Case Reports in Ophthalmology

Case Rep Ophthalmol 2024;15:607–613
DOI: 10.1159/000540051
Received: February 12, 2024
Accepted: June 23, 2024
Published online: August 8, 2024

Case Report

Primary Vitreoretinal Lymphoma Presenting Solely with Asymptomatic Peripheral Drusenoid Lesions

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Keywords

Intraocular lymphoma · B-cell lymphoma · Radiation therapy · Drusenoid lesions · Primary vitreoretinal lymphoma

Abstract

Introduction: Primary vitreoretinal lymphoma (PVRL) is a rare malignant tumor that typically involves the retina, vitreous, or optic nerve head. PVRL often occurs concurrently with central nervous system lymphoma. Here, we present the first report of a patient with biopsy-confirmed PVRL presenting solely with asymptomatic peripheral drusenoid lesions. ***Case Presentation:*** A woman in her 70s presented with new elevated amelanotic yellow lesions with overlying pigment in both of her eyes not previously seen prior to cataract surgery. Over the next 4 months, there was waxing and waning of lesions which resolved and first appeared in the right eye and then the left. A diagnostic vitrectomy of the left eye revealed B-cell lymphoma. The patient elected for initial treatment with radiation therapy of both orbits. A new lesion was identified in her right eye nearly 18 months after starting maintenance therapy with ibrutinib, following which systemic chemotherapy with methotrexate was initiated. ***Conclusion:*** Elevated clinical suspicion for a malignant process is needed for patients with progressive new retinal lesions in older age. Local radiation therapy to the orbits alone may not be sufficient to prevent progression despite initial presentation showing confinement of disease to the intraocular space.

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DOI: 10.1159/000540051

Introduction

First described in 1951, primary vitreoretinal lymphoma (PVRL) is a rare high-grade malignant tumor typically involving the retina, vitreous, or optic nerve head. PVRL constitutes less than 1% of non-Hodgkin lymphoma, with 95% representing diffuse large B-cell lymphomas [1, 2]. The epidemiology of PVRL is not well described; however, the incidence of primary central nervous system lymphoma (PCNSL) among immunocompetent patients has been reported as 0.046 per 100,000 person-years and 4–5 per 1,000 person-years in patients with acquired immune deficiency syndrome [3, 4]. Prior studies have found that CNS involvement will present in up to 80–90% of patients with PVRL, while bilateral ocular involvement will present in 15–25% of those with PCNSL [4, 5]. PVRL patients were typically elderly and female with B-cell type dominated binocular malignancy, according to a recent meta-analysis [6, 7]. PVRL is frequently misdiagnosed at its onset, as it may present with nonspecific symptoms that mimic uveitis [8, 9]. Delays in diagnosis of PVRL may lead to missed opportunities for comprehensive care and effective management, underscoring the importance of early detection [10, 11]. Timely diagnosis and treatment could lead to improved patient outcomes and increased survival.

Case Report

We report a single case of a woman in her 70s of Eastern European descent who presented with new supertemporal elevated amelanotic yellow lesions with overlying pigment in both of her eyes. She had a history of hypertension, dyslipidemia, diabetes, and previous transient ischemic attacks. On initial examination, her visual acuity was 20/25 bilaterally, and her anterior ocular exam was unremarkable. On fundoscopy, yellow lesions in the supertemporal quadrant of about four optic disc diameters in size were noted in both eyes (Fig. 1a, b). This presentation was consistent with bilateral peripheral drusen, a benign age-related finding. However, given that her referring ophthalmologist noted that these lesions were not present prior to cataract surgery performed earlier that year, a routine 3-month follow-up was scheduled. On follow-up examination, there was resolution of previously seen lesions in both eyes, but there were new lesions in the superotemporal macula of the right eye (Fig. 1c, d). The arteriovenous phase of intravenous fluorescein angiogram showed staining of the amelanotic yellow drusenoid lesions and widespread punctate leakage (Fig. 2a, b). Fluorescein angiogram demonstrated that the optic nerves were quiet and there was no central macular leakage in either eye (Fig. 2a, b). Autofluorescence images showed hypofluorescence of the drusenoid lesions (Fig. 2c, d), while optical coherence tomography through the macula and central fovea showed few typical subretinal drusen in the right eye (Fig. 2e) and intraretinal fluid/cystoid macular edema in the left eye (Fig. 2f). Follow-up 1 month later showed resolution of lesions in the right eye (Fig. 1e), and appearance of new drusenoid lesions in the inferior left retina (Fig. 1f). Workup for inflammatory (including serological markers, HLA typing, chest X-ray) and infectious causes (including tuberculosis, Borrelia, toxoplasmosis, Bartonella, syphilis) was negative. An MRI brain with Gadolinium also showed no intracranial abnormality. However, given the waxing and waning of her retinal findings, we had clinical suspicion for an atypical malignancy presentation. A diagnostic vitrectomy of the left eye revealed B-cell lymphoma (CD19 and CD20 positive) and she was referred urgently to our oncology colleagues. Unfortunately, she developed a macula-off retinal detachment shortly thereafter with hand motions and visual acuity in the left eye, which we repaired via pars plana vitrectomy.

Her oncological assessment included a lumbar puncture, bone marrow biopsy, and chemotherapy (CT) staging and this did not reveal any systemic evidence of lymphoma. As

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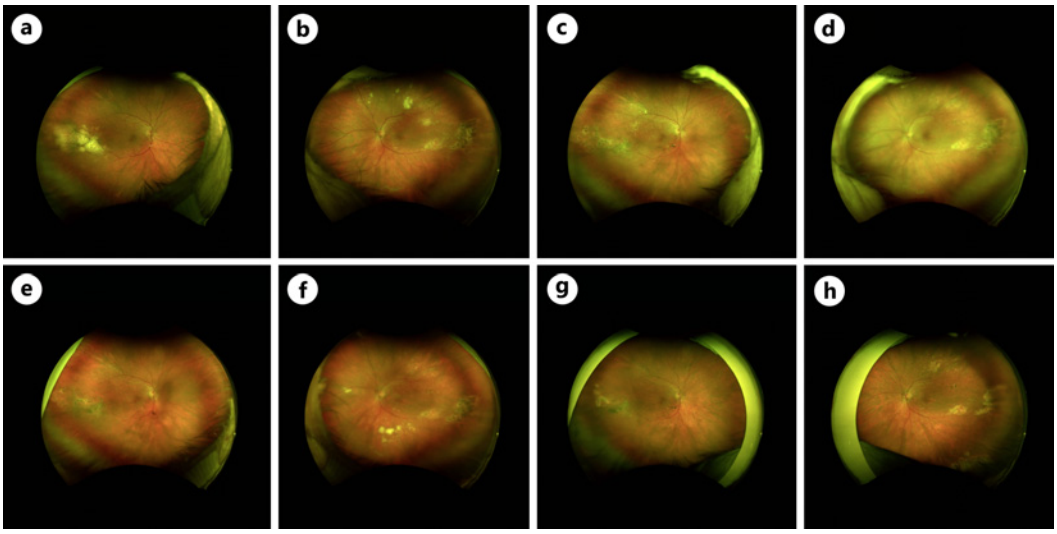

Fig. 1. Widefield fundus photographs show amelanotic yellow drusenoid lesions temporal to the macula of the right eye (**a**) and in the superotemporal quadrant of the left retina (**b**). Three months later, there is the resolution of previously seen lesions in both eyes (**c**), but there are new lesions in the superotemporal macula of the right eye (**d**). One month later, there is resolution of lesions in the right eye (**e**) and the appearance of new drusenoid lesions in the inferior left retina (**f**). Eighteen months after the initial visit and after bilateral RT, there is resolution of all visible lesions in both eyes (**g**, **h**).

such, she was given a diagnosis of PVRL. Given the high risk of eventual CNS involvement and uncommon presentation, we obtained consultations both from medical and radiation oncology specialists. Treatment options included intravitreal (IV) injections of methotrexate and rituximab with the option of including systemic CT, a treatment plan of four cycles of systemic rituximab and methotrexate in addition to radiation therapy (RT), systemic CT and orbital radiation to both eyes, or a 2-week course of RT to both eyes followed by surveillance. Our patient opted to proceed with RT only to both eyes (30 Gy in 10 fractions) and tolerated this well. She wished to defer CT as she wished to avoid becoming immunocompromised during the COVID-19 pandemic. As such, the patient elected to continue with MRI surveillance every 3 months. Unfortunately, 6 months later, an MRI revealed evolving brain parenchymal changes in the left posterior central gyrus concerning increasing tumor burden. A repeat lumbar puncture and CT staging once again revealed no signs of systemic lymphoma. At this time, she wished to proceed with four cycles of systemic therapy (methotrexate and rituximab), with an additional two cycles if treatment responsive. A total of eight cycles of CT and ten sessions of RT were completed, and maintenance therapy with ibrutinib was initiated in January 2021. At this time, she had resolution of all previously seen lesions in both eyes (Fig. 1g, h). Three months later, she developed increased ocular pressure (52 mm Hg) within her left eye that was believed to be due to impaired aqueous drainage secondary to her radiation treatment that was managed with selective laser trabeculoplasty.

She was otherwise stable from an oncologic perspective until June 2022, when a B-scan of the right eye detected a new ocular lesion. A PPV of the right eye was positive for B-cell lymphoma. Given that progression occurred despite localized RT to both eyes, systemic CT with methotrexate was initiated in August 2022.

The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000540051).

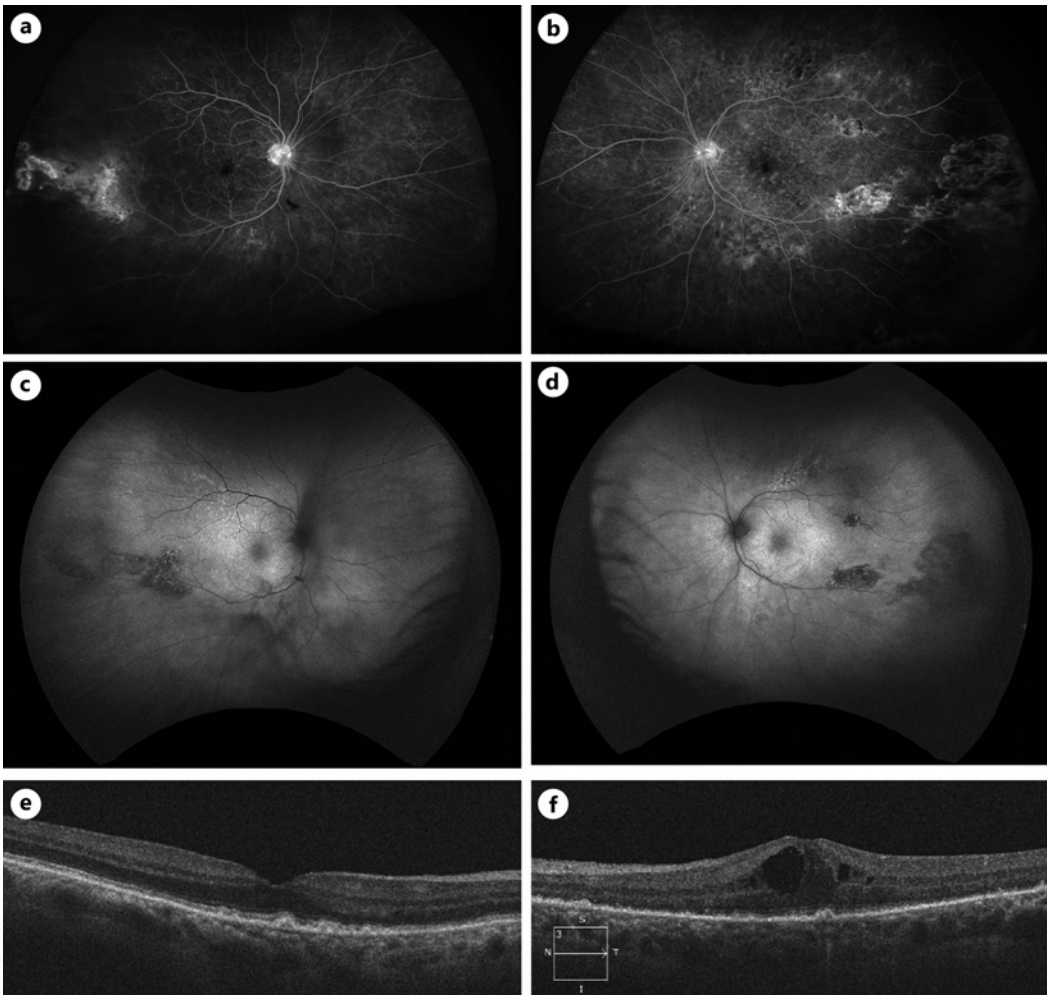

Fig. 2. Adjunctive imaging taken at the 3-month visit following the initial presentation. Arteriovenous phase of intravenous fluorescein angiogram of the right eye (**a**) and left eye (**b**), showing staining of the amelanotic yellow drusenoid lesions and widespread punctate leakage. Fluorescein angiogram demonstrated that the optic nerves were quiet and there was no central macular leakage in either eye. Autofluorescence images of the right eye (**c**) and left eye (**d**) showing hypofluorescence of the drusenoid lesions. Optical coherence tomography through the macula and central fovea showing few typical subretinal drusen in the right eye (**e**) and intraretinal fluid/cystoid macular edema in the left eye (**f**).

Discussion

Our patient presented with the sole finding of new bilateral peripheral drusen identified on a routine dilated fundus exam after cataract surgery. Although these lesions appeared drusenoid clinically, we note that it is possible they were located at the level of the choroid. Few other cases have been identified where patients presented with peripheral lesions alone with preserved visual acuity [12–14]. In one report, a man in his late 60s was initially presumed to have dry AMD, and a diagnosis of intraocular lymphoma was only made after a brain biopsy [15]. A key finding was the waxing and waning course of the lesions that raised clinical suspicion for malignancy, as described in other case reports [15–17]. Another case series identified vitelliform maculopathy as a preceding lesion of three PVRL cases [18]. Interestingly, in all cases, the lesions were transient and preceded the diagnosis of PVRL.

Drusenoid lesions in the macular area have been identified on optical coherence tomography 10 months prior to PVRL diagnosis, although these may be easily interpreted as normal aging processes or early dry AMD [19]. In our case, dilated fundus examinations both before and after cataract surgery were essential to identifying the new lesions, and in turn diagnosing PVRL, highlighting the importance of continuity of care.

Previously believed to be a form of PCNSL, PVRL is now suspected to arise from an infiltration of malignant lymphocytes from systemic circulation to the eye and brain [20]. One hypothesis postulates that permissive retinal endothelial receptors in conjunction with a lack of immune surveillance may allow preferential entry of malignant cells to the retina rather than the choroid [20]. Additionally, Bruch's membrane may serve as a barrier to further spread, confining proliferation to the uveal tract [20]. The prognosis of PVRL remains poor, largely due to the aggressive nature of the malignancy in addition to difficulties surrounding timely diagnosis [21]. Often mistaken as idiopathic uveitis, the differential diagnosis includes additional inflammatory and infectious etiologies including viral retinitis, tuberculosis, syphilis, sarcoidosis, Behçet's disease and Langerhans Cell Histiocytosis [22]. Delayed and misdiagnosed rates have been reported as high as 85% and 64%, with an average time of 1 year between symptom onset to diagnosis [2, 7, 21]. Prompt recognition is vital to ensure appropriate referral and treatment, prior to the development of CNS involvement. The most frequently described presenting symptoms include blurring of vision, decreased visual acuity, and new floaters, while common signs include vitreous inflammatory opacity, hyper-reflective foci in the posterior vitreous, yellow subretinal deposits ("leopard spotting"), and fine keratic precipitates [7]. Diagnosis of PVRL often requires a sample of malignant tissue obtained via vitrectomy [21].

Standardized treatment of isolated PVRL in the absence of PCNSL remains disputed, with focused ocular therapy and close follow-up argued by some [23]. Given that CNS lymphoma is the principal cause of death in PVRL, current guidelines recommend systemic high-dose methotrexate CT as this appears to improve overall survival [24, 25]. Due to high rates of relapse with systemic therapy alone, CT may be followed by consolidation RT for eradication of microscopic disease [24, 25]. Bilateral orbital RT or whole brain RT should be considered, although the risks of neurocognitive toxicity need to be weighed on an individual basis [24]. A recent meta-analysis by Zhao et al. [7] indicated that systemic CT with IV therapy should be used as a first-line treatment in PVRL. This study found that treatment with systemic and IV therapy conferred the lowest rates of CNS involvement and death rate, with the greatest 2- and 5-year survival rates [7]. Additionally, the combination of RT could further reduce rates of recurrence and death [7].

In our case, our patient initially received orbital radiation prior to CNS involvement. This protocol was supported by a multi-institutional Japanese study, which suggested that ocular RT alone was sufficient initial therapy with acceptable toxicity, as long as patients were closely followed for progression [26]. Once CNS disease was established, systemic CT with methotrexate and rituximab was initiated. After the completion of systemic CT and RT, ibrutinib was employed as maintenance therapy [2]. Median progression-free survival between 11 and 18 months and overall survival of 31–33 months have been reported by previous studies [21, 27]. This patient's case and review of the literature suggest that local RT alone is not sufficient to prevent CNS disease even in cases that confined intraocularly. Furthermore, systemic methotrexate-based CT in combination with local RT was initially effective in the treatment of PVRL with CNS involvement. However, CNS disease recurrence was not prevented despite CT, RT and ibrutinib maintenance therapy, in keeping with literature establishing high rates of recurrent disease [7].

In summary, here we present the first report of a patient with biopsy-confirmed PVRL presenting solely with asymptomatic peripheral drusenoid lesions. Complications from

disease progression included retinal detachment requiring repair, and high intraocular pressure requiring intervention. Initial treatment with RT to both orbits was insufficient to contain the progression and detection of new lesions resulted in the need for systemic CT. Our report emphasizes the importance of maintaining elevated clinical suspicion for a malignant process in older patients with new, progressive retinal lesions. This asymptomatic presentation of PVRL further highlights the insidious nature of initial presenting symptoms for some patients.

Statement of Ethics

This case report was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected patient health information was performed in a Health Insurance Portability and Accountability Act (HIPAA)-compliant manner. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local and national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

All authors attest that they meet the current ICMJE criteria for authorship. B.L., J.W., and J.K.: drafting of the manuscript, acquisition of data, and critical review of the manuscript. D.W.: supervision, conceptualization, and critical review of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. The data are not publicly available on legal or ethical grounds. Further inquiries can be directed to the corresponding author.

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