ORBITAL AND OCULAR ADNEXAL LYMPHOPROLIFERATIVE DISORDERS

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By

Sally Farouk Hussein Mohamed

(M.B.B.Ch)

Under supervision of

Prof. Dr. Beshr Atef Kenawy

Professor of Ophthalmology

Faculty of Medicine - Cairo University

Prof. Dr. Essam Ali El Tokhy

Assistant professor of Ophthalmology

Faculty of Medicine - Cairo University

Dr. Rania Ahmed Abd El Salam

Lecturer of Ophthalmology

Faculty of Medicine - Cairo University

Cairo University

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ABSTRACT

Orbital and ocular adnexal lymphoproliferative disorders account for 10-15% of orbital mass lesions. This spectrum includes the lymphocytic lesions, plasma cell tumors, histiocytic disorders and leukemic deposits. They represent a continuum of disorders ranging from benign to overtly malignant with considerable risk of systemic involvement. They develop as primary or secondary tumor manifestations in the orbit, conjunctiva, lid, lacrimal gland and sac.

Advancing immunohistochemistry and molecular biology allow more accurate immunophenotyping of individual clones of lymphoid cells and early and precise detection of genetic alterations. Specific immunobiologic diagnosis allows ophthalmologists to consider the lymphoproliferative lesions as a distinct clinicopathologic entity from idiopathic orbital inflammatory disease, with much different behavior.

Tissue biopsy remains mandatory for diagnosis with thorough systemic medical evaluation by hemato-oncologist. Radiotherapy is of choice for the majority of localized lesions while disseminated disease requires systemic chemotherapy or combined therapy. Recent immunotherapy is promising satisfactory results with low toxicity and risk of relapse. Long-term follow-up with half-yearly examination is recommended for detection of new lesions, late recurrence or systemic affection.

Key words:

Orbit - ocular adnexa – lymphoproliferative – biopsy - immunohistochemistry - molecular biology – Radiotherapy – chemotherapy - immunotherapy

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LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

page

****

Fig. 24: lacrimal sac lymphoma

Fig. 25: conjunctival lymphoma

Fig.26: Bilateral lymphoid lesions in the preseptal portion of eyelids

Fig. 27: ***:*** Superonasal anterior orbital mass presenting as a subcutaneous lesion in a 71-year-old woman with known lymphoma

Fig.28: CT scans of the orbit of a 35-year-old female with a history of non-Hodgkin's lymphoma and a recent onset orbital mass.

Fig.29**:** Axial orbital CT demonstrating an intraconal orbital mass with no bone destruction

Fig.30 : CT scan indicates a well-circumscribed mass confined to right lacrimal gland

Fig.31 : Lymphomatous infiltration of the extraocular muscles

Fig. 32: CT scan indicates a mass confined to the lacrimal gland bilaterally

Fig.33: MRI of the orbit of an 80 year old patient with right side proptosis

Fig.34: B and A scan of lymphoid lesion

Fig.36: Reactive lymphoid hyperplasia

Fig.37: immunophenotyping of reactive lymphoid hyperplasia showing polyclonality

Fig.38: Well-differentiated small lymphocytic lymphoma

Fig.39: Extranodal marginal zone lymphoma consisting of a heterogeneous population of cells

Fig.40: Extranodal marginal zone B cells with plasmacellular differentiation

Fig.41: Extranodal marginal zone lymphoma of MALT type showing lymphoepithelial lesions

Fig.42: Follicular lymphoma

Fig.43: Nodules stained with bcl-2 in FL

Fig.44: Mantle cell lymphoma

Fig. 45: MCL stains for bcl-1

Fig.46: Diffuse larbe B-cell lymphoma and transitional MALT lymphoma

Fig. 47: DLBCL showing the high proportion of cells in mitosis (90%) detected by labelling with MIB-1 antibodies

Fig. 48: African Burkitt's lymphoma

Fig.49: Non-African Burkitt's lymphoma

Fig.50 : AIDs-related Burkitt's lymphoma

Fig.51: Histopathology of Burkitt’s lymphoma showing sheets of lymphocytes with tingible-body macrophages with nuclear debris ("starry-sky pattern")

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LIST OF ABBREVIATIONS

AAPOX: Adult onset asthma and periocular xanthogranuloma

ACE: angiotensin-converting enzyme

AILD: angioimmunoblastic lymphadenopathy with dysproteinemia

ALCL: anaplastic large cell lymphomas of T-phenotype

ALH: Atypical lymphoid hyperplasia

ALHE: angiolymphoid hyperplasia with eosinophilia

ALL: acute lymphoblastic leukemia

AML: acute myelogenous leukemia

ANA: antinuclear antibody

ANCA: anti nuclear cytoplasmic antibody

AOX: Adult onset xanthogranuloma

APC: Antigen presenting cells

API2: apoptosis inhibitor-2 gene

ATLL: Adult T-cell leukemia-lymphoma

BCL: B-cell leukemia/lymphoma gene

BL: Burkitt's Lymphoma

BSAP: B cell specific activator protein

CBP: CREB binding protein

CD: Clusters of differentiation designation

CGH: Comparative genomic hybridization

cIg: cytoplasmic immunoglobulin

CNS: central nervous system

CLL: chronic lymphocytic leukemia

CR: complete remission

CT: Computed tomography

CTCL: Cutaneous T-Cell Lymphomas

DCR: dacryocystorhinostomy

DLBCL: diffuse large B-cell lymphomas

ECD: Erdheim-Chester disease

EG: Eosinophilic granuloma

EM: Electron microscopy

EMP: extramedullary plasnacytoma

EMZL: extranodal marginal zone lymphoma

ESR: erythrocyte sedimentation rate

FBGC: Foreign body giant cells

FISH: Interphase fluorescence in situ hybridization

FL: follicular lymphoma

FNAB: Fine-needle aspiration biopsy

Gy: grays

H&E: Hematoxylin and Eosin

HAMA: human antimouse antibody

HHV: human herpes virus

HTLV: Human T-cell lymphotropic virus

IFN α: interferon alpha

Ig: Immunoglobulin

IgH: immunoglobulin heavy chain gene

IH: Immunohistochemistry

IL: interleukin

ILSG: International Lymphoma Study Group

IOID: Idiopathic orbital inflammatory disease

JXG: Juvenile xanthogranuloma

KD: Kimura disease

LC: Langerhans' cells

LCH: Langerhans'C cell histiocytosis

mAbs: monoclonal antibodies

MALT: mucosa-associated lymphoid tissue

MCL: mantle cell lymphomas

ML: malignant lymphoma

MLT: MALT lymphoma-associated translocation gene

MM: multiple myeloma

MRI: magnetic resonance imaging

MUM1: multiple myeloma oncogene-1-protein

NBX: Necrobiotic xanthogranuloma

NHL: Non-Hodgkin lymphoma

NKTL: Natural killer/T-cell lymphomas

OAL: ocular adnexal lymphomas

OID: Orbital inflammatory disease

PAS: Periodic acid schiff

PCR: Polymerase chain reaction

PGE2: prostaglandin E2

PLC: pathologic Langerhans' cells

POL: Primary orbital lymphomas

PTCL: Peripheral T-cell lymphomas

RDD: Rosai Dorfman Destombes disease

REAL: Revised European-American Lymphoma

RLH: Reactive lymphoid hyperplasia

RT-PCR: Reverse transcriptase

SHML: Sinus histiocytosis with massive lymphadenopathy

sIg : surface immunoglobulin

SLL: Small lymphocytic lymphoma

TCR: T-cell antigen receptor

TdT: terminal deoxynucleotidyl transferase

WHO: World Health Organization

XLP: X-linked lymphoproliferative syndrome

XRT: External beam radiotherapy

INTRODUCTION

Orbital and ocular adnexal lymphoproliferative disorders constitute a fascinating and confusing disease complex ***(Kersten et al., 2003).*** They represent a heterogeneous group of lymphoid system neoplasm accounting only for 10-15% of orbital mass lesions (***Akansel et al., 2005***). They develop as primary or secondary tumor manifestations in the orbit, conjunctiva, lid, lacrimal gland and sac (***Auw-Haedrich et al., 2001***).

Both clinicians and pathologists have been always faced by considerable diagnostic dilemmas such as difficulty in differentiating between various subtypes, terminology and classification systems as well as treatment needs and prognosis. Both clinical and conventional histopathological parameters have always been challenging due to great overlap of lymphoproliferative disorders. With the advent of immunohistochemical and molecular biological studies, the spectrum of lymphoid disorders is being more clearly defined ***(Kersten et al., 2003).***

More than half of patients with histopathologically verified orbital or adnexal lymphoproliferative lesions have systemic disorders at the time of diagnosis or will develop the systemic disease (***Rootman et al., 2003***). Therefore, it is essential that all patients be investigated including a complete systemic evaluation by a haemato-onclogist at the time of diagnosis and at regular follow up intervals (***Auw-Haedrich et al., 2001***).

It is important for the ophthalmologist to distinguish orbital lymphoproliferative lesions from idiopathic orbital inflammatory disease, previously known as inflammatory pseudotumour, which behave in a much different fashion ***(Kersten et al., 2003).*** Subacute or chronic form is considered part of lymphoproliferative disorders by some authors and excluded by others (***Rootman et al., 2003***).

This work aims at reviewing the literature of clinical presentation and recent immunohistopathological classification of orbital and ocular adnexal lymphoproliferative disorders with their implication on prognosis as well as recent modalities in diagnosis and management.

Basic considerations in the diagnosis and treatment of lymphoproliferative disorders

I) Diagnosis:

A) Clinical considerations:

In spite of the diversity of lymphoproliferative and related hematopoietic disorders, four clinical syndromes can be recognized.

The most common presentation is insidious development of painless orbital mass (frequently anterior), with little functional interference due to low-grade, slowly-developing lesions. Patients may show rapid onset fulminant orbital infiltration due to aggressive disorders, late accelerated phase or secondary infections. Another category develops relatively rapid orbital manifestations secondary to involvement of adjacent bones, paranasal sinuses or skin. Neuro-ophthalmic complications may occur as a result of invasion of the central nervous system, ocular structures or both ***(Rootman et al., 2003).***

B) Imaging:

Orbital imaging allows greater specificity in diagnosis and management of orbital and adnexal lymphoproliferative lesions. This is achieved through determination of the lesion site, size, contour, tissue characteristics, dynamic effects (movement and positional change), capsular definition, relationship to vascular system and adjacent structures, as well as evidence of infiltration. In addition, changes in the lesion with time can help in diagnosis, timing of intervention, and assessment of progression or effect of treatment. Imaging can be useful in guided needle biopsy ***(Rootman, 2003).***

Plain films offer only a very basic assessment of bony details. Computed tomography (CT) scan and magnetic resonance imaging (MRI) are the corner stone of orbital diagnosis. They offer exquisite soft tissue detail and sensitivity to lesions within the orbit, delineate the extent of the tumor and invasion to the orbit and its vicinity. The results often lead to suggestion of the biology of the disease process, narrowing the differential diagnosis and setting the stage for development of an appropriate treatment plan ***(Ben Simon et al., 2005).*** These two modalities remain very complimentary ***(Rootman, 2003).***

1) Computed tomography (CT):

CT scanning is the imaging technique of choice for primary assessment of orbital disease and can be more readily carried out in many situations. It provides excellent soft tissue resolution because of the presence of orbital fat, which is low density on CT (fig.1). It demonstrates superb detail of bony anatomy and is exquisitely sensitive for calcification. It uses ionizing radiation; the dose to the lens is approximately 3 rads for a series of 3 mm axial slices. The cumulative lifetime dose associated with cataract formation is estimated at 200 to 600 rads ***(Rootman, 2003)***.

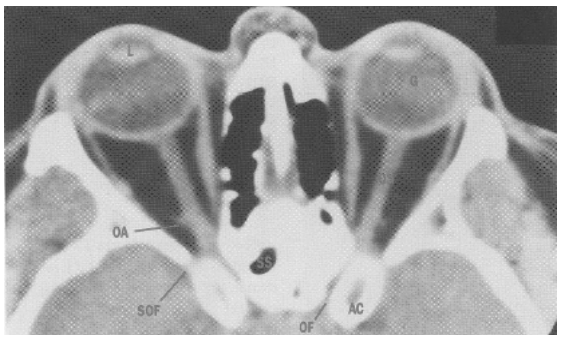

Fig. 1: Normal axial CT scan of the orbit
(Wirtschafter et al., 1992)

2) Magnetic resonance imaging (MRI):

MRI is assuming an increasing role in orbital imaging. It provides superb details of the globe, with better anatomic definition than CT as