1. Introduction

Mastocytosis is a group of disorders with a shared pathogenesis comprising aberrant mast cell proliferation and accumulation; adults commonly present with systemic mastocytosis (SM), characterized by mast cell accumulation in the bone marrow and other internal organs (Table 1). In advanced SM (advSM), mast cell infiltration causes organ dysfunction; advSM includes systemic mastocytosis with another hematologic malignancy (SM-AHN), aggressive SM (ASM), and mast cell leukemia (MCL), with ASM having the most favorable prognosis among the three. Ocular involvement is rare but has been reported in the orbit, lacrimal glands, lids, conjunctiva, cornea, and choroid. To our knowledge, only two cases of choroidal involvement in advSM have been reported previously. Choroidal infiltration by mast cells presents a challenging clinical situation, because it can cause vision loss, but there is no consensus on its treatment.

Midostaurin, approved by Food and Drug Administration FDA in 2017 for treatment of advSM, has shown better results compared with prior drugs, including interferon and cladribine. Midostaurin is a multiple kinase inhibitor targeting several steps in the molecular pathogenesis of SM, crucially mutant and wild type KIT. The KIT D816V (aspartate to valine at codon 816) is the most common mutation found in over 80% of all SM patients. In an open-label, single-arm trial of patients with advSM, midostaurin was efficacious in resolving one or more types of mast cell-induced end-organ damage. However, its efficacy in ocular involvement of SM is unknown. Herein, we describe the clinical course of an ASM patient with mast cell choroidal infiltrate.

2. Case report

A man in his fifties (no specific age for patient's confidentiality) presented with progressive right eye (OD) central visual field cloudiness for two months. He was referred to our service from an external ophthalmic workup showing subretinal fluid and macular lesion in OD. The patient previously had excellent vision in both eyes and had no prior ocular history. His medical history was notable for ASM with the KIT mutation. He was receiving interferon for treatment of ASM and had no history of other malignancies or vision changes.

The patient presented with visual complaints in the right eye, central visual field cloudiness, and decreased visual acuity. His visual acuity was 20/150 in the right eye and 20/25 in the left eye. Upon ophthalmic and radiologic imaging workup, the patient was diagnosed with presumed choroidal mast cell infiltration. The index of suspicion was high due to the prior SM diagnosis. External beam radiation and intravitreal injection treatments were offered but the patient declined. The patient was switched from interferon to a new targeted systemic therapy for ASM, midostaurin. Despite some mixed, temporary response in systemic symptoms/signs of ASM at four months, the choroidal lesion and subretinal fluid were stable with visual acuity at 20/125.

Conclusion and importance: Mast cell choroidal infiltration in ASM should be considered as part of the differential with acute/subacute vision changes. Diagnosis requires exclusion of other possibilities with ocular imaging and in this case, monitoring for development of other malignancies in which there were none. Midostaurin's ocular response was not on par with systemic response. Additional localized ocular therapies may be required.

Keywords: Central scotoma \ Choroidal lesion \ Malignancy \ Mastocytosis \ Midostaurin

ARTICLE INFO

A B S T R A C T

Purpose: To report a rare case of a unilateral choroidal mast cell infiltration in a patient with aggressive systemic mastocytosis (ASM).

Observations: The patient is a man in his fifties with a diagnosis of ASM. He developed visual complaints in the right eye associated with an area of subretinal fluid on fundus examination. Visual acuity at presentation was 20/150 in the right eye and 20/25 in the left eye. After ophthalmic and radiologic imaging workup, the patient was diagnosed with presumed choroidal mast cell infiltration. The index of suspicion was high due to the prior SM diagnosis. External beam radiation and intravitreal injection treatments were offered but the patient declined. The patient was switched from interferon to a new targeted systemic therapy for ASM, midostaurin. Despite some mixed, temporary response in systemic symptoms/signs of ASM at four months, the choroidal lesion and subretinal fluid were stable with visual acuity at 20/125.

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| Table 1 | | |
| --- | --- | --- |
| **Diagnosis** | **Clinical Features** | **Pathological Features** |
| Mastocytosis | | |
| **Type 1 (SM)** | | |
| **Type 2 (SM-AHN)** | | |
| **Type 3 (ASM)** | | |
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B-scan ultrasonography showed mildly increased echogenicity in the region of the choroidal in major criterion, minor criteria B and D, and “C findings” of bilineage cytopenia, hepatosplenomegaly, pelvic bone skeletal lesions, and GI tract involvement.

Table 1
Advanced systemic mastocytosis diagnostic (modified from Gotlib et al. and Valent et al.). Our patient with Aggressive systemic mastocytosis met the bone marrow major criterion, minor criteria B and D, and “C findings” of bilineage cytopenia, hepatosplenomegaly, pelvic bone skeletal lesions, and GI tract involvement.

Systemic mastocytosis (SM)
Requires one major + one minor criterion OR three minor criteria
Major criterion Multifocal dense infiltrates of mast cells (> 15 mast cells in aggregates) in bone marrow biopsies and/or in secretions of other extracutaneous organ(s)
Minor criteria A. > 25% of all mast cells are atypical cells (type I or type II) on bone marrow smears or are spindle-shaped in mast cell infiltrates detected on sections of visceral organs
B. KIT point mutation at codon 816 in the bone marrow or another extracutaneous organ
C. Mast cells in bone marrow or blood or another extracutaneous organ expresses CD2 or/and CD25
D. Baseline serum tryptase concentration > 20 ng/ml (in case of unrelated myeloid neoplasm, criterion D is not valid as an SM criterion)

SM Types
Indolent SM (ISM)
Smoldering SM (SSM)
Mast cell leukemia (MCL)

SM with associated hematologic neoplasm
Advanced SM SM plus another hematologic disorder, usually a myeloproliferative or myelodysplastic disorder with prognosis driven by the other hematologic disorder
Aggressive SM (ASM) A “mast cell cancer” where mast cells infiltrate peripheral tissue outside the marrow with at least 1 or more C findings
Mast cell leukemia (MCL) Highest mast cell burden with > 20% mast cells in bone marrow aspirate (not the biopsy) or > 10% mast cells in peripheral blood

D816V mutation, diagnosed 11 months prior to encounter with our service and was managed with interferon. At the time of initial ASM diagnosis, the patient had a positive tuberculosis QuantiFERON test result. Though there was no evidence of infection, a nine-month isoniazid course had been completed as precaution prior to onset of ocular symptoms.

On examination, visual acuity was 20/150 OD and 20/25 in the left eye (OS). Anterior segment examination was unremarkable in both eyes (OU). Funduscopy examination of OD showed a deep, cream-colored choroidal lesion in the nasal macula (Fig. 1a). Fundus autofluorescence imaging showed diffuse hyper-autofluorescence over and surrounding the involved area, suggestive of stressed retinal pigment epithelium (RPE) (Fig. 2). Optical coherence tomography (OCT) imaging showed a choroidal infiltrate with overlying subretinal fluid extending from the optic nerve to the fovea with a peripapillary subretinal lesion; there was also outer retinal atrophy over the involved area (Fig. 3a). Fluorescein angiography showed diffuse, deep leakage in the central/nasal macula, with late phase optic nerve head leakage, while indocyanine green angiography showed mainly blockage by the choroidal lesion (Fig. 4). B-scan ultrasonography showed mildly increased echogenicity in the region of the choroidal infiltrate and hyperechoic material within the optic nerve (Fig. 5a). As a precaution and due to a worsening central scotoma, magnetic resonance imaging (MRI) of the brain and orbits showed no optic nerve involvement.

Given the patient’s ASM diagnosis, the choroidal lesion was presumed to be mast cell infiltration. Biopsy was not considered because of high risks associated with the choroidal infiltrate’s posterior pole location and size. Therefore, proposed treatment was empiric. External beam radiation was offered given the neoplastic lesion characteristics and the single case report of treatment response by Fine et al. In addition, intravitreal bevacizumab or triamcinolone were offered to treat the subretinal fluid. Since the patient was imminently switching to midostaurin, he elected to monitor for response with new systemic therapy and declined any ocular treatments.

After four months of midostaurin (200 mg daily dose), his constitutional symptoms mildly improved and serum tryptase, hemoglobin, and leukocyte counts normalized. However, his visual acuity was still

Fig. 1. Fundus photos of macular choroidal infiltrate in a patient with aggressive systemic mastocytosis (ASM). (A) Initial visit: A nasal macular creamy choroidal infiltrate is visible (B) After 4 months of systemic midostaurin therapy; the lesion’s surface area expanded by 12.5%.

Fig. 2. Fundus autofluorescence at initial visit demonstrating patchy hyper- and hypo-autofluorescence overlying the lesions.
20/125 and there was no regression of the choroidal lesion with progression of the boundaries (Fig. 1b). The OCT images correlated, showing similar extent of the choroidal lesion, progression of atrophy in the outer retina, and new intraretinal fluid (Fig. 3b). Repeat ultrasound B scan was largely unchanged, except the previous optic nerve reflective material was no longer present (Fig. 5b). At four months follow-up, the patient elected to continue monitoring without localized ocular treatment.

Fig. 3. Optical coherence tomography images. (A) At initial visit: a choroidal infiltrate and a peripapillary subretinal lesion with correlating subretinal fluid. (B) Four months after initiating systemic midostaurin: the choroidal infiltrate appears similar but there is now intraretinal fluid and the peripapillary lesion appears larger.

Fig. 4. Fluorescein Angiogram (FA) and Indocyanine Green (ICG) at initial visit. (A) Left: FA late phase (3′09″) demonstrating leakage of the choroidal lesion and the optic nerve. (B) Right: FA at 10 minutes demonstrating further leakage from the lesion. No other choroidal or retinal lesions were noted. (A2) Left: ICG late phase (3′09″) reveals blockage of the choroidal fluorescence by the lesion. (B2) Right: ICG at 10 minutes demonstrating blockage by the lesion.
and the subretinal without any ocular treatment, the lesion remained stable on follow up mimicked the clinical presentation of a choroidal melanoma. However, presumed to be a choroidal mast cell in beam radiation for lesions in cases where systemic therapy does not

diagnosing the in

mented choroidal lesions were most likely mast cell choroidal in

pigmentary changes and serous retinal detachment.5 The lesion was

have been diagnosed in our patient with continued monitoring, there is

have progressed without systemic midostaurin.80 – 85%

show ocular response, and intravitreal medications to reduce fluid

exudation, such as bevacizumab or triamcinolone. Our patient’s choroidal infiltrate had developed despite systemic interferon therapy, so we offered more aggressive treatment with external beam radiation and intravitreal injections. The patient opted for the conservative option of allowing midostaurin therapy a chance to treat his choroidal infiltrate. Neither our team or the patient considered a biopsy due to the morbidity risks.

Midostaurin blocks the receptor tyrosine kinase on mast cells that have become constitutively active. Unfortunately, despite his initial systemic response, our patient’s ocular response was unimpressive. The visual acuity, subretinal fluid, and choroidal lesion remained stable, and new pockets of intraretinal fluid appeared at four months follow up. The discordance between the choroidal and systemic responses is not clear. It is possible that the drug penetration of the choroidal tissues was simply inadequate despite choriocapillaris fenestration. Since 80–85% of the blood supply to the eye is directed to the choroid,9 midostaurin molecules could be rapidly redistributed, reducing adequate effective concentration to reach the mast cells in the infiltrate. Explanations more specific to midostaurin non-response were proposed by Valent et al.10 Briefly, they include: 1) secondary mutations beyond the KIT D816V mutation, 2) midostaurin-induced selection of subclones with different driver pathways, 3) intrinsic resistance of stem cells (e.g. PD1 ligand), and pharmacological resistance from accumulation of midostaurin metabolites. It is not clear why these mechanisms would differ between the choroidal and systemic populations of mast cells. It is possible, of course, that the choroidal lesion’s stability was in fact a treatment response, and the lesion size and subretinal fluid would have progressed without systemic midostaurin.

3. Discussion

Choroidal involvement in systemic mastocytosis has been previously reported in two patients with aggressive systemic mastocytosis (ASM). Fine et al. reported a macular choroidal infiltrate with overlying pigmented changes and serous retinal detachment.5 The lesion was presumed to be a choroidal mast cell infiltrate and responded to his-tamine blockers and radiation. Michel et al. reported a pigmented macular lesion with overlying subretinal fluid; the lesion initially mimicked the clinical presentation of a choroidal melanoma. However, without any ocular treatment, the lesion remained stable on follow up and the subretinal fluid regressed. Both authors concluded that pigmented choroidal lesions were most likely mast cell choroidal infiltrates given their patient’s established ASM diagnoses. As with our patient, diagnosing the infiltrate was based on high clinical suspicion. Fine needle or open choroidal biopsy carried a high morbidity risk.

We also considered tuberculous (TB) granuloma, choroidal melanoma, and lymphoma. A TB granuloma was unlikely since latent TB treatment was completed prior to onset of vision symptoms, lack of other systemic signs/symptoms of TB, the stability of the lesion despite no anti-TB treatments, and examinations showing no vitritis or other markers of an infectious or inflammatory process. Moreover, the patient’s systemic symptoms mildly improved, which would be highly unlikely with disseminated TB, in addition to no history of pulmonary TB, immunosuppression/HIV infection, or salient social risk factors. A choroidal melanoma did not fit typical characteristics as determined by ophthalmic examination and characteristics on ultrasound and angiography. Lymphoma and leukemia were excluded mainly by clinical examination findings and patient history, including his young age, and his previously negative cervical lymph node biopsy. Furthermore, extramedullary leukemia with ocular involvement tends to occur within the context of acute myeloid leukemia or chronic myeloid leukemia in blast phase.6 Finally, a retrobulbar process and extraocular extension were ruled out by MRI of brain and orbits. Given no other malignancies have been diagnosed in our patient with continued monitoring, there is high confidence that the infiltrate was a mast cell infiltrate.

There is no standard treatment for mast cell choroidal infiltrate in advSM. Fine et al. reported success with radiation and systemic anti-histamine treatment, whereas Michel et al. reported improved visual acuity and lesion stability with systemic treatment, though the treatment details were not reported.7 Typical treatment options for more common choroidal metastases include systemic chemotherapy, external beam radiation for lesions in cases where systemic therapy does not
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