Case Report

Valsalva-Like Retinopathy Secondary to Pancytopenia following Induction of Etoposide and Ifosfamide

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1. Introduction

Sub-ILM hemorrhages have been reported in cases of Val- 
salva retinopathy, Terson’s syndrome, blood dyscrasias, and 
blunt facial trauma. Usually, these hemorrhages are induced 
by mechanical injury or pressure gradients associated with a 
central process, such as in Terson’s syndrome [1].

Spontaneous sub-ILM hemorrhages are rarely reported. 
A case described by de Maeyer et al. describes a patient 
with acute myeloid leukemia with severe thrombocytopenia 
who developed a sub-ILM hemorrhage. The case required 
vitrectomy and excision of the hemorrhagic cyst resulting in 
20/50 vision. The chemotherapy regimen in this case was not 
reported [1]. Another case described by Borges et al. describes 
a patient with non-Hodgkin’s lymphoma on chemotherapy 
who presented with hand-motions vision in both eyes. The 
right eye had a large preretinal hemorrhage that was treated 
promptly with vitrectomy and membrane peel. The patient 
recovered vision to 20/50. The other eye was operated a week 
later but did not achieve similar visual recovery. The authors 
suggested that early intervention may be beneficial in such 
cases [2].

Medical management may be an appropriate course in 
cases of sub-ILM hemorrhages. Sub-ILM hemorrhages have 
been reported in cases of blood dyscrasias such as idiopathic 
thrombocytopenic purpura (ITP) or aplastic anemia. These 
cases were also spontaneous and not secondary to trauma or 
Valsalva mechanism. In a reported case of ITP, vitrectomy was 
ofered to resolve a subhyaloid and vitreous hemorrhage, but 
the patient declined intervention. The underlying condition 
of ITP was treated medically and the hemorrhages improved 
with recovery of vision [3]. Mansour et al. reported a series 
of 37 patients with aplastic anemia who experienced retinal 
hemorrhages, some of which were sub-ILM. The patients 
were treated medically with red blood cell and platelet 
transfusions and followed by the ophthalmology service. The 
authors discuss various treatment options undertaken by the 
ophthalmology service including observation and Nd:YAG 
membranotomy. However, the authors do not report the 
outcomes of each modality [4]. Although Nd:YAG mem-
branotomy spares the patient the more invasive option of 
vitrectomy, it may not be possible if nonclearing vitreous 
hemorrhage precludes an adequate view. Vitrectomy with 
membrane peel has been shown to be effective in managing 
sub-ILM hemorrhages and may be preferred in such cases [1].

2. Case Report

A 19-year-old male with a history of metastatic Ewing’s 
sarcoma presented with vision loss in the right eye. He
endorsed headache but denied ophthalmalgia, pain with eye movements, recent vomiting, or other Valsalva-inducing activities.

His visual acuity was 20/400 in the right eye and 20/20 in the left eye. A relative afferent pupillary defect was present in the right eye with normal pupillary response in the left eye. Confrontational visual fields, extraocular movements, and intraocular pressures were all within normal limits. Dilated fundus exam of the right eye revealed a large preretinal hemorrhage encompassing a large area within the macula (Figure 1). Dot-blot and flame hemorrhages were noted along the arcades in the left eye sparing the fovea (Figure 2). Patches of myelinated nerve fibers were noted in both eyes. The patient was unable to see the color plates with his right eye due to central blurring. Color vision was normal in the left eye. Initial laboratory work-up was significant for hemoglobin of 4.9 g/dL and platelet count of 17 K/μL with a normal INR. Computerized tomography (CT) scan of the brain did not reveal any intracranial hemorrhages or other acute processes.

After treatment with packed red blood cells and platelets, his hemoglobin improved to 10.3 g/dL and platelet count improved to 78 K/μL. The patient was observed closely without aggressive surgical intervention given his systemic status. Ten days after presentation, the sub-ILM hemorrhage in the right eye was noted to have spontaneously drained into the vitreous, with only a minimal boat-shaped hemorrhage remaining inferiorly (Figure 3). This coincided with his improvement in vision to count fingers. Three months after presentation the hemorrhage in the right eye resolved and his vision improved to 20/20 with resolution of his relative afferent pupillary defect (Figure 4).

The patient had undergone two cycles of chemotherapy with ifosfamide and etoposide prior to presentation and was noted to be pancytopenic during his initial course of therapy with minimum values of hemoglobin and platelets occurring on the day of presentation (Figure 5). He was continued on ifosfamide and etoposide and was given prophylactic transfusions as needed prior to his chemotherapeutic infusions. There were no further ocular complications or hemorrhages for the duration of his treatment.

3. Discussion

Low platelet levels, high MCV, and anemia have been demonstrated to correlate with the prevalence of retinal
Etoposide is a topoisomerase inhibitor that interferes with the unwinding of DNA during replication [8]. Ifosfamide is an alkylating agent that adds an alkyl group to DNA, preventing replication enzymes from adequately accessing the template strand [9]. Both agents strongly affect neoplastic cells due to their tendency to proliferate more rapidly than normal cells. The major systemic toxicity associated with etoposide is bone marrow suppression [10]. Ifosfamide has also been documented to cause bone marrow suppression in addition to hemorrhagic cystitis, nephrotoxicity, and neurotoxicity [11]. In regard to ocular side effects, intra-arterial etoposide has been documented to cause arterial thrombosis with central retinal artery occlusion being one possible corollary [12]. Cisplatin and etoposide when used in conjunction have been reported to lead to symptomatic retinopathy with abnormal electroretinography (ERG) and visual evoked response (VER), though this was thought to be more attributed to the platinum component of cisplatin [13]. Ifosfamide has been reported to lead to blurring of vision, though the cause was not described. It is also known to cause florid conjunctivitis [14].

To our knowledge, the current case is the only report of etoposide and ifosfamide associated with anemia and thrombocytopenia resulting in spontaneous sub-ILM hemorrhage. As in the previously cited cases, we considered treatment with vitrectomy versus Nd:YAG membranotomy [15]. Delaying intervention runs the risk of scar formation in the pocket of hemorrhage and secondary vision loss. The mechanism of scarring is thought to be due to retinal pigment epithelial cell migration to the site of hemorrhage with the development of scar tissue similar to epiretinal membrane formation seen in proliferative vitreoretinopathy [16]. However, immediate vitrectomy was delayed in this patient due to the degree of his thrombocytopenia and anemia. Fortunately, his hemorrhage drained spontaneously after only ten days following platelet and packed red blood cell transfusions. In this case, close observation did not result in visual morbidity with the final visual acuity recovering to 20/20.

We report a case related to pancytopenia that resulted in a good outcome with observation only. This highlights the importance of treating the underlying mechanism of anemia-induced retinopathy with close observation while maintaining a low threshold to intervene when necessary.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

**References**

[1] K. de Maeyer, R. van Ginderdeuren, L. Postelmans, P. Stalmans, and J. van Calster, "Sub-inner limiting membrane haemorrhage: causes and treatment with vitrectomy," *British Journal of Ophthalmology*, vol. 91, no. 7, pp. 869–872, 2007.

[2] P. Borges, N. Correia, N. Ferreira, and A. Meireles, *Bilateral Retinal Hemorrhage—Case Report*, European VitreoRetinal Society, 2012.

[3] L. Wan-Wei, T.-J. Tengku-Norina, A.-A. Azma-Azalina, A.-G. Zulkifli, and E. Zunaina, "Spontaneous bilateral peripapillary, subhyaloid and vitreous hemorrhage with only minor platelet deficit in idiopathic thrombocytopenic purpura," *International Medical Case Reports Journal*, vol. 7, no. 1, pp. 15–17, 2014.

[4] A. M. Mansour, J. W. Lee, S. A. Yahng et al., "Ocular manifestations of idiopathic aplastic anemia: retrospective study and literature review," *Clinical Ophthalmology*, vol. 8, pp. 777–787, 2014.
M. C. Carraro, L. Rossetti, and G. C. Gerli, “Prevalence of retinopathy in patients with anemia or thrombocytopenia,” European Journal of Haematology, vol. 67, no. 4, pp. 238–244, 2001.

R. A. Rubenstein, M. Yanoff, and D. M. Albert, “Thrombocytopenia, anemia and retinal hemorrhage,” The American Journal of Ophthalmology, vol. 65, no. 3, pp. 435–439, 1968.

A. Agarwal and D. M. Gass, Gass’ Atlas of Macular Diseases, Saunders, Philadelphia, Pa, USA, 5th edition, 2012.

Y. Pommier, E. Leo, H. Zhang, and C. Marchand, “DNA topoisomerases and their poisoning by anticancer and antibacterial drugs,” Chemistry and Biology, vol. 17, no. 5, pp. 421–433, 2010.

L. P. Bignold, “Alkylating agents and DNA polymerases,” Anticancer Research, vol. 26, no. 2B, pp. 1327–1336, 2006.

S. P. Joel, R. Shah, P. I. Clark, and M. L. Slevin, “Predicting etoposide toxicity: relationship to organ function and protein binding,” Journal of Clinical Oncology, vol. 14, no. 1, pp. 257–267, 1996.

M. P. Goren, R. K. Wright, C. B. Pratt et al., “Potentiation of ifosfamide neurotoxicity, hematotoxicity, and tubular nephrotoxicity by prior cis-diamminedichloroplatinum(II) therapy,” Cancer Research, vol. 47, no. 5, pp. 1457–1460, 1987.

L. Schacter, “Etoposide phosphate: what, why, where, and how?” Seminars in Oncology, vol. 23, supplement 1, no. 6, pp. 1–7, 1996.

L. M. Hilliard, R. L. Berkow, J. Watterson, E. A. Ballard, G. K. Balzer, and C. L. Moertel, “Retinal toxicity associated with cisplatin and etoposide in pediatric patients,” Medical and Pediatric Oncology, vol. 28, no. 4, pp. 310–313, 1997.

I. A. Choonara, M. Overend, and C. C. Bailey, “Blurring of vision due to ifosfamide,” Cancer Chemotherapy and Pharmacology, vol. 20, no. 4, article 349, 1987.

O. Kuruvilla, M. Munie, M. Shah, U. Desai, J. A. Miller, and M. D. Ober, “Nd:YAG membranotomy for preretinal hemorrhage secondary to valsalva retinopathy,” Saudi Journal of Ophthalmology, vol. 28, no. 2, pp. 145–151, 2014.

S. K. Gibran, N. Kenawy, D. Wong, and P. Hiscott, “Changes in the retinal inner limiting membrane associated with Valsalva retinopathy,” British Journal of Ophthalmology, vol. 91, no. 5, pp. 701–702, 2007.