Central nervous system lymphoma presenting with a vitreoretinal disorder

Abdossalam M. Madkhali[1], Reem M. Alkulaibi[2], Taif N. Almutairi[2], Salman Aljarallah[3], Abdulrahman F. Albloushi[4]

Access this article online

Quick Response Code:

Website: www.saudijophthalmol.org

DOI: 10.4103/sjopt.sjopt_127_25

Abstract:

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma. Rarely, DLBCL presents as a vitreoretinal disorder. A 60-year-old female presented with progressive visual impairment in both eyes. Extensive investigations, including three chorioretinal biopsies, failed to identify the underlying cause. Eventually, the patient developed neurological symptoms, accompanied by atypical findings on magnetic resonance imaging. Following thorough deliberation, a brain biopsy was performed, revealing DLBCL. This case underscores the diagnostic challenges associated with vitreoretinal lymphoma, even when a biopsy is performed. It highlights the necessity of a high index of suspicion and a multidisciplinary approach, emphasizing the importance of persistent diagnostic efforts to achieve an accurate diagnosis and effective treatment.

Keywords:

Cutaneous lymphoma, diffuse large B-cell lymphoma, lymphoma, masquerade, uveitis

Introduction

Lymphomas are a diverse group of neoplasms originating in the lymphatic system, traditionally classified into two major categories: Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL).[1] Nearly 25% of NHL cases arise in extranodal locations, with most cases involving both nodal and extranodal sites.[2] The gastrointestinal (GI) tract and the head and neck region are the most common sites of primary extranodal NHL. In the GI tract, the stomach (66%) is most frequently affected, while in the head and neck region, the tonsils (33%) are the primary site of involvement.[3] The most common NHL subtypes are diffuse large B-cell lymphoma (DLBCL), accounting for about 30%, and follicular lymphoma, representing approximately 20%.[4]

Diffuse large B-cell lymphoma (DLBCL) typically presents with a rapidly enlarging, symptomatic mass.[5] Established risk factors for DLBCL include severe immune deficiency conditions, such as human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome, inherited immunodeficiency syndromes, and organ transplantation. In addition, chronic immune dysregulation, including autoimmune conditions (e.g. Sjögren syndrome, systemic lupus erythematosus, and rheumatoid arthritis), certain viral infections, and obesity, also contribute to the risk of DLBCL. A family history of Non-Hodgkin lymphoma/DLBCL, personal cancer history, and various genetic susceptibility loci are recognized risk factors for DLBCL.[6]

Although DLBCL most commonly presents as a rapidly enlarging lymph node, up to 40% of cases occur in extranodal sites. Approximately one-third of patients present with Stage IV disease, a similar proportion experience B symptoms, and more than half exhibit elevated serum lactate dehydrogenase levels.[7]

Rarely, DLBCL can present as a vitreoretinal disorder, complicating the diagnostic process. In this case, the diagnosis of DLBCL was ultimately confirmed through a brain biopsy.

Case Report

The CARE Checklist has been completed by the

[1]Department of Medicine, Oncology, Hematology and Radiation Oncology Unit, [2]Medical Students/Interns, [3]Department of Medicine, Neurology Section, [4]Department of Ophthalmology, College of Medicine, King Saud University, Riyadh, Saudi Arabia

Address for correspondence:
Dr. Abdossalam M. Madkhali, Department of Medicine, Oncology, Hematology and Radiation Oncology Unit, College of Medicine, King Saud University, Riyadh, Saudi Arabia.
E-mail: ammadkhali@ksu.edu.sa

Submitted: 16-Apr-2025
Revised: 29-May-2025
Accepted: 05-Aug-2025
Published: 20-Nov-2025

How to cite this article: Madkhali AM, Alkulaibi RM, Almutairi TN, Aljarallah S, Albloushi AF. Central nervous system lymphoma presenting with a vitreoretinal disorder. Saudi J Ophthalmol 0;0:0.

authors for this case report. A timeline of the patient's hospital course is illustrated in Figure 1.

A 60-year-old woman presented to the ophthalmologist with progressive visual impairment over 6 months affecting both eyes. In addition, the patient reported a history of low-grade fever, headache, a 5-kg weight loss over 1 year, and skin lesions that appeared 6 months before presentation. At the initial presentation, her best-corrected visual acuity (BCVA) was no light perception in the right eye and hand motion (HM) in

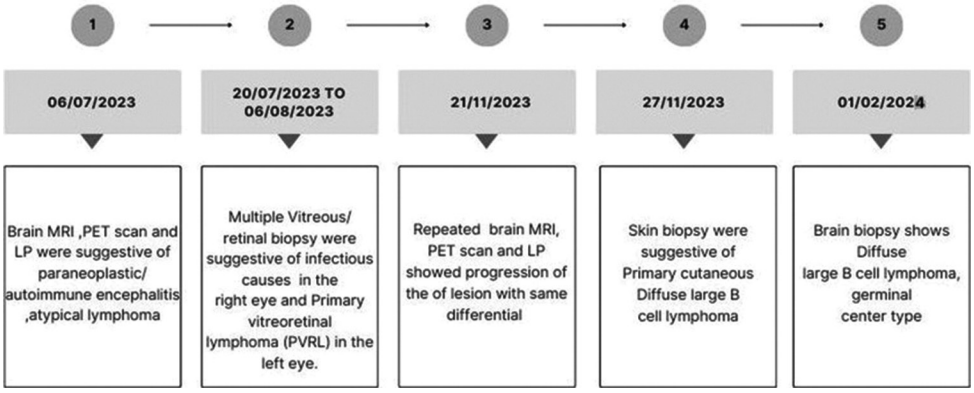

Figure 1: Timeline of the case along with investigation and differential diagnosis. PET: Positron emission tomography, MRI: Magnetic resonance imaging, LP: Lumbar puncture

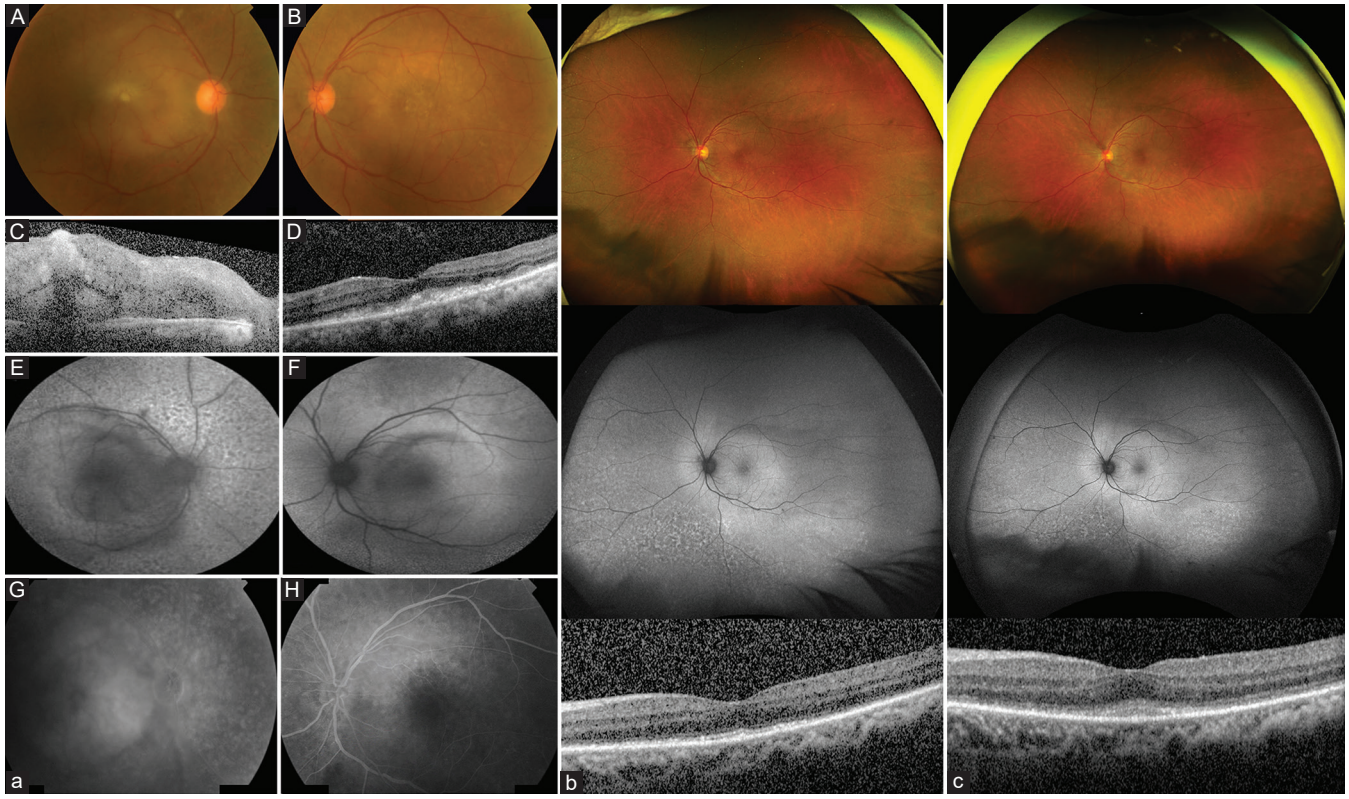

Figure 2: (a) (A and B) At presentation, color fundus photographs of both eyes showing bilateral mild vitreous haze, yellowish retinal infiltration involving the fovea, and a cotton wool spot superior to the macula in the right eye; scattered multiple creamy subretinal deposits in the left eye. (C and D) Optical coherence tomography of the macula showed diffuse retinal thickening, disorganization of inner and outer retinal layers, subretinal hyperreflective material in the right eye, and diffuse hyperreflective subretinal deposit in the left eye. (E and F) Fundus autofluorescent images show a granular pattern of slight hyperautofluorescence and hypoautofluorescence spots, more prominent in the right eye. (G and H) Fluorescein angiography of both eyes revealed late diffuse hyperfluorescence and a leopard pattern in the right eye, with no optic disc leakage or staining observed in either eye. (b) After 3 weeks of treatment with six intravitreal methotrexate injections, the patient's visual acuity improved to 20/60. Note the resolution of subretinal infiltration and vitreous haze. The fundus autofluorescent image shows a granular pattern with slight hyperautofluorescence and hypoautofluorescence spots in the inferior retina. (c) Two months after the last intravitreal injection, the patient's visual acuity dropped to counting fingers at three feet, with a recurrence of vitreous haze and the subretinal infiltrative lesion

the left eye. Intraocular pressure was 15 mmHg in both eyes. Slit-lamp examination showed bilateral nuclear sclerosis with a clear cornea and quiet anterior chamber. A dilated fundus examination revealed bilateral 1+ vitreous haze. A yellowish retinal infiltration involving the fovea and a cotton wool spot superior to the macula was noted in the right eye, while the left eye showed scattered multiple creamy subretinal deposits [Figure 2a; A and B].

Optical coherence tomography of the macula showed diffuse retinal thickening, disorganized inner and outer retinal layers, subretinal hyperreflective material in the right eye, and diffuse hyperreflective subretinal deposits in the left eye [Figure 2a; C and D]. Fundus autofluorescent images displayed a granular pattern of slight hyperautofluorescence and hypoautofluorescence spots, more prominent in the right eye [Figure 2a; E and F]. Fluorescein angiography of both eyes revealed late diffuse hyperfluorescence and a leopard pattern in the right eye, with no optic disc leakage or staining in either eye [Figure 2a; G and H].

The ocular findings suggested either an infectious cause, such as herpes virus infection or toxoplasmosis, or a neoplastic process like lymphoma, given the systemic symptoms.

The patient was hospitalized for further investigation. The workup included a complete blood count with differential, erythrocyte sedimentation rate, electrolytes, blood glucose, blood chemistry, liver function tests, tuberculin test, syphilis serology, antinuclear antibodies, antineutrophil cytoplasmic antibodies, QuantiFERON TB Gold test, and chest X-ray, all of which were unremarkable. Magnetic resonance imaging (MRI) of the brain and whole spine with contrast revealed multiple hyperintense, small, nonenhancing white matter lesions in the bilateral periventricular areas, which were deemed nonspecific. There were no parenchymal or meningeal lesions to suggest lymphoma [Figure 3a].

Because the ocular phenotype did not align with any specific uveitic entity and given the multimodal imaging results, a suspicion of vitreoretinal lymphoma was raised. Additional workup was undertaken, including a vitreous and chorioretinal biopsy of the right eye, which was inconclusive for malignancy. Two weeks later, a larger chorioretinal biopsy was performed from the right eye, and this, too, was negative for malignancy. The biopsies were examined for histopathology, cytopathology, immunohistochemistry, and flow cytometry. Unfortunately, specific biomarkers such as MYD88, the chorioretinal interleukin (IL)-10/IL-6 ratio, and immunoglobulin H clonality were unavailable at our hospital.

Further workups were performed, including computed tomography (CT) of the chest, abdomen, and pelvis, as well as a breast mammogram, all of which were normal. A positron emission tomography (PET) scan detected a left leg subcutaneous soft-tissue lesion suspected to be either infectious or inflammatory, with an enhanced MRI recommended for further correlation. A diagnostic lumbar puncture was also performed for cerebrospinal fluid (CSF) analysis, including microscopic cytology, flow cytometry, paraneoplastic panel, and infectious screening, all of which were negative.

Given the clinical presentation and suspicion of vitreoretinal lymphoma, a plan to start intravitreal methotrexate (400 µg/0.1 mL) for the left eye was discussed and agreed upon with the patient. The protocol of treatment was decided to be once weekly for 2 months, then once monthly for 7 months, after discussing with the ocular oncologist. Initially, six injections were administered (once per week). The patient reported significant improvement in her left eye BCVA, which improved from HM to 20/60, with decreased vitritis and resolution of the subretinal hyperreflective material [Figure 2b]. Unfortunately, after the sixth injection, the patient developed corneal toxicity in the left eye and was, therefore, referred to a specialist center in Europe for further evaluation and management. She subsequently underwent cataract removal in the right eye and a vitreous biopsy, which was negative for any infiltrative or infectious entities.

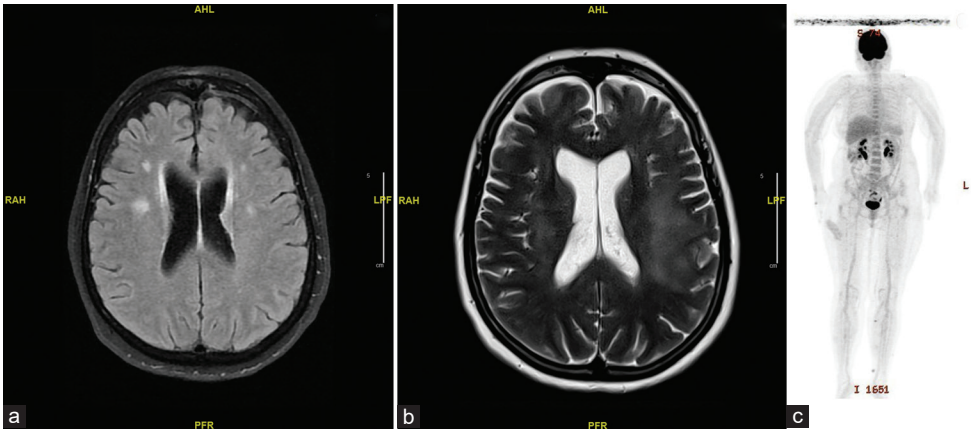

Figure 3: (a) Baseline brain magnetic resonance imaging (MRI) showing small hyperintense, nonenhancing white matter lesions in the bilateral periventricular areas on T2/fluid attenuated inversion recovery sequences. (b) Repeated brain MRI showing interval progression of the ill-defined, confluent T2 hyperintense signal abnormality in the supratentorial and infratentorial parenchyma. (c) Follow-up positron emission tomography-fluorodeoxyglucose 18 scan showing resolution of previously noted lower limb lesions

About a month later, the patient reported behavioral changes and difficulty walking. She was hospitalized in our center for further investigation. Neurological examination revealed restricted lateral gaze in the right eye and mild weakness in the right upper and lower extremities, with normal muscle tone and symmetrical deep tendon reflexes. The patient exhibited a bilateral intention tremor and dysmetria on both finger-to-nose and heel-to-shin tests. She was unable to stand unsupported due to a severe wide-based ataxic gait. Ophthalmologic examination showed pseudophakia in the right eye, granulomatous keratic precipitates, two cells in the anterior chamber with no light perception, and total retinal detachment. Examination of the left eye revealed a quiet anterior segment, stable retinal findings, and unchanged BCVA (20/60), with no new lesions noted.

A repeat MRI of the brain showed interval progression of an ill-defined, confluent T-two hyperintense lesion in the supratentorial and infratentorial parenchyma. Central nervous system (CNS) lymphoma was considered possible at this point, although radiologically, it was not strongly supported due to the lack of typical intense enhancement seen in CNS lymphoma and the spontaneous improvement of some lesions [Figure 3b]. A repeated CSF analysis showed acellular fluid with normal protein and glucose levels. Aquaporin-four antibodies were <1:10, and myelin oligodendrocyte glycoprotein antibodies and ACE were negative. Further workup was also negative for HIV, hepatitis markers, syphilis, tuberculosis, cytomegalovirus, and Brucella, as well as for paraneoplastic markers in both serum and CSF.

A repeated PET scan showed no evidence of F-fluorodeoxyglucose (FDG)-avid lymphoma, though the FDG-avid cutaneous/subcutaneous lesions in the left leg remained unchanged [Figure 3c]. The patient presented with three skin nodules – two on the left upper leg and one on the left foot – that appeared violaceous, were firm, and measured approximately 0.5 cm × 0.7 cm. The biopsy results of these lesions revealed dermal infiltration by large lymphocytes within a background of small lymphocytes, which is consistent with localized lymphoma. Immunohistochemistry results are detailed in Table 1.

Given the indolent nature of the lesions and the patient's poor performance status, the skin lesions were treated with radiotherapy (25 Gy in five fractions).

One month later, the patient presented with worsening visual acuity in the left eye, declining to counting fingers, along with a subretinal infiltrative lesion [Figure 2c]. Her neurological condition had also deteriorated, with increased ataxia, frequent falls, and weakness in the lower limbs. Given the progressive clinical and radiological findings and a high suspicion of CNS lymphoma, a brain biopsy was performed, revealing changes consistent with DLBCL, germinal center type. Details of the immunohistochemistry staining are shown in Table 2. The presentation and immunohistochemistry may suggest two different clonal populations and possibly two entities.

Table 1: Immunohistochemistry result of cutaneous lesions

Marker	Result	Cells
CD45	+	Large and small lymphocytes
CD20	+	Large lymphocytes
CD3	+	Small lymphocytes
CD30	−	N/A
CD10	−	N/A
BCL-2	+	Large lymphocytes
BCL-6	+	Large lymphocytes
MUM-1	+	Large lymphocytes
ALK-1	−	N/A

+: Positive, -: Negative, BCL: B-cell lymphoma, N/A: Not available

Table 2: Immunohistochemistry result of brain biopsy

Marker	Percentage
CD20	70
PAX-5	70
CD10	70
BCL-2	<20
C-MYC	<5
CD30	Negative
EBV (LMP1)	Negative
MUM1	10
Ki-67	>80
CD3	Highlights small T cells in the background

BCL: B-cell lymphoma

The patient was treated with high-dose methotrexate and rituximab, using an alkalizing regimen and prehydration with intravenous (IV) sodium bicarbonate and potassium chloride before methotrexate administration, followed by oral sodium bicarbonate until methotrexate levels dropped below 0.1 micromol/L and urine pH was seven or greater. This regimen was repeated every 14 days until either remission or signs of toxicity. Her response to therapy was monitored with MRI, and regular follow-up with the ophthalmology team was maintained to assess her left eye cataract. The patient adhered to the therapy schedule, tolerated the treatment well, and experienced no adverse events.

At the time of writing this report, the patient was still receiving systemic high-dose methotrexate and 4th monthly intravitreal methotrexate (total of 10 doses, six weekly and 4 monthly). Her most recent imaging showed mild improvement in some of the brain findings from earlier studies.

Discussion

This case presented a real diagnostic and management challenge. The clinical appearance was asymmetric, and the phenotype in the right (blind) eye was not very typical for lymphoma, suggesting infectious causes such as toxoplasmosis and herpes infections. However, findings in the left eye were suggestive of primary vitreoretinal lymphoma (PVRL) rather than metastatic disease. Furthermore, PVRL and primary uveal lymphoma are very rare entities; apart from CNS involvement, they are not generally associated with systemic involvement. In this case, the presence of subcutaneous lymphomatous lesions

indicated it was likely part of systemic lymphoma, as primary cutaneous lymphomas rarely metastasize to the subretinal space and vitreous cavity.[8,9]

Conventionally, intraocular PVRL is thought to manifest as vitritis and retinal/subretinal infiltrates, whereas intraocular lymphomatous metastases are more commonly present in the uvea due to hematogenous spread. Interestingly, this case presented with vitritis and a subretinal infiltrate but not choroidal infiltrates, mimic the characteristic presentation of PVRL. Reviewing the various radiology images, MRI findings in our case were not suggestive of lymphoma, despite evaluation by our neuroradiology team, which deals daily with malignant presentations, including lymphoma, in large volumes. The findings were instead more suggestive of nonneoplastic processes. In addition, PET-CT showed skin nodules, but the avidity was more indicative of an infectious or inflammatory process rather than infiltrative lesions.

This report presents an unusual and rare presentation of lymphoma, challenging the medical team and demanding significant time and effort from the patient. The close interdisciplinary cooperation and discussion ultimately led to a successful diagnosis, albeit after an exhaustive and costly series of investigations. Documenting and publishing such rare cases is important, though with limited resources and expertise in many centers worldwide, they may provide limited guidance for managing similar cases. Notably, in this case, a final diagnosis was reached only after a brain biopsy.

This complex case of DLBCL presented with progressive visual impairment and systemic symptoms, including weight loss and skin lesions. Despite extensive initial workups and inconclusive biopsies, a definitive diagnosis was ultimately reached through brain and subcutaneous biopsies. This case underscores the importance of maintaining a high index of suspicion for systemic lymphoma in atypical presentations and highlights the need for a multidisciplinary approach to ensure accurate diagnosis and effective treatment. Successful management and significant clinical improvement were achieved with targeted therapy, emphasizing the critical role of comprehensive evaluation and follow-up.

Acknowledgment

This work was supported by the College of Medicine Research Center, Deanship of Scientific Research, King Saud University, Riyadh, Saudi Arabia.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

This study was financially supported by College of Medicine Research Center, Deanship of Scientific Research, King Saud University, Riyadh, Saudi Arabia.

Conflicts of interest

There are no conflicts of interest.

References

1. Müller AM, Ihorst G, Mertelsmann R, Engelhardt M. Epidemiology of non-Hodgkin's lymphoma (NHL): Trends, geographic distribution, and etiology. Ann Hematol 2005;84:1-12.
2. Bowzyk Al-Naeeb A, Ajithkumar T, Behan S, Hodson DJ. Non-hodgkin lymphoma. BMJ 2018;362:k3204.
3. Arican A, Dinçol D, Akbulut H, Onur H, Demirkazik A, Cay F, *et al.* Clinicopathologic features and prognostic factors of primary extranodal non-Hodgkin's lymphomas in Turkey. Am J Clin Oncol 1999;22:587-92.
4. Thandra KC. Epidemiology of Non-Hodgkin's Lymphoma; 2021. Available from: https://www.mdpi.com/2076-3271/9/1/5. [Last accessed on 2025 Aug 05].
5. Møller MB, Pedersen NT, Christensen BE. Diffuse large B-cell lymphoma: Clinical implications of extranodal versus nodal presentation – A population-based study of 1575 cases. Br J Haematol 2004;124:151-9.
6. Wang SS. Epidemiology and etiology of diffuse large B-cell lymphoma. Semin Hematol 2023;60:255-66.
7. Hunt KE, Reichard KK. Diffuse large B-cell lymphoma. Arch Pathol Lab Med 2008;132:118-24.
8. Chong DY, Johnson MW, Shen D, Chan CC, Callanan DG. Vitreous metastases of primary cutaneous B-cell lymphoma. Ocul Immunol Inflamm 2009;17:342-4.
9. Rozati S, Kempf W, Ostheeren-Michaelis S, Bode-Lesniewska B, Zimmermann DR, Dummer R, *et al.* Cutaneous diffuse large B-Cell lymphoma, leg type, with bilateral intraocular involvement and infiltration to the CNS. J Clin Oncol 2016;34:e93-6.