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Choroidal Neovascular Membrane Formation and Retinochoroidopathy in a Patient with Systemic Langerhans Cell Histiocytosis: A Case Report and Review of the Literature

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Key Words

Langerhans cell histiocytosis · Choroidal neovascular membrane · Intraocular involvement

Abstract

We report a case of bilateral atrophic retinochoroidopathy with choroidal neovascular membrane (CNVM) formation in a patient with systemic Langerhans cell histiocytosis (LCH). A 35-year-old female, diagnosed with LCH at the age of 3, experienced an episode of acute vision loss in her right eye. Visual acuity was counting fingers. Dilated fundus exam and fluorescein angiography revealed the presence of CNVM along with bilateral widespread areas of chorioretinal atrophy. The patient underwent removal of CNVM with excellent postoperative visual acuity (20/25); however, indolent progression of her disease led to gradual deterioration of visual acuity (20/80 in the right eye and 20/320 in the left). This case shows that in contrast to previous reports, intraocular involvement of LCH does not need to be dramatic and clinically evident but it can acquire a chronic degenerative form. This report aims to raise awareness among ophthalmologists concerning the potential intraocular sequelae of LCH.

Introduction

Langerhans cell histiocytosis (LCH), formerly known as histiocytosis X, encompasses a wide spectrum of diseases seen in children and young adults, which are characterized by the abnormal proliferation of cells with Langerhans cell characteristics. Terms such as Letterer-Siwe disease, Hand-Schüller-Christian syndrome and eosinophilic granuloma refer to various clinical syndromes of LCH mostly now of historical significance. Although the underlying pathophysiology is still unclear, there is evidence to suggest a cytokine-mediated process. Bone, skin, lungs and lymph nodes are frequently affected. Ophthalmic involvement is seen in 10–23% of patients, most often involving the soft tissues of the orbit resulting in proptosis [1]. Intraocular involvement is rare and has been reported both as an isolated focus [2] or as diffuse infiltrative disease [3].

We report here the first case, to our knowledge, of an adult patient with LCH and bilateral atrophic retinochoroidopathy with development of choroidal neovascular membrane (CNVM). Despite successful removal of CNVM with submacular surgery and stable good vision for almost 6 years, subsequent slow progression of the disease led to bilateral visual disability.

Case Report

In 1978, disseminated LCH was diagnosed in a 3-year-old girl involving the skull, central nervous system (CNS) and lower extremities. Despite being critically ill for several months, supportive care resulted in near complete recovery. No systemic chemotherapy was administered. Cerebellar disturbance manifesting as ataxia and dizziness were residual symptoms from CNS involvement by the disease.

At 23 years of age (October 1998), the patient presented to our clinic complaining of decreased vision in her right eye. Visual acuity was counting fingers in the right eye and 20/25 in the left eye. Dilated fundus examination was significant for bilateral symmetric widespread areas of pigmentary disturbance and chorioretinal atrophy. These areas were well demarcated, punched out, and located at the posterior pole involving the macula and perimacular area (fig. 1a, b). There was mild peripapillary atrophy in both eyes. The anterior chamber and vitreous were clear in both eyes. No signs of active inflammation were present. There was no relative afferent pupillary defect. Fluorescein angiography revealed the presence of CNVM in the right eye along with blockage of fluorescence corresponding to the areas of atrophy with late staining at their edges (fig. 1c, d).

The patient underwent extraction of the CNVM by subretinal surgery. There were no intraoperative complications.

Results

In January 1999, three months after surgery, the patient's visual acuity improved from counting fingers at initial presentation to 20/25 and remained stable for the next 5 years. An extensive work-up to identify the etiology of the bilateral chorioretinal atrophic areas was undertaken: CBC, ESR, ACE, RPR, FTA-ABS, HIV, hepatitis B and C, HSV, as well as chest X-ray were all normal. Further testing for toxoplasmosis and tuberculosis was also noncontributory. The patient did not have any history of in utero infections, or any history of histoplasmosis exposure. Past medical history was insignificant other than LCH. There was no history of trauma or use of tobacco. The

patient did not have hypertension or any type of diabetes. No medications were prescribed after resolution of LCH symptoms and the disease was in remission ever since that initial episode at the age of 3. There was no other significant past ocular history nor any family history of eye disease.

In 2005, the patient started to complain of increasing dyschromatopsia in both eyes and increased number of dark spots in her right central visual field. Ishihara plate reading was 0/8 for the right eye and 1/8 for the left. Fluorescein and ICG angiography did not reveal the recurrence or new development of a CNVM, nor any signs of active disease that could explain these symptoms. Goldman visual fields (GVF) in the right eye revealed a relative and absolute central scotoma, which was attributed to scarring. GVF on the left was normal. On March 2007, visual acuity has deteriorated to 20/80 in the right eye and 20/160 in the left eye. Dilated fundus examination, fluorescein and ICG angiography (fig. 1g, h) did not reveal any significant fundus changes or any areas of new inflammatory involvement from her last exam and a plausible explanation for this decline of vision was not identified. Cirrus spectral-domain optical coherence tomography (SD-OCT, Cirrus, Zeiss) images ([fig. 2](#)) were significant for areas of outer retinal irregularity, RPE elevation and chorioretinal scarring. Visual acuity in the left eye continued to decline until her last visit on March 2009 when it was 20/320, compared to that of the right eye which remained stable at 20/80.

Discussion

Intraocular involvement in LCH is rare. A review of the literature ([table 1](#)) indicates that the disease can affect multiple structures within the eye, with choroid being the most common among them. Choroidal involvement may present either in a diffuse infiltrative pattern or as a solitary mass lesion. Aberrant infiltration of abnormal Langerhans cells has been histologically identified in the retina [4], vitreous, sclera [5], aqueous humor [6] and optic nerve sheath [7]. From the reported cases with intraocular involvement, the majority of patients (10/15) were less than 10 years old with concurrent multisystemic disease involving either the spleen, lymph nodes, skin, bones and liver [3–11]. The risk of progression to an unfavorable visual outcome is very high when diffuse infiltration is present. In adults there have been 5 cases reported. Tsai et al. [12] reported of an 18-year-old male with reactivation of LCH and concurrent anterior uveitis with iris nodules. This is the only case demonstrating anterior uveal tract involvement without evidence of disease in the posterior segment of the eye. Patton et al. [13] reported of a 29-year-old man who presented with a choroidal mass several years after resection of a solitary cerebral LCH lesion. Diffuse infiltration of ocular tissues by proliferating histiocytes in adults is rare and only one case has been demonstrated to date in a patient with aggressive multisystemic LCH [14]. Intraocular involvement as the single manifestation of LCH is extremely rare and only 2 cases have been reported thus far [2, 15]. Interestingly, both cases presented in adults as a solitary choroidal mass. Cancer-associated retinopathy as a result of systemic LCH has also been recently reported in a 3-year-old patient [16].

The differential diagnosis of bilateral chorioretinal scars with or without CNVM formation is extensive and includes both infectious causes and inflammatory retinochoroidopathies, such as punctate inner choroidopathy (PIC), multifocal

choroiditis with panuveitis (MCP) and serpiginous choroidopathy, among others. However, along with our patient's negative work-up, no criteria were met to support the diagnosis of any of these entities. More precisely, the patient never had any vitreous cells, which is considered a *sine qua non* for MCP diagnosis. Furthermore, the multifocal and symmetric distribution of the lesions was unlikely to be consistent with MCP or serpiginous choroidopathy. The patient did not have any myopia to support a diagnosis of PIC.

Our patient presented at the age of 23 with bilateral atrophic chorioretinal scars, which indicated that the initial inflammatory insult occurred before her first visit in October 1998. Considering the negative past ocular history, the unremarkable laboratory work-up and her systemic disease at the age of 3, we concluded that disseminated LCH was responsible for the observed fundus abnormalities. Our diagnosis was further supported by the fact, that similar fundus findings have been reported by Epstein and Grant [6] in a case of a 5-month-old child with disseminated LCH. The authors described multiple round symmetrical punched-out choroidal lesions in both eyes. Additionally, another report from François and Bacsulin [10] described an 8-year-old child with disseminated LCH who developed bilateral circular pigmented areas as well as areas of depigmentation in the posterior pole. In both of these cases and the vast majority of pediatric LCH cases, aggressive disease progression led to acute severe vision loss. In our case, however, initial eye involvement was mild and remained asymptomatic, led to the development of the choroidal atrophic spots after the disease subsided and became symptomatic 20 years later with the development of CNVM. A possible explanation for this phenotypic clinical variation is that the severity and extent of inflammation was milder in our patient compared to the reported cases. Finally, our patient experienced a gradual deterioration of visual acuity over the years, which can be attributed to slow progression of the disease. Comparison of the fundus photographs and fluorescein angiographies obtained from our patient's visits revealed mild enlargement in the size and pigmentation of the atrophic scars over the years (fig. 1a, b, i, j).

In summary, this rare case illustrates that intraocular involvement in LCH does not need to be dramatic and clinically evident, leading to acute vision loss as previously reported but it can have a more chronic degenerative course. This case report underlines the importance of a fundus examination in children with multisystemic LCH.

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Disclosure Statement

No authors have any financial/conflicting interests to disclose.

Table 1. Previously reported cases of Langerhans cell histiocytosis

No.	Authors	Year	Age	Sex	Manifestations/findings	Comment/outcome	Ref.
<i>Reports in children</i>							
1	Boztug et al.	2006	Neonate	F	Bilateral diffuse infiltration of histiocytes	Multisystemic LCH – bilateral total vision loss	3
2	Lahav and Albert	1974	Neonate	M	Bilateral diffuse infiltration of uveal tract and optic nerve sheath – iris nodules	Multisystemic LCH – patient succumbed to the disease	7
3	Rupp and Holloman	1970	3 months	F	Bilateral iris nodules and diffuse infiltration of the choroid	Multisystemic LCH – patient succumbed to disease	8
4	Epstein and Grant	1977	9 months	F	Bilateral multiple punched out choroidal lesions – secondary open-angle glaucoma	Multisystemic LCH – enucleation of the left eye	6
5	Heath	1959	16 months	M	Bilateral diffuse infiltration of sclera, uveal tract retina and vitreous	Multisystemic LCH – patient succumbed to the disease	5
6	Mozziconacci et al.	1966	2	F	Severe retinal and vitreous involvement	Multisystemic LCH – bilateral total vision loss	4
7	Hayashi et al.	2007	3	F	Cancer-associated retinopathy – no intraocular infiltration of histiocytes	Multisystemic LCH – successfully treated with chemotherapy	16
8	Angell and Burton	1978	5	F	Unilateral choroidal mass	Multisystemic LCH – in remission	9
9	François and Bacskulin	1967	8	M	Bilateral circular pigmented areas as well as areas of depigmentation in the posterior pole – tapetoretinal degeneration of ocular fundi	Multisystemic LCH – bilateral severe vision loss	10
10	Mittelman et al.	1973	3	M	Bilateral diffuse choroidal infiltration, extensive retinal degeneration and loss of photoreceptors	Multisystemic LCH – patient succumbed to the disease	11
<i>Reports in adults</i>							
11	Tsai et al.	2005	18	M	Unilateral anterior uveitis and iris nodules	Multisystemic LCH – successfully treated with topical corticosteroids	12
12	Patton et al.	2006	29	M	Intraocular choroidal mass	Presumed diagnosis after documented solitary cerebral LCH lesion – treated successfully with external beam radiotherapy	13
13	MacCumber et al.	1990	43	M	Histiocytic infiltration of choroid, sclera, optic nerve	Multisystemic LCH – patient succumbed to the disease	14
<i>Intraocular unifocal LCH</i>							
14	Kim and Lee	2000	49	M	Solitary choroidal tumor	No systemic findings – involved eye was enucleated	15
15	Narita et al.	1993	61	F	Solitary tumor, anterior uveitis, diffuse infiltration of intraocular tissues by histiocytes	No systemic findings – involved eye was enucleated	2

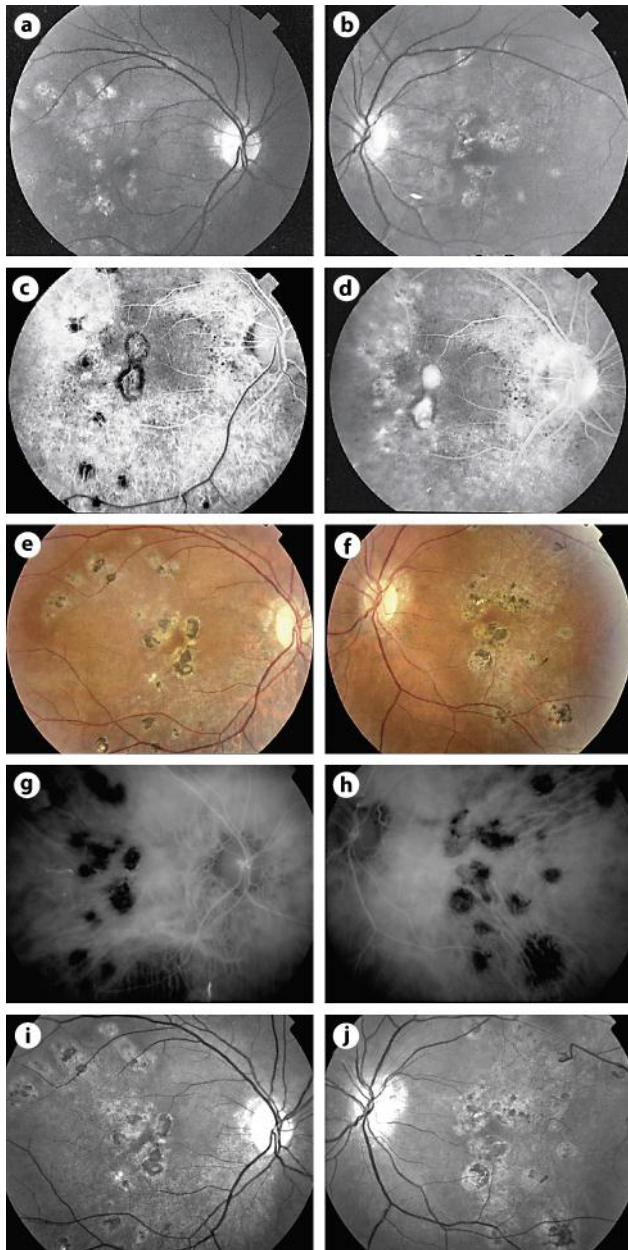


Fig. 1. **a–d** October 1998. Red-free fundus photographs (**a, b**) demonstrating the widespread areas of atrophy in both eyes. Early (**c**) and late (**d**) phase fluorescein angiography of the right eye reveals the presence of choroidal neovascular membrane. September 2001. Color fundus photographs (**e, f**) showing multiple areas of pigmentary changes. March 2007. ICG angiography shows multiple scattered hypofluorescent spots without any signs of new inflammatory involvement (**g, h**). April 2009. Comparison of the red free photographs taken from patient's initial (**a, b**) and last follow-up visit (**i, j**) reveals mild enlargement of the size as well as in the pigmentation of the chorioretinal scars.

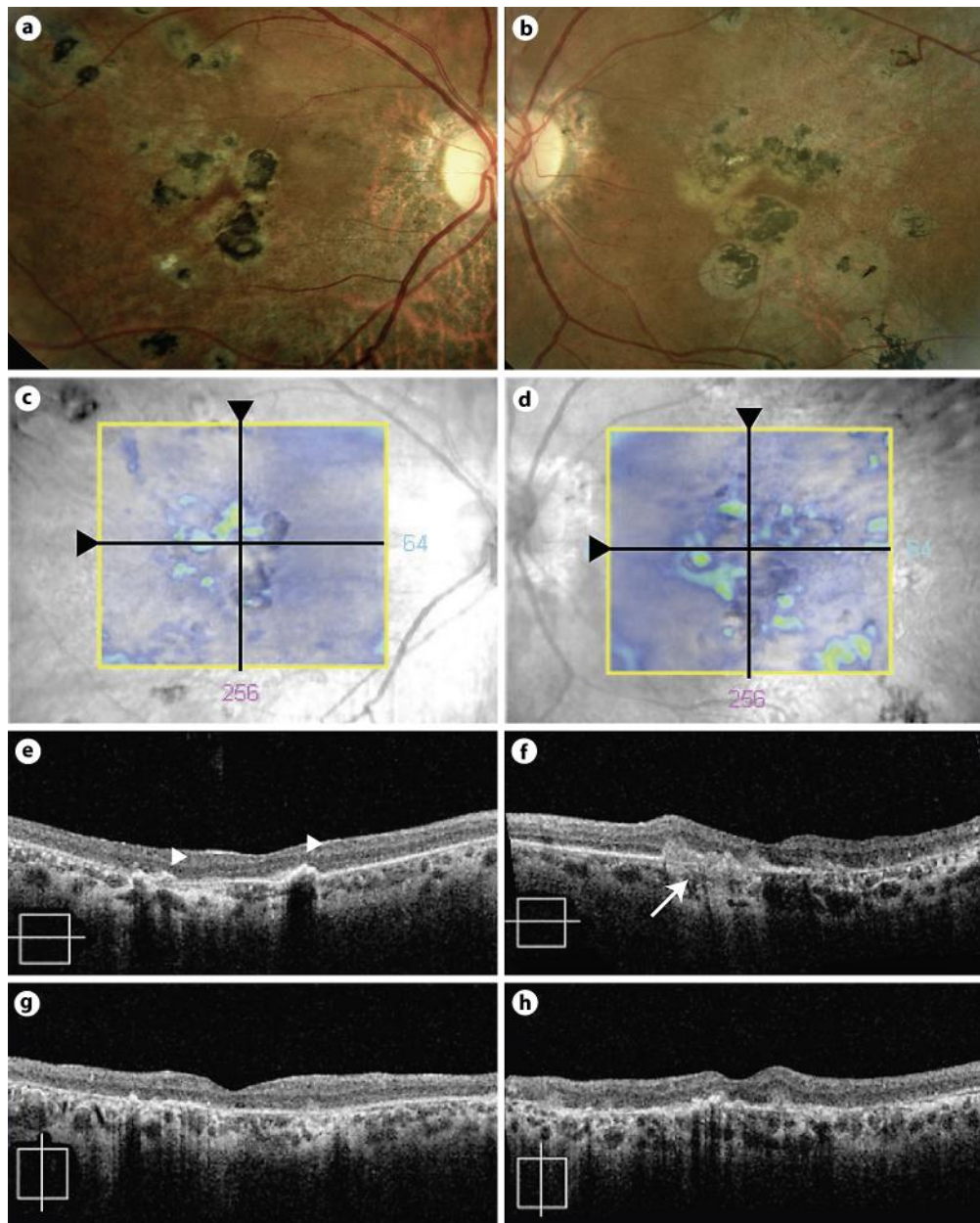


Fig. 2. Imaging with Cirrus SD-OCT reveals hyper-reflective areas of outer retinal irregularity (**f**, arrow), RPE elevation (**e**, arrowheads) and chorioretinal scarring (**e–h**).

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