**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.

**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](http://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](http://www.nccn.org), [www.esmo.org](http://www.esmo.org), [www.evidence.nhs.uk](http://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**

1. 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.
2. Benign reactive lymphoid hyperplasia of the iris: The photomicrograph shows an almost similar looking iris mass, less prominent in size.
3. Iris melanoma: A typical brown mass within the iris in this photography is the key feature to discriminate between iris lymphoma and melanoma.
4. 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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