

## **REVIEW**

# **Ophthalmic Manifestations of Lymphoma**

**<sup>1</sup>A. E. Omoti and <sup>2</sup>C. E. Omoti**

Departments of <sup>1</sup>Ophthalmology and <sup>2</sup>Haematology, University of Benin Teaching Hospital, Benin City, Nigeria  
Reprint requests to: Dr. A. E. Omoti, Department of Ophthalmology, University of Benin Teaching Hospital,  
Benin City, Nigeria. E- mail: [afeomoti@yahoo.com](mailto:afeomoti@yahoo.com)

### **Abstract**

**Background:** Ophthalmic involvement in lymphoma is a relatively rare condition that can result from a primary intraocular lymphoma or an intraocular manifestation of systemic lymphoma. This report reviews the ophthalmic manifestations of lymphoma.

**Methods:** Review of relevant information from journal articles and Internet search.

**Results:** Almost all the structures in the orbit, adnexiae and eye can be involved in lymphoma. Lymphoma of the eye and adnexiae are most frequently of B lineage. Most of the ocular manifestations frequently masquerade as other more benign intraocular conditions including allergic or infectious conjunctivitis, uveitis, multiple evanescent white dot syndrome, acute retinal necrosis or herpetic retinitis. Correct diagnosis thus depends on a high index of suspicion and frequently requires radiologic imaging, histologic analysis, particularly vitreous biopsy or flow cytometry, subretinal aspiration and retinal biopsy. Diagnosis is often delayed and may lead to a fatal outcome. Recognition of its modes of presentation facilitates early diagnosis and treatment that may improve prognosis.

**Conclusions:** It is important to review the ocular manifestations of lymphoma to assist the ophthalmologist to play a pivotal role in the prompt diagnosis and treatment of ocular lymphoma, and the haematologist/oncologist to recognize the need for a complete ophthalmic evaluation in the diagnosis, follow-up and management of lymphoma patients.

**Key words:** lymphoma, ophthalmic manifestations, masquerade, vitreous biopsy

### **Résumé**

**Introduction:** La participation ophtalmique dans lymphome est une condition relativement rare qui peut être provoqué par lymphome intraoculaire primaire ou une manifestation intraoculaire du lymphome systémique. Ce rapport fait une rétrospective des manifestation ophtalmique du lymphome.

**Méthodes:** Une rétrospective des informations pertinentes des articles dans les journaux et des recherches dans l'internet.

**Résultats:** Prèsque toutes les structures dans l'orbite, adnexiae et l'oeil peuvent participer dans lymphome. Lymphome de l'oeil et d'adnexiae sont le plus souvent du lignage B. La plupart des manifestations oculaires les plus souvent mascarade comme d'autre conditions intraoculaire plus bénigne y compris des infections conjunctivite ou allergique, uveite, syndrome tacheté du blanc évanescent multiple, nécrose aigue rétine ou rétinite herpetique. Donc diagnostique correcte dépend d'index plus élevé du soupçon et l'imaging radiologique est très fréquemment exigé, analyse histologique, la biopsie vitreuse en particulier ou bien écoulement cytométrie, aspiration sousrétine et la biopsie rétine. Le diagnostique est souvent retardé et pourrait aboutir à un résultat sérieux. Reconnaissance de son mode de présentation facilitera un diagnostique précoce et un traitement qui pourrait améliorer la prognose.

**Conclusion:** C'est très important de faire une rétrospective des manifestations oculaires du lymphome afin d'aider l'ophtamologiste de jouer un rôle clef dans un diagnostique précoce et traitement du lymphome oculaire, et pour aider l'hématologiste et oncologiste de reconnaître le besoin pour une évaluation ophtalmique dans le diagnostique, des soins post-hospitaliers et la prise en charge des patients atteints du lymphome.

**Mots-clés:** Lymphome, manifestation ophtalmiques, mascarade, biopsie vitreuse

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## Introduction

Lymphoid proliferations can affect the eye in various ways. Intraocular and orbital structures can be affected by non-Hodgkin's primary central nervous system lymphoma (PCNSL), reactive lymphoid hyperplasia, and systemic non-Hodgkin's lymphoma.<sup>1-7</sup> Rare cases of cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome) with ocular involvement have also been reported.<sup>8,9</sup> Hodgkin's lymphoma may also affect the ocular structures.<sup>10</sup>

There are two distinct forms of intraocular lymphoma.<sup>4</sup> One originates within the central nervous system (CNS) and is called primary CNS lymphoma. The second form arises outside the CNS and metastasizes to the eye. When primary CNS lymphoma initially involves the retina, it is named primary intraocular lymphoma (PIOL).

Intraocular lymphoma is probably the most elusive intraocular tumor to diagnose. It frequently masquerades as other more benign ocular lesions.<sup>2,3,5,7,11</sup> Correct diagnosis thus depends on a high index of suspicion and frequently requires radiologic imaging, histologic analysis, particularly vitreous biopsy or flow cytometry, subretinal aspiration and retinal biopsy.<sup>3-5,11</sup> Diagnosis can be difficult and it is frequently delayed as the clinical condition can mimic a number of other ocular conditions.<sup>2,7</sup> Furthermore, ocular manifestations of lymphoma are generally rare events.<sup>12</sup> It is thus important to review the ocular manifestations of lymphoma to assist the ophthalmologist to play a pivotal role in the prompt diagnosis and treatment of ocular lymphoma which must be regarded as a sight and life threatening condition. It will also assist the haematologist/oncologist to recognize the need for a complete ophthalmic evaluation in the diagnosis, follow-up and management of lymphoma patients.

## Epidemiologic Characteristics

Most reports of ocular involvement in lymphoma are case reports or reports of few patients. This may reflect its relative rarity. Since an indeterminate number of unreported and isolated cases have occurred, meaningful data regarding incidence and prevalence are not available. In general, the primary non-Hodgkin's lymphoma of the CNS is rare, accounting for 1% of all non-Hodgkin's lymphomas, 1% of intracranial tumors and less than 1% of all intraocular tumors.<sup>2,13</sup> It typically affects elderly patients,<sup>2,12,14-16</sup> with mean age around 63 years,<sup>16</sup> but can occur in young children.<sup>1,17</sup> There is no reported racial predilection. There is no sex predilection.<sup>5</sup>

## Mechanism of Ocular Manifestations

Cancer may affect the eye and orbit as a direct result of metastatic neoplastic infiltration, compression, or circulating antibodies involving paraneoplastic retinal

degeneration.<sup>18</sup> In the case of lymphoma, ocular involvement may be due to the disease itself, or side effects of the treatment. Most of the ophthalmic manifestations are the consequence of direct infiltration of the adnexiae, intraocular and orbital tissues. Presence of a mass lesion in the orbit can result in compression of orbital tissues and displacement of the eyeball resulting in proptosis.<sup>1,16</sup> The ocular symptoms may be due to inflammation of the infiltrated tissues and this is largely responsible for the variability of ophthalmic manifestations ranging from typical uveitis to retinitis and vasculitis.<sup>19</sup> Eyes with retinal infiltrates and haemorrhagic retinal necrosis are usually believed to harbor a microbial infection.<sup>20</sup> An acute change of refractive error has been reported to be due to a lymphomatous deposit in the choroid.<sup>21</sup> Lymphomas of the eye and its adnexia are frequently of B lineage but may rarely be affected by non-B-cell non-Hodgkin's lymphoma.<sup>16</sup>

## Ophthalmic Manifestations

The lack of pathognomonic features, high clinical variability and the limited value of imaging techniques and histopathological measures often lead to serious delay in diagnosis.<sup>19</sup> Intraocular lymphoma often has a fatal outcome, but recognition of its modes of presentation facilitates early diagnosis and treatment that may improve prognosis.<sup>7</sup> Almost all the ocular tissues may be affected by lymphoma. They will be grouped as the orbit and adnexial structures, anterior segment, posterior segment and neuro-ophthalmic manifestations.

### *Orbit and adnexial structures*

Infiltration of the orbit by lymphoma can result in proptosis.<sup>1,16</sup> The protrusion may be gross depending on the size of the mass lesion.<sup>16</sup> Infiltration of the eyelids may result in periorbital swelling and ptosis.<sup>21</sup> Lymphoma may also present as a localized eyelid mass or nodule.<sup>16,22,23</sup>

Cutaneous T cell lymphoma (mycosis fungoides and Sezary syndrome) may involve the skin of the eyelids and may result in lower eyelid ulceration or cicatricial ectropion.<sup>8,24</sup> In a report on cutaneous T-cell lymphoma, cicatricial eyelid ectropion was the most common ophthalmic manifestation occurring in 17(40.4%) of the 42 patients studied.<sup>8</sup>

### *Anterior segment*

Infiltration of the conjunctiva may give rise to conjunctival swellings or masses.<sup>16,22</sup> In a study of 39 children with leukaemias and malignant lymphomas, the most frequent ocular findings were seen in the conjunctiva, occurring in 33.4% of patients.<sup>1</sup> Marked chronic follicular conjunctivitis has been reported in a patient with mantle cell lymphoma.<sup>23</sup> The follicular appearance of the lymphocyte hyperplasia may mimic the clinical picture of infectious or allergic conjunctivitis, and may cause diagnostic difficulties and delay in diagnosis and appropriate treatment.

The cornea may be affected in adult T-cell leukaemia/lymphoma which is caused by Human T-cell lymphotropic virus type 1 infection (HTLV-1).<sup>25</sup> It is an RNA retrovirus that primarily affects CD4+ T-cells. Corneal involvement in HTLV-1 infection and adult T-cell leukaemia/lymphoma include corneal haze, central corneal opacities with thinning, scarring, bilateral immunoprotein keratopathy, peripheral corneal thinning, scarring and neovascularization.<sup>25</sup> It is believed that the novel corneal findings in these patients are most likely a consequence of the hypergammaglobulinaemia induced by the HTLV-1 infection or the T-cell malignancy. Keratoconjunctivitis sicca has also been reported in adult T-cell leukaemia/lymphoma.<sup>25</sup>

Episcleritis and scleritis may occur following lymphoma infiltration.<sup>25,26</sup> The differential diagnosis of lymphoma should be considered when scleritis is resistant to corticosteroid therapy.<sup>26</sup> Mucosa-associated lymphoid tissue (MALT) lymphoma has been reported to masquerade as anterior scleritis.<sup>26</sup> The anterior scleritis may be associated with uveal effusion syndrome.<sup>26</sup>

Lymphoma may masquerade as iritis, anterior uveitis or panuveitis.<sup>2, 3, 7, 12, 25-27</sup> Incorrect diagnosis of the uveitic syndrome may have severe consequences. Uveal involvement may be the initial manifestation of extranodal lymphoma.<sup>12</sup> It is a differential diagnosis of recurrent uveitis-like symptoms evolving to painful blind eye. In a study of 40 patients with uveitic masquerade syndromes identified in a cohort of 828 consecutive patients with uveitis, 19 patients had intraocular malignancy (48% of all with uveitis masquerade syndrome; 2.3% of all with uveitis), mainly intraocular lymphoma (n=13) and leukaemia (n=3).<sup>27</sup> The ophthalmologist was the first to recognize malignant disease in 11 of 19 patients (58%). Uveitis in lymphoma is resistant to corticosteroid therapy<sup>7</sup> and may be associated with hypopyon.<sup>28</sup> An iridic nodular lesion has been reported in the evolution of non-Hodgkin's lymphoma.<sup>17</sup> Vogt-Koyanagi-Harada disease (VKH), an inflammatory ocular disorder characterized by bilateral granulomatous panuveitis and a variety of extraocular manifestations, has been reported to be associated with various immune disorders and recently with malignant lymphoma.<sup>29</sup> There is evidence that VKH can be induced by immune disorders caused by high sIL-2R in malignant lymphoma.<sup>29</sup>

Glaucoma may occur in lymphoma.<sup>2, 28</sup> It may occur secondary to neovascularization of the iris and iridocorneal angle (neovascular glaucoma),<sup>2</sup> or may be due to direct obstruction of the trabecular meshwork by tumor cells.<sup>28</sup>

### Posterior segment

The vitreous may be infiltrated by cells<sup>20</sup> or there may be vitritis.<sup>3,4</sup> In a study of 14 patients with intraocular lymphoma, vitritis was present in 85.7% of cases.<sup>3</sup> The typical clinical presentation include blurred vision and floaters.<sup>4,15</sup> Vitreous haemorrhage may also occur.<sup>2</sup>

The choroid may be involved by lymphoma either alone<sup>4,26</sup> or as part of panuveitis.<sup>2,7,26</sup> Posterior uveitis may be associated with retinochoroidal infiltration and in more severe cases may be associated with serous retinal detachment.<sup>26</sup> A choroidal tumor has also been reported in large-cell lymphoma.<sup>22</sup>

The retina is frequently involved in ocular lymphoma. The various retinal lesions reported in lymphoma include retinal and subretinal infiltrates,<sup>4,11,30</sup> necrotizing granulomatous retinal vasculitis and retinitis,<sup>5,7,19,31</sup> retinal pigmentary degeneration,<sup>14,25</sup> haemorrhagic retinal necrosis,<sup>20</sup> retinal periphlebitis,<sup>10</sup> and perivascular exudates and sheathing.<sup>20,32</sup> The retinal and subretinal infiltrates and pigmentary alterations may mimic a diagnosis of multiple evanescent white dot syndrome.<sup>11</sup> The typical yellowish-white infiltrates may occur at the level of the subretinal pigment epithelial layer.<sup>30</sup> Subretinal pigment epithelium tumors may also be seen.<sup>7</sup> However, other presentations may include multiple deep white dots in the retina secondary to tumor infiltration; retinal infiltration causing a necrotizing retinitis; or infiltration of the retinal vasculature causing arterial or venous obstruction.<sup>7</sup> The fundus may also show tumorous subretinal lesions suggestive of proliferation of tumor cells.<sup>31</sup> Electrooculogram may show findings suggestive of widespread impairment of the retinal pigment epithelium.<sup>31</sup> In adult T-cell leukaemia/lymphoma, ocular lesions may result from HTLV-1 infection, including direct infiltration by adult T-cell leukaemia/lymphoma cells, cytomegalovirus retinitis and HTLV-1-associated uveitis.<sup>33</sup> The ocular lesion may simulate acute retinal necrosis or herpetic retinitis.<sup>34</sup>

### Neuro-ophthalmic manifestations

Primary intraocular lymphoma is a variant of primary central nervous system lymphoma in which lymphoma cells are initially present only in the eyes without evidence of disease in the brain or cerebrospinal fluid.<sup>15</sup> The prognosis is mostly determined by involvement of the central nervous system and/or visceral organ.<sup>19</sup> Completely different extraocular features are induced by long-standing local infiltrates within basal ganglia, a diffuse infiltration of the brain leading to an acute increase in intracranial pressure.<sup>19</sup> These may result in neuro-ophthalmic manifestations. Optic nerve invasion may occur in primary intraocular lymphoma.<sup>7,10,28,35</sup> Optic neuritis can occur due to tumor cell infiltration of the optic nerve,<sup>28,35</sup> and this may progress to optic atrophy and visual loss.<sup>35</sup> The clinical course may mimic multiple sclerosis.<sup>35</sup> Bilateral optic disc swelling may occur in Hodgkin's disease.<sup>10</sup> The incidence of non-Hodgkins lymphoma of the central nervous system has trebled over the past 15 years.<sup>36</sup> HIV/AIDS and other causes of immunosuppression may be responsible.

### Diagnosis

Diagnosis is based on a good history, clinical examination and investigations. A history of systemic

lymphoma will raise a suspicion that the ophthalmic disorder may be due to lymphoma. With the aid of a pen torch and slit lamp biomicroscope, anterior segment lesions can be identified. Fundoscopy and fluorescein angiography can identify posterior segment lesions. Orbital and intraocular mass lesions can be identified by radiological examinations such as ultrasound scan, computed tomography scan and magnetic resonance imaging.<sup>11, 35</sup> Definitive diagnosis is based on biopsy of the affected tissue. Diagnosis of the systemic disease is established based on tissue samples that are studied by histological examination of a surgical biopsy from an accessible lymph node site.

Of importance in ocular lymphoma is pars plana vitrectomy and cytology, aqueous tap, subretinal aspiration or retinal biopsy.<sup>11,14, 30</sup> Lumbar puncture with cytology of the cerebrospinal fluid is important in central nervous system involvement.

### Treatment and Prognosis

Treatment of ocular lymphoma is by radiation therapy and this may be combined with chemotherapy in the presence of central nervous system involvement.<sup>11</sup> For non-Hodgkin's lymphoma, chemotherapy involves the use of iv Cyclophosphamide 750mg/m<sup>2</sup> on days 1 and 8, iv Adriamycin 45mg/m<sup>2</sup> on days 1 and 8, iv Vincristine 1.5mg/m<sup>2</sup> on days 1 and 8 and oral Prednisolone 20mg 8 hourly for 10days. For Hodgkin's lymphoma, chemotherapy involves the use of ABVD regimen (iv Adriamycin 25mg/m<sup>2</sup> on days 1and15; iv Bleomycin 10U/m<sup>2</sup> on days 1and15; iv Vinblastine 6mg/m<sup>2</sup> on days 1and15 and iv Dacarbazine 375mg/m<sup>2</sup> on days 1and15). High dose methotrexate and Leucovorin rescue may also be used for ocular lymphoma.<sup>2</sup>

Prognosis for visual recovery is good if diagnosis is made early and therapy started on time. Dramatic improvements in visual acuity have been reported in patients with retinal involvement after x-irradiation.<sup>11</sup> Intraocular lymphoma often has a fatal outcome but recognition of its mode of presentation facilitates early diagnosis and treatment that may improve prognosis.<sup>3,7,31</sup> Compared with primary intraocular lymphoma, metastatic systemic lymphomas have a better prognosis and is less likely to create a diagnostic dilemma.<sup>15</sup> The survival from the establishment of the diagnosis has been reported to 20.6 months on the average.<sup>3</sup>

### Conclusion

Lymphoma of the eye and adnexia are most frequently of B lineage. The lack of pathognomonic features, high clinical variability and the limited value of imaging techniques and histopathological measures often lead to serious delay in diagnosis. Almost all ocular structures can be involved in lymphoma and it frequently masquerades as other more benign intraocular conditions. Diagnosis is thus often delayed

and this may lead to a fatal outcome. Early diagnosis and treatment may be facilitated by recognition of its modes of presentation and this may improve prognosis.

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