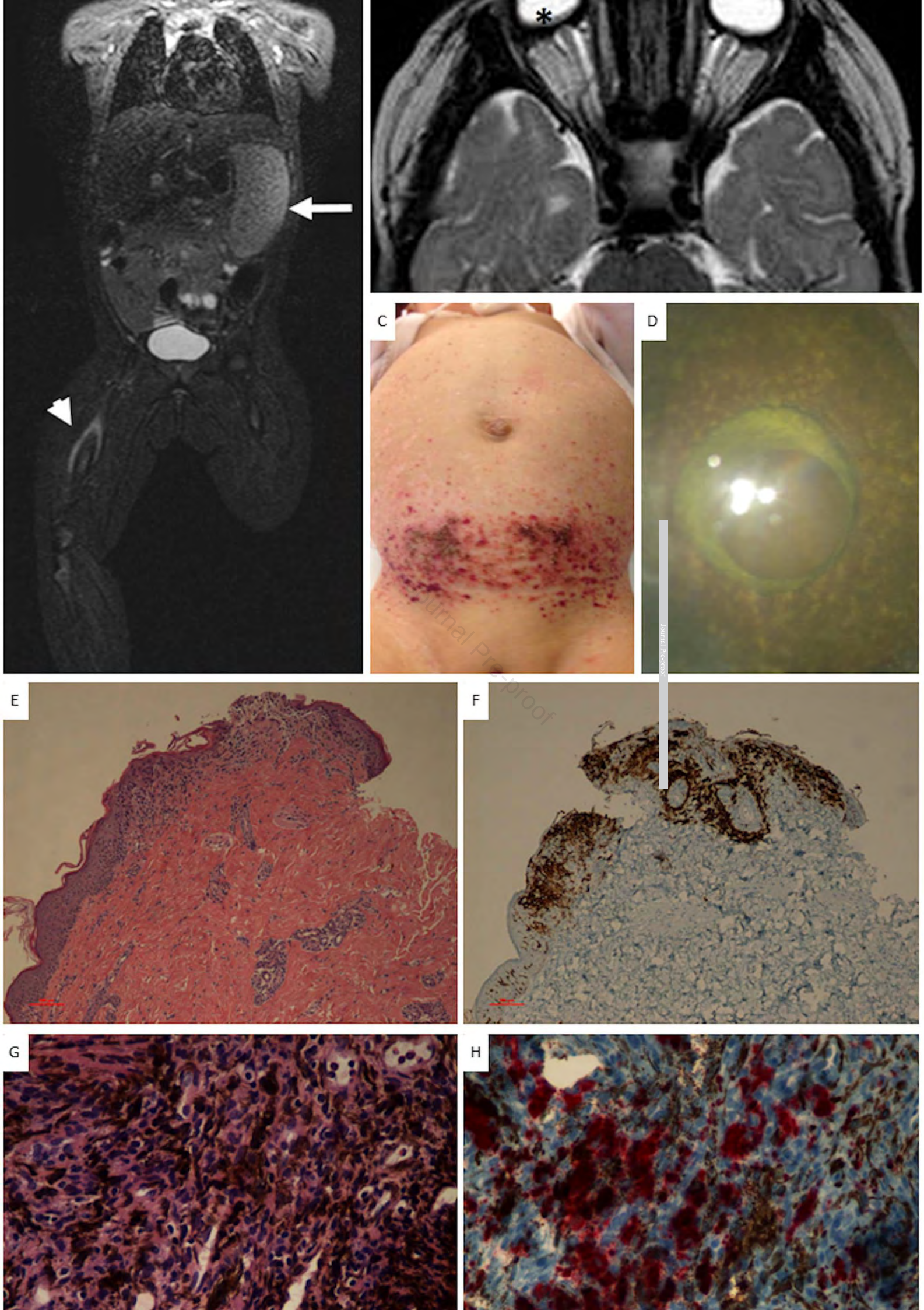
Figure: Iconography of radiology, clinical and pathology findings.

A: STIR coronal image of whole-body magnetic resonance imaging (MRI) shows increased volume of the spleen (arrow) and high signal intensity of the right femoral diaphysis with associated periosteal reaction. **B**: MRI T2w axial image of the orbits detects an asymmetry of the eyeballs (the right eye is smaller than left eye); the anterior chambers are narrow, the ciliary bodies are thickened (arrow), with further thickening of the retinal-choroid layer (asterisk). **C**: Cutaneous LCH reactivation consistent of papular and ecchymotic lesions of the abdomen. **D**: Post-surgical aphakia of the left eye with granulomatous infiltration of the iris. **E-F**: Langerhans cells in the superficial dermis with epidermotropism (Original Magnification 10x); Haematoxylin and Eosin (E) and CD1a positive reaction (brown chromogen) (F). **G-H**: Langerhans cells more readily visible in the immunostained slides due to abundant pigment (Original Magnification 40X); Haematoxylin and Eosin (G) and CD1a positive reaction (red chromogen) (H).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