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Iris lymphoma – a systematic guide for diagnosis and treatment

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Abstract:	Iris lymphomas are rare malignant neoplasms arising either as primary tumors in the iris or as secondary tumors involving the iris. We summarize previously published data and make recommendations for work-up strategies for cases of suspected iris lymphoma. Our objective is to provide a structured overview of the typical clinical symptoms and signs, the pathologic, ophthalmic as well as hematologic work-up for diagnosis, treatment, and follow-up of iris lymphomas and offer a flowchart on how to diagnose and treat these tumors.
Response to Reviewers:	

Old Cover Letter

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Cologne, 18-NOV-2019

Submission Review Article

"Iris lymphoma – a systematic concept for diagnosis and treatment"

Dear Editor-in-Chief,

Dear Professor Gittinger Jr,

May we kindly ask you to consider our enclosed manuscript "Iris lymphoma – a systematic concept for diagnosis and treatment" - as appropriate for publication in "Survey of Ophthalmology".

In August 2018 you accept our outline focussing on iris lymphoma, an important and special entity that deserve specific attention indepently from as well as in addition to the well-described vitreoretinal lymphomas. Herein, we describe the current multidisciplinary concepts for diagnosis, staging and treatment in iris lymphoma.

For further discussion please do not hesitate to contact me by phone (+49 221 478 4300), by fax (+49 221 478 5094) or by email (ludwig.heindl@uk-koeln.de) at your convenience.

With many thanks and best regards,

Sincerely yours,

L. M. Heindl.

Ludwig M. Heindl, MD
Ass. Professor of Ophthalmology
Director, Ophthalmic Oncology and Ophthalmic Plastic and Reconstructive Surgery Service

RE: Outline "Iris Lymphoma - Concepts for Diagnosis, Staging and Treatment"

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Anlagen: Author information letter ~1.doc (32 KB) ; Author information package~1.doc (54 KB)

Dear Dr Heindl,

Thank you for your interest in submitting a review on Iris Lymphoma - Concepts for Diagnosis, Staging and Treatment. I think this is an important topic and your outline covers it well. Attached is a copy of the journal's information for authors packet. Please review the instructions before submitting.

I look forward to receiving the manuscript.

Best wishes,

John

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Subject: Outline "Iris Lymphoma - Concepts for Diagnosis, Staging and Treatment"

Dear Editor-in-Chief,
Dear Professor Gittinger Jr,

May we kindly ask you to consider our enclosed outline - "Iris Lymphoma - Concepts for Diagnosis, Staging and Treatment" - as appropriate for a review submission to "Survey of Ophthalmology".

The proposed review will focus on iris lymphoma, an important and special entity that deserve specific attention indepently from as well as in addition to the well-described vitreoretinal lymphomas. Herein, we describe the current multidisciplinary concepts for diagnosis, staging and treatment in iris lymphoma.

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Iris lymphoma – a systematic guideline for diagnosis and treatment

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Short title: Diagnosis and treatment of iris lymphoma

Key words: iris lymphoma – diagnosis – treatment – staging – lymphopoiesis

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Abstract

Iris lymphomas are rare malignant neoplasms arising either as primary tumors in the iris or as secondary tumors involving the iris. This review on iris lymphomas summarizes previously published data and puts forward recommendations for work-up strategies of suspected iris lymphoma cases. Our objective is to provide a structured overview of the typical clinical symptoms and signs, the pathologic, ophthalmic as well as hematologic work-up for diagnosis, treatment, and follow-up of iris lymphomas. Further, this review offers a flowchart how to diagnose and treat these tumors.

Symptoms and clinical signs of iris lymphoma may mimic a fulminant anterior uveitis. Careful evaluation of these signs by experienced uveitis or tumor specialists, together with the patient's medical records, may lead to the suspicion of an iris lymphoma. State-of-the-art diagnostics includes either a biopsy or fine needle aspiration of the iris or anterior chamber, respectively, and its subsequent pathologic work-up. Adjunctive analyses, - e.g. immunohistochemistry, clonality analysis and possibly mutational testing -, aid the diagnosis. In the case of lymphoma diagnosis, hematological staging including magnetic resonance imaging, serological testing and bone marrow analyses are required to determine the extent of the disease and allow for decision-making in subsequent patient management. Discussions within a multidisciplinary tumor board (including the ophthalmologists as well as the hematologists) will lead to the appropriate selection of treatment(s), including local and/or systemic therapies. Based on a review of the literature and on the combined authors' experience, this article provides recommendations as to how to schedule and perform the follow-up of iris lymphoma patients after treatment.

1.Introduction

Intraocular lymphoma is subdivided by anatomic localization.[14] Lymphomatous involvement of the iris is an extremely rare condition, with very little being known about the demographics and epidemiology of this disease. It is defined as a lymphoma with predominant involvement of the iris, and can be either a primary or secondary manifestation, with most cases in the literature being a secondary manifestation of an underlying systemic Non-Hodgkin lymphoma (NHL; Figure 1).[13,14] The diagnosis of 'primary iris lymphoma' is reached if there is no evidence of an underlying systemic lymphoma at the time of ocular diagnosis and staging examinations. It is to be distinguished from a primary ciliary body lymphoma with predominant involvement of the ciliary body; a primary choroidal lymphoma arising predominantly within the choroid; and primary vitreo-retinal lymphoma, occurring mainly within the vitreous and/or retina (usually *without* any choroidal disease; Figure 1).[14]

Most iris lymphomas are B-cell NHL, but T-cell lymphomas can also occur in the iris; no iridal Hodgkin lymphoma has been described to date.[36,40] Nevertheless, iris lymphomas tend to be a high-grade lesions, and are associated with aggressive subtypes of systemic lymphoma and thereby a poor prognosis.[36,40] This clinical outcome also may be due to diagnosis delay, which is quite common, varying between weeks and months. Typically, iris lymphoma patients present with inflammatory clinical signs, and are often misdiagnosed initially with an anterior uveitis. A definitive diagnosis is ultimately achieved by tissue sampling or aqueous cytology.

The purpose of this review is to provide diagnostic and therapeutic recommendations as well as a 'work-up' chart for patients with this disease.

2. Review of the iris lymphoma literature

To date ~30 publications describing ~50 cases of iris lymphoma has been published in PubMed during the last 40 years (Table 1).[1,2,5,8,9,18,19,24,25,27,28,32,36,37,40-42,44,45,52-54,60,61,64,66-68]

Most are single case reports, but there are also a couple of small case series. As mentioned above, B-cell NHL was the most dominant lymphoma subgroup, followed by T-cell lymphoma, and plasma cell myeloma (also termed multiple myeloma). More than 70% of the cases of iridal lymphoma were unilateral.

Apart from a dominant iris involvement, scattered lymphoma cells were also observed within the adjacent anterior chamber and ciliary body in some patients. In the latter cases, it is not clear from the descriptions provided whether these lymphomas were primarily arising in the iris or whether they secondarily infiltrated the iris stroma by contiguous spread. In our review of the literature, it was indeed difficult to discriminate between cases that were primarily arising in the iris, and those that may have arisen within the anterior choroid/ciliary body and then secondarily infiltrated the iris. Therefore, for the purposes of this review, 'iris lymphoma' was strictly defined as that with predominant disease in the iris, to distinguish it from a ciliary body lymphoma with the bulk of the disease within the ciliary body, from a choroidal lymphoma with predominant lymphoma in this location, and from a vitreo-retinal lymphoma, with the disease occurring mainly within the vitreous and/or retina. This definition correlates with that provided by the Tumor Node Metastatis system for uveal melanoma.[4] Consequently, iris lymphoma cases with combined and extensive ciliary body-, choroidal- or vitreo-retinal lymphoma were excluded from this review. Taking this anatomical definition into account, it would appear that ~25% of the cases reported in the literature are primary iris lymphoma, and the remainder of the cases are secondary iris NHL (Table 2).

The age range of patients with iris lymphomas was between 1 - 89 years with a peak in late 50s and early 60s (Table 2). The predilection of male and female patients with primary or secondary lymphoma as the same. Depending on the extent and subtype of the disease, patients were treated with either external beam irradiation, local intraocular treatments (e.g., Rituximab), systemic therapy or enucleation. Table 1 summarizes the data of all iris lymphoma case reports found in our literature review.

3. Lymphopoiesis - opportunities for lymphocyte mutation towards lymphoma

Knowledge of lymphopoiesis is critical in the understanding of the pathological mechanisms behind lymphoma development. At any stage of the differentiation pathway of lymphocytes, genetic alterations may arise in them leading to uncontrolled proliferation of a particular clone, and ultimately the initiation of a lymphoma.[26,34,48] These may arise in specific niches within the body (nodal or extranodal), potentially remain localized or spread and become systemic.[26,34,48]

In the healthy person, an intact immune function depends on the regular production of lymphocytes in the bone marrow and thymus. Pluripotent hematopoietic stem cells, also the precursor cells for erythrocytes and platelets, are regulated by different cytokines and chemokines (e.g., interleukin-1, -6, -7 or stem cell factor) and develop into lymphatic precursor cells.[26,34,48] These cells further differentiate into T- or B-lymphocyte stem cells. The T-lymphocyte stem cell migrate into the thymus and undergo a positive or negative selection.[26,34,48] After this selection process, these cells differentiate into either CD4+ or CD8+ cells, and are released into the lymph and blood system. Well-defined subtypes of T-cells are known with differing functions in the immune system.[26,34,48]

B-lymphocyte stem cells are located in the bone marrow and spleen, and generate pro-and pre-B-cells, which differentiate into ‘immature’ B-cells. They are released as immune naïve competent B-cells into the blood and ultimately the lymph system. During this maturation phase, a key step is the production of a B-cell-receptor (BCR). B-cells without a competent BCR or one with insufficient antigenicity undergo apoptosis.[26,34,48]

The bone marrow and thymus are considered the primary lymphatic organs, as both are the locations where hematopoietic stem cells develop into B- or T-lymphocytes. In contrast, lymph nodes, spleen, tonsil or mucosa-associated lymphatic tissue (M.A.L.T.) are considered as secondary lymphatic organs, where the B- or T-lymphocytes undergo further activation and maturation in lymphatic follicles.[26,34,48]

Immunocompetent naïve lymphocytes circulate in the blood or reside in the lymphatic follicles of the secondary lymphatic organs. In these lymphatic follicles, most cells are B-lymphocytes, but also T-lymphocytes as well as macrophages and other antigen presenting cells. Before antigen exposure, these lymphoid follicles are called “primary follicles”. After first antigen contact, they differentiate into “secondary follicles” with a

specific architecture. For example, B-lymphocytes, such as naïve B-lymphocytes and memory cells, are mostly found in the cortex of a follicle. In the capsule of the follicle, B-lymphocytes proliferate with support of T-lymphocytes after a contact with an extrinsic antigen, and then differentiate also into plasma cells, providing the humoral response. B-lymphocyte that are considered inadequate on antigen exposure undergo apoptosis in the ‘germinal center’ of the secondary follicle.[26,34,48] Figure 2 displays the different steps of lymphopoiesis, and the proposed stages during which mutations can occur resulting in the differing B- and T-cell lymphomas.

4. Clinical signs and symptoms of iridal lymphoma

Clinical signs and symptoms of an iridal lymphoma may overlap with those of an anterior uveitis, including visual acuity reduction, intraocular pressure elevation and pain, haze of the cornea, cells and flare in the anterior chamber, pseudohypopyon and hyphema. Apart from these unspecific features, a whitish mass in the iris with or without neovascularization, differs from an anterior uveitis as well as the appearance of 'pseudo-hypopyon' (Figure 3a).[36,40] Further, cell clumps or aggregates on a lytic background are more likely to comprise lymphoma cells. Due to its rarity and the similarity of its signs and symptoms to anterior uveitis, the diagnosis of an iris lymphoma, and thereby the commencement of its treatment, might be delayed.

In addition to the ophthalmic signs and symptoms, so-called 'B-symptoms' associated with lymphoproliferative disorders, including unclear fever above 38°C, night sweats, and unexpected weight loss (more than 10% in 6 months), may be apparent, and ultimately guide the differential diagnosis and subsequent investigation of these patients to its lymphomatous nature.

5. Differential diagnosis - benign reactive lymphoid hyperplasia of the iris and other differential diagnoses

One of the main differential diagnoses of iris lymphoma is “Benign reactive lymphoid hyperplasia” (BRLH) of the iris, which has been defined as a condition characterized by a mass of benign polyclonal B and T-lymphocytes and plasma cells infiltrating the iris stroma.[12,56] Iridal BRLH appears either as a circumscribed lesion or as a diffuse amelanotic thickening of the iris stroma (Figure 3b). It typically shows an indolent course and may even self-resolve. BRLH can occur in association with other systemic conditions, such as the Castleman’s syndrome.[7] BRLH may have been misclassified in the past with small cell B-NHL, such as extranodal marginal zone B-cell NHL or small lymphocytic lymphoma/leukemia being overlooked.[12,56,58] Malignant transformation of BRLH can occur, but it appears to be very uncommon.[33,38]

Because of its benign nature, BRLH of the iris is by nature less aggressive and shows well-circumscribed uveal involvement, thus implying that a ‘watch-and-wait’ follow-up investigation may help to discriminate between BRLH and any malignant disease.

Further differential diagnoses for iris lymphoma include amelanotic iris nevi, amelanotic iris melanoma (Figure 3c), as well as other rare neoplasms, such as iris hemangiomas, adenoma of the iris pigment epithelium, leiomyoma as well rhabdomyosarcoma, or metastatic carcinoma (Figure 3c).[43,59]

In particular, differentiation between an amelanotic iris melanoma and iris lymphoma can be difficult, due to similar and overlapping clinical signs of these lesions. There are certain features, however, which strongly hint towards the diagnosis of melanoma. These include a more densely appearing tumor with corectopia, ectropium uveae, glaucoma, hyphema and extraocular extension as well as feeder vessels.[57] Nevertheless, in unclear cases, histological analysis of a tissue or fine needle aspitation biopsy may be necessary, as the diagnosis obviously has a major impact on treatment choice.

Finally, an inflammatory condition in the anterior chamber (e.g., juvenile xanthogranuloma of the iris or Koeppe nodes of the iris in sarcoidosis) may mimic an iris lymphoma, displaying similar clinical signs and symptoms, as described before.

6. Ophthalmic work-up and fine needle aspiration biopsy/iris biopsy

The first step of the ophthalmic work-up of iris lymphoma is a comprehensive ophthalmic examination, including taking a detailed medical history; visual acuity testing, formal visual field testing; intraocular pressure measurement; and investigating the anterior chamber with a slit lamp, followed by a fundoscopy (if possible). Formal visual field testing is performed to assess possible posterior segment/optic nerve involvement or CNS disease. Standardized echography including A- and B-scans, ultrasound bio microscopy (UBM), anterior chamber optical coherence tomography (AC-OCT) help to discriminate from other differential diagnoses. Both UBM and AS-OCT provide information with respect to status of the iris pigment as well as to the density of the mass. Further, UBM displays the ciliary body and allows for examination of ciliary body infiltration, which AS-OCT is not able to provide.

Apart from the usual comprehensive description of the clinical signs, photographic documentation of the anterior chamber and the iris is mandatory, in order to follow any progression of anterior chamber inflammation and/or the tumor itself including during treatment. Additionally, quantification of anterior chamber inflammation by laser flare photometry or by the use of the Standardized Uveitis Nomenclature allows for the quantification of aqueous flare and cells.[30]

If all signs and symptoms suggest a clinical diagnosis of lymphoma, biopsy is mandatory to confirm the diagnosis and to allow for its exact subtyping according to the WHO Lymphoma Classification, updated in 2016.[47] This is key for the subsequent choice of treatment.

To undertake an iris biopsy, two approaches are possible: to date, there is no evidence that one approach is better than the other. The first is an incisional surgical biopsy to obtain material from the suspicious iridal mass to get sufficient material for diagnostic purposes, without removal of the whole tumor.[11,22,23,46] The second is an excisional resection of the tumor mass to obtain sufficient material for histopathological diagnostics but also with potential cure.[62] Both approaches have their advantages and disadvantages. A small specimen procedure may be able to provide the diagnosis, and the residual tumor is then treated by either radiotherapy and/or chemotherapy. To date, there are no data indicating that a small sample biopsy might lead to a higher rate of recurrence, metastasis or earlier cancer-associated death. On the other hand, complete tumor excision is difficult in iris lymphoma, as these tumors are often not well-delineated and, thereby, difficult to accurately remove from the eye. Further,

inflammation in the anterior chamber and corneal clouding may make complete tumor excision impossible. In addition to incisional or excisional resections, a careful fine needle aspiration biopsy (FNAB) of the anterior chamber would be of value in cases where there is a reasonable scattering of lymphoma cells within the aqueous. Because of the small amount of material likely to be obtained, only a limited number of investigations would able to be performed on this FNAB; these would be determined by the morphology of the cells (see below).

In some cases, unfortunately, the lymphomatous infiltration within the iris may be quite extensive involving the entire circumference of the iris, and also infiltrating into the chamber angle leading to secondary glaucoma and a painful eye. In such advanced cases, enucleation may be the only option for diagnosis and treatment (Figure 4).

7. Morphological, immunohistological and molecular biological diagnostics.

Critical to the diagnosis of iris lymphoma is the morphological analysis of the biopsied cells. Following surgery, tissue biopsies and FNAB can be placed in a soft fixative, such as Cytolyt, and sent to the laboratory for further processing.[16] Where tissue pieces are present, these would be embedded in paraffin and sectioned for conventional (e.g., hematoxylin and Eosin; H&E) and immunohistochemical staining. In contrast, the FNAB would be processed as cytospins, and stained with May Grunewald Giemsa (MGG), with spare cytospins being prepared for immunocytology. On the basis of the cytomorphology, the immunoprofile is selected, taking into account the limited amount of material and the main intent to subclassify the tumor as precisely as possible. The most common B-NHL involving the iris is a 'diffuse large B-cell lymphoma', whilst the small cell B-NHL can vary significantly according to the underlying systemic malignancy (e.g. chronic lymphocytic leukemia, mantle cell lymphoma).[13,17] Should the lymphomatous lesion demonstrate a plasmacellular differentiation, a plasma cell myeloma must be excluded. Finally, in the case of immunosuppressed patients, an Epstein Barr virus-related lymphomatous lesion must be considered.[8,50] Table 1 shows the available immune profile analyses in all case reports and series of iris lymphomas.

By definition, an autonomic clonal proliferation of B- or T-lymphocytes is a lymphoma. Polymerase chain reaction of the immunoglobulin genes (IgH-PCR) and of the T-cell receptor (TCR-PCR) is of value in confirming the diagnosis of B- and T-cell lymphomas, respectively, of the iris. In addition, cytogenetic features of the iris lymphoma cells may enable the exact lymphoma subtyping.[13] This is essential in determining whether this is a primary or secondary manifestation in the eye. Newer next generation sequencing techniques, enabling the detection of both copy number alterations and mutations within tumor cells on very small intraocular samples, have recently been introduced into the diagnostic repertoire.[21]

8. Subsequent clinical analyses

8a. Hematologic work-up (MRI, blood analyses, bone marrow analysis; depending on patient's lymphoma history)

As above, based on the review of the literature, 75% of iris lymphoma patients have an underlying systemic NHL. Therefore, after diagnosing an iridal lymphoma, the patient should be referred to the hematological team for staging investigations, which entail radiological imaging, as well as serological- and bone marrow examinations.[63] Clinical outcome of iridal lymphomas is very much dependent on the lymphoma stage and subtype.[13,15]

The gold standard for imaging the extent of systemic lymphomatous infiltration includes magnetic resonance imaging (MRI) and positron emission tomography (PET).[49,65] An alternative to MRI for staging is computed tomography (CT), particularly in cases with contraindications for MRI (e.g., patients with heart pacemaker) and PET, or bone infiltration.

As can be ascertained from the above, strong inter-disciplinary cooperation between clinical teams is required, i.e., between the ophthalmologists, pathologists, hematologists, radiologists, and radiotherapists.

8b. Staging

Apart from the molecular pathological classification, hematological staging of the lymphoma in each patient is of great significance, particularly with respect to patient management. Using the information from the hematological work-up, most hematologists use the Ann Arbor classification, which has been defined for Hodgkin-lymphoma and for NHLs.[51] The Ann Arbor "Lugano" classification for Non-Hodgkin-lymphoma is summarized in Table 3.[10]

9. Treatment concepts for iris lymphoma

9a. General considerations

As above, after the establishment of the diagnosis, cases of iris lymphoma must be presented and discussed in internal multidisciplinary tumor boards. There are no standardized protocols for the treatment of iris lymphoma, due to the rarity of this disease. However, a personalized approach to patient treatment would include consideration of not only the particular iris lymphoma but also of the general condition of the patient and their particular personal circumstances and preferences. All treatment decisions should be made together with the patient.

Some treatment options are applicable for disease limited to the iris, whilst others must take into account systemic disease. For example, a secondary leukemic manifestation in the iris must include both localized and systemic therapy.

Iris lymphoma case reports describe the diagnoses and respective treatments in these patients, and these are summarized in Table 1. General considerations and assumptions for treatment of iris lymphoma are evaluated and described below. Figure 5 demonstrates a possible work-up for iris lymphoma including information, how to diagnose iris lymphoma and how to develop a treatment concept for these patients.

9b. Systemic medical drug treatment

Most iris lymphomas are treated by systemic chemotherapy, chemo-immune-therapy, checkpoint inhibitors, or further targeted therapies.[20,35] A combination of the mentioned therapy is often required and are most likely established by an experienced hematologist.

9c. External beam radiation

In cases of primary lymphoma, external beam irradiation could also be a treatment option.[39] This is also the case with secondary iris lymphomas with disturbing or sight-threating ocular symptoms. The dose is dependant on lymphoma type, usage of additional systemic medication and the purpose of treatment (curative versus palliative), is usually between 40-80 Gray. Further, different options such as linear accelerator, proton beam radiation, gamma knife radiation or cyber knife radiation may also be used in this condition.[6]

9d. Ocular medical drug treatment

In some cases, iris lymphoma is treated locally with intraocular injections. To date, the most experience has been gained using intravitreal methotrexate and/or rituximab.[35] These reagents are administered either into the anterior chamber or into the vitreous.

The latter offers the advantage of having a depot effect up to 4 weeks, with little risk of it being washed out as quickly via the trabecular meshwork. Similar to external beam irradiation, ocular injection of chemotherapeutic agents only makes sense in isolated primary iris lymphoma or to support systemic therapy.

9e. Surgery

Surgical treatment options are less likely to cure iris lymphoma, unless the area affected is well-contained. However, it may be undertaken should the patient have developed a secondary glaucoma as a result of the iridal lymphoma.[6]

9f. Watch and Wait – palliative approach

In some very rare cases, depending of the patient's age and general condition, a 'watch-and-wait' approach (i.e. without the administration of any treatment) might be considered appropriate after appropriate clinical diagnostics and deliberation. The benefit and the disadvantages of therapy options should be discussed within the internal tumor board and with the patient.

9g. Online Tool to choose treatment

An important online tool to care lymphoma and cancer in general has been established with the National Comprehensive Cancer Network (www.nccn.org). For many lymphoma types, guidelines and recommendations are provided on this website. Here, oncological ophthalmologists find valuable information regarding lymphoma, which might be very helpful in secondary manifestation of these tumors in the iris.

10. Follow-Up and further care (recommendation for ophthalmic and hematologic follow-up, psycho-oncology)

After treatment, all patients with iris lymphoma must be monitored frequently. An ophthalmic follow-up of every 6 weeks for the first 3 months, and then every 3 months for the first three years are recommended by the authors. In the event of sight-threating conditions or painful symptoms these intervals might be shortened. A follow-up visit in the ophthalmology department should include visual acuity testing, visual field testing, intraocular pressure measuring, and investigating the anterior chamber using a slit lamp, followed by fundoscopy, standardized echography, UBM, anterior chamber OCT, and laser flare photometry. Most important for the monitoring of the tumor is photographic documentation of the iris and of the anterior chamber, pre- and post-treatment.

In addition to the ophthalmic follow-up, a hematological follow-up must be undertaken by the hematology team. Intervals are to be defined by the hematologist and might vary between 3 and 6 months initially.

In the case of tumor recurrence either within the eye or systemically, the patient's case has to re-evaluated by the internal tumor board.

Within the medical care, all lymphoma patients should be offered a psycho-oncological support with diagnosis and throughout the complete treatment and after-care process. This practice is in accordance with all major lymphoma guidelines (www.nccn.org, www.esmo.org, www.evidence.nhs.uk, www.onkopedia.com).

11. Conclusions:

To date, there are no standardized protocols for the treatment of iris lymphoma. Conclusions, concepts and experience in the diagnostics and treatment of systemic, and other intraocular lymphomas allow us here to extrapolate and draw-up recommendations for the treatment of iris lymphoma patients. As in all cancers, the multidisciplinary tumor board is key for therapeutic decision-making in iris lymphoma patients. Due to the rarity of this tumor, randomized clinical trials are very unlikely; however, an international multicenter register might enable best practice documentation.

12.Method of literature search:

A PubMed search was performed using the search word combination „iris lymphoma“, “anterior chamber lymphoma”, “iris leukemia”, “anterior chamber leukemia”, “iris multiple myeloma”, “anterior chamber multiple myeloma”, “iris plasma cell myeloma”, “anterior chamber myeloma”, “iris plasmacytoma”, and “anterior chamber plasmacytoma”. English language literature listed in PubMed has been have been screened and included, if iris lymphoma cases have been described or otherwise excluded. Literature in general on lymphoma have been included, only if they contributed significant information or recommendations on characteristics, diagnosis or treatment of iris lymphoma. Further, as menitoned above ‘iris lymphoma’ has been defined as lymphoma predominantly within the iris; ciliary body lymphoma as disease predominantly within the ciliary body; choroidal lymphoma as that predominantly located within the choroid; and vitreo-retinal lymphoma as that arising predominately within the vitreous and/or retina (usually without uveal involvement). Accordingly, iris lymphoma cases with combined ciliary body-, choroidal- or vitreo-retinal lymphoma were excluded from our review.

13.Abbreviations:

AC-OCT	anterior chamber optical coherence tomography
BCR	B-cell-receptor
BRLH	Benign reactive lymphoid hyperplasia
CD	Cluster of differentiation
CNS	Central nervous system
CT	computer tomography
MALT	Mucosa-associated lymphatic tissue
MRI	magnetic resonance imaging
NHL	Non-Hodgkin lymphoma
PET	positron emission tomography
UBM	Ultrasound bio microscopy
WHO	World health organization

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16.Disclosure

Declarations of interest for all authors: none

Figures' Legends

Fig. 1 Anatomical classification of intraocular lymphomas

This figure shows the current understanding of intraocular lymphoma based primarily on the affected anatomic structure. Iris lymphoma has been defined as lymphoma predominantly affecting the iris; ciliary body lymphoma, as that affecting predominantly the ciliary body; choroidal lymphoma as that occurring predominantly within the choroid; and vitreo-retinal lymphoma as that arising mainly within the vitreous and/or retina. This correlates with the TNM/AJCC definition of uveal melanomas (i.e. iris, ciliary body and choroidal melanomas).

* Lymphomatous disease is predominant in the iris and iris root

** Lymphomatous disease is dominant in ciliary body

*** Lymphomatous disease is dominant in choroid

(modified from [14]).

Fig. 2 Lymphopoiesis

The figure shows the process of lymphopoiesis and therefore also potential stages for lymphoma development, as previously modified published.[31,55]

Fig. 3 Iris tumors

a) Iris lymphoma: The photograph shows a whitish mass and pseudohypopyon in the anterior chamber filling the whole chamber angle and touching the cornea at 6 o'clock.
b) Benign reactive lymphoid hyperplasia of the iris: The photomicrograph shows an almost similar looking iris mass, less prominent in size.
c) Iris melanoma: A typical brown mass within the iris in this photography is the key feature to discriminate between iris lymphoma and melanoma.
d) Metastasis within the iris and in the anterior chamber of a bronchial carcinoma patient: Massive infiltration of the whole anterior chamber, including a 'pseudohypopyon' can be seen in this photomicrograph.

Fig. 4 Histopathological photomicrograph

Extensive secondary iris lymphoma: The histopathological photographs show a secondary manifestation of a diffuse large cell B-cell lymphoma in a 68-year old male (a) Hematoxylin-and-eosin (H&E) stain, showing the cornea (left) and the lymphomatous infiltration in the iris (right), with tumour cell 'spillage' into both the anterior and posterior chambers. The iris pigmented epithelium is detached from the iris stroma due to the large number of lymphoma cells. b) H&E stain of the iris lymphoma at higher magnification demonstrating the morphology of the large B-cells with numerous mitoses and occasional apoptotic bodies. c) PAX5 staining of the lymphoma cells; d) high magnification of the lymphoma cells seen in the anterior chamber within fibrin strands. The patient was initially treated with low-dose radiotherapy to the eye; however, unfortunately there was not a significant reduction in the lymphomatous infiltrate. Due to the secondary glaucoma and intractable pain, the eye was removed.

Fig. 5 Work-up chart

This schematic summarizes the suggested concept of how to diagnose and treat iris lymphoma.

Tables' Legends

Tab. 1 Iris lymphoma case report overview

The table summarizes clinical features of all case reports found following the described research rules in this manuscript. Case reports have been divided into a) all lymphoma case reports without plasma cell myeloma; b) case series; and c) plasma cell myeloma case reports.

Tab. 2 Summary of biodata for reviewed iris lymphoma cases

The table summarizes the biodata of all predominate iris lymphoma case reports without plasma cell myeloma. Altogether, 43 cases have been analyzed for age range, gender, unilateral vs bilateral, lymphoma type, eye morphology involvement and therapy.

Tab. 3 Lugano classification-modified Ann Arbor classification for Non-Hodgkin Lymphoma

The table displays the most updated version of the Ann Arbor classification.[10]

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Iris lymphoma – a systematic guideline for diagnosis and treatment

We are thankful that the Reviewers appear to be happy with all of our modifications to the text.

Concerning the request to provide better histopathology figures, we have been able to find an example of an advanced iris lymphoma, which has been added into the text as a replacement Figure 4 to the original one of the biopsy sample. Unfortunately, the slides of the iris biopsy still remain barred doors within the University of Liverpool and are likely to be inaccessible for another one month or two; however, we hope that he would find this case a suitable alternative.

Figure 1

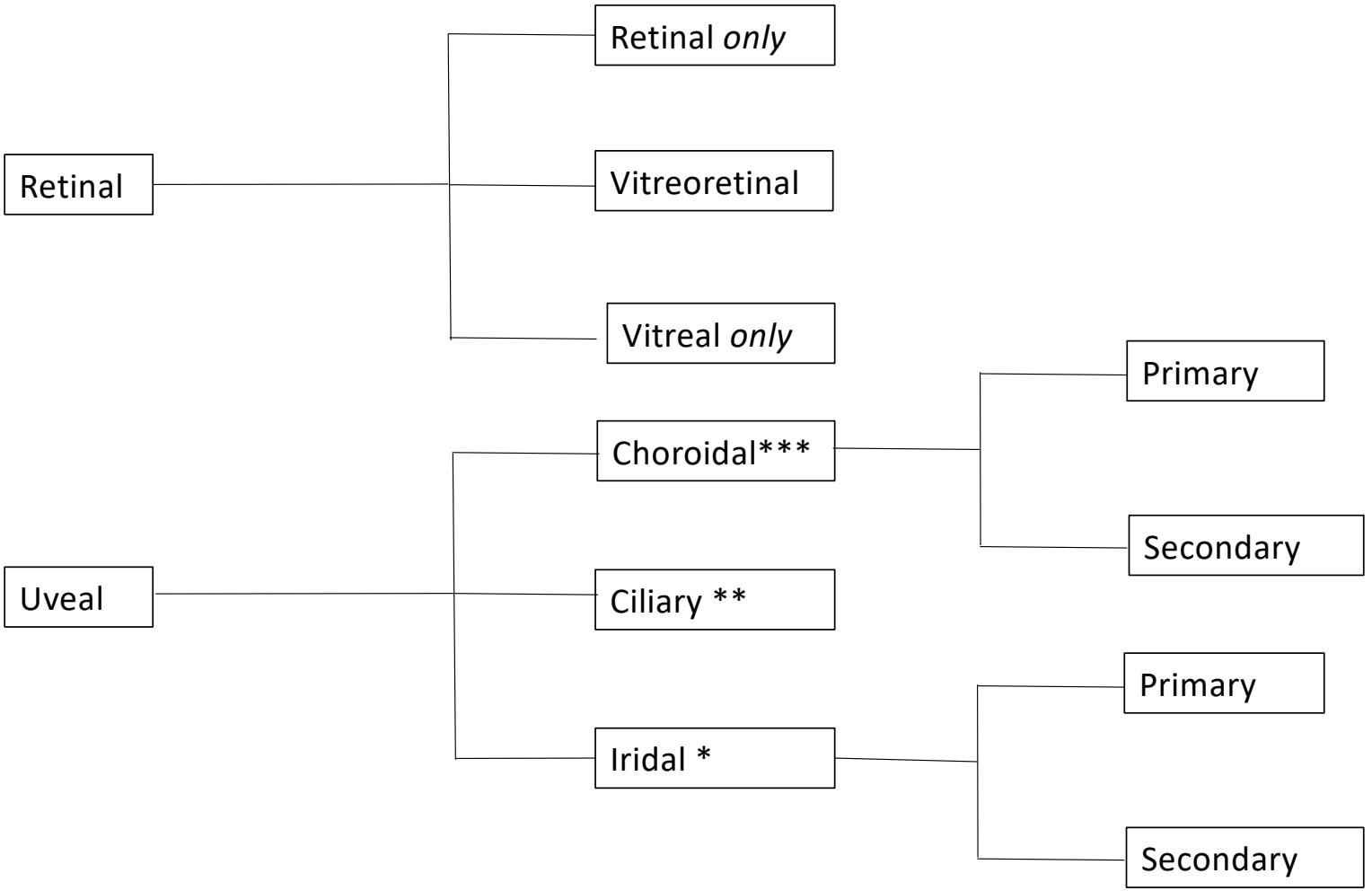
Retinal
Retinal only
Vitreoretinal
Vitreal only
Uveal
Choroidal***
Primary
Secondary
Ciliary **
Iridal *
Primary
Secondary

Figure 2

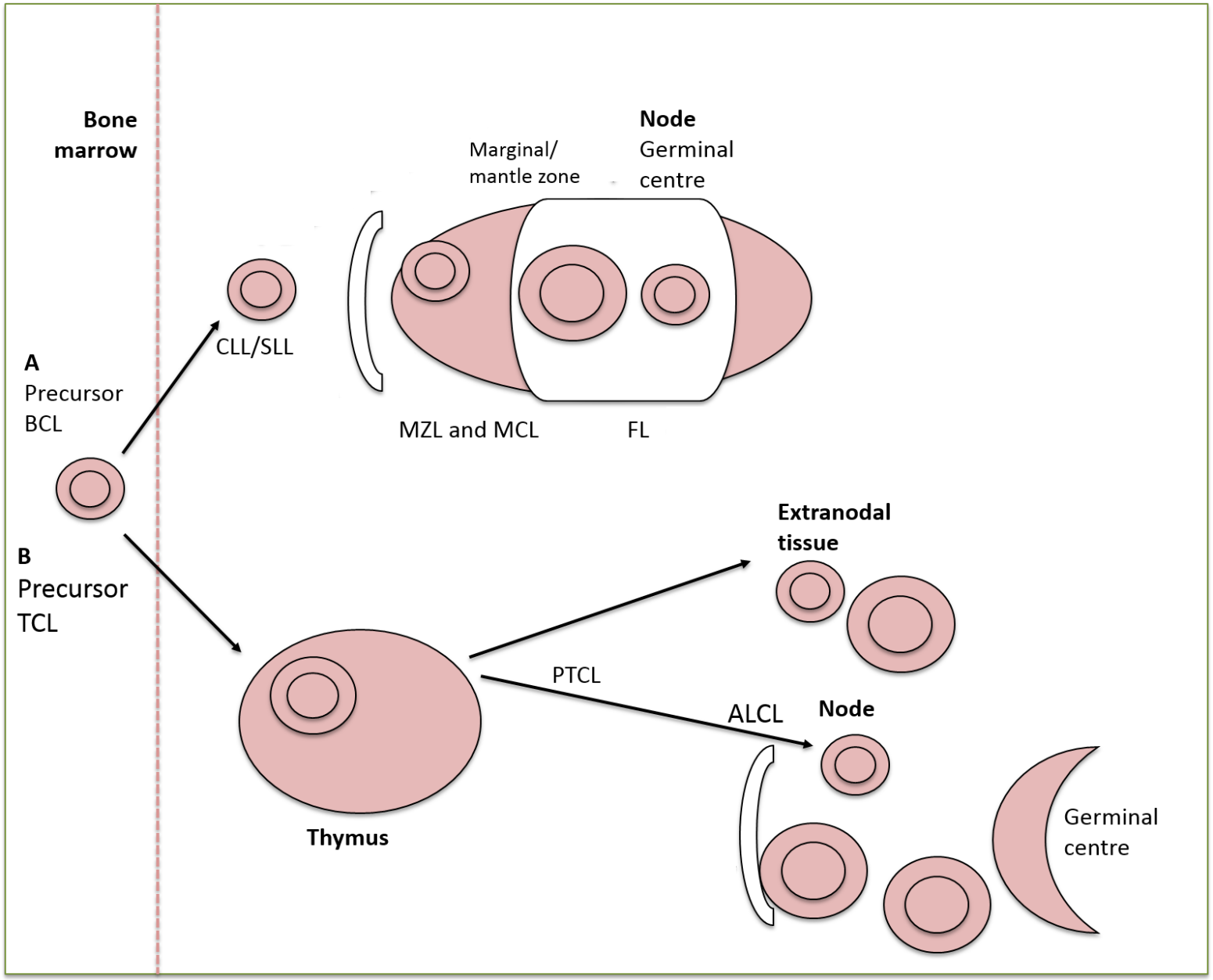
Bone marrow
Node
Germinal centre
Marginal/ mantle zone
CLL/SLL
A
Precursor BCL
MZL and MCL
FL
B
Precursor TCL
Extranodal tissue
PTCL
ALCL
Node
Thymus
Germinal centre

Figure 3a

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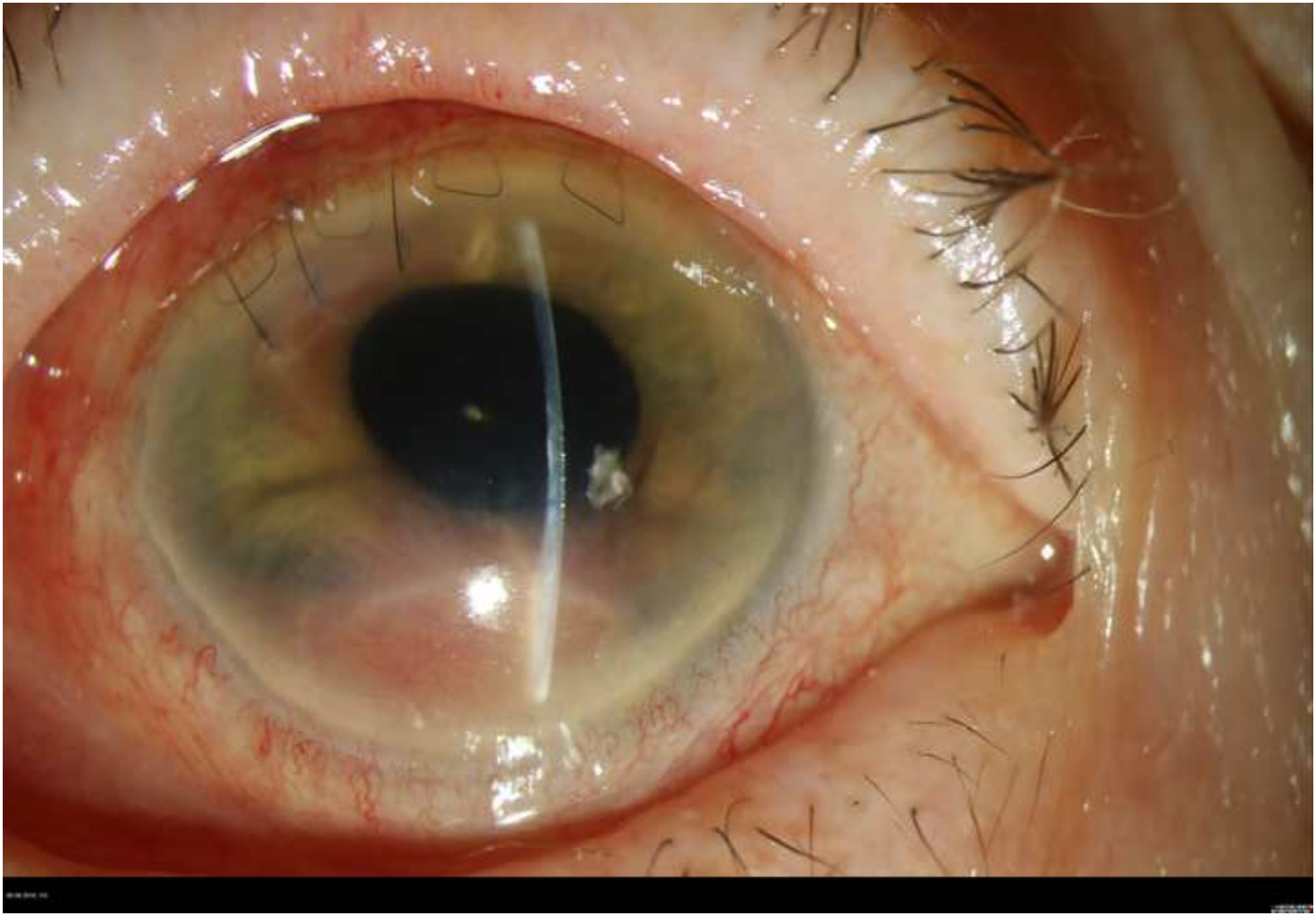

Figure 3b

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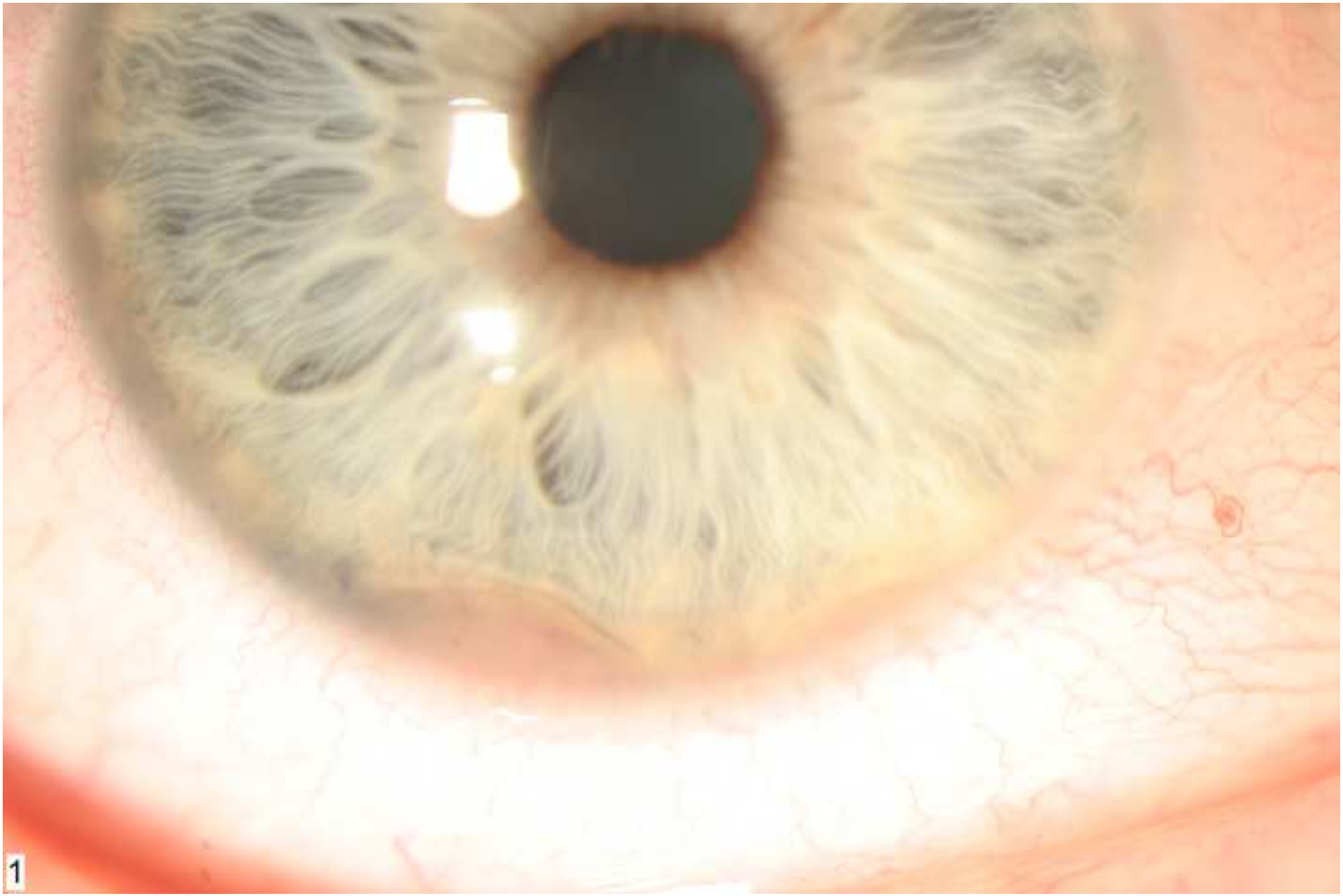

Figure 3c

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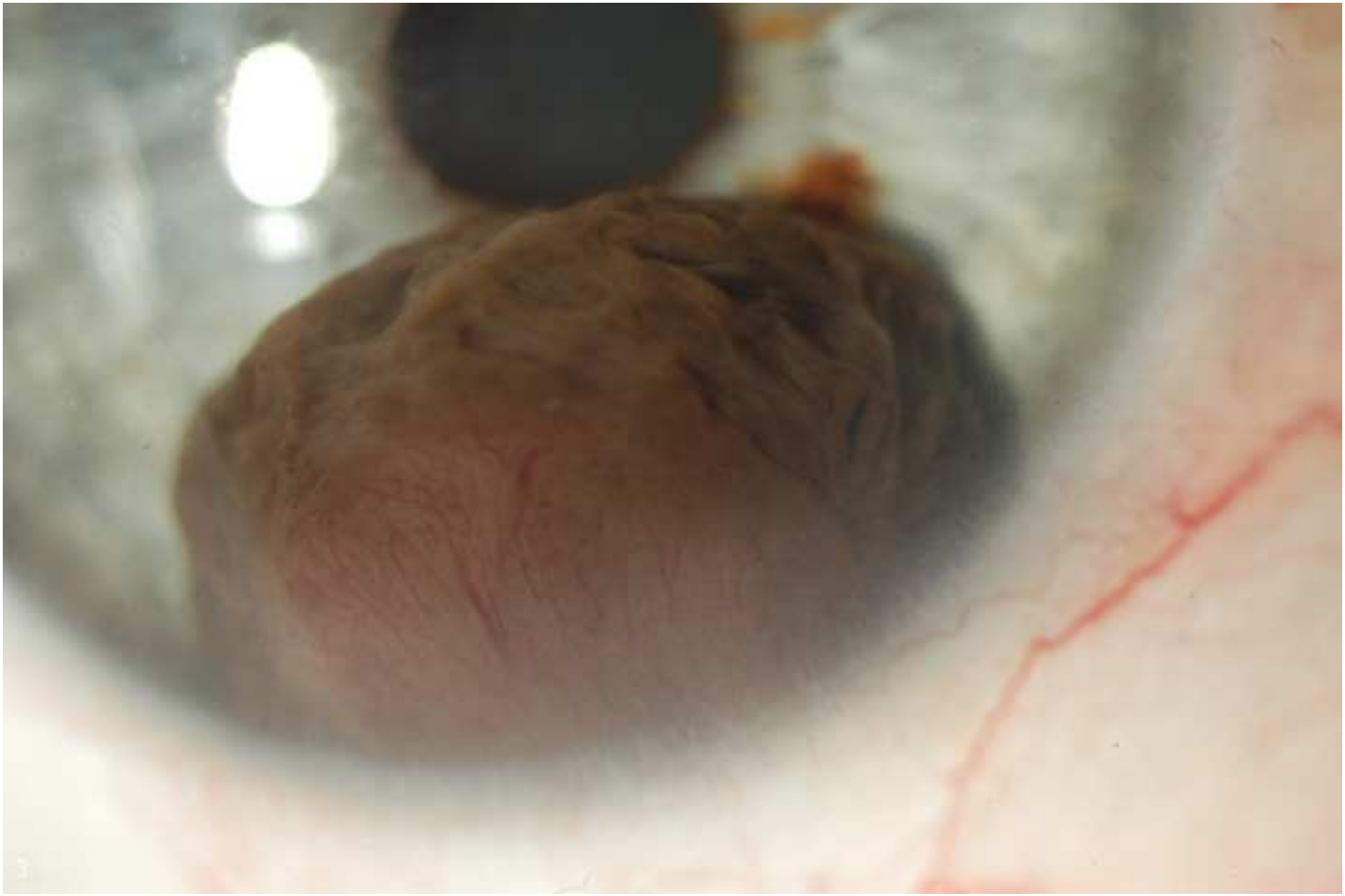

Figure 3d

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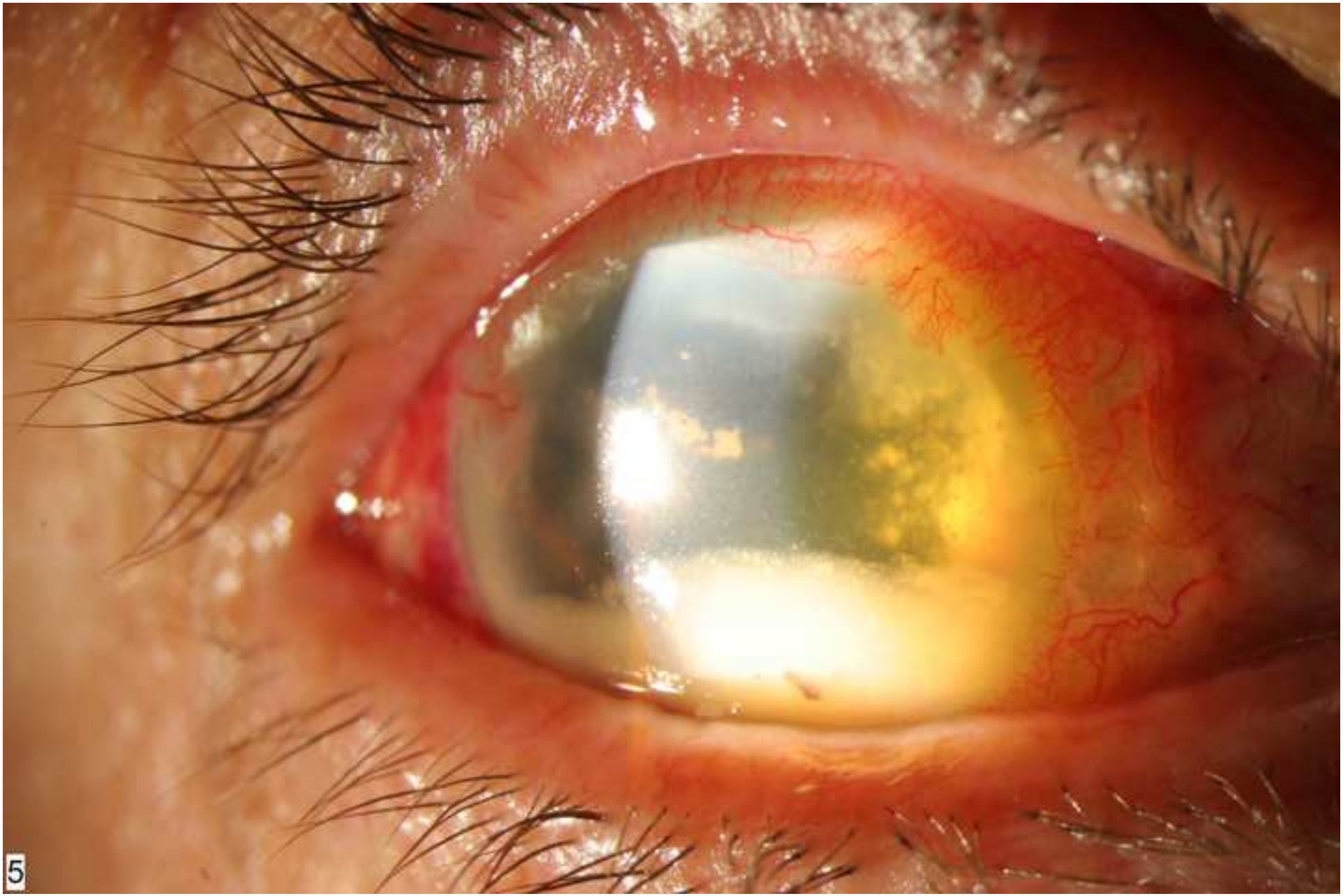

Figure 4

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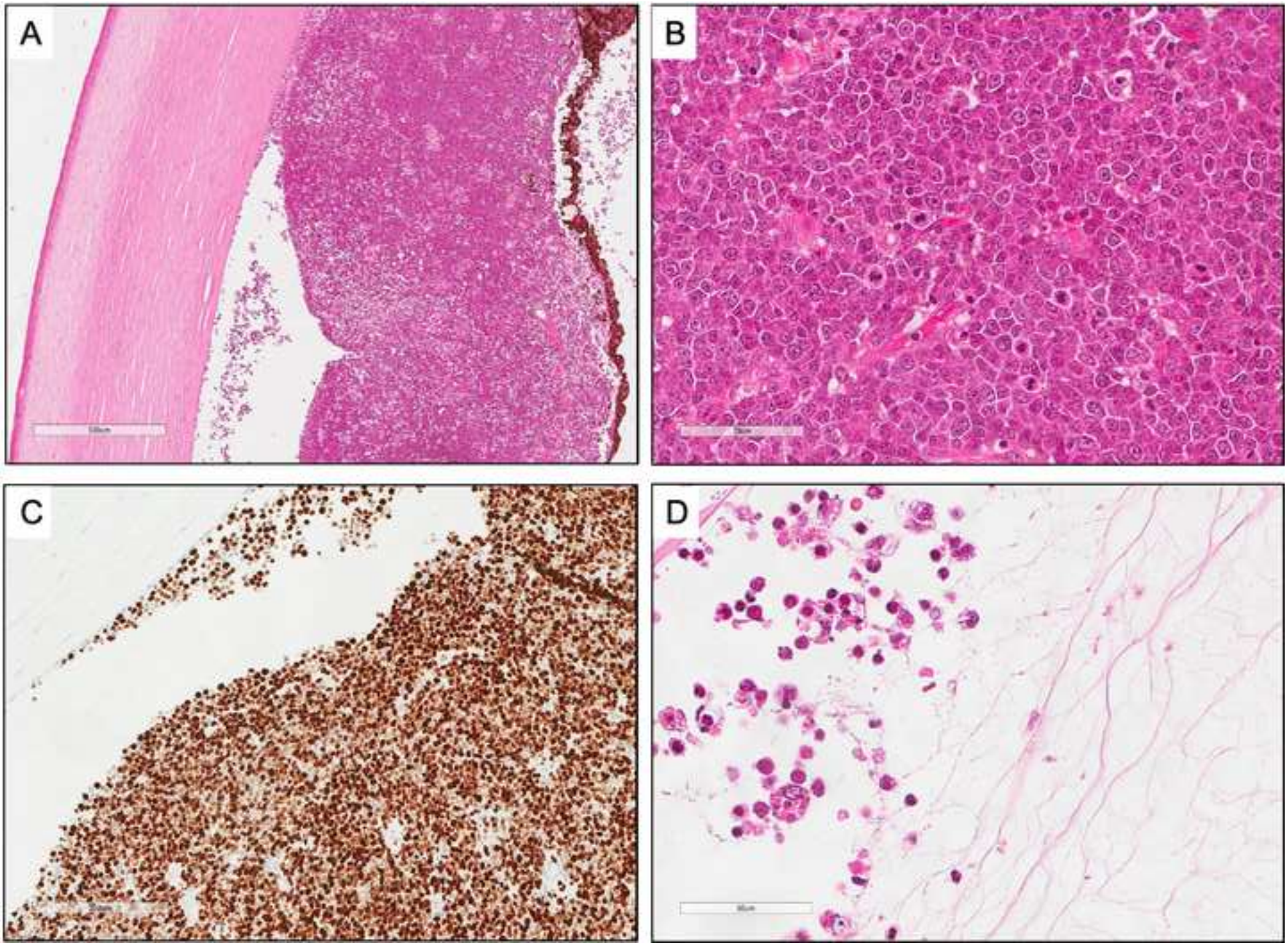

Figure 5

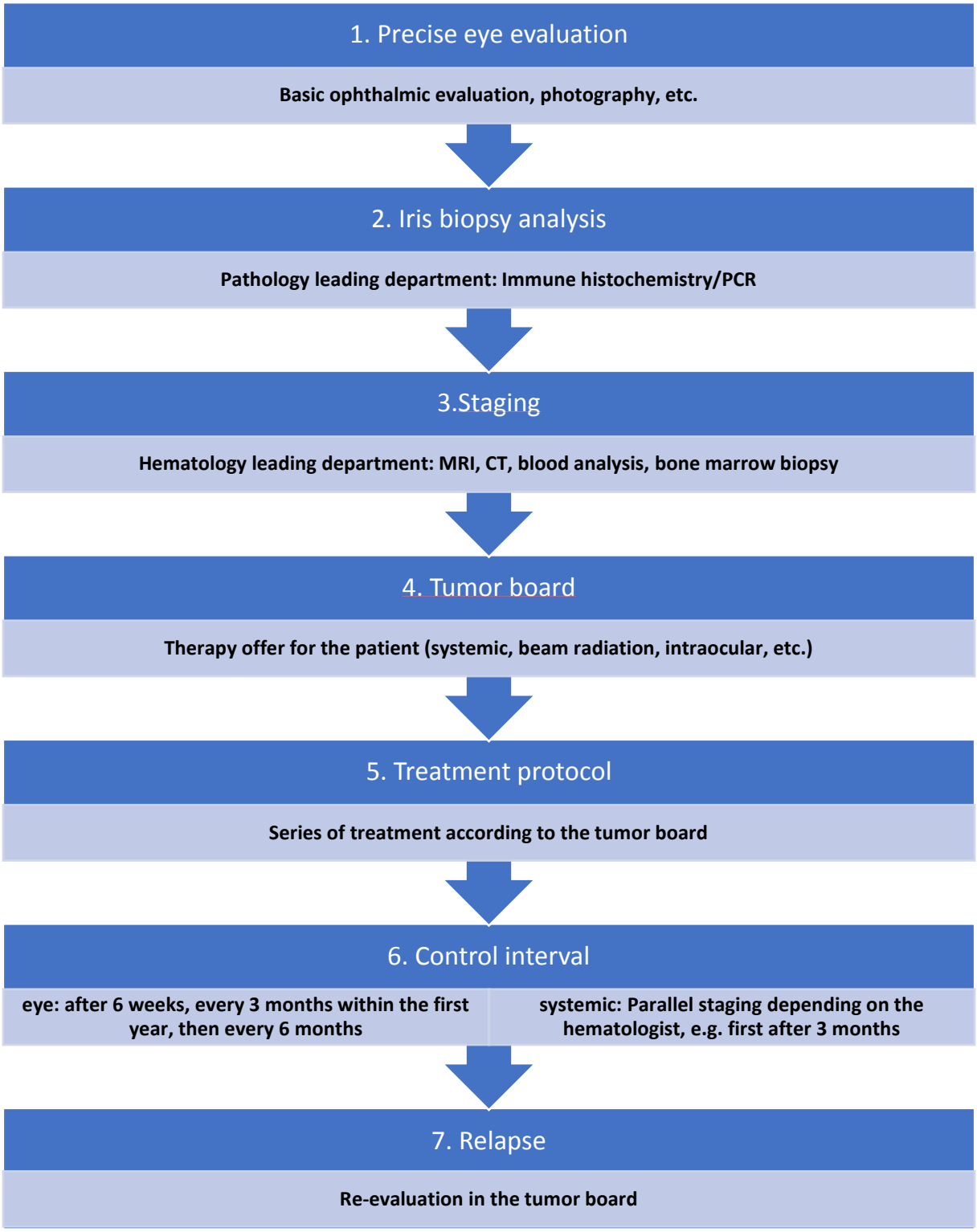
1. Precise eye evaluation
Basic ophthalmic evaluation, photography, etc.
2. Iris biopsy analysis
Pathology leading department: Immune histochemistry/PCR
3.Staging
Hematology leading department: MRI, CT, blood analysis, bone marrow biopsy
4. Tumor board
Therapy offer for the patient (systemic, beam radiation, intraocular, etc.)
5. Treatment protocol
Series of treatment according to the tumor board
6. Control interval
eye: after 6 weeks, every 3 months within the first year, then every 6 months
systemic: Parallel staging depending on the hematologist, e.g. first after 3 months
7. Relapse
Re-evaluation in the tumor board

Table 1

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Table

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Table 2

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Table

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Table 3

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Each author must complete a statement of disclosure.

Manuscript Title: **Iris lymphoma - a systematic concept for diagnosis and treatment**

Authors: **Vinodh Kakkassery, Sarah E. Coupland, Ludwig M. Heindl**

PLEASE LIST:

A) Any commercial or similar relationships of the authors or members of their families to products or companies mentioned in or related to the subject matter of the article being submitted

Kakkassery: NONE
Coupland: NONE
Heindl: none.

B) Any source of funding for the article being submitted

Kakkassery: NONE
Coupland: NONE Heindl: none.

C) Any corporate appointments of the authors or members of their families relating to or in connection with products or companies mentioned in the article or otherwise bearing on the subject matter of the article being submitted

Kakkassery: NONE
Coupland:
Heindl: none.

D) Any other pertinent financial relationships of the authors or members of their families, such as consultancies, stock ownership or other equity interests or patent-licensing arrangements to products mentioned in the article being submitted

Kakkassery: NONE
Coupland: NONE
Heindl: none.

E) Has any portion of this manuscript been submitted for publication elsewhere and/or is it under consideration for publication in another journal, website or textbook? (If yes, please provide details)

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All authors must sign to assure that the statements listed above are truthful and complete to the best of their knowledge.

V. Kakkassery S. Coupland

L. M. Heindl

18-NOV-2019

Iris lymphoma – a systematic guide for diagnosis and treatment

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Short title: Diagnosis and treatment of iris lymphoma

Key words: iris lymphoma – diagnosis – treatment – staging – lymphopoiesis

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Abstract

Iris lymphomas are rare malignant neoplasms arising either as primary tumors in the iris or as secondary tumors involving the iris. We summarize previously published data and make recommendations for work-up strategies for cases of suspected iris lymphoma. Our objective is to provide a structured overview of the typical clinical symptoms and signs, the pathologic, ophthalmic as well as hematologic work-up for diagnosis, treatment, and follow-up of iris lymphomas and offer a flowchart on how to diagnose and treat these tumors.

1.Introduction

Intraocular lymphoma is subdivided by anatomic localization.[14] Lymphomatous involvement of the iris is an extremely rare condition, with little being known about the demographics and epidemiology of this disease. It is defined as a lymphoma with predominant involvement of the iris and can be either a primary or secondary tumor, with most cases in the literature being a secondary manifestation of an underlying systemic non-Hodgkin lymphoma (NHL; Figure 1).[13,14] The diagnosis of primary iris lymphoma is reached if there is no evidence of an underlying systemic lymphoma at the time of ocular diagnosis and staging examinations. This is to be distinguished from a primary ciliary body lymphoma with predominant involvement of the ciliary body, primary choroidal lymphoma arising predominantly within the choroid, and primary vitreo-retinal lymphoma occurring mainly within the vitreous and/or retina (usually *without* any choroidal disease--Figure 1).[14]

Most iris lymphomas are B-cell NHL, but T-cell lymphomas may also occur in the iris. No iris Hodgkin lymphoma has been described to date.[36,40] Nevertheless, iris lymphomas tend to be high-grade lesions, aggressive subtypes of systemic lymphoma with a poor prognosis.[36,40] This clinical outcome also may be due to diagnosis delay, which is quite common, often weeks or months. Typically, iris lymphoma patients present with inflammatory clinical signs and are misdiagnosed initially as anterior uveitis. A definitive diagnosis is ultimately achieved by tissue sampling or aqueous cytology.

We provide diagnostic and therapeutic recommendations, as well as a chart to guide work-up for patients with this disease.

2. Review of the iris lymphoma literature

To date ~30 publications describing ~50 cases of iris lymphoma are indexed in PubMed over the last 40 years (Table 1).[1,2,5,8,9,18,19,24,25,27,28,32,36,37,40-42,44,45,52-54,60,61,64,66-68]

Most are single case reports, but there are also a couple of small case series. As mentioned above, B-cell NHL was the most dominant lymphoma subgroup, followed by T-cell lymphoma and plasma cell myeloma (also termed multiple myeloma). More than 70% of the cases of iris lymphoma were unilateral.

Apart from a dominant iris involvement, scattered lymphoma cells were also observed within the adjacent anterior chamber and ciliary body in some patients. In the latter cases, it is not clear from the descriptions provided whether these lymphomas were primarily arising in the iris or whether they secondarily infiltrated the iris stroma by contiguous spread. In our review of the literature, it was indeed difficult to discriminate between cases that were primarily arising in the iris and those that may have arisen within the anterior choroid/ciliary body and then secondarily infiltrated the iris. Therefore, for the purposes of this review, iris lymphoma was strictly defined as that with predominant disease in the iris, to distinguish it from a ciliary body lymphoma with the bulk of the disease within the ciliary body, from a choroidal lymphoma with predominant lymphoma in this location, and from a vitreo-retinal lymphoma, with the disease occurring mainly within the vitreous and/or retina. This definition correlates with that provided by the Tumor Node Metastatis system for uveal melanoma.[4] Consequently, iris lymphoma cases with combined and extensive ciliary body-, choroidal- or vitreo-retinal lymphoma were excluded from this review. Taking this anatomical definition into account, it would appear that ~25% of the cases reported in the literature are primary iris lymphomas, and the remainder of the cases are secondary iris NHL (Table 2).

The age range of patients with iris lymphomas was between 1 - 89 years, with a peak in the late 50s and early 60s (Table 2). The distribution of male and female patients with primary or secondary lymphoma is the same. Depending on the extent and subtype of the disease, patients were treated with external beam irradiation, local intraocular treatments (e.g., rituximab), systemic therapy, or enucleation. Table 1 summarizes the data on all iris lymphoma cases found in our literature review.

3. Lymphopoiesis - opportunities for lymphocyte mutation towards lymphoma

Knowledge of lymphopoiesis is critical in the understanding of the pathological mechanisms behind lymphoma development. At any stage of the differentiation pathway of lymphocytes, genetic alterations may arise leading to uncontrolled proliferation of a particular clone and ultimately the initiation of a lymphoma.[26,34,48] These may arise in specific niches within the body (nodal or extranodal), potentially remain localized, or spread and become systemic.[26,34,48]

In the healthy person, an intact immune function depends on the regular production of lymphocytes in the bone marrow and thymus. Pluripotent hematopoietic stem cells, also the precursor cells for erythrocytes and platelets, are regulated by different cytokines and chemokines (e.g., interleukin-1, -6, -7 or stem cell factor) and develop into lymphatic precursor cells.[26,34,48] These cells further differentiate into T- or B-lymphocyte stem cells. The T-lymphocyte stem cell migrate into the thymus and undergo a positive or negative selection.[26,34,48] After this selection process, these cells differentiate into either CD4+ or CD8+ cells and are released into the lymph and blood system. Well-defined subtypes of T-cells are known with differing functions in the immune system.[26,34,48]

B-lymphocyte stem cells are located in the bone marrow and spleen and generate pro-and pre-B-cells, which differentiate into ‘immature’ B-cells. They are released as immune naïve B-cells into the blood and ultimately the lymphatic system. During this maturation phase, a key step is the production of a B-cell-receptor (BCR). B-cells without a competent BCR or one with insufficient antigenicity undergo apoptosis.[26,34,48]

The bone marrow and thymus are considered the primary lymphatic organs, as both are the locations where hematopoietic stem cells develop into B- or T-lymphocytes. In contrast, lymph nodes, spleen, tonsil or mucosa-associated lymphatic tissue (M.A.L.T.) are considered as secondary lymphatic organs, where the B- or T-lymphocytes undergo further activation and maturation in lymphatic follicles.[26,34,48]

Immunocompetent naïve lymphocytes circulate in the blood or reside in the lymphatic follicles of the secondary lymphatic organs. In these lymphatic follicles, most cells are B-lymphocytes, but they also contain T-lymphocytes, as well as macrophages and other antigen presenting cells. Before antigen exposure, these lymphoid follicles are called “primary follicles”. After first antigen contact, they differentiate into “secondary

follicles” with a specific architecture. For example, B-lymphocytes, such as naïve B-lymphocytes and memory cells, are mostly found in the cortex of a follicle. In the capsule of the follicle, B-lymphocytes proliferate with support of T-lymphocytes after a contact with an extrinsic antigen, and then differentiate also into plasma cells, providing the humoral response. B-lymphocyte that are considered inadequate on antigen exposure undergo apoptosis in the ‘germinal center’ of the secondary follicle.[26,34,48] Figure 2 displays the different steps of lymphopoiesis and the proposed stages during which mutations can occur, resulting in the differing B- and T-cell lymphomas.

4. Clinical signs and symptoms of iris lymphoma

Clinical signs and symptoms of an iris lymphoma may overlap with those of an anterior uveitis, including visual acuity reduction, intraocular pressure elevation and pain, haze of the cornea, cells and flare in the anterior chamber, pseudohypopyon, and hyphema. Apart from these nonspecific features, a whitish mass in the iris with or without neovascularization differs from an anterior uveitis as well as the appearance of ‘pseudohypopyon’ (Figure 3a).[36,40] Further, cell clumps or aggregates on a lytic background are more likely to comprise lymphoma cells. Owing to its rarity and the similarity of its signs and symptoms to anterior uveitis, the diagnosis of an iris lymphoma, and thereby the commencement of its treatment, may be delayed.

In addition to the ophthalmic signs and symptoms, so-called ‘B-symptoms’ associated with lymphoproliferative disorders, including fever above 38°C, night sweats, and unexpected weight loss (more than 10% in 6 months) may be apparent, and ultimately guide the differential diagnosis and subsequent investigation of these patients to its lymphomatous nature.

5. Differential diagnosis - benign reactive lymphoid hyperplasia of the iris and other differential diagnoses

One of the main differential diagnoses of iris lymphoma is benign reactive lymphoid hyperplasia (BRLH) of the iris, which has been defined as a condition characterized by a mass of benign polyclonal B and T-lymphocytes and plasma cells infiltrating the iris stroma.[12,56] Iris BRLH appears either as a circumscribed lesion or as a diffuse amelanotic thickening of the iris stroma (Figure 3b). It typically shows an indolent course and may even self-resolve. BRLH can occur in association with other systemic conditions, such as Castleman syndrome.[7] BRLH may have been misclassified in the past with small cell B-NHL, such as extranodal marginal zone B-cell NHL or small lymphocytic lymphoma/leukemia.[12,56,58] Malignant transformation of BRLH can occur, but appears to be very uncommon.[33,38]

Because of its benign nature, BRLH of the iris is by nature less aggressive and shows well-circumscribed uveal involvement, thus implying that a 'watch-and-wait' follow-up investigation may help to discriminate between BRLH and any malignant disease.

Further differential diagnoses for iris lymphoma include amelanotic iris nevi, amelanotic iris melanoma (Figure 3c), as well as other rare neoplasms, such as iris hemangiomas, adenoma of the iris pigment epithelium, leiomyoma or rhabdomyosarcoma, or metastatic carcinoma (Figure 3c).[43,59]

In particular, differentiation between an amelanotic iris melanoma and iris lymphoma can be difficult due to similar and overlapping clinical signs. There are certain features, however, that strongly suggest the diagnosis of melanoma. These include a more densely appearing tumor with corectopia, ectropium uveae, glaucoma, hyphema, extraocular extension, as well as feeder vessels.[57] Nevertheless, in unclear cases, histological analysis of a tissue or fine needle aspiration biopsy may be necessary, as the diagnosis obviously has a major impact on treatment choice.

Finally, an inflammatory condition in the anterior chamber (e.g., juvenile xanthogranuloma of the iris or Koeppe nodules of the iris in sarcoidosis) may mimic an iris lymphoma, displaying similar clinical signs and symptoms, as described before.

6. Ophthalmic work-up and fine needle aspiration biopsy/iris biopsy

The first step of the ophthalmic work-up of iris lymphoma is a comprehensive ophthalmic examination, including taking a detailed medical history; visual acuity testing, formal visual field testing; intraocular pressure measurement; and investigating the anterior chamber with a slit lamp, followed by a funduscopy,if possible. Formal visual field testing is performed to assess possible posterior segment/optic nerve involvement or CNS disease. Standardized echography including A- and B-scans, ultrasound biomicroscopy (UBM), and anterior chamber optical coherence tomography (AC-OCT) help to narrow the differential. Both UBM and AS-OCT provide information with respect to status of the iris pigment as well as to the density of the mass. Further, UBM displays the ciliary body and allows for examination of ciliary body infiltration, which AS-OCT is not able to provide.

Apart from the usual comprehensive description of the clinical signs, photographic documentation of the anterior chamber and the iris is mandatory, in order to follow any progression of anterior chamber inflammation and/or the tumor itself including during treatment. Additionally, quantification of anterior chamber inflammation by laser flare photometry or by the use of the Standardized Uveitis Nomenclature allows for the quantification of aqueous flare and cells.[30]

If signs and symptoms suggest a clinical diagnosis of lymphoma, biopsy is mandatory to confirm the diagnosis and to allow for its exact subtyping according to the WHO Lymphoma Classification, updated in 2016.[47] This is key for the subsequent choice of treatment.

To undertake an iris biopsy, two approaches are possible To date, there is no evidence that one approach is better than the other. The first is an incisional surgical biopsy to obtain material from the suspicious iris mass sufficient for diagnostic purposes, without removal of the whole tumor.[11,22,23,46] The second is an excisional resection of the tumor mass to obtain material for histopathological diagnosis, but also with the potential for cure.[62] Both approaches have their advantages and disadvantages. A small specimen procedure may be able to provide the diagnosis, and the residual tumor is then treated by either radiotherapy and/or chemotherapy. There are no data indicating that a small sample biopsy might lead to a higher rate of recurrence, metastasis or earlier cancer-associated death. On the other hand, complete tumor excision is difficult in iris lymphoma, as these tumors are often not well-delineated and, thereby, difficult to remove completely from the eye. Further,

inflammation in the anterior chamber and corneal clouding may make complete tumor excision impossible. In addition to incisional or excisional resections, a careful fine needle aspiration biopsy (FNAB) of the anterior chamber would be of value in cases where there is a reasonable scattering of lymphoma cells within the aqueous. Because of the small amount of material likely to be obtained, only a limited number of investigations would able to be performed on this FNAB; these would be determined by the morphology of the cells (see below).

In some cases, unfortunately, the lymphomatous infiltration within the iris may be involve the entire circumference of the iris, also infiltrating into the chamber angle leading to secondary glaucoma and a painful eye. In such advanced cases, enucleation may be the only option (Figure 4).

7. Morphological, immunohistological, and molecular biological diagnostics.

Critical to the diagnosis of iris lymphoma is the morphological analysis of the biopsied cells. Following surgery, tissue biopsies and FNAB can be placed in a soft fixative, such as Cytolyt, and sent to the laboratory for further processing.[16] Where tissue pieces are present, these would be embedded in paraffin and sectioned for conventional (e.g., hematoxylin and eosin; H&E) and immunohistochemical staining. In contrast, the FNAB would be processed as cytospins, and stained with May Grunewald Giemsa (MGG), with spare cytospins being prepared for immunocytology. On the basis of the cytomorphology, the immunoprofile is selected, taking into account the limited amount of material and the main intent to subclassify the tumor as precisely as possible. The most common B-NHL involving the iris is a 'diffuse large B-cell lymphoma', whilst the small cell B-NHL can vary significantly according to the underlying systemic malignancy (e.g. chronic lymphocytic leukemia, mantle cell lymphoma).[13,17] Should the lymphomatous lesion demonstrate a plasmacellular differentiation, a plasma cell myeloma must be excluded. Finally, in the case of immunosuppressed patients, an Epstein Barr virus-related lymphomatous lesion must be considered.[8,50] Table 1 shows the available immune profile analyses in all case reports and series of iris lymphomas.

By definition, an autonomic clonal proliferation of B- or T-lymphocytes is a lymphoma. Polymerase chain reaction of the immunoglobulin genes (IgH-PCR) and of the T-cell receptor (TCR-PCR) is of value in confirming the diagnosis of B- and T-cell lymphomas, respectively, of the iris. In addition, cytogenetic features of the iris lymphoma cells may enable the exact lymphoma subtyping.[13] This is essential in determining whether this is a primary or secondary manifestation in the eye. Newer next generation sequencing techniques, enabling the detection of both copy number alterations and mutations within tumor cells on small intraocular samples, have recently been introduced into the diagnostic repertoire.[21]

8. Subsequent clinical analyses

8a. Hematologic work-up (MRI, blood analyses, bone marrow analysis; depending on patient's lymphoma history)

As above, based on review of the literature, 75% of iris lymphoma patients have an underlying systemic NHL. Therefore, after diagnosing an iris lymphoma, the patient should be referred to a hematologist team for staging investigations, which entail radiological imaging, as well as serological and bone marrow examinations.[63] Clinical outcome of iris lymphomas is very much dependent on the lymphoma stage and subtype.[13,15]

The techniques for imaging the extent of systemic lymphomatous infiltration include magnetic resonance imaging (MRI) and positron emission tomography (PET).[49,65] An alternative to MRI for staging is computed tomography, particularly in cases with contraindications for MRI (e.g., patients with pacemakers) or bone infiltration.

As can be ascertained from the above, strong interdisciplinary cooperation between clinical teams is required, i.e., between the ophthalmologists, pathologists, hematologists, radiologists, and radiotherapists.

8b. Staging

Apart from the molecular pathological classification, hematological staging of the lymphoma in each patient is of great significance, particularly with respect to management. Using the information from the hematological work-up, most hematologists use the Ann Arbor classification, which has been defined for Hodgkin lymphoma and for NHL.[51] The Ann Arbor "Lugano" classification for NHL is summarized in Table 3.[10]

9. Treatment concepts for iris lymphoma

9a. General considerations

As above, after the establishment of the diagnosis, cases of iris lymphoma must be presented and discussed in internal multidisciplinary tumor boards. There are no standardized protocols for the treatment of iris lymphoma, due to the rarity of this disease; however, a personalized approach to patient treatment would include consideration of not only the particular iris lymphoma, but also of the general condition of patients and their particular personal circumstances and preferences. All treatment decisions should be made together with the patient.

Some treatment options are applicable for disease limited to the iris, while others must take into account systemic disease. For example, a secondary leukemic manifestation in the iris must include both localized and systemic therapy.

Iris lymphoma case reports describe the diagnoses and respective treatments in these patients, and these are summarized in Table 1. General considerations and assumptions for treatment of iris lymphoma are evaluated and described below. Figure 5 demonstrates a possible work-up for iris lymphoma including information on how to diagnose iris lymphoma and how to develop a treatment concept for these patients.

9b. Systemic medical drug treatment

Most iris lymphomas are treated by systemic chemotherapy, chemo-immune-therapy, checkpoint inhibitors, or further targeted therapies.[20,35] A combination of the mentioned therapy is often required and are most likely established by an experienced hematologist.

9c. External beam radiation

In cases of primary lymphoma, external beam irradiation could also be a treatment option.[39] This is also the case with secondary iris lymphomas with disturbing or sight-threating ocular symptoms. The dose is dependent on lymphoma type, usage of additional systemic medication, and the purpose of treatment (curative versus palliative), is usually between 40-80 Gray. Further, different options such as linear accelerator, proton beam radiation, gamma knife radiation, or cyber knife radiation may also be used in this condition.[6]

9d. Ocular medical drug treatment

In some cases, iris lymphoma is treated locally with intraocular injections. To date, the most experience has been gained using intravitreal methotrexate and/or

rituximab.[35] These reagents are administered either into the anterior chamber or into the vitreous. The latter offers the advantage of having a depot effect up to 4 weeks, with little risk of it being washed out as quickly via the trabecular meshwork. Similar to external beam irradiation, ocular injection of chemotherapeutic agents only makes sense in isolated primary iris lymphoma or to support systemic therapy.

9e. Surgery

Surgical treatment options are less likely to cure iris lymphoma, unless the area affected is well-contained. However, it may be undertaken should the patient have developed a secondary glaucoma as a result of the iris lymphoma.[6]

9f. Watch and wait – palliative approach

In some rare cases, depending of the patient's age and general condition, a 'watch-and-wait' approach (i.e. without the administration of any treatment) might be considered appropriate after appropriate clinical diagnostics and deliberation. The benefit and the disadvantages of therapy options should be discussed within the internal tumor board and with the patient.

9g. Online tool to choose treatment

An important online tool to care lymphoma and cancer in general has been established with the National Comprehensive Cancer Network (www.nccn.org). For many lymphoma types, guidelines and recommendations are provided on this website. Here, oncological ophthalmologists find valuable information regarding lymphoma, which might be very helpful in secondary manifestation of these tumors in the iris.

10. Follow-Up and further care (recommendation for ophthalmic and hematologic follow-up, psycho-oncology)

After treatment, all patients with iris lymphoma must be monitored frequently. An ophthalmic follow-up of every 6 weeks for the first 3 months, and then every 3 months for the first three years are recommended. In the event of sight-threating conditions or painful symptoms, these intervals might be shortened. A follow-up visit in the ophthalmology department should include visual acuity and field testing,, intraocular pressure measurement, and visualizing the anterior chamber using a slit lamp, followed by funduscopy, standardized echography, UBM, AC-OCT, and laser flare photometry. Most important for the monitoring of the tumor is photographic documentation of the iris and of the anterior chamber, pre- and post-treatment.

In addition to the ophthalmic follow-up, follow-up must be undertaken by the hematology team. Intervals are to be defined by the hematologist and might vary between 3 and 6 months initially.

In the case of tumor recurrence either within the eye or systemically, the case has to re-evaluated by the multidisciplinary tumor board.

Within the medical care, all lymphoma patients should be offered a psycho-oncological support with diagnosis and throughout the complete treatment and after-care process. This practice is in accordance with all major lymphoma guidelines (www.nccn.org, www.esmo.org, www.evidence.nhs.uk, www.onkopedia.com).

11. Conclusions:

There is no current standardized protocol for the treatment of iris lymphoma. Our experience in the diagnostics and treatment of systemic and other intraocular lymphomas allows us to extrapolate from the data available and draw up recommendations for the treatment of iris lymphoma patients. As in all cancers, the multidisciplinary tumor board is essential for therapeutic decision-making in iris lymphoma patients. Owing to the rarity of this tumor, randomized clinical trials are unlikely to occur; however, an international multicenter register might enable best practice documentation.

12.Method of literature search:

A PubMed search was performed using the search word combination „iris lymphoma“, “anterior chamber lymphoma”, “iris leukemia”, “anterior chamber leukemia”, “iris multiple myeloma”, “anterior chamber multiple myeloma”, “iris plasma cell myeloma”, “anterior chamber myeloma”, “iris plasmacytoma”, and “anterior chamber plasmacytoma”. English language literature listed in PubMed has been have been screened and included, if iris lymphoma cases have been described or otherwise excluded. Literature in general on lymphoma have been included, only if they contributed significant information or recommendations on characteristics, diagnosis or treatment of iris lymphoma. Further, as menitoned above ‘iris lymphoma’ has been defined as lymphoma predominantly within the iris; ciliary body lymphoma as disease predominantly within the ciliary body; choroidal lymphoma as that predominantly located within the choroid; and vitreo-retinal lymphoma as that arising predominately within the vitreous and/or retina (usually without uveal involvement). Accordingly, iris lymphoma cases with combined ciliary body-, choroidal- or vitreo-retinal lymphoma were excluded from our review.

13.Abbreviations:

AC-OCT	anterior chamber optical coherence tomography
BCR	B-cell-receptor
BRLH	Benign reactive lymphoid hyperplasia
CD	Cluster of differentiation
CNS	Central nervous system
CT	computer tomography
MALT	Mucosa-associated lymphatic tissue
MRI	magnetic resonance imaging
NHL	Non-Hodgkin lymphoma
PET	positron emission tomography
UBM	Ultrasound bio microscopy
WHO	World health organization

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16.Disclosure

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Figures' Legends

Fig. 1 Anatomical classification of intraocular lymphomas

This figure shows the current understanding of intraocular lymphoma based primarily on the affected anatomic structure. Iris lymphoma has been defined as lymphoma predominantly affecting the iris; ciliary body lymphoma, as that affecting predominantly the ciliary body; choroidal lymphoma as that occurring predominantly within the choroid; and vitreo-retinal lymphoma as that arising mainly within the vitreous and/or retina. This correlates with the TNM/AJCC definition of uveal melanomas (i.e. iris, ciliary body and choroidal melanomas).

* Lymphomatous disease is predominant in the iris and iris root

** Lymphomatous disease is dominant in ciliary body

*** Lymphomatous disease is dominant in choroid

(modified from [14]).

Fig. 2 Lymphopoiesis

The figure shows the process of lymphopoiesis and therefore also potential stages for lymphoma development, as previously modified published.[31,55]

Fig. 3 Iris tumors

a) Iris lymphoma: The photograph shows a whitish mass and pseudohypopyon in the anterior chamber filling the whole chamber angle and touching the cornea at 6 o'clock.
b) Benign reactive lymphoid hyperplasia of the iris: The photomicrograph shows an almost similar looking iris mass, less prominent in size.
c) Iris melanoma: A typical brown mass within the iris in this photography is the key feature to discriminate between iris lymphoma and melanoma.
d) Metastasis within the iris and in the anterior chamber of a bronchial carcinoma patient: Massive infiltration of the whole anterior chamber, including a 'pseudohypopyon' can be seen in this photomicrograph.

Fig. 4 Histopathological photomicrograph

Extensive secondary iris lymphoma: The histopathological photographs show a secondary manifestation of a diffuse large cell B-cell lymphoma in a 68-year old male (a) Hematoxylin-and-eosin (H&E) stain, showing the cornea (left) and the lymphomatous infiltration in the iris (right), with tumour cell ‘spillage’ into both the anterior and posterior chambers. The iris pigmented epithelium is detached from the iris stroma due to the large number of lymphoma cells. b) H&E stain of the iris lymphoma at higher magnification demonstrating the morphology of the large B-cells with numerous mitoses and occasional apoptotic bodies. c) PAX5 staining of the lymphoma cells; d) high magnification of the lymphoma cells seen in the anterior chamber within fibrin strands. The patient was initially treated with low-dose radiotherapy to the eye; however, unfortunately there was not a significant reduction in the lymphomatous infiltrate. Due to the secondary glaucoma and intractable pain, the eye was removed.

Fig. 5 Work-up chart

This schematic summarizes the suggested concept of how to diagnose and treat iris lymphoma.

Tables' Legends

Tab. 1 Iris lymphoma case report overview

The table summarizes clinical features of all case reports found following the described research rules in this manuscript. Case reports have been divided into a) all lymphoma case reports without plasma cell myeloma; b) case series; and c) plasma cell myeloma case reports.

Tab. 2 Summary of biodata for reviewed iris lymphoma cases

The table summarizes the biodata of all predominate iris lymphoma case reports without plasma cell myeloma. Altogether, 43 cases have been analyzed for age range, gender, unilateral vs bilateral, lymphoma type, eye morphology involvement and therapy.

Tab. 3 Lugano classification-modified Ann Arbor classification for Non-Hodgkin Lymphoma

The table displays the most updated version of the Ann Arbor classification.[10]

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