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Case report

Lymphoma masquerading as occlusive retinal vasculitis: A case study

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ABSTRACT

Purpose: To describe a case of retinal lymphoma presenting as an occlusive retinal vasculitis without vitritis that was exquisitely responsive to intravitreal dexamethasone implant (IVDI).
Observation: A 66-year old male presented with decreased vision in the right eye and was diagnosed with occlusive retinal vasculitis and prominent cystoid macular edema though he lacked vitritis. A complete systemic workup for infectious, inflammatory, and infiltrative etiologies was unremarkable. Intravenous methylprednisolone and cyclophosphamide had no clinical effect. Due to persistent perivascular exudates and refractory macular edema, IVDI was administered with marked improvement in vision and clinical findings. Subsequent retinal vasculitis in the left eye responded to IVDI as well. The patient remained disease free for months while on weekly adalimumab. He then presented with acute vision loss in the left eye due to a lymphomatous subretinal infiltration and a new lesion in the corpus callosum. He has remained disease free for more than two years after intravitreal methotrexate injections and rituximab with an autologous stem cell transplant.
Conclusion and importance: Lymphoma may present as an occlusive retinal vasculitis without vitritis and can be masked due to its response to IVDI.

Introduction

Retinal vasculitis is an inflammatory response characterized by perivascular inflammation that may result in vascular occlusion.[1,2] Rarely primary vitreoretinal lymphoma can present as a retinal vasculitis though it often is accompanied by other signs and symptoms such as vitritis. A high suspicion is when the patient deviates from the expected clinical course.[3,4]

We describe a patient with presumed idiopathic occlusive retinal vasculitis that was resistant to conventional therapy with oral and intravenous (IV) steroids, as well as IV cyclophosphamide. Clinical and visual improvement occurred after a single intravitreal dexamethasone implant (IVDI), an FDA-approved treatment of non-infectious posterior uveitis.[5] Recurrent cystoid macular edema in the fellow eye responded to several IVDI, but subsequently developed a subretinal infiltrate and biopsy revealed lymphoma. Magnetic resonance (MR) imaging of the brain also showed a new lesion in the splenium of the corpus callosum that was absent one year prior. This case demonstrates a profound effect of local steroid implantation, the protean manifestations of ocular lymphoma and the need for continued vigilance despite a seemingly successful treatment of suspected occlusive retinal vasculitis.

Case report

A 66-year old male presented with an abrupt decrease in right eye vision with an associated nasal field deficit. Visual acuity (VA) was 20/100 and 20/25 in the right and left eye, respectively. Pupillary response, intraocular pressures, and anterior segment exam was unremarkable. Fundus exam of the right eye showed periarteriolar exudates in the temporal macula with associated cystoid macular edema (CME) and subtle retinal whitening (Fig. 1). There was no vitritis or optic disc edema. The anterior and posterior exam of the left eye was normal. Angiographic studies of the right eye showed mild hyperfluorescence of the optic nerve, hyperfluorescence in the macula and vascular staining with peripheral nonperfusion. A thorough history and review of systems was obtained, revealing only asthma that required oral prednisone for episodic flares. Oral valacyclovir was initiated while awaiting laboratory results and a rheumatology consultation was obtained. At 1-week follow-up, VA declined to 20/200 in the right eye and was 20/20 in the left eye. Repeat fundus exam of the right eye showed worsening

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central macular edema, temporal retinal whitening, and intraretinal hemorrhages, while the left eye developed a new cotton-wool spot along the superior arcade. An aqueous tap was performed for PCR testing of VZV, HSV, CMV, and Toxoplasmosis, all of which were negative. The valacyclovir was discontinued and he was admitted for a 3-day course of intravenous methylprednisolone and a single 1g infusion of cyclophosphamide. The laboratory workup and rheumatologic consultation revealed no systemic etiology. (CBC, BMP, ESR, CRP, ACE, C- ANCA and P-ANCA, Rheumatoid factor, ANA, HLA-A29, HLA-B51 were within normal limits; FTA-ABS and HIV were non-reactive). Chest x-ray and brain MRI were also unremarkable.

Upon discharge, the patient continued 325 mg of aspirin and 40mg of oral prednisone daily. Right eye VA was unchanged at 20/200 during follow-up at week 3 and OCT imaging showed persistent edema. IVDI was administered in the right eye. Ten days later, visual acuity improved to 20/60 with marked reduction of the central retinal thickness on OCT from 1067 μm to 282 μm (Fig. 2). The perivascular exudates also decreased (Fig. 2). The patient was gradually tapered off oral steroids and his visual acuity remained stable at 20/60 in the right eye following a single IVDI.

At 4-month follow-up the patient presented with a temporal field cut in the left eye though his VA was 20/20. New perivascular exudates were noted in the nasal peripheral retina of the left eye (Fig. 3). The options of initiating therapy with biologics or local treatment with IVDI were discussed at length. A course of 60 mg oral prednisone was started instead. The patient underwent another evaluation by rheumatology for possible systemic association as well as the consideration of systemic therapy with adalimumab injections. An IVDI injection was administered in the left eye. Three weeks later, the perivascular exudates and retinal whitening resolved. The VA remained at 20/60 on the right and 20/20 on the left.

He developed recurrent CME with a decrease in vision while on weekly adalimumab without vasculitis. IVDI was administered two additional times with visual acuity improvement. Two months following the last IVDI and one year following initial presentation he had a sudden profound drop in left eye VA to 20/400. Examination showed a yellowish retinal lesion and hemorrhage (Fig. 4). OCT showed hyperreflectivity and thickening of the neurosensory retina with underlying fluid. The patient was admitted for repeat high dose steroids and AC tap was repeated for PCR analysis. Repeat brain MRI showed a new lesion in the splenium of the corpus callosum, giving the clinical impression of demyelinating disease or possible lymphoma. Lumbar puncture was negative. A standard 3 port pars plana vitrectomy was performed. Diathermy was applied over the involved retina and yellowish exudate was aspirated and submitted to pathology along with a vitreous specimen. Cellular morphology showed large cell lymphoma consistent with the clinical suspicion. The specimen from the vitreous was paucicellular and negative for malignancy. Oncology recommended systemic induction therapy consisting of methotrexate, rituximab, and temozolomide followed by autologous hematopoietic stem cell therapy with cytarabine for one year. He also underwent 10 intravitreal injections of methotrexate 400 μg/0.1 ml in the left eye. The retinal lesion resolved (Fig. 5). The lesion in the splenium of the corpus callosum was successfully treated with systemic rituximab and autologous stem cell therapy. The right eye remained disease free throughout the entire course and maintained visual acuity at 20/50. The left eye remained 5/200 without lesion recurrence over one year following the last methotrexate injection. No systemic signs of lymphoma were evident more than 28 months after the initial presentation.

Discussion

Primary vitreoretinal lymphoma often masquerades as vitritis leading to diagnostic delay or infiltrate the retina and sub retinal space.[6] This case of ocular lymphoma is unique given the lack of vitritis and complete resolution of a vasculitis and CME after a single IVDI.[3,4] Katoch et al. describe persistent vitritis in addition to vasculitis occurring prior to lymphomatous subretinal deposits.[4] The present case differs in that

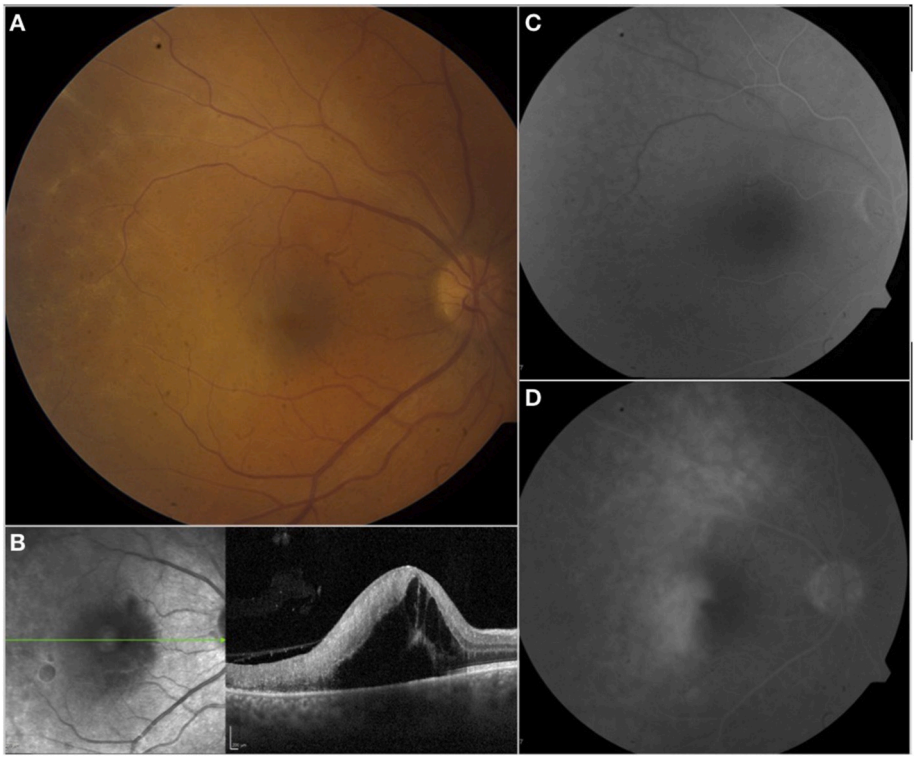

Fig. 1. Fundus photograph of the right eye showing perivascular exudates in the temporal macula with macular edema and retinal whitening in an otherwise healthy 66 yo male. There was no vitritis. (A) OCT demonstrates hyperreflectivity with cystoid macular edema and sub retinal fluid. (B). There is poor arterial fill after 30 seconds on fluorescein angiography. (C) Macular leakage is seen in later frames with vascular staining and peripheral nonperfusion. (D).

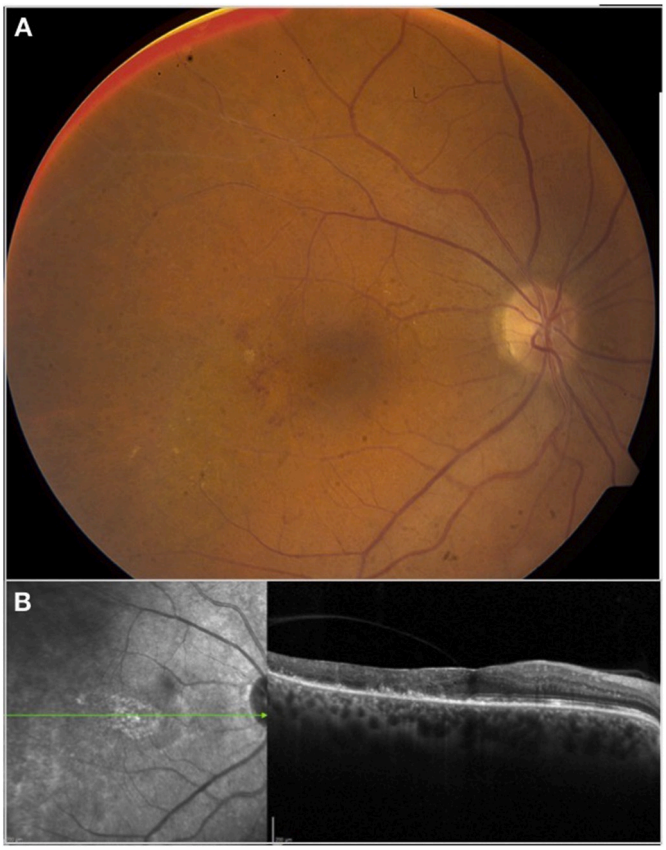

Fig. 2. The perivascular exudates resolved 10 days after a single IVDI though there is persistent petechial hemorrhages, peripheral vascular sheathing and ischemic changes (A). Resolution of the macular edema and temporal thinning with disruption of outer retinal layers is noted on OCT. (B).

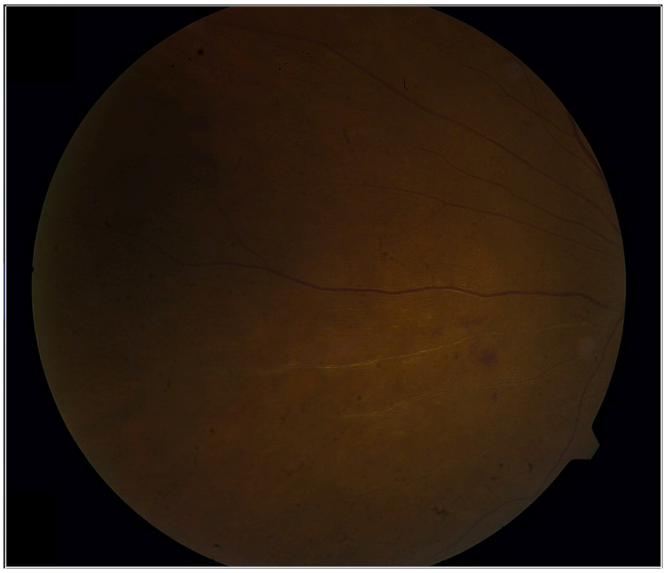

Fig. 3. Fundus photo at 4 month follow up demonstrates new perivascular exudates in the nasal peripheral retina of the left eye without vitritis. He complained of temporal field loss though his visual acuity was 20/20.

there was no vitritis and the initial vasculitis was exquisitely responsive to IVDI. In a case of lymphoma causing an arterial occlusion Damato et al. hypothesized that primary vitreoretinal lymphoma results from hematogenous spread of systemic loci although it remains unclear why

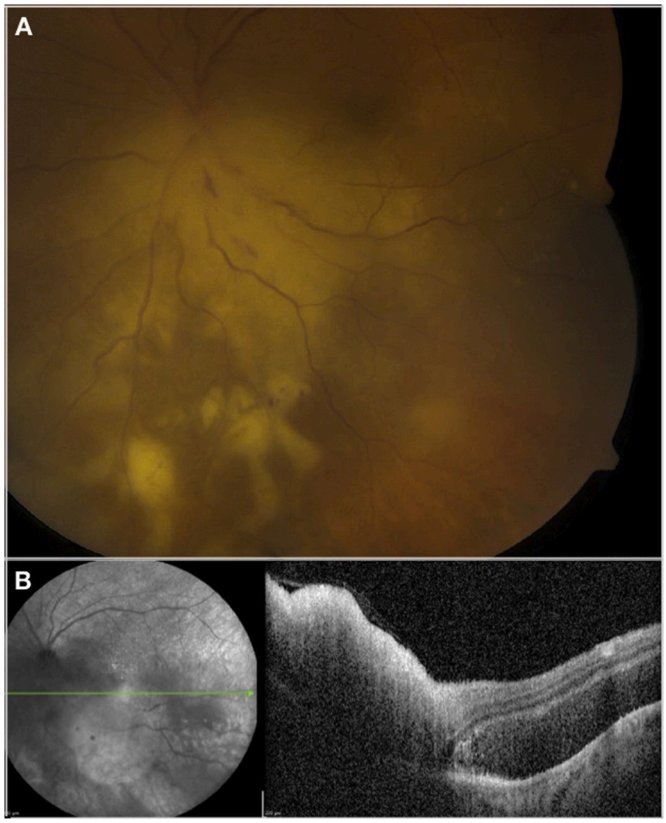

Fig. 4. Fundus photo of left eye shows a large yellow lesion inferior to nerve with intraretinal hemorrhages and associated retinal detachment without vitritis. (A) OCT demonstrates full thickness involvement of the neurosensory retina and subretinal fluid. (B) Pathology of subretinal aspirate confirmed large cell lymphoma. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

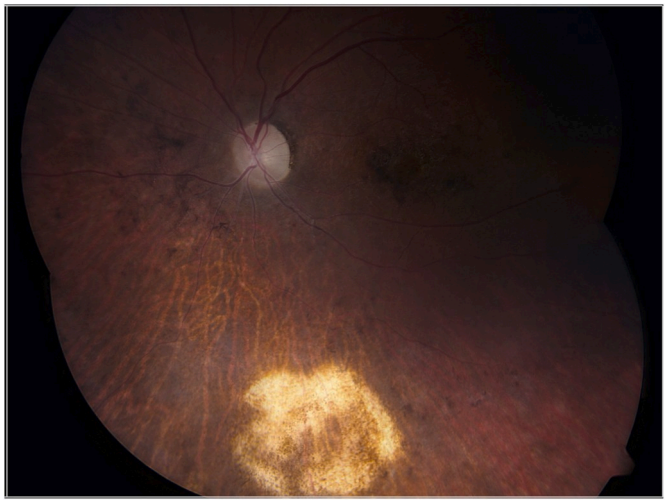

Fig. 5. Repeat photo shows resolution of lymphoma following 10 intraocular injections with methotrexate and systemic therapy with rituximab and autologous stem cells.

the disease remains limited to the CNS.[7] Indeed, pathologic specimens have demonstrated its angiocentric distribution[8–11] Furthermore, ultra widefield fluorescein angiography may reveal vascular leakage prior to the development of other ocular manifestations.[12] Differing degrees of perfusion status may explain the protean manifestations of primary

vitreoretinal lymphoma in this case with subretinal infiltration of lymphomatous cells in the left eye, but not the right. However, this hypothesis remains unproven without the availability of corresponding pathologic specimens at each stage of disease presentation.

The effect of steroids on ocular lymphoma can cause delay in diagnosis or a falsely negative biopsy specimen.[3,13,14] This case showed no response to systemic steroids. However, localized delivery of IVDI with its lack of dependency on perfusion resulted in profound and sustained resolution after one treatment in the right eye.[15–20] Natural history could have resulted in increasing subretinal infiltration that would have prompted earlier biopsy. However, the declining vision in the setting of a presumed occlusive inflammatory process with negative systemic workup led to the use of IVDI. Though spontaneous improvement of ocular lymphoma has been reported, it was not likely in this case given the immediate unequivocal improvement with IVDI and subsequent disease activity in the fellow eye.[21]

It is possible that our patient had an idiopathic inflammatory occlusive retinal vasculitis with subsequent lymphoma resulting from an induced immunosuppressed state. The link between immunosuppression and lymphoma is well documented and the use of cyclophosphamide and adalimumab in this patient was a risk factor for its development.[22–27] Although the lack of CNS findings on his initial MR may support this possibility, ocular lymphoma can predate cerebral disease in 42–92% of cases while only one third of cases have intracranial involvement at the time of presentation.[28–30] A biopsy specimen was not obtained during the patient's initial presentation due to unequivocal resolution with a single IVDI. Likewise, his second eye had a vasculitis that responded to IVDI followed by two episodes of CME also responding to IVDI. Additionally, intraocular lymphoma has not been reported after use of anti-TNF therapy and cyclophosphamide has previously been used as part of a treatment algorithim for intraocular lymphoma.[31] Nevertheless, this case underscores the need for continued vigilance when treating with immunosuppressants due to the risk of secondary malignancy.

Conclusions

In summary, we describe an interesting case of intraocular lymphoma presenting as a retinal vasculitis without vitritis and an exquisite sensitivity to IVDI. It underscores the need for continued vigilance despite an initial negative workup with initial successful treatment. Definitive biopsy should be considered when the clinical course changes or an expected response to treatment does not occur.

Patient consent

Written consent to publish the case report was obtained. This report does not contain any protected health information (PHI) that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

None of the authors have any financial disclosures.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2020.100777.

References

1. Rosenbaum JT, Ku J, Ali A, et al. Patients with retinal vasculitis rarely suffer from systemic vasculitis. *Semin Arthritis Rheum*. 2012;41(6):859–865.
2. Kwon SJ, Park DH, Shin JP. Frosted branch angiitis as ocular manifestation of Behçet's disease: unusual case report and literature review. *Kor J Ophthalmol*. 2013;27(6):466–469.
3. Brown SM, Jampol LM, Cantrill HL. Intraocular lymphoma presenting as retinal vasculitis. *Surv Ophthalmol*. 1994;39(2):133–140.
4. Katoch D, Bansal R, Nijhawan R, Gupta A. Primary intraocular central nervous system lymphoma masquerading as diffuse retinal vasculitis. *BMJ Case Rep*. 2013;30.
5. Lowder C, Belfort Jr R, Lightman S, et al. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. *Arch Ophthalmol*. 2011;129(5):545–553.
6. Grange LK, Kouchouk A, Dalal MD, et al. Neoplastic masquerade syndromes in patients with uveitis. *Am J Ophthalmol*. 2014;157(3):526-531.
7. Damato BE, Bever GJ, Afshar AR, Rubenstein JL. Insights from a case of vitreoretinal lymphoma. *Ocul Oncol Pathol*. 2019;5(1):13–19.
8. Gass JD, Trattler HL. Retinal artery obstruction and atheromas associated with non-Hodgkin's large cell lymphoma (reticulum cell sarcoma). *Arch Ophthalmol*. 1991;109(8):1134–1139.
9. Jack Jr CR, O'Neill BP, Banks PM, Reese DF. Central nervous system lymphoma: histologic types and CT appearance. *Radiology*. 1988;167(1):211–215.
10. Kohno T, Uchida H, Inomata H, Fukushima S, Takeshita M, Kikuchi M. Ocular manifestations of adult T-cell leukemia/lymphoma. A clinicopathologic study. *Ophthalmology*. 1993;100(12):1794–1799.
11. Ridley ME, McDonald HR, Sternberg Jr P, Blumenkranz MS, Zarbin MA, Schachat AP. Retinal manifestations of ocular lymphoma (reticulum cell sarcoma). *Ophthalmology*. 1992;99(7):1153–1161.
12. Lavine JA, Singh AD, Sharma S, et al. Ultra-widefield multimodal imaging of primary vitreoretinal lymphoma. *Retina*. 2019;39(10):1861–1871.
13. Mulay K, Narula R, Honavar SG. Primary vitreoretinal lymphoma. *Indian J Ophthalmol*. 2015;63(3):180–186.
14. Whitcup SM, de Smet MD, Rubin BI, et al. Intraocular lymphoma. Clinical and histopathologic diagnosis. *Ophthalmology*. 1993;100(9):1399–1406.
15. Saatci AO, Ayhan Z, Takeş Ö, Yaman A, Bajin FM. Single bilateral dexamethasone implant in addition to panretinal photocoagulation and oral azathioprine treatment in IRVAN syndrome. *Case Rep Ophthalmol*. 2015;6(1):56–62.
16. Karagiannis D, Soumplis V, Georgalas I, Kandarakis A. Ranibizumab for idiopathic retinal vasculitis, aneurysms, and neuroretinitis: favorable results. *Eur J Ophthalmol*. 2010;20(4):792–794.
17. Akesbi J, Brousseaud FX, Adam R, Rodallec T, Nordmann JP. Intravitreal bevacizumab (Avastin) in idiopathic retinitis, vasculitis, aneurysms and neuroretinitis. *Acta Ophthalmol*. 2010;88(2):e40–e41.
18. Empeslidis T, Banerjee S, Vardarinos A, Konstas AG. Dexamethasone intravitreal implant for idiopathic retinal vasculitis, aneurysms, and neuroretinitis. *Eur J Ophthalmol*. 2013;23(5):757–760.
19. Fabiani C, Emmi G, Lopalco G, et al. Intravitreal dexamethasone implant as an adjunct weapon for severe and refractory uveitis in behçet's disease. *Isr Med Assoc J*. 2017;19(7):415–419.
20. Coşkun E, Celemler P, Kimyon G, et al. Intravitreal dexamethasone implant for treatment of refractory behçet posterior uveitis: one-year follow-up results. *Ocul Immunol Inflamm*. 2015;23(6):437–443.
21. Kase S, Namba K, Jin XH, Kubota KC, Ishida S. Spontaneous regression of intraocular lymphoma. *Ophthalmology*. 2012;119(5):1083–1084.
22. Xu Y, Wang H, Zhou S, et al. Risk of second malignant neoplasms after cyclophosphamide-based chemotherapy with or without radiotherapy for non-Hodgkin lymphoma. *Leuk Lymphoma*. 2013;54(7):1396–1404.
23. Paul C, Le Tourneau A, Cayuela JM, et al. Epstein–Barr virus-associated lymphoproliferative disease during methotrexate therapy for psoriasis. *Arch Dermatol*. 1997;133(7):867–871.
24. Pietersma F, Piriou E, van Baarle D. Immune surveillance of EBV-infected B cells and the development of non-Hodgkin lymphomas in immunocompromised patients. *Leuk Lymphoma*. 2008;49(6):1028–1041.
25. Kasiskie BL, Snyder JJ, Gilbertson DT, Wang C, et al. Cancer after kidney transplantation in the United States. *Am J Transplant*. 2004;4(6):905–913.
26. Biggar RJ, Chaturvedi AK, Goedert JJ, Engels EA. AIDS-related cancer and severity of immunosuppression in persons with AIDS. *J Natl Cancer Inst*. 2007;99(12):962–972.
27. Bernatsky S, Clarke AE, Suissa S. Hematologic malignant neoplasms after drug exposure in rheumatoid arthritis. *Arch Intern Med*. 2008;168(4):378–381.
28. Ferreri AJ, Blay JY, Reni M, et al. Relevance of intraocular involvement in the management of primary central nervous system lymphomas. *Ann Oncol*. 2002;13(4):531–538.

29. Cassoux N, Merle-Beral H, Leblond V, et al. Ocular and central nervous system lymphoma: clinical features and diagnosis. *Ocul Immunol Inflamm*. 2000;8(4):243–250.
30. Sagoo MS, Mehta H, Swampillai AJ, et al. Primary intraocular lymphoma. *Surv Ophthalmol*. 2014;59(5):503–516.
31. Soussain C, Choquet S, Fourme E, et al. Intensive chemotherapy with thiotepa, busulfan and cyclophosphamide and hematopoietic stem cell rescue in relapsed or refractory primary central nervous system lymphoma and intraocular lymphoma: a retrospective study of 79 cases. *Haematologica*. 2012;97(11):1751-1756.