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Intraocular Lymphoma With B Cells

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ABSTRACT

Intraocular lymphoma includes a group of malignant tumors, originating in the lymphohematopoietic tissue, with reserved prognosis. The risk factors are multiple: chromosomal translocation, infections (Epstein Barr), immunodeficiency, chemotherapy, radiation exposure. Intraocular lymphoma can be primary (vitreoretinal and uveal), and secondary. The uveal one is choroidal or with damage to the iris and ciliary body. Primary vitreoretinal lymphoma, more common bilaterally asymmetric, present at 50-70 years old, can be associated with primary CNS lymphoma or by CNS dissemination with malignant cells, B lymphocytes. Clinically, the anterior pole is not affected, but the posterior pole presents cloudy vitreous with vision in haze, "leopard spot" retinal changes with subretinal infiltrates and lymphomatous foci. In choroidal uveal lymphoma, the anterior pole and vitreous are not affected or show minor signs, but multiple chorioretinal infiltrates, retinal detachment, optic disc edema, sometimes macular damage are present. Lymphoma of the iris and ciliary body, often unilateral, has an iridociliary reaction of variable intensity, with an average vitreous reaction. Secondary lymphoma is metastasis from systemic lymphoma. Treatment in lymphoma depends on the tumor's stage of evolution, stage I-II or III-IV, but also on the type of lymphoma: indolent or aggressive. Treatment options are selected depending on the age, general condition, volume, extent, histology of the tumor. Rituximab can be effective alone, or combined with: cyclophosphamide, doxurubicin, vincristine, prednisone, in repeated courses. If necessary, STEM cell transplantation can be performed, autologous, repeated with allogeneic STEM cells, CAR-T cells. If necessary, local chemotherapy can be applied with intravitreal methotrexate, rituximab, associated with systemic chemotherapy. Surgical treatment might be necessary in some cases with enucleation, exenteration.

Keywords

Primary, Secondary intraocular lymphoma, Vitreoretinal lymphoma, Uveal lymphoma, Rituximab, Chemotherapy.

Introduction

Lymphomas are a heterogeneous group of malignant tumors, present in the reticuloendothelial and lymphatic tissue, with a reserved prognosis, which includes two large groups of neoplasms.

- Non-Hodgkin lymphoma, NHL 85% with:
  - Affecting B cells with multiple subtypes
  - Damage to T cells

- Hodgkin's disease

NHL is the most common hematopoietic neoplasm, 5 times more common than Hodgkin's disease, being more common in men 1.4/1.

NHL has 2 forms: indolent and aggressive

Lymphomas affect the immune system with anarchic, excess lymphocytes that migrate into the bloodstream, locating in various organs.

- Benign lymphomas are slowly progressive, respond to treatment, but are not curative
- Aggressive lymphomas are rapidly progressive, respond to treatment, and some may even be curable
- In children, nonHodgkin lymphoma is always aggressive (Burkitt lymphoma, large B-cell lymphoma).

Intraocular lymphoma B-cell nonHodgkin is a rare form of heterogeneous lymphocytic neoplasia, often undiagnosed, unrecognized or diagnosed late

- NHL is likely to spread, with the incidence and spread of the disease increasing with age
- The incidence of intraocular lymphoma is estimated at 1.86% of malignant intraocular tumors.
- The patient with NHL requires a careful clinical, systemic and ocular examination with a complete assessment of the patient's health status.

Risk Factors

During the various stages of lymphocyte development, a malignant clonal expansion may occur that favors the appearance of lymphoma; this correlated with gene recombination processes causes malignant changes of B and T cells.

The risk factors for NHL are multiple:

- Chromosomal translocation
- Infections
  - Epstein Barr virus, binds to an antigen on the B lymphocyte and causes the transformation of the B lymphocyte into lymphoblast cells
  - Endemic malaria generates decreased T-cell immunity, with B-cell proliferation
  - Hepatitis C virus
  - HSV associated with Kapossi sarcoma
  - Exposure to pesticides, herbicides, chemotherapy, radiation exposure
  - Immunodeficiency (AIDS)
  - Chronic inflammation in patients with autoimmune diseases (Syogreen syndrome, Hashimoto's thyroiditis)

Clinical Forms

Intraocular lymphoma can be primary and secondary. The primitive lymphoma is: vitreoretinal and uveal and this one with 2 forms: choroidal and iris and ciliary body.

Primitive Intraocular Lymphoma [1-3]

- Primitive intraocular lymphoma is a malignant tumor with a reserved prognosis located predominantly in the vitreous and retina, sometimes also at the choroidal level. Many intraocular lymphomas are undiagnosed, and receive incorrect treatment because they can mimic other eye diseases, most commonly uveitis.
- In most cases, intraocular lymphoma presents as uveitis, but there may be other clinical manifestations: intraocular mass, neovascular glaucoma, posterior scleritis (some cases can be detected at autopsy).
- Functional explorations
  - AFG and AVI show localized hyperfluorescence in the temporal sector of the optic disc corresponding to areas of leakage points located in the choroid.
  - Ultrasound biomicroscopy reveals suprachoroidal effusion and choroidal thickening. Bscan can reveal neuroepithelial detachment, thickening of the choroidal layer and retina.
  - OCT shows neuroepithelial detachment, thickening of the choroidal layer, significant presence of subretinal fluid.

Primitive Vitreoretinal Lymphoma [4-6]

- Tumor that predominates in the retina and vitreous, present at 50-70 years, more than 50% bilaterally asymmetric, with an incidence of 0.0146% of patients per year
- is associated with CNS lymphoma, which can be primary or through CNS dissemination with malignant cells, B lymphocytes
  - If lymphoma initially occurs ocularly, in 55-80% patients may develop CNS lymphoma at 60-70 years of age or in immunocompromised youth
  - If the primary lymphoma is initially CNS, the tumor may also appear ocularly at the same time
  - Clinical:
    - The anterior pole is not affected
    - Symptoms: blurred vision, AV decrease in varying degrees, myodesopsia
    - Ophthalmoscopic:
      - Vitreous: diffuse cellular infiltrates with motile cells that cloud the transparency of the vitreous and give blurred vision
      - Retina: EPR changes, with subretinal infiltrates and lymphomatous foci with geographic appearance, yellowish white under bilateral EPR in 80-90%, with its change, "leopard spot" appearance, visualized and AFG; independent non-metastatic foci of primitive CNS lymphoma are present

There is correlation between ocular and CNS lymphoma, therefore all patients must undergo a complete clinical examination, with neurological, oncological, ophthalmological evaluation, parallel with imaging investigations, MRI gadolinum, cerebral, spinal, HIV tests.

- Many patients may present functional cognitive changes with neurological decline

Primary Uveal Lymphoma [4,7]

- It is more common in men 50-70 years old, it predominates unilaterally but also bilaterally
- Can have 2 different locations: choroidal or iris and ciliary body (the iris possible with B,T cells)

Choroidal Uveal Lymphoma [5,7-10]

Choroidal lymphoma may take on variable non-specific clinical aspects. The patient may have atypical symptoms or persistent clinical signs and symptoms of uveitis and/or scleritis unresponsive to treatment, requiring immediate biopsy to establish the correct diagnosis.

- Symptoms:
  - Recurrent episodes of decreased vision, metamorphopsia
  - If the disease progresses, pain appears (possibly due to secondary angle-closure glaucoma), decreased vision
  - Diplopia, proptosis may be present in the episcleral extension

- Choroidal lymphoma can be associated with systemic lymphoma
- The anterior pole may (or may not) show signs of anterior uveitis, + iris infiltrate, ciliary body, rubeosis iridis
- Ophthalmoscope
  - vitreous - minor or absent signs with the presence of cellular reaction
  - yellowish creamy infiltrates, single or multiple, chorioretinal
  - retinal detachment with tendency to extension
  - choroidal folds, optic disc edema, lipofuscin pigment
  - possible macular localization with cystoid macular edema, with decreased vision
- Episcleral extension, with congested episcleral vessels

Iris and Ciliary Body Lymphoma [8,11,12]

- Often unilateral
- Symptoms: moderate with decreased vision, blurred vision
- Anterior pole: present iridociliary reaction of variable intensity, with perikeratic hyperemia, corneal precipitates, Tindal positive, iris and ciliary body infiltrate, rubeosis iridis, secondary glaucoma.
- Average vitreous reaction, minimal ophthalmoscopic changes
- Differential diagnosis
- Primary vitreoretinal lymphoma, metastatic carcinoma, parsplanitis, leukemic infiltrate, chronic idiopathic vitritis, primary uveal lymphoma, choroiditis, benign lymphoid reactive hyperplasia, posterior scleritis, Hodgkin's disease.

Secondary Intraocular Lymphoma [8,9,13]

- It is metastasis from systemic lymphoma

- **Paraclinical explorations** they are useful for confirming the positive diagnosis of lymphoma [5,7,8,14].

B scan shows:

- Detachment of the neuroepithelium
- Thickening of the choroidal layer
- Significant presence of subretinal fluid

Biomicroscopic ultrasound reveals:

- Suprachoroidal effusion
- Choroidal thickening

October

- Changes in the retinal pigment epithelium (RPE) and the presence of subretinal fluid
- Thickening of the choroidal layer and detachment of the neuroepithelium
- Subretinal lesions, granular, between Bruch's membrane and EPR
- Retinal changes, reactive changes of Bruch's membrane
- Individualize choroidal metastases

AFG

- Early hypofluorescence, late hyperflorescence
- Punctate leakage in metastases
- Uveal effusion under the neuroepithelium

Indocyanine green angiography - AVI - shows:

- Hypofluorescent spots of various sizes in the early to late phase corresponding to multiple choroidal lesions
- AFG and AVI show localized hyperfluorescence in the temporal scotoma of the optic disc corresponding to punctate areas of choroidal leakage.

Biopsy by vitreous aspiration or by vitrectomy and retinal puncture [6]

- Cytological examination may reveal neoplastic, pleomorphic lymphocytes with oval or round nuclei, occasionally prominent nucleoli, with frequent mitoses, insufficient cytoplasm
- It is not always conclusive

PCR

- Can detect the MVD88 gene mutation, frequently present in lymphoma
- Allows measurement of IL-6, IL-10 in vitreous, aqueous humor
- Immunohistochemistry can be conclusive for diagnosis

Mandatory clinical investigations

- Lungs radiograph
- CT, MRI, for diagnosis of disease, response to treatment and / or detection of recurrences
- Scan Pet positron emission tomography is useful for post-therapeutic evaluation to highlight early recurrence; has predictive value for relapse

Prognosis

The prognosis in NHL is variable and is dependent on the histological type, extent; tumor size: age older than 60 years, general condition, tumor location, stages of evolution III-IV. In NHL the prognosis is reserved for recurrence 22% after treatment.

- **Positive diagnosis** of intraocular lymphoma is difficult to establish, the tumor can generate clinical manifestations similar to other eye diseases.
- The positive diagnosis must highlight the exact clinical diagnosis, tumor staging and functional evaluation with cure or palliation [1,2].

Treatment in Intraocular Lymphoma

- Treatment in intraocular lymphoma depends on the stage of the lymphoma [2,3,5,13,14].

Stage I-II

- ***Localized lymphoma with relatively benign evolution***, can benefit from local radiation therapy, which can control the disease for a long time, but relapses can occur even after 10 years
- ***Aggressive localized lymphoma***requires intensive associated chemotherapy

Stage III-IV

- ***Lymphoma with benign evolution***, require a single alkylating drug or treatment regimens with 2-3 associated drugs
  - Treatment options are selected depending on the age, general condition, extension, volume, histology of the tumor
  - Rituximab can be effective alone or in combination
- ***Aggressive lymphoma*****,** requires association, rituximab, with cyclophosphamide, doxurubicin, vincristine, prednisone.
  - Autologous STEM cell transplantation
  - Bone marrow transplant when unresponsive to treatment
  - Permanently monitored patients with periodic control

Treatment Indications

- Stage I-II
  - Indolent lymphoma
    - Radiotherapy 30-40gy, divided into daily sessions 1.5-2gy, with possible side effects
  - Aggressive lymphoma
    - Rituximab associated with cyclophosphamide, vincristine, doxorubicin, prednisone
    - Associated chemotherapy, short 3 cycles, associated with monoclonal antibody, rituximab, followed by radiotherapy
    - If PET positron emission tomography is positive, 2 more cycles are administered before radiotherapy
    - Relapse, requires stage IV treatment
- Stage III-IV
  - Indolent lymphoma in advanced stages
    - The initial treatment is extended with monitoring 6-8 cycles of chemotherapy associated with rituximab, + radiotherapy
    - Rituximab plus associated chemotherapy at 21 days, 6 cycles, + radiotherapy
    - If PET is positive, after 4 cycles, 2 cycles of radiotherapy are administered
  - Unilateral lymphoma limited to the eye may benefit from intravenous treatment with rituximab or methotrexate, with possible side effects, cataracts, conjunctival hyperemia, keratopathy
  - Relapse, patient up to 70 years old, with good general condition
    - 2 more courses of associated chemotherapy, plus rituximab
    - patient up to 70 years old in good general condition can benefit from autologous STEM cell transplant, repeated if necessary, from allogeneic STEM cell transplant (sibling, compatible donor)

Patients who cannot receive aggressive treatment may benefit from radioimmunotherapy, with a lymphoma-specific monoclonal antibody combined with a radioactive isotope.

CAR – T cell therapy, in which T cells are taken from the patient, modified in the laboratory and reintroduced into the patient's circulation to change their affinity to destroy malignant cells.

- Bilateral lymphoma requires:
  - Radiotherapy 40gy, in daily fractions, with variable response, with possible complications: optic neuropathy, retinopathy, dry eye, cataract, glaucoma
  - Systemic chemotherapy plus rituximab

- If intraocular lymphoma is associated with CNS lymphoma, intravenous chemotherapy with high-dose methotrexate, 8g/m2 (the most used) is indicated

- If necessary, local chemotherapy, + systemic chemotherapy can be administered.
  - Intravitreal methotrexate: 400 micrograms / 0.1ml x 2/ week – 4 weeks, x1/week – 4 weeks, 1/month – 12 months, alternatively with radiotherapy
  - Rituximab, intravitreal, 1mg/0.1ml, if methotrexate intolerant
- **Surgical treatment**, enucleation, exenteration, in the extensive forms.
- **For therapeutic efficiency in intraocular lymphoma, an early diagnosis and specific treatment (chemotherapy + radiotherapy) is required immediately, necessary for a good local clinical prognosis, and the prevention of systemic metastases (if they have NOT occurred) [3,8,13].**

Conclusions

Intraocular B-cell lymphoma is a rare form of lymphocytic neoplasia, sometimes undiagnosed, unrecognized, or diagnosed late, with higher incidence and dissemination after 60 years, with reserved prognosis. Intraocular lymphoma is primitive and secondary, the primitive is vitreoretinal and uveal, the uveal is choroidal or iris and of the ciliary body.

Clinical manifestations depend on the location, extent and evolution of the tumor. Paraclinical explorations OCT, AFG, aspiration biopsy with cytological examination, immunohistochemistry, PCR, confirm the tumor diagnosis and the stage of evolution. Treatment indications are appropriate to the stage of tumor evolution, differentiated into unilateral and bilateral lymphoma, intraocular lymphoma associated with CNS lymphoma or systemic lymphoma, relapsed lymphoma. Lymphoma is radiosensitive, using 40gy radiotherapy. The essential treatment in lymphoma is systemic chemotherapy in short or long treatment courses, of 3-6 cycles, with rituximab + associated with cyclophosphamide, vincristine, doxurubicid, prednisone. If necessary, transplantation of autologous STEM cells, allogenes, radioisotopes, CAR-T cells. Local intravitreal chemotherapy with methotrexate or rituximab may be necessary. Surgical treatment, enucleation, exenteration might be indicated. The patient with intraocular lymphoma requires permanent medical control, ophthalmologist, neurologist, oncologist, with careful periodic evaluation of tumor stage, intraocular, CNS, systemic and appropriate treatment.

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