American Journal of Ophthalmology Case Reports 10 (2018) 221–225

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.elsevier.com/locate/ajoc

Case report

Vogt-Koyanagi-Harada disease like presentation in patients with chronic myeloid leukemia

Saurabh Mistry[a], S. Sudharshan[a,*], Suganeswari Ganesan[a], Ashraf Banu Akbar[b], Jyotirmay Biswas[a]

[a] Sankara Nethralaya, Medical Research Foundation, Chennai, India
[b] Sankara Nethralaya, Vision Research Foundation, Chennai, India

ARTICLE INFO

Keywords:
Chronic myeloid leukemia
Panuveitis
Vogt-Koyanagi-Harada disease
Tyrosine kinase inhibitors
Dasatinib
Imatinib

ABSTRACT

Purpose: To report two rare cases of chronic myeloid leukemia (CML) on tyrosine kinase inhibitors presenting as bilateral serous retinal detachment and ocular inflammation, simulating Vogt-Koyanagi-Harada (VKH) disease.
Methods: Case series and review of literature.
Result: Two young patients (one male and one female) with CML on treatment with tyrosine kinase inhibitors (imatinib and dasatanib) under remission presented with bilateral sudden vision loss. One patient had bilateral multiple pockets of serous retinal fluid while the other had panuveitis with exudative retinal detachment. There was neither prodromal symptoms nor systemic signs and symptoms suggestive of VKH in both cases. They responded well to systemic steroid therapy without recurrences with complete visual recovery.
Conclusion and importance: CML patients can have features similar to VKH even during stable hematological phase and may be possibly associated with the use of tyrosine kinase inhibitors. Hence it is important not to misdiagnose and treat such patients with long term immunomodulators.

1. Introduction

Patients with leukemia often have ocular manifestations. These occur either from direct infiltration of neoplastic cells or from indirect causes, including hematologic abnormalities, central nervous system involvement, opportunistic infections, or from drug toxicity. Awareness of the ophthalmic manifestations of leukemia is important as they may precede the diagnosis of leukemia or can occur during the course of the disease.[1]

Although nearly all ocular structures can be affected, leukemic retinopathy is often the most clinically apparent manifestation. Typically, manifestations of leukemic retinopathy are florid, with vascular changes such as retinal vein tortuosity or obstruction, flame-shaped hemorrhages, dot-and-blot hemorrhages, Roth spots, and even optic nerve edema.

Serous retinal detachment is not commonly seen in patients with chronic myeloid leukemia (CML), although anecdotal cases in lymphoblastic leukemia have been reported.[2–8] There are no reports of such ocular presentation associated with drugs used in the treatment of CML especially tyrosine kinase inhibitors. We report two rare cases of CML on hematological remission who presented with bilateral serous retinal detachment simulating Vogt-Koyanagi-Harada (VKH) disease. These patients were on tyrosine kinase inhibitors namely imatinib and dasatinib and their possible role as the cause of ocular inflammation was considered.

2. Case details

2.1. Case 1

A 32-year young female, a known case of CML since 8 years on hematological remission presented to us with complaints of sudden bilateral painless loss of vision since 10 days duration. Her recent blood counts were within normal limits. She was on treatment with imatinib mesylate since the past 6 years. Her best corrected visual acuity in the right eye was 6/36, N18 and in the left eye was 3/60, N36. Anterior chamber was quiet and fundus examination of both eyes revealed hyperemic discs and multiple pockets of subretinal fluid in posterior pole along with multiple confluent yellowish placoid lesions in choroid simulating VKH. The patient did not have any similar ocular history in the past nor had any prodromal symptoms or neurological, auditory or integumentary signs or symptoms. Fundus fluorescein angiography of

* Corresponding author. Dept of Uveitis, Sankara Nethralaya, Medical Research Foundation, 18, College Road, Nungambakkam 600 006, Chennai, India.
E-mail addresses: drsaurabhmistry@yahoo.com (S. Mistry), drdharshan@gmail.com (S. Sudharshan), drgsi@snmail.org (S. Ganesan), ashrafbanuakbar@gmail.com (A.B. Akbar), drjb@snmail.org (J. Biswas).

https://doi.org/10.1016/j.ajoc.2018.03.010
Received 14 November 2017; Received in revised form 8 February 2018; Accepted 8 March 2018
Available online 10 March 2018

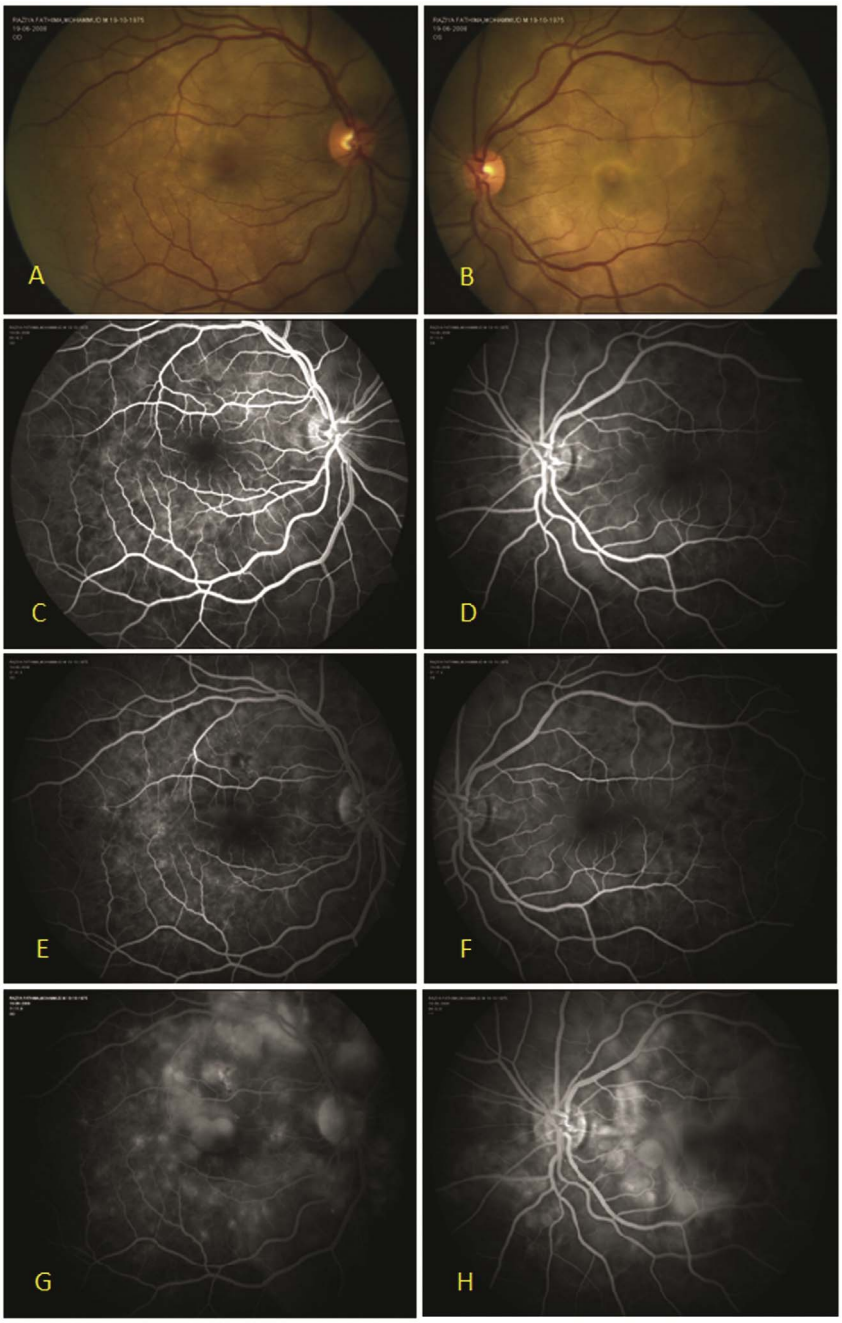

Fig. 1. Case 1 findings at presentation.
A & B) Fundus examination of both eyes shows hyperemic discs and multiple pockets of subretinal fluid in posterior pole along with multiple confluent yellowish placoid lesions in choroid; C & D) Fluorescein angiography of both eyes in early phase revealed hypofluorescent spots corresponding to the placoid lesions in choroid; E & F) followed by multiple hyperfluorescent pinpoint leaks in the mid phase; G & H) which showed pooling of the dye in the subretinal space during the late phase.

both eyes in early phase revealed hypofluorescent spots corresponding to the placoid lesions in choroid, followed by multiple hyperfluorescent pinpoint leaks in the mid phase which showed pooling of the dye in the subretinal space during the late phase. [Fig. 1]. Ultrasonography (USG) B scan of both eyes showed increased choroidal thickness and did not reveal any choroidal mass. Investigations revealed a normal chest X-ray and a negative Quantiferon-TB Gold (QFT-G) and Mantoux tests. Patient underwent bone marrow trephine biopsy which showed markedly hypocellular bone marrow. Although CSF analysis was not done during the ocular presentation, she was re-evaluated by oncologist and was found to be haematologically stable.

Patient was treated with pulse therapy of intravenous methyl prednisolone (IVMP) 1G for 3 days followed by tapering course of systemic steroids at 1 mg/kg body weight after hematologist and physician's clearance. BCVA improved to 6/6 with complete resolution of subretinal fluid in both eyes at 6 weeks. Oral steroids were tapered over a period of 3 months with complete resolution of inflammation. There was no reactivation of ocular inflammation and the patient continued to remain in hematological remission till the last follow-up period of 20 months.

2.2. Case 2

A 41-year old male, on treatment for CML since 10 years and in hematological remission, presented with complaints of sudden painful loss of vision in both eyes since 5 days. The patient did not have any

prior ocular history nor prodromal symptoms or any integumentary findings, neurologic or auditory findings which have been described commonly in association with VKH. His recent blood counts were within normal limits. Patient was on treatment with imatinib mesylate since 4.5 years and was recently switched over to dasatinib 9 days ago. Best corrected visual acuity at presentation in right eye was CF and in left eye was 6/18. Anterior segment evaluation revealed fine keratic precipitates, fibrinous anterior chamber reaction, posterior synechiae and vitreous cells in both eyes. Fundus examination of right eye revealed hyperemic discs and multiple pockets of subretinal fluid in posterior pole and peripheral 360-degree choroidal detachment. Left eye fundal view was hazy due to intense fibrinous reaction in anterior chamber. There was gross hypotony in right eye and normal intraocular pressure in left eye.

Ultrasonography of right eye revealed serous choroidal detachment and subretinal fluid pocket at macula with choroidal thickness of 1.6mm, whereas left eye showed subretinal fluid pocket at macula with choroidal thickness of 1.3mm. Fundus fluorescein angiography of right eye revealed multiple hyperfluorescent pinpoint leaks in the mid phase which showed pooling of the dye in the subretinal space during the late phase; left eye media was hazy due to inflammation. Anterior chamber tap was done, and aqueous aspirate cytopathology did not reveal any leukemic cells [Fig. 2].

Investigations revealed a normal chest X-ray and negative QFT-G and Mantoux tests. Patient was evaluated by the treating oncologist and was found to be haematologically stable.

Patient was treated with pulse therapy of IVMP 1G per day for 3 days followed by tapering course of systemic steroids at 1 mg/kg/day after clearance from treating hematologist. At 1-month follow-up, BCVA improved to 6/6, N6 in the right eye and 6/9, N8 in the left eye. Optical coherence tomography showed complete resolution of subretinal fluid in right eye, whereas trace subretinal fluid was noted in the left eye [Fig. 3]. Oral steroids were slowly tapered over the next 3 months after complete resolution of inflammation. There were no recurrences and at 1 year followup, patient developed posterior subcapsular cataract in both eyes. He underwent uneventful phacoemulsification with in the bag foldable acrylic intraocular lens implantation in both eyes under steroid cover.

During the final follow-up visit after 7 years from presentation, patient maintained BCVA of 6/7.5 in both eyes without any recurrence. The patient was also maintained on dasatinib throughout the course and he continued to remain in hematological remission till the last

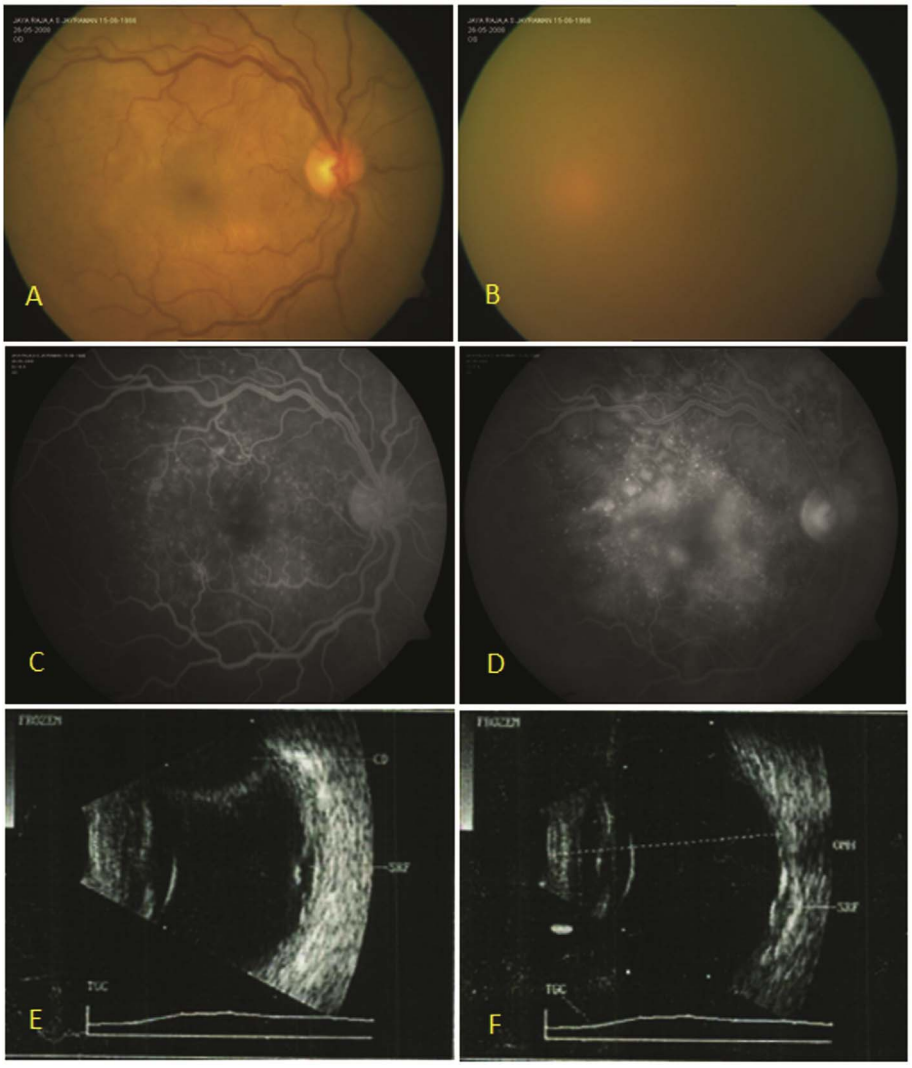

Fig. 2. Case 2 findings at presentation.
A & B) Fundus examination of right eye revealed hyperemic discs and multiple pockets of subretinal fluid in posterior pole and left eye view was hazy due to intense fibrinous reaction in anterior chamber; C & D) Fluorescein angiography of right eye revealed multiple hyperfluorescent pinpoint leaks in the mid phase which showed pooling of the dye in the subretinal space during the late phase; E & F) Ultrasonography of right eye revealed serous choroidal detachment and subretinal fluid pocket at macula, whereas left eye showed subretinal fluid pocket at macula.

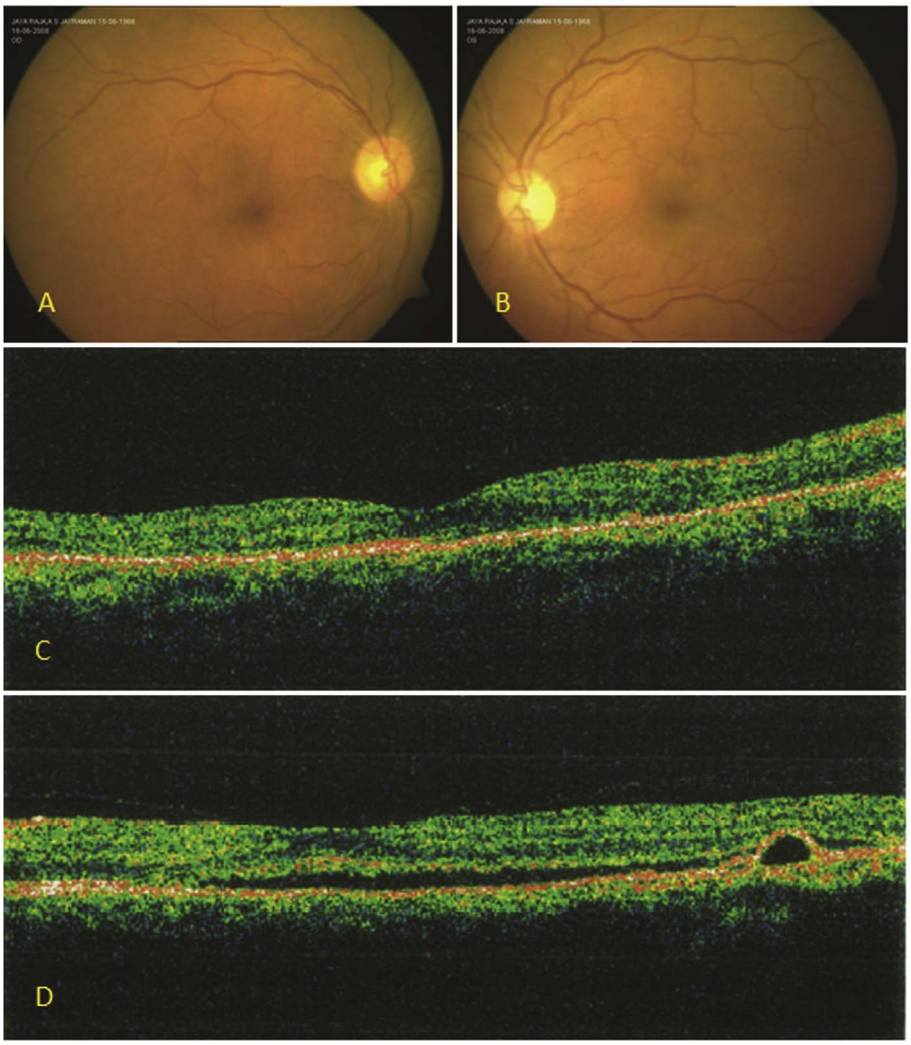

Fig. 3. Case 2 findings at 1 month follow-up visit.
A & B) Fundus picture showing resolution of ocular inflammation; C & D) Optical coherence tomography showing complete resolution of subretinal fluid in right eye, whereas in left eye trace subretinal fluid was present.

follow-up period.

3. Discussion

Ocular inflammation in patients with CML has been reported during the blast crisis, as a relapse of central nervous system (CNS) involvement or even as an initial manifestation of undetected CML.

CML in blast crisis and relapsing acute myeloid leukemia have been reported to present as masquerade syndromes.[9–12] These patients often develop a severe anterior segment cellular infiltration with hypopyon. Anterior chamber tap and cytopathology of the aqueous has been reported to be diagnostic. In our patient in whom aqueous analysis for cytopathology was done, did not yield any leukemic cells as he was in hematological remission stage of the disease.

Exudative retinal detachment and panuveitis as a possible drug related side effect was considered. Both our patients were on long term Imatinib and one of the patients was switched over to dasatanib. Imatinib mesylate is a selective inhibitor of the bcr/abl, c-kit and PDGF receptor tyrosine kinases. Common ocular side effects reported with imatinib include periorbital oedema (70%), epiphora (18%), glaucoma, recurrent retinal and conjunctival haemorrhage and optical neuritis especially with dosages of 600–800 mg/day.[13,14] Both our patients were on long term treatment with imatinib mesylate (range - 4.5–6 years) with a cumulative daily dose of 400 mg/day. Dasatinib is a tyrosine kinase inhibitor indicated in cases resistant or intolerant to imatinib. While systemic side effects such as headache, diarrhea, peripheral edema and skin rash have been reported with dasatanib, not many ophthalmic side effects with the same are found in literature.[15,16] Recently a case of optic neuropathy secondary to dasatinib has been reported in the treatment of CML[17]. Serous retinal detachments either with imatinib or dasatanib have not been reported in the literature.

Among the various side effects of dasatanib, especially in those with severe adverse reactions, fluid accumulation in cavities such as pleural and pericardial effusion or ascites have been reported.[15,16] A possible hypothesis of a similar presentation with fluid accumulation in the sub retinal space was considered. This could not be conclusively proven in our series based on Naranjo's criteria for drug association, since both our patients continued their respective drugs, and had no recurrences.[18] There is still a reason to strongly believe a drug associated reaction especially in Case 2, since he had a severe ocular inflammatory reaction within a short period of switching over from imatinib to dasatinib. An idiosyncratic or a dose related reaction in select patients of CML on long term imatinib with variable pharmacokinetics could be a possible explanation for a less aggressive VKH like presentation in Case 1.

Chawla et al. reported a case of incomplete VKH disease in a 39-year old patient of CML, on imatinib, in hematological remission[8] While their patient had prodromal symptoms and other meningismal signs suggestive of VKH, both our patients did not have any of those. With a

long follow-up, even the typical signs of convalescent phase of VKH such as sunset glow fundus, integumentary findings were not seen in both our patients. Significantly both our patients did not have any recurrence of ocular inflammation during the follow-up period.

AlZamil et al. reported a VKH like presentation in a patient that was eventually diagnosed as acute lymphocytic leukemia (ALL).[7] They believe the prodromal symptoms may misdirect to the clinical diagnosis of incomplete VKH. They hypothesise that it may be due to leukemic infiltration into the CSF and microvasculopathy due to hyperleukocytosis. The choroid is the most frequently involved ocular tissue in leukemia. The possible mechanism of bilateral serous retinal detachment in such cases could be due to choroidal ischemia and secondary retinal pigment epithelial (RPE) dysfunction.[19] Ocular histologic findings by autopsy in leukemic patients have documented the features of choroidal thickening and leukemic cell infiltration that may cause partial occlusion of the choriocapillaries and delay of choroidal circulation leading to choroidal ischemia.[19] Secondary dysfunction of the Bruch's membrane and retinal pigment epithelium may ultimately develop into serous retinal detachments.[20]

4. Conclusion

Presentation and course in our patients ruled out VKH and a possible drug association was considered although could not be conclusively proven based on Naranjo's criteria. Our study shows that ocular inflammation in CML, which is usually associated with blast crisis can occur even during stable hematological phase especially in patients on tyrosine kinase inhibitors such as imatinib and dasatinib.

VKH like presentation in patients with CML can occur due to choroidal ischemia and secondary RPE dysfunction or due to the drugs and hence it is important not to misdiagnose and treat such patients with long term immunomodulators or systemic steroids. Our cases were a rare presentation simulating VKH in patients with CML on tyrosine kinase inhibitors in hematological remission phase.

Disclosure

Ethics approval and consent to participate

Written informed consent was obtained from the patients for the publication of this report and any accompanying images. Ethics approval was granted to us by our own institute's IRB.

Funding

None.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

None.

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