Lymphome primaire intraoculaire: le syndrome mascarade

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Definitions

• Ocular lymphoma includes:
  - Intraocular lymphoma
  - Extraocular lymphoma (orbital and adnexa) (Dr Moulin)

• Intraocular lymphoma may be:
  - Primary
  - Secondary
  - Uveal
Definitions

• Primary intraocular lymphoma (PIOL):
  - Subset of primary central nervous system (CNS) lymphoma
  - May precede, be concomitant, or be subsequent to CNS lymphoma
  - Lymphoma cells located within the vitreous and the retina → sometimes referred to as primary vitreoretinal lymphoma
Definitions

- Secondary intraocular lymphoma:
  - Arises outside the CNS, usually from non-Hodgkin’s lymphoma, and metastasizes to the eye, mainly the choroid
  - Different clinical features and prognosis than PIOL
  - Lymphoma cells located within the uvea
Definitions

• Uveal lymphoma (PD Dr Schalenbourg):
  - Choroidal (primary uveal lymphoma, with no associated CNS involvement)
  - Iris
  - Ciliary body

• Coupland and Damato suggested the term PIOL be replaced with anatomical description of lymphomatous infiltrates: vitreoretinal, uveal (choroidal), iridal, ciliary body lymphoma

Epidemiology of PIOL

- No exact data, rare
- Most data from larger cohorts of primary CNS lymphoma
  - 4-6% of primary brain tumors, < 2000 cases/year USA
  - 1-2% of all extranodal lymphomas, < 1% of all intraocular tumors
- Incidence has tripled over the past 15 years, USA & Europe
- Mostly adults, range 20-80 years of age, more prevalent in older individuals; mean age at presentation 40-60 years
- Sex ratio M:F 1:2, no racial predilection
- 80% PIOL associated with primary CNS (frontal lobe, medulla, leptomeninges, intravascular CNS lymphoma)
WHO classification - nomenclature

• Based on morphology, immunophenotype, genotype and clinical features
• Hematopoietic and lymphoid tissue tumors classified into:
  - Myeloid
  - Lymphoid
  - Histiocytic
• Most PIOL are of the diffuse large-B cell type (DLBCL)
Hematopoietic and lymphoid tissue tumors

Lymphoid
- Hodgkin
- Non-Hodgkin
  - B-cell
    - Lymphoblastic (precursor cell)
    - Mature (peripheral)
      - Leukemic (disseminated) and primary extranodal
  - T-/NK cell
    - Lymphoblastic (precursor cell)
    - Mature (peripheral)
      - Leukemic (disseminated) and primary extranodal

Myeloid

Histiocytic

Solid (predominantly nodal)
Etiology of PIOL

- Unknown, hypotheses
- Infectious antigen(s) may cause B-cell expansion, which then becomes clonal
- Hematological transfer of neoplastic cells from nodal and extranodal sites to ocular and CNS tissues
- Role of EBV
Clinical features

• **MASQUERADE SYNDROME!**:  
  - Unilateral or bilateral (65-83% of cases) involvement, often asymmetric  
  - Blurred vision, floaters, but visual acuity generally better than what would be expected considering intense cellularity

*Modified from Coupland SE et al. Ocul Immunol Inflamm 2009; 17:227-237*
Clinical features

- **MASQUERADE SYNDROME!**
  - Little or no anterior segment inflammation (no synechiae, no ciliary flush)
  - Anterior chamber cells and flare may occur with keratic precipitates
  - Rarely, infiltration of AC angle, or pseudohypopyon

Modified from Coupland SE et al. Ocul Immunol Inflamm 2009; 17:227-237
Clinical features

- **MASQUERADE SYNDROME!**:
  - Vitritis: clumps/sheets/strands of cells, haze
  - Subretinal/sub-RPE creamy lesions, yellow-orange, may be confluent, “leopard-skin” appearance
  - Isolated, punctate, multifocal subretinal infiltrates
  - Exsudative retinal detachment, vasculitis
  - Gen no cystoid macular edema

Modified from Coupland SE et al. Ocul Immunol Inflamm 2009; 17:227-237
Differential diagnosis (clinical)

• Intermediate/posterior uveitides and panuveitides
  - Non-infectious
    Behçet’s disease (ischemia!)
    VKH (fluorescein and ICG angiographic features)
    Retinal vasculitis
    Sarcoidosis
  - Infectious
    Tuberculosis
    Syphilis
    Fungal or bacterial endophthalmitis

• Choroidal metastasis (pale, subretinal fluid, no vitreous cells/haze)
The “typical” clinical scenario

- Patient is > 60 years of age
- Chronic uni- or bilateral intermediate or posterior uveitis with relatively good visual acuity
- No cystoid macular edema despite intense cellularity in the vitreous
- Good initial response to oral corticosteroids, then refractory
- Delayed diagnosis because of aspecific clinical presentation
- Blood workup for specific uveitic entities negative
- Definitive diagnosis made after several vitreous biopsies
Diagnosis

• Fluorescein angiography: punctate window defects, hypofluorescent lesions (masking effect), vascular leakage, generally no macular leakage, late staining of subretinal infiltrates

• ICG angiography: hypocyanescent lesions early phase, isocyanescent lesions late phase

Fluo + ICG: positive predictive value 89%, negative predictive value 85%

Diagnosis

- OCT

Hyperreflective sub-RPE material

Modified from Vasconcelos-Santos DV. *J Ophthalmic Inflamm Infect* 2011

Modified from Forooghian F. *Ophthalmic Surg Laser Imaging* 2011
Diagnosis

• Blood studies: to rule out differential diagnoses (infectious uveitides, sarcoidosis)
• Neuroimaging: to confirm/rule out CNS involvement; MRI > CT-scan
• Vitreous/retinal biopsy
  - Fine needle aspiration or vitrectomy, multiple biopsies often needed
  - Retinotomy with aspiration from subretinal fluid/material
  - Uveal biopsies often non-diagnostic
• Biopsy specimens must be transported quickly since lymphoma cells undergo degradation within 60 minutes
• If ongoing corticosteroid therapy → discontinue for at least 2 weeks
Diagnosis

• Cytology: sensitivity 30% (often due to little number of cells), specificity 100%

• Immunohistochemistry: phenotyping of cells by their surface markers; improves sensitivity from 30% to 70%

• PCR \(\rightarrow\) clonality, IgH rearrangement: high sensitivity and specificity

• Cytokine dosage:
  - IL-10: if elevated, sensitivity 90%, specificity 93%
  - IL-10/IL-6 ratio: if > 1, sensitivity and specificity 75%
Therapy

- Radiotherapy: brain and orbits, total 20-50 Gy
- Systemic chemotherapy: high-dose IV methotrexate if CNS involvement
- Combination of initial brain & eye radiotherapy followed by chemotherapy
- Intraocular chemotherapy (intravitreous):
  - Methotrexate: 0.4 mg/0.1 ml, total 25 injections; CAVE endothelium!
  - Rituximab: anti-CD20 monoclonal antibody, 1 mg/0.1 ml
Conclusion – message to take home

- PIOL is a rare disease
- Differentiate PIOL (subset of primary CNS lymphoma) from secondary intraocular lymphoma (extra-CNS lymphoma metastatizing to the eye)
- Mostly diffuse large B-cell lymphoma (DLBCL)
- Delayed diagnosis, diagnostic challenge, refractory chronic uveitis, particularly if isolated vitreous involvement → MASQUERADE!
- Typical subretinal and sub-RPE lesions
- Definitive diagnosis: vitreous biopsy, several biopsies often needed
- Cytology, immunohistochemistry, PCR, cytokine levels (IL-10, IL-6)
- Multidisciplinary diagnosis, therapy and follow-up
Quizz #1

What is the difference between primary and secondary intraocular lymphoma (only one answer):

1. There is no difference
2. Primary involves younger patients than secondary
3. Primary is a subset of CNS lymphoma, secondary is not
4. Primary means lymphoma is B-cell, secondary means it is T-cell
5. Primary means the patient was never diagnosed with ocular lymphoma before, secondary means recurrent ocular lymphoma
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Quizz #2

What is the most common lymphoma type in PIOL (only one answer):

1. Mantle cell lymphoma
2. Hodgkin’s lymphoma
3. Burkitt’s lymphoma (EBV-related)
4. Peripheral T-cell lymphoma
5. Diffuse large B-cell lymphoma
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Quizz #3

Which of the following regarding PIOL is FALSE (only one answer):

1. Often presents as non-specific, chronic intermediate uveitis
2. Results from intraocular metastases of Hodgkin’s lymphoma
3. Usually involves patients > 50-60 years of age
4. May respond to oral corticosteroids
5. Typical location of lesions is beneath the RPE
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Quizz #4

Which of the following is TRUE regarding PIOL (only one answer):

1. Cytology of vitreous has a poor sensitivity
2. PCR of vitreous has a high specificity
3. Elevated IL-10 concentration is highly suggestive of PIOL
4. Vitreous specimens must be handled as quickly as possible
5. All of the above
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