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Original Research Paper

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SURGICALLY TREATED EXUDATIVE RETINAL DETACHMENT IN A PATIENT WITH WALDENSTROM MACROGLOBULINEMIA: A CASE REPORT

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ABSTRACT Waldenstrom macroglobulinemia (WM) is a lymphoplasmacytic lymphoma characterized by malignant B cells and elevated serum Immunoglobulin M (IgM) levels. WM can result in hyperviscosity syndrome, which can lead to dilatation of veins and exudates and complications in the posterior eye segment, such as an exudative retinal detachment (RD). Herein, we report a rare case of bilateral RD in WM, which was successfully treated surgically. In September 2020, a 62-year-old female patient was admitted to the Eye Clinic of Clinical Center of Montenegro (Podgorica, Montenegro), due to a sudden vision loss. Just 24 hours upon hospital admission the BCVA in the right eye decreased from 20/200 (ETDRS letter score 35) to light perception and projection. As the right eye fundus revealed exudation, tortuous venous dilatation, and multiple hemorrhages consistent with hyperviscosity syndrome, the patient underwent additional examinations, which uncovered WM as a cause of RD. Given that RD was nonrespondent to the standard WM treatment protocol, we decided to treat RD in the right eye surgically. After three surgeries, the retina was reattached with pars plana vitrectomy, retinotomy, and silicone oil implantation of 5000 centistoke. The patient was extremely satisfied after we restored partial vision. To the best of our knowledge, this is the first case of serous RD in WM treated surgically after failing conventional treatments such as plasmapheresis, chemotherapy, and intrabulbar steroid injections. Nevertheless, in order to draw conclusions about the effectiveness of pars plana vitrectomy in treating serous RD in WM, more cases of successful surgery are needed.

KEYWORDS : Waldenstrom macroglobulinemia, exudative retinal detachment, vitrectomy, visual acuity

INTRODUCTION

Waldenström macroglobulinaemia (WM) is a lymphoplasmacytic lymphoma characterized by malignant B cells and the serum accumulation of Immunoglobulin M (IgM)(Hobbs et al., 2020). In the majority of patients, WM follows Monoclonal Gammopathy of Undetermined Significance (MGUS). It accounts for 1-2% of hematological cancers(Hobbs et al., 2020).

WM is primarily considered a sporadic disease, but some studies have suggested a possibility of a single genetic defect. Activating mutations of the myeloid differentiation primary response 88 (MYD88) are present in over 90% of patients with WM and the most common one is MYD88 L265P(Guerrera Maria Luisa, 2018).

This gene encodes a protein involved in the toll-like receptor (TLR) and interleukin-1 (IL-1) signaling pathways(Guerrera Maria Luisa, 2018). MYD88 mutations cause constitutive expression of the anti-apoptotic transcription factor nuclear factor kappa B (NF-kB), allowing the abnormal IgM-producing B cells to survive(Guerrera Maria Luisa, 2018).

The accumulation of IgM leads to both serum hyperviscosity and high intravascular osmotic pressure(Hobbs et al., 2020).

The force of viscous serum tears the venule wall, resulting in retinal vascular dilatation and microvascular hemorrhage (Hobbs et al., 2020).

Fundoscopic abnormalities are seen in 30-40% of patients with WM(Hobbs et al., 2020). Common fundus exam findings include bilateral retinal vein engorgement, lipid exudates, central and branch retinal vein thrombosis and flame-shaped hemorrhages, which typically manifest once serum viscosity rises to near 4.0 cp(Dammacco et al., 2022; Hobbs et al., 2020). A less common ocular finding is the accumulation of subretinal fluid(Hobbs et al., 2020).

We report a case of WM presenting with vision loss due to a bilateral RD. The case we report is unique not only because this is an unusual presentation of WM, but also because this is the first RD in WM in literature successfully treated surgically to the best of our knowledge.

The case demonstrates how surgery can be an effective mode of treatment for exudative RD in WM, especially when other treatments, such as plasmapheresis, chemotherapy, and intravitreal injections of corticosteroids and anti-vascular endothelial growth factor (anti-VEGF), have failed.

Case Presentation

We present a case of a 62-year-old Caucasian female patient who was admitted to the Eye Clinic, Clinical Center of Montenegro (Podgorica, Montenegro) in September 2020, due to a sudden bilateral vision loss, with onset 2 days prior to admission.

The patient considered herself generally healthy and her medical history prior to admission was insignificant.

A complete eye examination was performed, followed by ocular echography.

The patient's best corrected visual acuity (BCVA) in the right and left eyes was 20/200 (ETDRS letter score 35) and light perception, respectively.

Fundus examination of the right eye showed exudation, tortuous venous dilatation and multiple vitreous preretinal, intraretinal, and subretinal hemorrhages, most prominent superiorly (Figure 1).

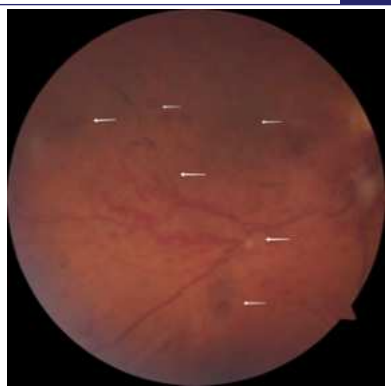

Figure 1. On the first examination of the right eye, the fundus revealed tortuous dilatation of veins, exudation, flame hemorrhages and dot and blot hemorrhages, most prominent superiorly (pointed out by arrows). These findings are typical manifestations of branch retinal vein occlusion (BRVO) caused by hyperviscosity syndrome. In the 24 hours following this image, retinal detachment developed due to subretinal exudation.

Fundus examination of the left eye revealed vitreous hemorrhage (Figure 2). Retinal detachment (RD) was confirmed by ocular echography. RD appeared as a folded, shriveled, poorly mobile membrane, which gave the impression that RD was long standing. Right eye might have compensated for left eye with RD, and patient didn't complain about vision loss until exudation and detachment developed in the right eye.

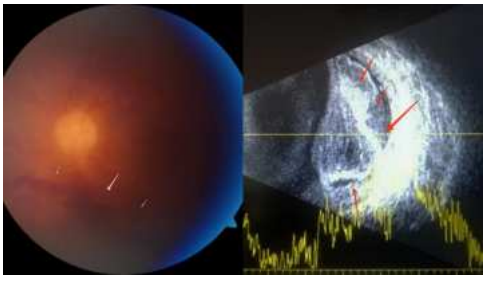

Figure 2. Fundus of the left eye revealed vitreous hemorrhage (pointed out by white arrows). To get a better understanding of the posterior segment changes, we needed to do an ultrasound of the eye. A V-shaped membrane is noted extending from the optic disc to the ora serrata, typical of RD (pointed out by red arrows).

With 24 hours from admission, the patient's BCVA in the right eye deteriorated from 20/200 (ETDRS 35) to only light perception. Vision deterioration in the right eye was caused by a complete exudative RD, confirmed by fundus examination and ocular echography.

Due to a severe RD in both eyes, we used ocular echography to further monitor patient's condition.

Hyperviscosity retinopathy was the likely diagnosis based on tortuous venous dilatation and multiple dot and blot hemorrhages(Bhavsar Mayur, 2021). Given that hyperviscosity retinopathy was suspected, additional laboratory testing including complete blood count (CBC), quantitative immunoglobulins, and serum protein electrophoresis, were requested to properly diagnose the etiology and treat accordingly(Bhavsar Mayur, 2021). CBC showed leukocytosis (24.69x10^9/L), iron deficiency anemia (hemoglobin 65g/L, serum iron 9.1 μmol/L), and thrombocytopenia (135x10^9/L). The patient had hyperproteinemia (107 g/L), hyperglobulinemia, hypoalbuminemia, and a low albumin/globulin ratio (0.33). Serum protein electrophoresis showed increased IgM levels (78.9 g/L), with a predominance of kappa chains and an elevated kappa/lambda ratio (14.71). Serum protein immunofixation confirmed IgM kappa monoclonal gammopathy. B2 macroglobulin levels were elevated (3400 ng/ml).

Patient was emergently transferred to the Hematology clinic. Bone marrow biopsy showed intertrabecular lymphoplasmacytic infiltration. Immunohistochemistry showed that the lymphoplasmacytic cells obtained from the bone marrow aspirates were positive for CD20. The allele-specific real-time polymerase chain reaction (PCR) analysis was negative for MYD88L265P mutation.

Hepatosplenomegaly was confirmed by ultrasonography and computerized tomography (CT) examination of the abdomen. The patient underwent four sequential courses of plasma exchange therapy, followed by six cycles of chemo- and immunotherapy according to the R-CHOP protocol, consisting of rituximab (Rituxan, Roche of Basel), cyclophosphamide (Ciklofosfamid Accord, Accord Healthcare Polska), doxorubicin (Doxorubicin Ebewe, Sandoz pharmaceuticals) and vincristine (Vincristine Pfizer, Pfizer) and prednisone (Pronison, Galenika AD, Belgrade). The patient showed very good partial response (VGPR) to systemic therapy, with a 90% reduction in serum IgM level from baseline (IgM 8.98 in December 2020), complete resolution of enlarged lymph nodes and splenomegaly. However, RD did not respond to plasmapheresis and chemotherapy.

We tried to reduce subretinal fluid with peribulbar injections of triamcinolone acetonide (Kenalog, Krka-farma d.o.o, Belgrade), but the treatment was not successful.

We then decided to treat RD in the right eye surgically. Because of the long-term nature of RD in the left eye, we considered the risks outweighed the benefits of surgery and decided against it. The detached retina appeared as a folded membrane with minimal movement, characteristic of long-standing detachments (Figure 2). We suspect that the RD in the left eye was exudative and related to WM, given the presence of other hyperviscosity syndrome effects, such as vitreous hemorrhage, observed during the eye examination. However, it could have other origins, including rhegmatogenous detachment, but this could not be confirmed.

After three surgeries, we successfully reattached the retina of the right eye and improved the patient's BCVA from light perception and projection to 20/50.

The first surgery consisted of phacoemulsification with implantation of the flex posterior chamber intraocular lens (PC IOL). We also performed pars plana vitrectomy, and transscleral drainage of subretinal fluid followed by silicone oil tamponade with 300-centistoke silicone. The surgery went well and the patient's BCVA in the right eye was restored from light perception and projection to 20/63 (ETDRS 60). Nevertheless, optical coherence tomography (OCT) examination one month after the surgery revealed the recurrence of exudative RD caused by subretinal fluid accumulation, as well as the epiretinal membrane (ERM) formation.

We scheduled second surgery, in order to remove subretinal fluid and ERM and reattach the retina. We performed re-vitrectomy with peeling of the ERM and internal limiting membrane (ILM). On a one-month follow-up exam, there was a recurrence of exudative RD.

We then decided to do the third and final surgery which consisted of re-vitrectomy, evacuation of the 300-centistoke

silicone oil, peripheral drainage retinotomy of 180 degrees and injection of the 5000-centistoke silicon oil. An OCT performed one month after the final surgical treatment showed a complete resorption of subretinal fluid and reattachment of retina (Figure 3). Ultra-wide field retinal imaging (UWF) showed retinal reattachment (Figure 4). Patient's BCVA in the right eye gradually improved to 20/50 (letter score 65) and she was extremely satisfied.

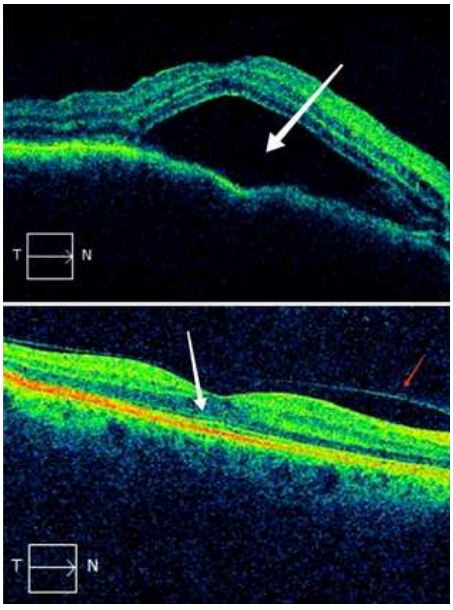

Figure 3. Horizontal OCT B-scans of macula of the right eye before the surgical procedures (above) and after the third and final surgery (below). The image above shows exudative retinal detachment due to accumulation of subretinal fluid. The image below shows retinal reattachment and epiretinal membrane pointed out by red arrow.

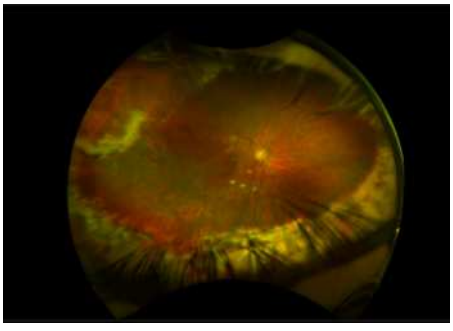

Figure 4. Ultra wild field (UWF) fundus image of the right eye at 1 month after the third surgery shows retinal reattachment.

The patient is in clinical remission and is regularly followed up by hematologists and ophthalmologists. During the last follow-up by the hematologist in March 2024, there were no signs or symptoms of active disease. A follow-up ophthalmology examination in April 2024 confirmed that the right retina was still attached and the patient's BCVA was light perception and projection and 20/70 for left and right eyes, respectively. Three years after her final surgery, the patient's BCVA in her right eye has slightly declined to 20/70, yet she remains satisfied with the result.

Written informed consent was obtained from the patient for the publication of this case report.

DISCUSSION

This case is unique for several reasons.

First of all, men (0.8/100.000) are more likely to develop WM than women (0.4/100.000)(Bhavsar Mayur, 2021). However, we present a female patient. Secondly, in this case, WM was diagnosed due to a sudden vision impairment caused by exudative RD. Initial symptoms of WM are usually nonspecific, including fatigue, malaise, weight loss, and fever(Bhavsar Mayur, 2021). Our patient did not have these symptoms and she considered herself as a healthy and fit 62-year-old prior to the vision loss. She denied having symptoms of iron-deficiency anemia such as shortness of breath, lethargy, headache, palpitations and this can be explained by the fact that the anemia developed slowly over time. According to literature, 35% of patients with WM present with hyperviscosity symptoms, as it was in this case(Hobbs et al., 2020). Our patient was MYD88 L265P negative and was therefore in the minority of patients with WM who do not have this mutation(Guerrera Maria Luisa, 2018). According to the International Prognostic Scoring System (IPSS) key risk factors prior to initiation of therapy include age > 65, hemoglobin ≤ 115 g/L, platelet count ≤ 110, serum B2 microglobulin > 3000 ng/L, and serum monoclonal protein > 70 g/L and three or more risk factors are associated with high-risk disease and a median survival of 43 months(Kyle). Our patient had 3 out of 5 risk factors and still achieved VGPR to plasmapheresis and chemotherapy and is in remission with no signs of active disease to date.

Fundoscopic abnormalities are seen in approximately 30-40% of patients with WM(Hobbs et al., 2020). Common fundoscopic abnormalities in WM include bilateral retinal vein engorgement, lipid exudates, central and branch retinal vein thrombosis, and flame-shaped hemorrhages, which typically manifest once serum viscosity rises to near 4.0 cp(Hobbs et al., 2020). A less common ocular finding is the accumulation of subretinal fluid(Hobbs et al., 2020), as seen in this patient. In addition, there are only a few cases in literature which report an exudative bilateral RD on account of WM(Kapoor et al., 2017; Lai & Chang, 2022; Leskov Ilya, 2021; Lin Albert B., 2019; Vasileiou et al., 2020). Lai and Chang reported a case of a WM which presented with a bilateral serous macular detachment in a 63-year-old male patient and was also resistant to plasmapheresis and chemotherapy, possibly due to a long-term toxicity of IgM to the retinal pigment epithelium(Lai & Chang, 2022). Lin et al. reported a case of a 56-year-old female patient with bilateral serous RD at the time of diagnosis with WM(Lin Albert B., 2019). The authors concluded that IgM levels play a crucial role in RD pathophysiology, and that reducing IgM levels rapidly and efficiently leads to improved vision(Lin Albert B., 2019). Vasileiou et al. also reported a case of a WM presenting with bilateral vision loss due to hyperviscosity syndrome and RD. An intravitreal anti-VEGF injection was administered to both eyes in combination with systemic treatment for WM, but there was no improvement in visual acuity despite a minor reduction of retinal thickness on OCT(Vasileiou et al., 2020). On the other hand, Quhill et al. reported a case of bilateral RD in WM successfully treated with systemic therapy(Quhill et al., 2009). Leskov et al. reported a case of a serous macular detachment in a patient with WM and MYD88 L265P mutation(Leskov Ilya, 2021). Macular detachment was successfully treated with ibrutinib, inhibitor of Bruton's tyrosine kinase. In our patient, however, such treatment would most likely fail since she was found to be MYD88 L265P negative(Leskov Ilya, 2021).

It is important to note that fluorescein angiography (FA) imaging, which is an important auxiliary method for diagnosing RD in WM, was not performed as part of this study(Vasileiou et al., 2020). Namely, serous macular detachments in gammopathies are silent in FA, with no leakage over the area of neurosensory detachment(Vasileiou et al., 2020). Therefore, vascular exudation does not seem to be the primary mechanism of subretinal fluid accumulation(Vasileiou et al., 2020). The current hypothesis behind the formation of these detachments is that venous congestion in the choroid and retina leads to hypoxia of the

retinal vascular endothelial cells, ischemic breakdown of the blood-RPE barrier and leakage of fluid into the subretinal space(Bhavsar Mayur, 2021; Leskov Ilya, 2021; Vasileiou et al., 2020). We presume that if it was performed, FA would support the diagnosis of and show no signs of retinal vascular leakage.

Another limitation to our study is not using anti-VEGF therapy to reduce subretinal fluid. By blocking the VEGF downstream pathway, anti-VEGF drugs reduce vascular permeability, intra- and subretinal fluid accumulation(Heloterä Hanna, 2022). Treatment of RD in WM has yielded in part conflicting results. It was successful in some cases and resulted in improvement of visual acuity(Kapoor & Wagner, 2015; Ratanam et al., 2015; Xu et al., 2015), and in others, fluid accumulation was reduced but visual acuity did not improve despite anti-VEGF injections(Besirli, 2013; Watson). The failure of anti-VEGF therapy could indicate that VEGF is not responsible for subretinal fluid accumulation in WM(Watson).

Given the range of treatment responses described in the literature, there are insufficient data for an established treatment protocol for retinopathy secondary to WM. Hyperviscosity retinopathy seems most responsive to systemic treatments that rapidly lower IgM levels and serum viscosity, such as plasmapheresis in conjunction with systemic chemotherapy to prevent paraprotein production. However, in some cases, such as the case we present, RD is unresponsive to systemic therapy and further treatment options are needed. Local treatment with intravitreal injections of steroids and anti-VEGF therapy has had mixed results. To our knowledge, this is the first reported case of surgically treated RD in WM. After 2 unsuccessful surgeries, we performed pars plana vitrectomy and drainage retinotomy with 5000-centistoke silicone oil implantation which resolved RD, improved patient's BCVA and quality of life.

CONCLUSION

This case report sheds light on surgery as a possible treatment option for persistent exudative RD secondary to Waldenstrom macroglobulinemia. We need more cases of successful surgically treated RD in order to draw conclusions that it could be considered an effective and reliable treatment option.

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REFERENCES

1. Besirli, C. G., Johnson, Mark W. (2013). Immunogammopathy maculopathy associated with Waldenström macroglobulinemia is refractory to conventional interventions for macular edema. Retinal Cases & Brief Reports, 7(4), 319-324. https://doi.org/10.1097/ICB.0b013e31828ef0dc
2. Bhavsar Mayur, C. J., Chiu Caterine. (2021). Waldenstrom Macroglobulinemia and the Eye: A case report and review. Canadian Journal of Optometry, 83(3), 29-35. https://doi.org/10.15353/cjo.v83i3.1786
3. Dammacco, R., Lisch, W., Kivela, T. T., Terpos, E., Kastritis, E., Sisto, D., Mavilio, A., Ria, R., Alessio, G., Vacca, A., & Dammacco, F. (2022). The Spectrum of Ocular Manifestations in Patients with Waldenstrom's Macroglobulinemia. Ocul Immunol Inflamm, 30(7-8), 1659-1668. https://doi.org/10.1080/09273948.2021.1933068
4. Guerrera Maria Luisa, T. N., Xu Lian, Yang Guang, Demos Maria. (2018). MYD88 mutated and wild-type Waldenström's Macroglobulinemia: characterization of chromosome 6q gene losses and their mutual exclusivity with mutations in CXCR4. Haematologica, 103(9), e408-e411. https://doi.org/10.3324/haematol.2018.190181
5. Heloterä Hanna, K. K. (2022). A Linkage between Angiogenesis and Inflammation in Neovascular Age-Related Macular Degeneration. Cells, 11(21), 3453. https://doi.org/10.3390/cells11213453
6. Hobbs, M., Fonder, A., & Hwa, Y. L. (2020). Waldenstrom Macroglobulinemia: Clinical Presentation, Diagnosis, and Management. J Adv Pract Oncol, 11(4), 381-389. https://doi.org/10.6004/jadpro.2020.11.4.5
7. Kapoor, K. G., & Wagner, M. S. (2015). Bevacizumab in macular serous detachments associated with Waldenstrom's macroglobulinemia. Ophthalmic Surg Lasers Imaging Retina, 46(1), 95-97. https://doi.org/10.3928/23258160-20150101-18
8. Kapoor, P., Ansell, S. M., Fonseca, R., Chanan-Khan, A., Kyle, R. A., Kumar, S. K., Mikhael, J. R., Witzig, T. E., Mauermann, M., Dispenzieri, A., Ailawadhi, S., Stewart, A. K., Lacy, M. Q., Thompson, C. A., Buadi, F. K., Dingli, D., Morice, W. G., Go, R. S., Jevremovic, D., . . . Reeder, C. B. (2017). Diagnosis and Management of Waldenstrom Macroglobulinemia: Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) Guidelines 2016. JAMA Oncol, 3(9), 1257-1265. https://doi.org/10.1001/jamaoncol.2016.5763
9. Kyle, R. A., Larson Dirk R., McPhail Ellen D, Therneau Terry M., Dispenzieri Angela. Fifty-Year Incidence of Waldenström Macroglobulinemia in Olmsted County, Minnesota, From 1961 Through 2010: A Population-Based Study With Complete Case Capture and Hematopathologic Review. Mayo Clin Proc, 93(6), 739-746. https://doi.org/10.1016/j.mayocp.2018.02.011
10. Lai, C. C., & Chang, C. H. (2022). Hyperviscosity-related retinopathy and serous macular detachment in Waldenstrom's macroglobulinemia: A mortal case in 5 years. Eur J Ophthalmol, 32(4), NP109-NP114. https://doi.org/10.1177/11206721211002066
11. Leskov Ilya, K. A., Gill Manjot K. (2021). SEROUS MACULAR DETACHMENT ASSOCIATED WITH WALDENSTROM MACROGLOBULINEMIA MANAGED WITH IBRUTINIB: A CASE REPORT AND NEW INSIGHTS INTO PATHOGENESIS. Retinal Cases & Brief Reports, 15(4), 490-494. https://doi.org/10.1097/ICB.0000000000000837
12. Lin Albert B., S. A. T., Jampol Lee M. . (2019). UNUSUAL SEROUS RETINAL DETACHMENT IN A PATIENT WITH WALDENSTROM MACROGLOBULINEMIA: A CASE REPORT. Retinal Cases & Brief Reports, 13(1), 1-4. https://doi.org/10.1097/ICB.0000000000000540
13. Quhill, F., Khan, I., & Rashid, A. (2009). Bilateral serous macular detachments in Waldenstrom's macroglobulinaemia. Postgrad Med J, 85(1005), 382. https://doi.org/10.1136/pgmj.2008.071886
14. Ratanam, M., Ngim, Y. S., Khalidin, N., & Subrayan, V. (2015). Intravitreal bevacizumab: a viable treatment for bilateral central retinal vein occlusion with serous macular detachment secondary to Waldenstrom macroglobulinaemia. Br J Haematol, 170(3), 431-434. https://doi.org/10.1111/bjh.13307
15. Vasileiou, V., Kotoula, M., Tsironi, E., Androudi, S., & Papageorgiou, E. (2020). Bilateral vision loss in Waldenstrom's macroglobulinemia. Ann Hematol, 99(1), 193-194. https://doi.org/10.1007/s00277-019-03879-5
16. Watson, J. A., Olson, Daniel J., Zhang, Alice Jang Hyperviscosity Retinopathy Due to Waldenström Macroglobulinemia: A Case Report and Literature Review. Journal of VitreoRetinal Diseases, 5(6), 520-524. https://doi.org/10.1177/2474126420987142
17. Xu, L. T., Courtney, R. J., & Ehlers, J. P. (2015). Bevacizumab therapy and multimodal ultrawide-field imaging in immunogammopathy maculopathy secondary to Waldenstrom's macroglobulinemia. Ophthalmic Surg Lasers Imaging Retina, 46(2), 262-265. https://doi.org/10.3928/23258160-20150213-06