Unexpected Occurrence of an Occult Macular Hole in a Case of Dense Sub-internal Limiting Membrane Hemorrhage

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ABSTRACT

Sub-internal limiting membrane (sub-ILM) hemorrhage is relatively uncommon and associated with various etiologies. It often results in significant visual impairment due to its tendency to affect the macular region. We present the case of a patient diagnosed with hairy cell leukemia undergoing cladribine treatment, who experienced sudden vision loss due to dense sub-ILM hemorrhage in the macular region, confirmed by optical coherence tomography (OCT), and associated with concurrent anemia and thrombocytopenia. Due to the patient's leukopenic condition, he was treated with pneumatic tamponade with 100% octafluoropropane (C3F8) gas and prone positioning to facilitate faster visual recovery by displacing the hemorrhage from the fovea. Although the sub-ILM hemorrhage was completely resolved, a macular hole appearance was detected on fundus examination, confirmed by OCT as Stage 1B occult macular hole. The aim of this report is to highlight occult macular hole formation after sub-ILM hemorrhage and discuss the underlying mechanisms proposed as causes of macular hole development after sub-ILM hemorrhage.

Key Words: Leukemic retinopathy, macular hole, pneumatic displacement, sub-internal limiting membrane hemorrhage

INTRODUCTION

Hairy cell leukemia (HCL) is a rare type of chronic leukemia characterized by an indolent course, resulting in pancytopenia due to infiltration of the bone marrow.[1] Ocular manifestations in patients with leukemia are common and can occur in up to 90% of cases.[2] These manifestations can be divided into two categories: primary or direct infiltration of leukemic tumor cells, which manifests as direct infiltration of eye tissues such as the anterior segment, uveal tract, vitreous, retina, and orbital tissues, as well as neuro-ophthalmic signs of central nervous system leukemia. The secondary or indirect changes result from hematological abnormalities associated with leukemia, including anemia, thrombocytopenia, hyperviscosity and immunosuppression. These manifestations can present as retinal hemorrhages occurring at all levels, vitreous hemorrhages, vascular occlusions, opportunistic infections or various chemotherapy-related disorders.[3] Although all ocular structures can be affected, the most common presentation of leukemia often involves leukemic retinopathy which describes retinal manifestations associated with anemia, thrombocytopenia, and hyperviscosity rather than leukemic infiltration.[2]

In this report, we present a case of HCL that developed dense sub-internal limiting membrane (sub-ILM) hemorrhage in the macular region due to leukemic retinopathy, treated with pneumatic displacement using octafluoropropane (C3F8) gas and prone positioning to displace the sub-ILM hemorrhage while the patient was receiving treatment for neutropenic fever. In the case of the patient, whose close follow-up was postponed due to treatment in the intensive care unit, a Stage 1B occult macular hole was

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detected on optical coherence tomography (OCT) during his subsequent examination. Since sub-ILM hemorrhage is not common, there are limited studies available on the long-term complications associated with it.[4] Our aim in this case is to discuss the potential cause of the occult macular hole formation following sub-ILM hemorrhage.

CASE REPORT

A 37-year-old male, receiving cladribine treatment for hairy cell leukemia, admitted to the intensive care unit due to a persistent fever of 39°C, severe leukopenia, anemia, and thrombocytopenia, was referred to us for decreased vision in both eyes. Prior to the onset of current symptoms, the patient did not report any history of vision problems. Best-corrected visual acuity (BCVA) was hand motion in the right eye and 20/40 in the left eye. No elevation of IOP was noted. Funduscopy showed dense hemorrhage, approximately 2 disc diameters in size, occupying the central macula with an incomplete double-ring sign in the right eye, consistent with sub-ILM hemorrhage as the blood forms a concentric ring around the hemorrhage, usually appearing as flakes that demarcate the posterior hyaloid. Additionally, intraretinal hemorrhages, with multiple white-centered hemorrhages scattered throughout the retina, were seen in the right eye, indicating the presence of Roth spots. In the left eye, flame-shaped retinal hemorrhages extending from the optic disc to the four quadrants, Roth spots, and small hemorrhagic spot temporal to the fovea were observed. (Figure 1) On OCT, a dome-shaped, well-demarcated blood clot was observed beneath a hyper-reflective band corresponding to the ILM, obscuring deeper foveal details, indicative of sub-ILM hemorrhage in the right eye. An overlying patchy membrane with low optical reflectivity was present above the hemorrhage, consistent with the posterior hyaloid. A hyper-reflective band was also visible beneath the hemorrhage, resulting from the compression of the underlying retinal nerve fiber layer. In the left eye, moderately reflective hyperreflective bands corresponding to flame-shaped retinal hemorrhages and minimal intraretinal cystic changes in the macula were noted. (Figure 2) Since vitrectomy was not an option for the right eye due to leukopenia, 0.3 mL of pure octafluoropropane (C3F8) was injected through the pars plana followed by the patient changing to a prone position. On the day following pneumatic displacement treatment, minimal reabsorption of the sub-ILM hemorrhage was observed. (Figure 3) The follow-up examination was conducted in the 14th week due to the patient's medical condition. BCVA improved to 20/100 and 20/20 in the right and left eyes respectively. At funduscopy, complete clearing of the sub-ILM hemorrhage and intraretinal hemorrhages spread across the retina was observed in the right eye while a macular hole appearance was seen. OCT revealed loss of the foveal depression associated with a bridge-like ILM, along with

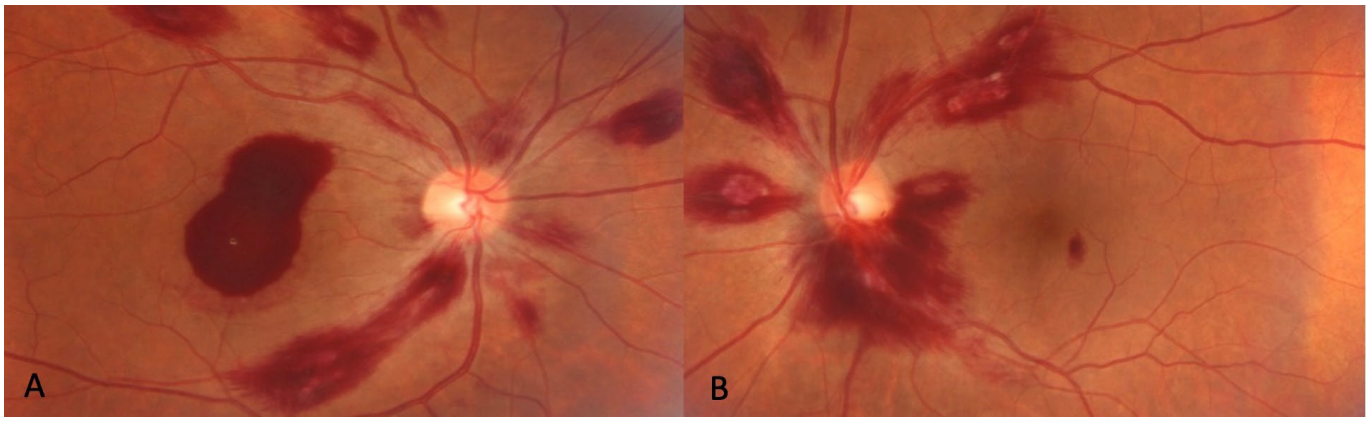

Figure 1: *Fundus photographs of the right eye (A) and the left eye (B) at the first examination*

A showing dense hemorrhage, approximately 2 disc diameters in size, occupying the central macula with an incomplete double-ring sign in the right eye, consistent with sub-ILM hemorrhage as the blood forms a concentric ring around the hemorrhage, usually appearing as flakes that demarcate the posterior hyaloid.

B showing flame-shaped retinal hemorrhages extending from the optic disc to the four quadrants, Roth spots and small hemorrhagic spot temporal to the fovea.

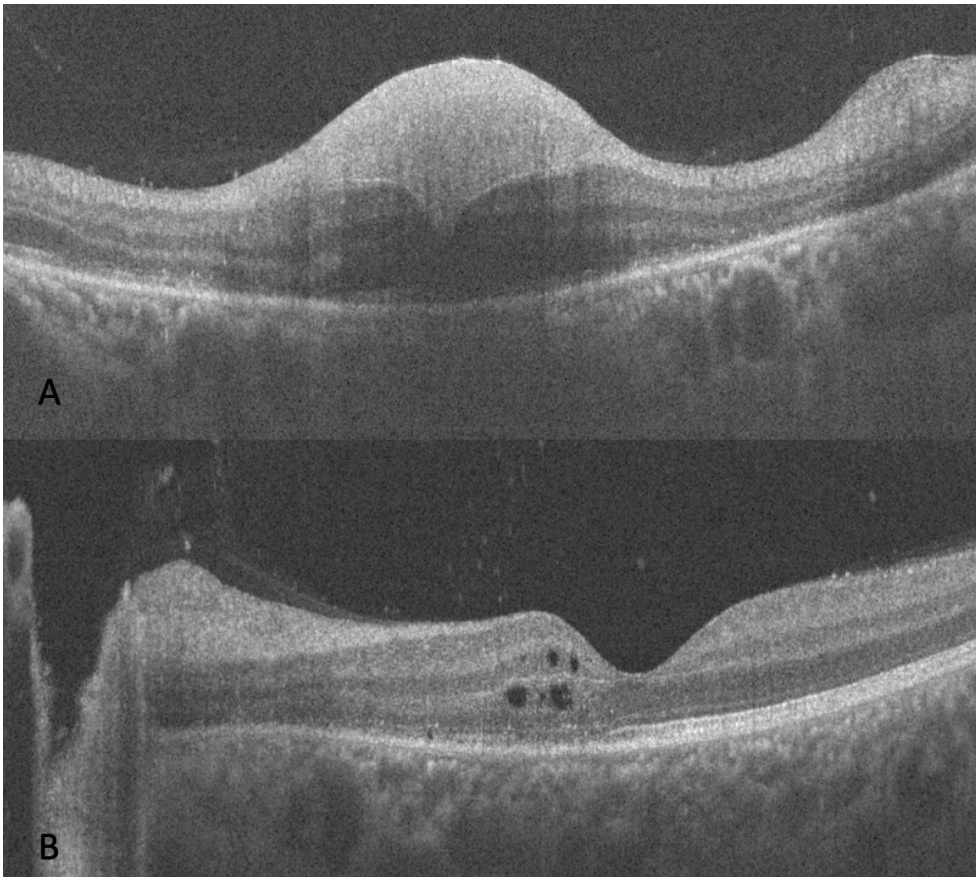

Figure 2: *Optical coherence tomograpy of the right eye (A) and the left eye (B) at the first examination*

A showing a dome-shaped, well-demarcated blood clot was observed beneath a hyper-reflective band corresponding to the ILM, obscuring deeper foveal details, indicative of sub-ILM hemorrhage in the right eye. An overlying patchy membrane with low optical reflectivity was present above the hemorrhage, consistent with the posterior hyaloid. A hyper-reflective band was also visible beneath the hemorrhage, resulting from the compression of the underlying retinal nerve fiber layer. B showing minimal intraretinal cystic changes in the macula.

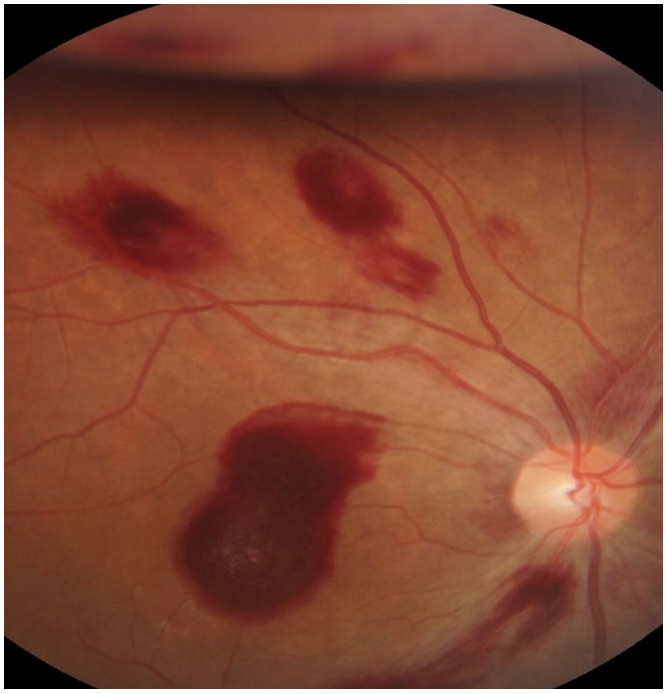

Figure 3: *Fundus photograph of the right eye after intravitreal gas injection showing minimal reabsorption of the sub-ILM hemorrhage and C3F8 gas in the vitreous cavity.*

a hyporeflective cystic formation extending into the outer retina, causing disruption in the photoreceptor layer in the right eye. Additionally, small circular cysts were observed in the outer plexiform layer. In the left eye, complete resolution of intraretinal cystic changes within the macula with normal foveal contour and intraretinal hemorrhages was noted. (Figure 4)

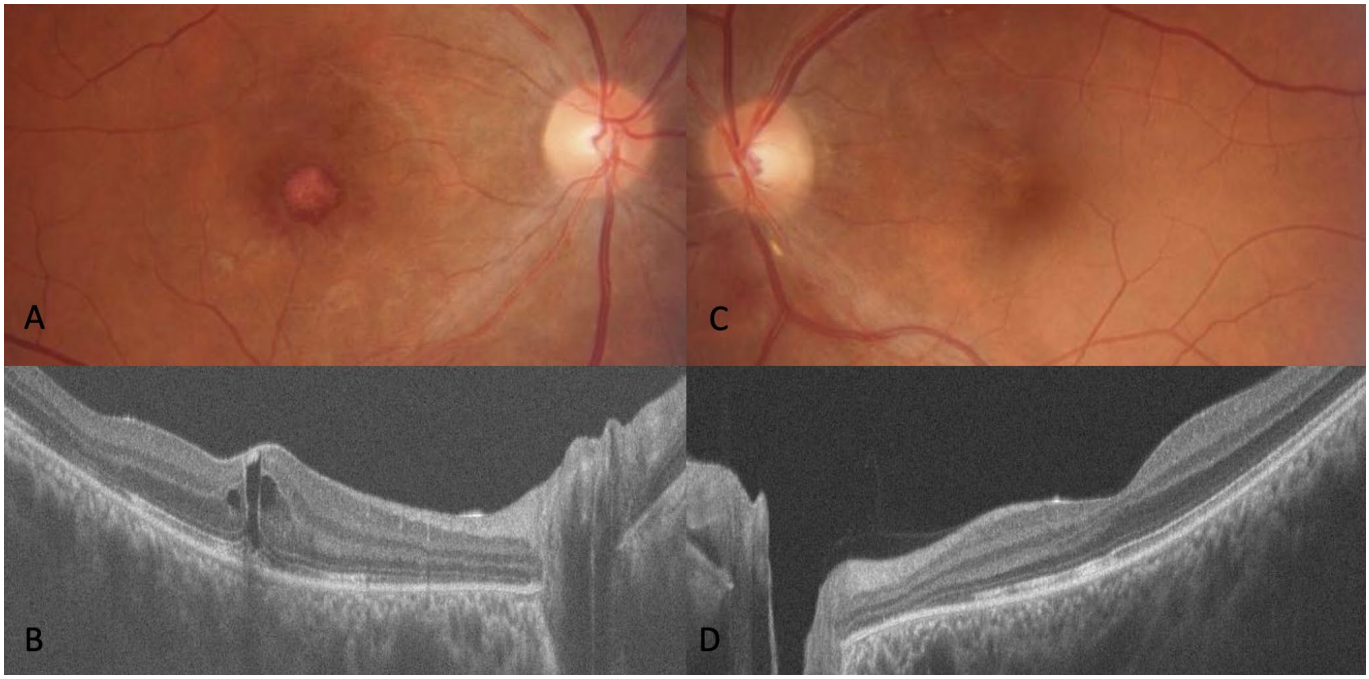

Figure 4: *Fundus photographs of the right eye (A) and the left eye (C) along with optical coherence tomography images of the right eye (B) and the left eye (D), taken during the 14th-week examination following pneumatic displacement*

A showing complete clearing of the sub-ILM hemorrhage and intraretinal hemorrhages as well as disappearance of Roth spots with a macular hole appearance.

B confirms the macular hole appearance by showing loss of the foveal depression associated with a bridge-like internal limiting membrane (ILM), along with a hyporeflective cystic formation extending into the outer retina, causing disruption in the photoreceptor layer. Additionally, small circular cysts in the outer plexiform layer are observed.

C and D showing complete resolution of intraretinal cystic changes within the macula with normal foveal contour and intraretinal hemorrhages.

DISCUSSION

Sub-ILM hemorrhages are located in the superficial retina between the ILM and the retinal nerve fiber layer.[5] These sharply demarcated, dome-shaped hemorrhages tend to occur more frequently in the macular region due to the lack of tight adhesion of the ILM in the macula, thereby leading to severe visual impairment.[5,6] Various causes of sub-ILM hemorrhage have been reported including Valsalva retinopathy, Terson's syndrome, ocular trauma, ruptured retinal macroaneurysms (RAM) and hematological disorders.[5-7] Blood dyscrasias, such as anemia and thrombocytopenia, have been associated with sub-ILM hemorrhages in a number of reports. When both conditions are present simultaneously, the likelihood of developing retinopathy is higher. The reduced endothelial cell integrity of the retinal vasculature and reduced coagulability allow the leakage of blood through the endothelial barrier of the retinal capillaries.[8]

Pre-retinal hemorrhages typically resolve within a short period if they are smaller than one disk diameter. However, the spontaneous resolution of large and dense hemorrhages may take months, potentially resulting in irreversible visual impairment. This could be due to pigmentary macular changes, formation of epiretinal membranes or toxic damage to the retina caused by prolonged exposure to hemoglobin and iron.[9] To prevent blood-related complications, various management approaches for sub-ILM hemorrhage have been reported including Nd:YAG laser puncture, pars plana vitrectomy and pneumatic displacement with intraocular gas tamponade with or without tissue plasminogen activator (tPA)injection.[5] In our case, we treated sub-ILM hemorrhage resulting from concurrent anemia and thrombocytopenia with intravitreal C3F8 injection, considering both the hemorrhage size and the patient's ongoing treatment for neutropenic fever. At the next examination, which was conducted at the 14-week

follow-up, a stage 1B occult macular hole was observed. Macular hole development associated with sub-ILM and subretinal hemorrhage following ruptured RAM has been reported in studies, and sub-ILM hemorrhage has been identified as a risk factor for the development of macular holes. [10]

The exact mechanism of macular hole development following sub-ILM hemorrhage remains unclear. Highly elevated pressure in the sub-ILM space can result in microlaceration or retinal degeneration between retinal layers, which may lead to the formation of a macular hole.[11] Additionally, direct chemical toxicity to the retina from iron, hemosiderin, or fibrin, along with the deterioration of oxygenation and nutrient supply due to large sub-ILM hemorrhage, can also contribute. Furthermore, the contraction of a blood clot can cause mechanical damage to the retinal layers, further contributing to stage 1B occult macular hole with disruption in the photoreceptor layer.[4,12] Sub-ILM hemorrhage can also cause structural changes to the ILM, leading to alterations in anterior-posterior vitreous traction, which may further contribute to macular hole formation.[12] Due to the patient's condition, close follow-up after pneumatic displacement was not possible, making it difficult to monitor the effect of the gas on the vitreoretinal interface. Consequently, a macular hole may have developed due to vitreomacular traction during the separation of the posterior vitreous.

A study reported characteristic OCT findings following surgery for sub-ILM hemorrhage caused by RAM rupture.[13] Vertical hyperreflectivity with photoreceptor (ellipsoid and interdigitation zone) disruption on OCT may indicate central foveal fragility and could be mechanistically linked to the hyperreflective stress line commonly observed before macular hole development. In our case, an occult macular hole developed from the region where this hyperreflective stress line was observed, along with photoreceptor layer disruption.

CONCLUSION

Several mechanisms have been proposed as underlying causes of occult macular hole development following sub-ILM hemorrhage. Further large-scale and long-term studies with more frequent follow-up are needed for a better understanding.

REFERENCES

1. Nagy ZF, Ferenczi K, Istenes I, Eid H, Bödör C, Timár B, Demeter J. Case Report: Development of Diffuse Large B Cell Lymphoma a Long Time After Hairy Cell Leukemia. Pathol Oncol Res. 2022 Apr 29;28:1610338.
2. Talcott KE, Garg RJ, Garg SJ. Ophthalmic manifestations of leukemia. Curr Opin Ophthalmol. 2016 Nov;27(6):545-551.
3. Sharma T, Grewal J, Gupta S, Murray PI. Ophthalmic manifestations of acute leukaemias: the ophthalmologist's role. Eye (Lond). 2004 Jul;18(7):663-72.
4. Chou YK, Huang YM, Lin PK. Sub-internal limiting membrane hemorrhage treated with intravitreal tissue plasminogen activator followed by octafluoropropane gas injection. Taiwan J Ophthalmol. 2015 Oct-Dec;5(4):198-201.
5. De Maeyer K, Van Ginderdeuren R, Postelmans L, Stalmans P, Van Calster J. Sub-inner limiting membrane haemorrhage: causes and treatment with vitrectomy. Br J Ophthalmol. 2007 Jul;91(7):869-72.
6. Meyer CH, Mennel S, Rodrigues EB, Schmidt JC. Persistent premacular cavity after membranotomy in valsalva retinopathy evident by optical coherence tomography. Retina. 2006 Jan;26(1):116-8.
7. Alamri OS, Alsulami RE, Alqahtani BS, Alqahtani A. Spontaneous Resolution of Foveal Sub-internal Limiting Membrane Hemorrhage with Excellent Visual and Anatomical Outcome in a Patient with Acute Myeloid Leukemia. Middle East Afr J Ophthalmol. 2020 Apr 29;27(1):56-58.
8. Carraro MC, Rossetti L, Gerli GC. Prevalence of retinopathy in patients with anemia or thrombocytopenia. Eur J Haematol. 2001 Oct;67(4):238-44.
9. García Fernández M, Navarro JC, Castaño CG. Long-term evolution of Valsalva retinopathy: a case series. J Med Case Rep. 2012 Oct 10;6:346.
10. Sagara N, Kawaji T, Koshiyama Y, Inomata Y, Fukushima M, Tanihara H. Macular hole formation after macular haemorrhage associated with rupture of retinal arterial macroaneurysm. Br J Ophthalmol. 2009 Oct;93(10):1337-40.
11. Nourinia R, Behnaz N, Hassanpour H, Karjoo Z, Hassanpour K. Macular hole and submacular hemorrhage secondary to retinal arterial macroaneurysm - successfully treated with a novel surgical technique. GMS Ophthalmol Cases. 2020 Aug 6;10:Doc31.
12. Nourinia R, Behnaz N, Hassanpour H, Karjoo Z, Hassanpour K. Macular hole and submacular hemorrhage secondary to retinal arterial macroaneurysm - successfully treated with a novel surgical technique. GMS Ophthalmol Cases. 2020;10
13. Hayamizu, R., Totsuka, K., Azuma, K. et al. Optical coherence tomography findings after surgery for sub-inner limiting membrane hemorrhage due to ruptured retinal arterial macroaneurysm. Sci Rep 12, 16321 (2022).