



Extranodal marginal zone lymphoma associated with Vogt-Koyanagi-Harada disease

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Introduction

Vogt-Koyanagi-Harada (VKH) disease is an autoimmune syndrome characterized by progressive multisystem inflammation due to immune targeting of melanocytic antigens. Early-stage VKH presents with prodromal phase symptoms including fever, meningeal signs, and audio-vestibular manifestations preceding ocular involvement. Inflammation of the choroid and adjacent structures may contribute to early stages of VKH disease such as retinal pigmented epithelium (RPE) dysfunction with subretinal fluid accumulation and subsequent exudative retinal detachment. Extraocular manifestations include tinnitus, alopecia, poliosis, and vitiligo. If untreated, permanent vision loss may develop from complications of chronic inflammation and associated sequelae of subretinal fibrosis and choroidal neovascularization.¹

Although the precise pathophysiology of VKH disease remains under investigation, autoimmune T cell targeting of host melanocytic antigens has been described.² The relationship between autoimmune disease syndromes and neoplasm is of particular interest in our case. Lymphoma in association with VKH disease has rarely been reported, but lymphoproliferative disease or diffuse B-cell lymphoma with concurrent VKH has been characterized.⁸ Moreover, lymphoma and leukemia may mimic VKH disease, emphasizing the importance

of recognizing similarities in clinical manifestations and the potential for lymphoproliferative disease in this context.

Herein, we report a patient who developed findings consistent with complete VKH disease who later developed extranodal marginal zone lymphoma (EMZL) of mucosa-associated lymphoid tissue in the context of immunosuppressive therapy. The clinical findings, pathology features, multidisciplinary management, and potential relationships between the autoimmune syndrome and lymphoma are described.

Case Report

A 61-year-old male of Hispanic descent presented to our uveitis service for the evaluation of exudative retinal detachment in the left eye secondary to suspected VKH disease. His past medical history was significant for tinnitus, poliosis, alopecia, vitiligo, and chronic headaches (Figure 1). His ocular history was significant for bilateral asymmetric panuveitis, affecting the left eye more than the right eye. The patient had a prior episode of acute angle closure glaucoma in the left eye at age 58. Following this episode, he was treated with laser peripheral iridotomy and Ahmed valve glaucoma drainage device implantation in the left eye. Poliosis and alopecia were also observed around the time of glaucoma onset. Brain magnetic resonance imaging (MRI) from the referring provider showed bilateral peripheral globe enhancement greater in the left than right with a small fluid component in the left globe posteriorly. A review of systems was also notable for chronic headache, episodic neck pain, tinnitus and dizziness. The referring ophthalmologist noted subretinal fluid in the right eye and a macula-involving cyst with inferior retinal detachment in the left eye 6 weeks prior to presentation.

At presentation, his ocular medications consisted of brimonidine-timolol and twice daily prednisolone in the left eye. On examination, best corrected visual acuities (BCVA) were 20/20 in the right eye and light perception (LP) in the left eye. Intraocular pressure (IOP) was 15 mmHg in the right eye and 11 mmHg in the left eye. Slit lamp examination showed rare anterior chamber (AC) cells in the right eye and trace AC cells, 2+ vitreous cells, and peripheral anterior synechiae in the left eye. Fundusoscopic examination revealed mild pigmentary changes in the right eye and choroidal effusions, large macular cyst, inferior exudative retinal detachment and optic nerve pallor in the left eye (Figures 2A, C). Optical coherence tomography (OCT) demonstrated subretinal fluid with mild serous pigment epithelium detachment (PED) in the right eye and severely thickened choroid with large intraretinal cyst in the left eye (Figures 2B, D). Fluorescein angiography (FA) revealed small multifocal punctate areas of leakage in the macula in the right eye and staining in areas of choroidal effusion and pigmentary change without vasculitis in the left eye.

Uveitis work-up including syphilis serology, toxoplasma serology, erythrocyte sedimentation rate, and angiotensin-converting enzyme were unremarkable; however, tuberculosis (TB) interferon-gamma release assay was positive. Given the patient's history and exam findings, the patient was diagnosed with complete VKH based on the revised VKH diagnostic criteria.³ He was started on topical prednisolone acetate 1% in the left eye twice daily and oral prednisone at 60 mg/day for two weeks. The patient was also diagnosed with latent TB, prompting a 4-month course of rifampin. The rheumatology and infectious disease teams elected to defer systemic immunosuppression therapy until anti-TB therapy was completed.

The patient was lost to follow-up until 5 months later. BCVA at this time was 20/25 in the right eye and no light perception (NLP) in the left eye. The IOP was 12 mmHg in the right eye and 8 mmHg in the left eye. The subretinal fluid resolved in the right eye but remained persistent in the left eye. At this time, he continued topical prednisolone acetate 1% in the left eye twice daily.

The patient was lost to follow-up and subsequently presented 9 months later with complaints of mild left eye irritation. He remained on topical corticosteroids and otherwise denied other ocular complaints. The VA and exam were unchanged from previous visit and right eye remained stable. The topical prednisolone acetate 1% was increased to four times daily with a weekly taper. Mycophenolate mofetil 500 mg twice daily was also initiated at this time.

Six weeks later, the patient presented with significant pain in the left eye. BCVA was NLP in the left eye with an IOP of 71 mmHg. Subretinal fluid remained. A B-scan ultrasound showed a detached retina with underlying choroidal thickening and extrascleral extension with low internal reflectivity (Figure 3). Maximum medical therapy including topical dexamethasone, atropine, dorzolamide-timolol, and brimonidine-timolol was started to reduce the IOP. Despite therapy, IOP remained persistently over 70 mmHg in the left eye. At this time, glaucoma and oculoplastic services were consulted. Mycophenolate mofetil was increased to 1000 mg twice daily. Given significant ocular pain and vision loss, the patient opted for enucleation of the left eye. Pre-operative computed tomography (CT) of the orbits revealed diffuse thickening of the left globe with a 1.8 cm posterior mass-like lesion. Six weeks after onset of ocular hypertension, enucleation was performed. Grossly, at the time of enucleation surgery, there was nodular thickening noted along the posterior globe.

Pathologic examination revealed a nodular subretinal lesion abutting the optic nerve and ciliary body. Microscopically, there was proliferation of small lymphoid cells with moderate amount of clear cytoplasm and few scattered large cells involving the entire choroid, optic nerve and infiltrating within the eye. Focally, germinal centers were also observed. Immunohistochemistry revealed lymphoid cells positive for CD20, PAX5, CD43, MNDA, and BCL-2 with partial and dim CD10 positivity and without co-expression of BCL-6 or CD5. *In situ* hybridization showed these B-cells to be lambda-restricted, consistent with small, mature lymphoma of B-cell origin. The germinal centers were positive for CD10 and BCL-6, and BCL-2 negative (Figure 4). These histological and phenotypic findings were consistent with a diagnosis of EMZL. Fluorescence *in situ* hybridization (FISH) studies detected trisomy 18 (69% of interphase cells).

The patient was referred to hematology/oncology and radiation oncology. Mycophenolate mofetil was continued for 3 months following enucleation. A whole-body positron emission tomography (PET) scan was negative for additional lesions, and the patient underwent local radiation therapy to the left orbit. Radiation therapy was initiated 5 months post-enucleation. Following 12 treatments over 16 days, no evidence of recurrent lesion was observed at 10 months post-radiation. Three years later, BCVA has remained stable at 20/20 in the right eye with resolution of subretinal fluid. Ophthalmic and systemic surveillance remain ongoing with no recurrences of uveitis or lymphoma to date.

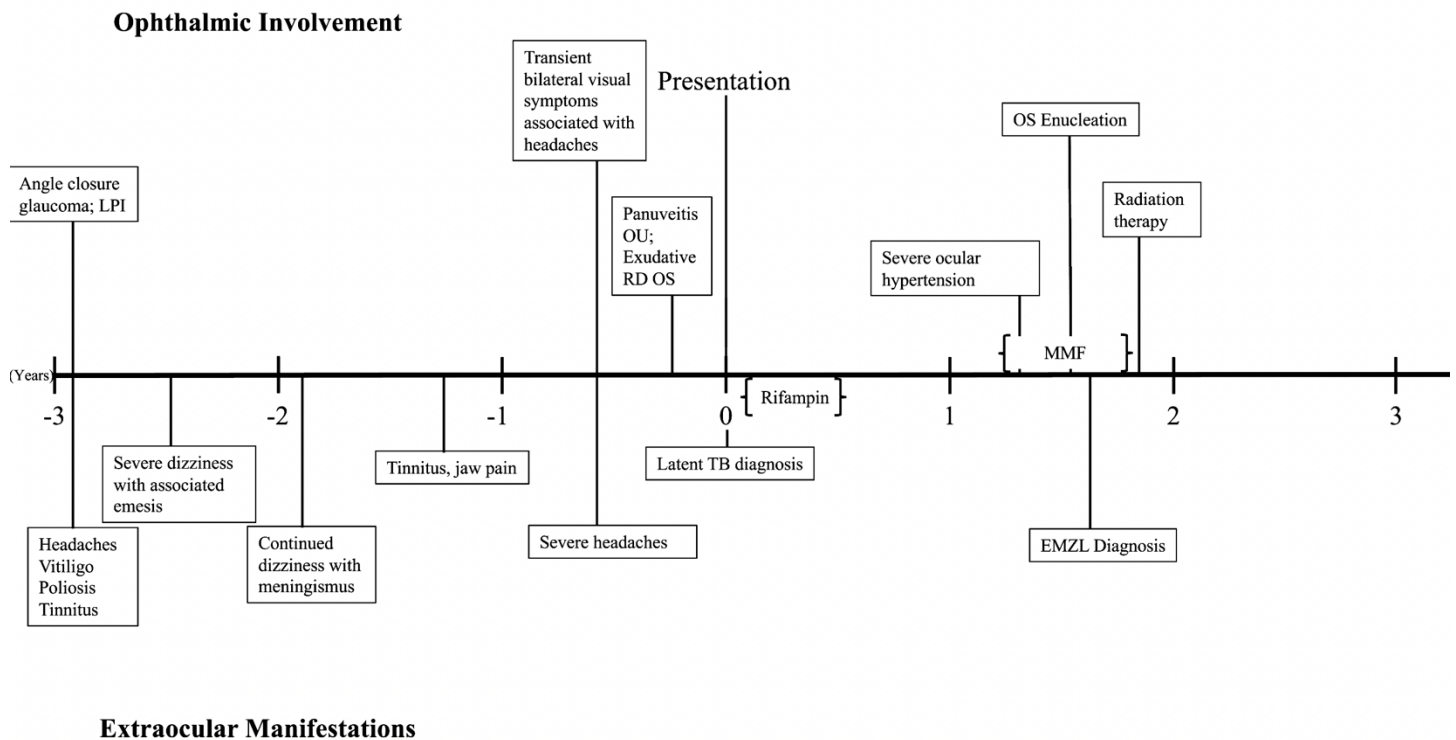


Figure 1. Timeline of clinical course, disease management, and major interventions. The X axis is represented in years, where year 0 corresponds to clinical presentation. A negative year value reflects a time point prior to presentation, and positive years reference events after presentation. Duration of relevant systemic medications has been added in brackets. Abbreviations: LPI, Laser Peripheral Iridotomy; OU, both eyes; RD, retinal detachment; OS, left eye; mo, month; F/U, follow-up; MMF, mycophenolate mofetil; EMZL, extranodal marginal zone lymphoma.

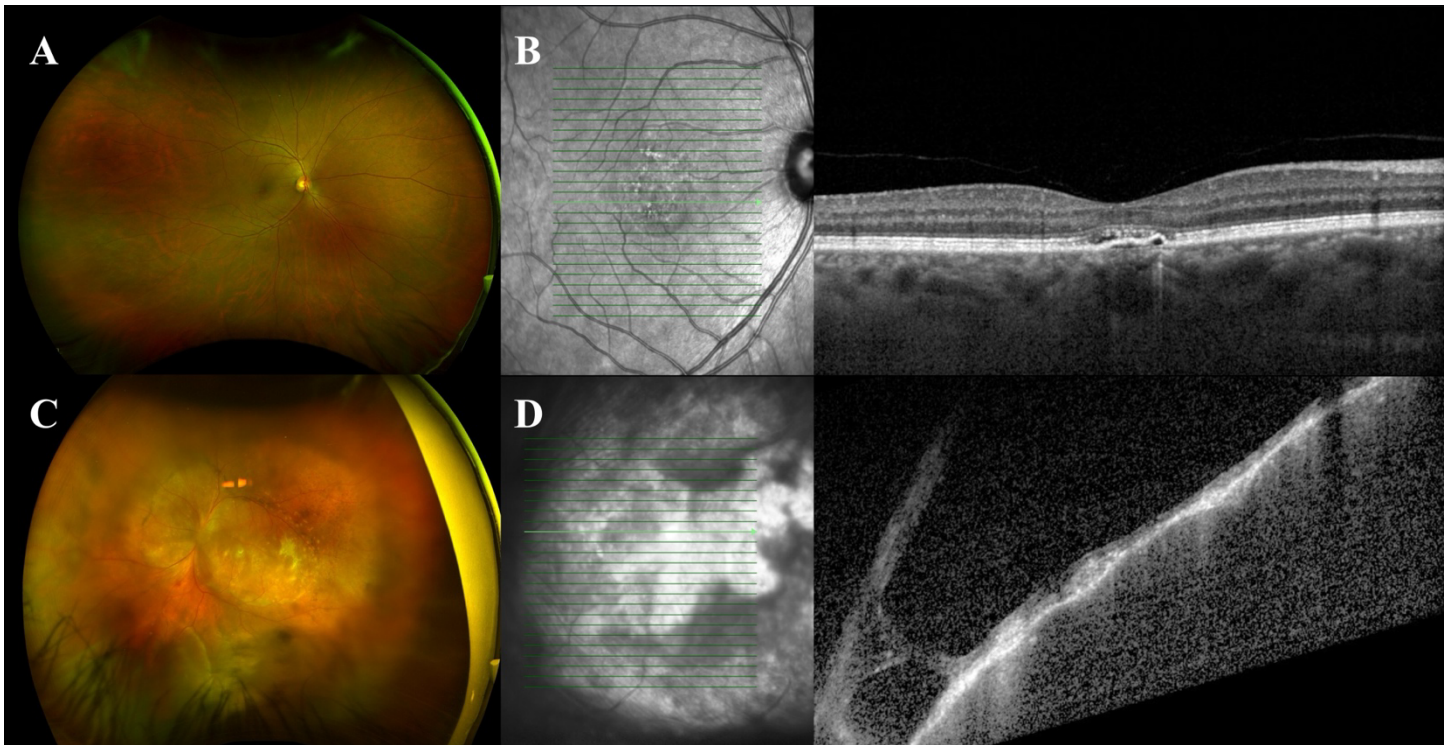


Figure 2. Ultra-widefield fundus photography and optical coherence tomography (OCT) images of both eyes. A. Fundus photograph of the right eye shows mild pigmentary changes in the central macula. B. OCT of the right eye reveals a small pigment epithelium detachment and mild subretinal fluid. C. Fundus photograph of the left eye demonstrates choroidal effusions, a large macular cyst, and underlying retinal pigmented epithelial change. D. OCT of the left eye shows thickened choroid, subretinal septate, and subretinal fluid with thin overlying retina.

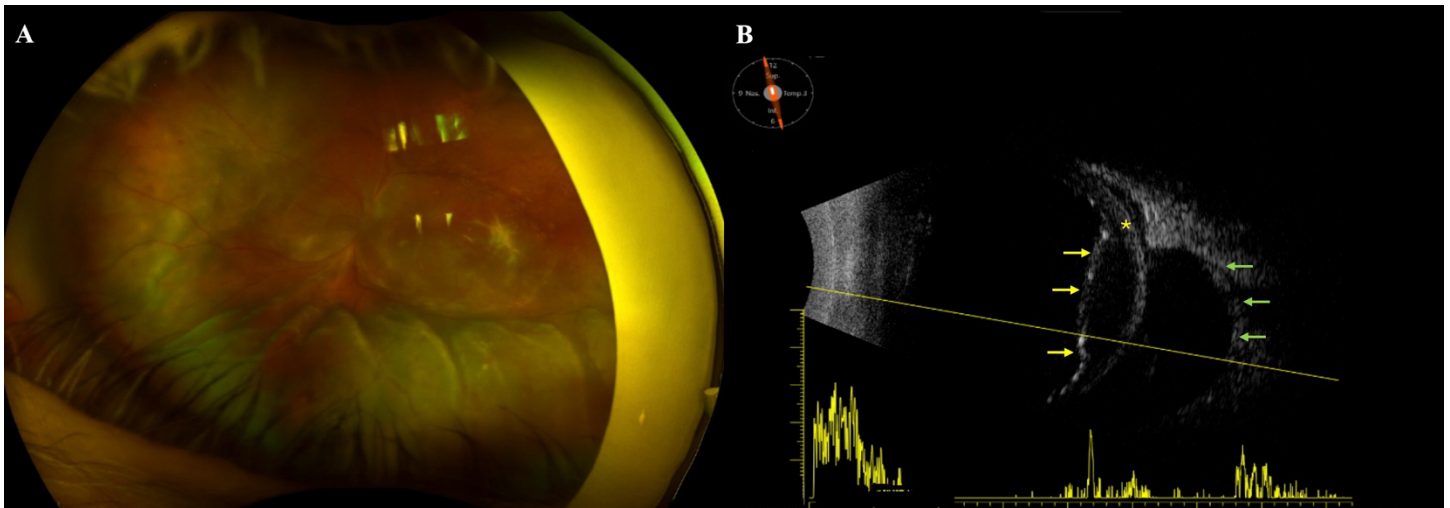


Figure 3. A. Ultra-widefield fundus photograph of the left eye demonstrates an extensive, inferior exudative retinal detachment. B. B-scan ocular ultrasound of left eye shows subretinal fluid consistent with exudative retinal detachment (yellow arrows). Choroidal thickening is observed (*) along with extrascleral extension (green arrows) with low internal reflectivity.

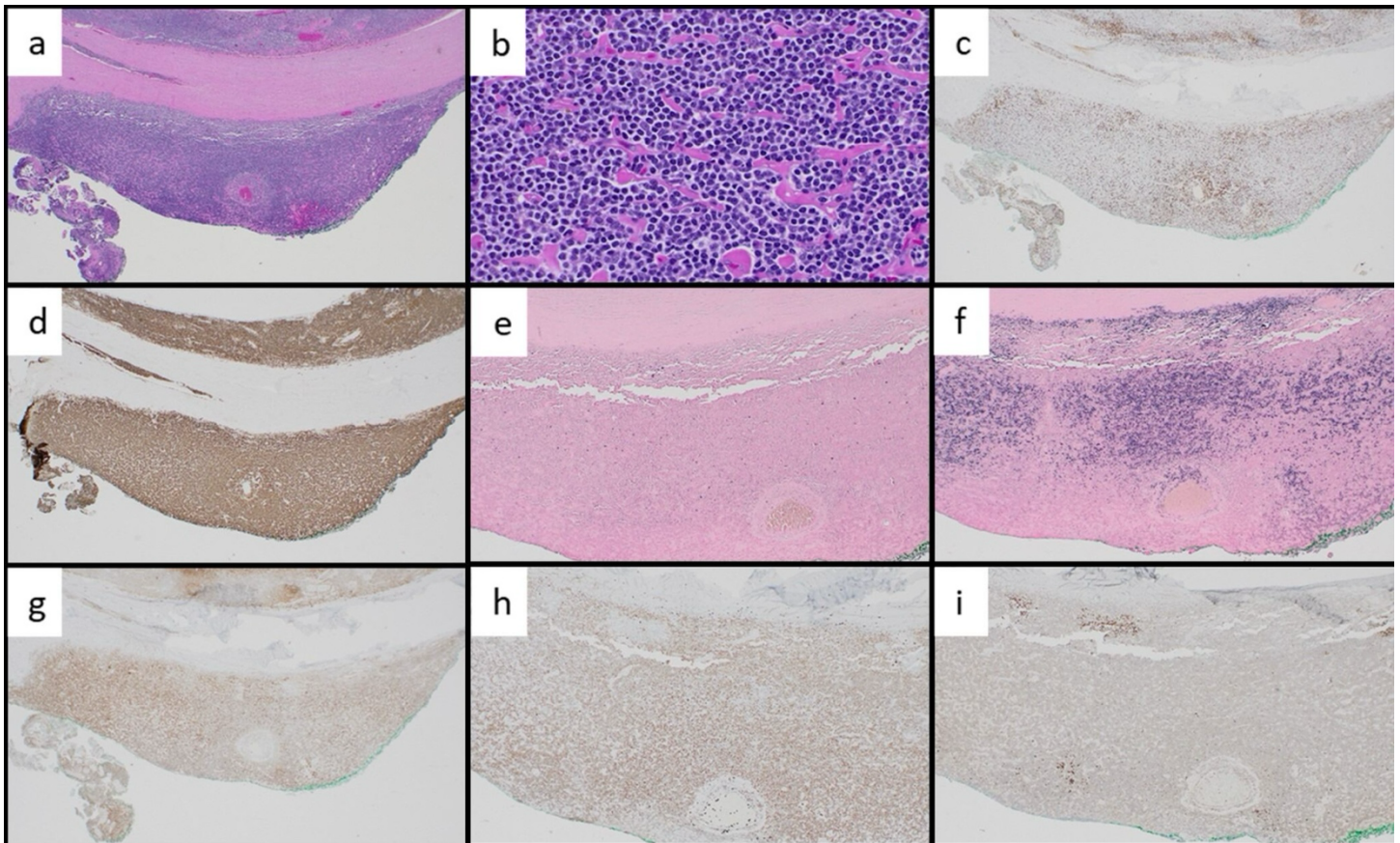


Figure 4. Histopathologic and immunophenotypic characterization of extranodal marginal zone lymphoma. A. Hematoxylin and Eosin (H&E) stain 2x magnification and B. H&E stain 40x magnification show a diffuse proliferation of small lymphoid cells with abundant clear cytoplasm. C. CD3 positive cells indicate presence of scattered small T cells. D. CD20 positive cells demonstrate the majority of lymphocytes are B cells. E. Kappa *in situ* hybridization (ISH) and F. Lambda ISH show light chain restriction with predominant expression of lambda supporting clonality. G. CD10 positive cells and H. Myeloid nuclear differentiation shows positive staining in neoplastic B cells. I. BCL6 positive staining supports presence of neoplastic cells.

Discussion

In this report, we describe a patient with clinical findings that met criteria for complete VKH disease including the combination of panuveitis with exudative retinal detachment as well as dermatologic and neurologic findings. The patient developed a blind, painful eye and underwent enucleation with a globe specimen that showed EMZL. The inflammatory flares were managed with topical corticosteroids and 500-1000 mg of mycophenolate mofetil twice daily for 6 months. Challenges in management included inconsistent follow-up, chronic inflammation, and laboratory findings consistent with prior TB exposure. Ultimately, the constellation of findings led to a diagnosis of EMZL, prompting definitive oncology treatment.

The patient initially experienced classic prodromal symptoms of VKH including headache, dizziness, and meningeal signs at least 3 years prior to his presentation to our clinic. We hypothesize that chronic antigen stimulation and local inflammation may have been associated with disease evolution. Although the inflammation was significantly greater in the left eye, the systemic features and local signs of intraocular

inflammation in the right eye was consistent with a diagnosis of VKH. Asymmetric disease severity, while atypical, has been reported.⁴ Given the final diagnosis of lymphoma, whether the patient may have had an underlying neoplasm masquerading as VKH also remains a possibility.

Lymphoma may masquerade as intraocular inflammation, potentially presenting with AC cells, vitreous cell and haze, and choroidal thickening.⁵ While this was considered in the initial differential diagnosis, several clinical and imaging features led us to suspect lymphoma developed in the setting of VKH disease rather than representing a lymphoma-associated masquerading syndrome at presentation although this remains a possibility. A history of meningismus, audio-vestibular symptoms, and cutaneous depigmentation are characteristic of VKH disease and cannot be explained by ocular lymphoma. Additionally, bilateral involvement, evidence of chronic RPE changes, and brain imaging without presence of mass lesion from referring clinician decreased our suspicion for an underlying neoplasm at presentation.

An association between VKH and malignant lymphoma has been rarely described.⁶ Hashida et al. reported an elevated serum concentration of tumor marker sIL-2R and speculated that tumor cells from recurrent malignant lymphoma resulted in clinical features characteristic of VKH.⁶ Recently, additional cases of systemic lymphoma presenting with retinal findings masquerading as VKH disease have also been reported.^{7,8} Another report described a lymphoproliferative disorder in a patient with VKH disease undergoing mycophenolate mofetil therapy.⁹ Systemic immunosuppression is recommended in the management of VKH disease. Prior reports have described the association of immunosuppression (i.e., thiopurines and mycophenolate mofetil) with lymphoproliferations and lymphoma and thus require vigilance in monitoring.^{10,11} The inconsistent follow-up and the need to defer mycophenolate initially owing to the positive TB test reduce the likelihood of a direct causal relationship between mycophenolate mofetil and lymphoma development, although whether it was a contributing factor remains a possibility.

The pathologic findings were distinct from prior reports in the literature. Extranodal marginal zone lymphomas typically consist of small CD20+/CD5-/CD10- lymphocytes with architectural disruption, while the EMZL in our patient was CD10+. CD10+ expression is unusual in EMZL and is observed in follicular lymphoma. It is possible that these cells represent non-neoplastic germinal center B cells rather than tumor cell clones. EMZL is known to colonize pre-existing reactive follicles.¹² We hypothesize stimulation of the follicle secondary to VKH-associated inflammation contributed to EMZL formation. Therefore, the presence of CD10+ cells may reflect residual B cells from the previously non-neoplastic, active follicle. EMZL is postulated to occur secondary to recurrent antigen stimulation in the context of infection, autoimmune disease, or other chronic inflammatory conditions.^{13,14} In our patient, chronic melanocytic antigen inflammatory stimuli may have precipitated a B- and T- cell proliferative response that resulted in the development of lymphoma in the context of VKH associated panuveitis. Although distinct molecular pathways that relate autoimmunity with non-Hodgkin's lymphoma remain under investigation, chronic antigen stimulation, inflammation, and B-cell activation are factors that may contribute to malignant cell clones.¹⁵

Conclusion

This case highlights the potential relationship between panuveitis associated with VKH and EMZL. Judicious monitoring is recommended for patients with VKH disease, and consideration should be given to the possibility of masquerade syndromes in the management of patients with VKH who fail to respond to immunosuppressive therapy.

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Statement of Ethics

This case report adheres to patient confidentiality and ethical principles in accordance with the guidelines of the Declaration of Helsinki and relevant local regulations.

Patient Consent and Privacy

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors declare no conflicts of interest related to this topic.

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