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Case report

# Presumed mast cell choroidal infiltrate in aggressive systemic mastocytosis

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ABSTRACT

*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 infiltrate. The index of suspicion was high due to the prior ASM 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.

## 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).[1–3] 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.[4] 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.[5,6] 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*.[7] The *KIT* D816V (aspartate to valine at codon 816) is the most common mutation found in over 80% of all SM patients.[2] 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.[7] 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*

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**Table 1**
Advanced systemic mastocytosis diagnostic (modified from Gotlib et al.[3] and Valent et al.[2]). 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<br>B. *KIT* point mutation at codon 816 in the bone marrow or another extracutaneous organ<br>C. Mast cells in bone marrow or blood or another extracutaneous organ expresses CD2 or/and CD25<br>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) | | Benign with good prognosis |
| Smoldering SM (SSM) | | Abnormally high mast cell burden with 2 of 3 B findings but no C findings.<br>B findings (end-organ involvement)<br>1. Bone marrow biopsy > 30% infiltration by mast cells and serum tryptase level > 200 ng/ml<br>2. Signs of dysplasia or myeloproliferation, in non-mast cell lineage(s)<br>3. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging (> 2cm)<br>C findings (end-organ damage)<br>1. Bone marrow dysfunction manifested by 1 or more cytopenias (ANC $< 1 \times 10^9$/L, Hgb < 10 g/dL, or platelets $< 100 \times 10^9$/L)<br>2. Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension<br>3. Skeletal involvement with large osteolytic lesions and/or pathologic fractures<br>4. Palpable splenomegaly with hypersplenism<br>5. Malabsorption with weight loss from gastrointestinal tract mast cell infiltrates |
| SM with associated hematologic neoplasm (SM-AHN) | 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). Funduscopic 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.

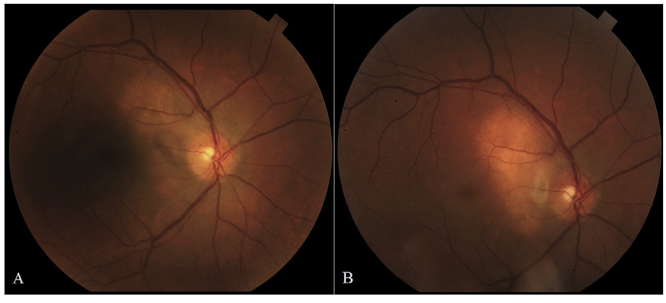


**Fig. 1.** Fundus photos of macular choroidal infiltrate in a patient with aggressive systemic mastocytosis (ASM). (A) Initial visit: A nasal macular creamy choroidal infiltrate is visible (B) After 4 months of systemic midostaurin therapy: the lesion's surface area expanded by 12.5%.

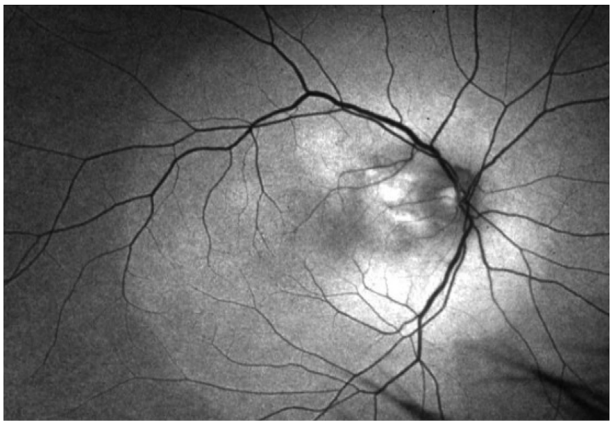

**Fig. 2.** Fundus autofluorescence at initial visit demonstrating patchy hyper- and hypo-autofluorescence overlying the lesions.

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.[5] 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

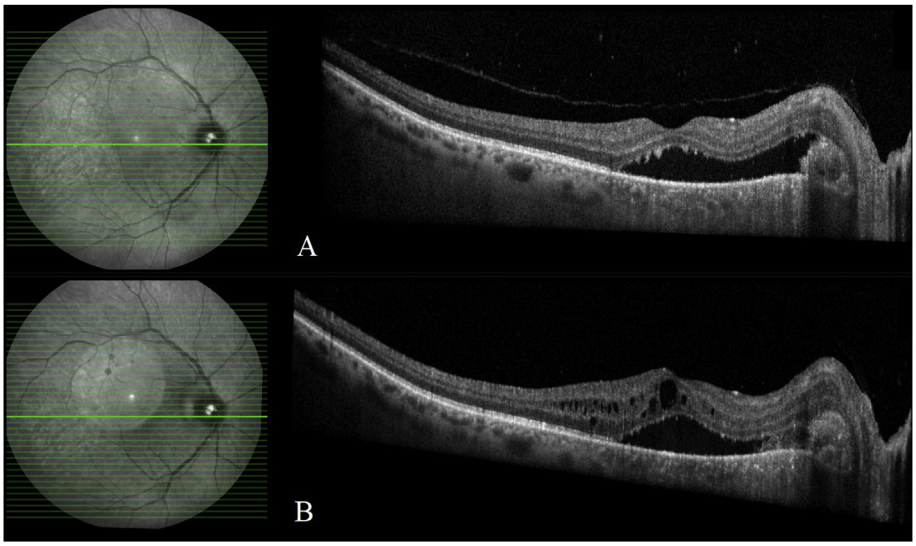


**Fig. 3.** Optical coherence tomography images. (A) At initial visit: a choroidal infiltrate and a peripapillary subretinal lesion with correlating subretinal fluid. (B) Four months after initiating systemic midostaurin: the choroidal infiltrate appears similar but there is now intraretinal fluid and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

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.

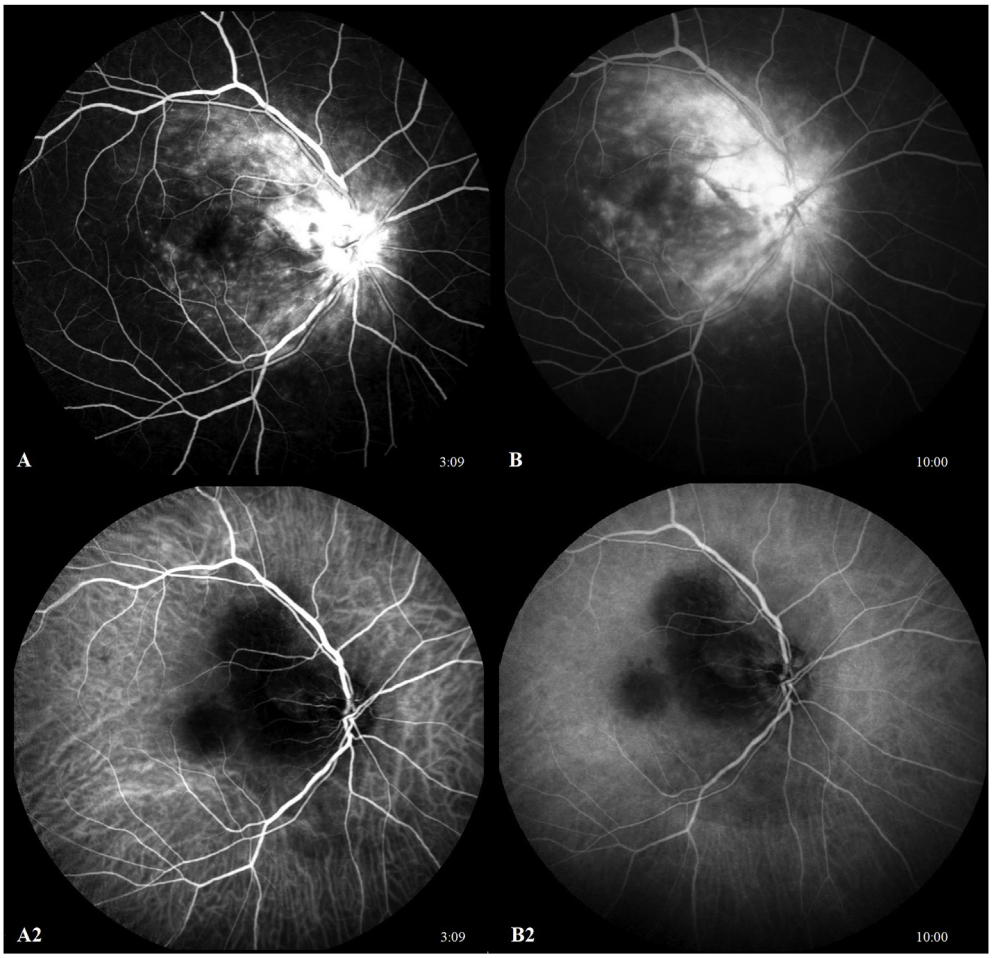


**Fig. 4.** Fluorescein Angiogram (FA) and Indocyanine Green (ICG) at initial visit. (A) Left: FA late phase (3′09″) demonstrating leakage of the choroidal lesion and the optic nerve. (B) Right: FA at 10 minutes demonstrating further leakage from the lesion. No other choroidal or retinal lesions were 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.

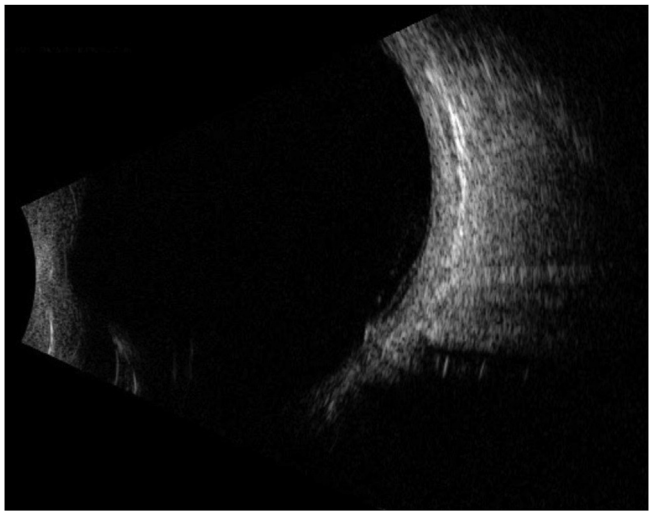

**Fig. 5.** B scan ultrasonography at initial visit: increased echogenicity in the region of the infiltrate and hyperechoic material at optic nerve. At four months, the B scan was virtually the same suggesting stability of the lesion.

## 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 pigmentary changes and serous retinal detachment.[5] The lesion was presumed to be a choroidal mast cell infiltrate and responded to histamine 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.[8] 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 antihistamine treatment,[5] whereas Michel et al. reported improved visual acuity and lesion stability with systemic treatment, though the treatment details were not reported.[6] Typical treatment options for more common choroidal metastases include systemic chemotherapy, external beam radiation for lesions in cases where systemic therapy does not 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.

## 4. Conclusion

This case highlights the consideration of mast cell infiltrate in patients presenting with acute/subacute central vision loss in context of ASM. This is a uniquely challenging clinical situation plagued by impracticality of tissue-based diagnosis, necessitating diagnosis by exclusion with careful examination and multimodal imaging coupled to clinical suspicion if an establish ASM diagnosis is known. An update on systemic therapy for ASM is provided, in which midostaurin is promising in treating ASM systemically, but additional localized ocular therapies may be required during close monitoring of the patient's visual symptoms and changes in visual acuity.

## Patient consent

The patient reviewed this case report and provided oral consent for publication.

## Funding and conflict of interests

The authors declare no conflicts of interest and no funding sources.

## Authorship

All authors attest to satisfying the ICMJE criteria for Authorship.

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