IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 18, Issue 4 Ser. 1 (April. 2019), PP 05-09
www.iosrjournals.org

Orbital Lymphoma Review of Literature

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Disclosure
The authors have no financial interests in any of the products mentioned in the article.
AIM: To discuss presentation, investigation, diagnosis and treatment of orbital lymphoma

Date of Submission: 20-03-2019 Date of acceptance: 06-04-2019

I. Background:

Lymphoid tumours are the most common primary orbital malignancy in adults constituting about 10% of all orbital tumors[1] and about 2% of all lymphomas.[2] Lymphoma represents about 13% of primary malignant eyelid tumors.[3] Orbital lymphoma may present as in localized form (orbit, lacrimal gland, lids, and conjunctiva) of systemic lymphoma .

Majority of orbital lymphomas are non Hodgkin's type and are seen primarily in adults in the 50 to 70 year age group.

Orbital lymphoma can affect the conjunctiva, eyelid, and orbit/lacrimal gland as well as the nasolacrimal drainage system. The reported frequencies of involvement in these sites are the conjunctiva 20–33%, orbit/lacrimal gland 46–74%, and eyelid 5–20%.[4,5]

Orbital lymphomas are usually unilateral but may involve both orbits and demonstrate a predilection for the lacrimal gland. Bilaterality is reported in 10–20% of cases. Recent studies have shown a higher incidence , presumably due to the ability of new methods and classifications to distinguish previously ambiguous cases. Patient with orbital lymphoma usually present with a painless proptosis of insidious onset, downward displacement of globe, eyelid edema, palpable non-tender orbital mass and ptosis.[6]

II. Review Results

Owing to Nonspecific clinical sign and symptoms diagnostic delay can occur, adequate imaging studies followed by early surgical biopsy will contribute to early diagnosis.[7] Primary lymphomas isolated to the orbit, the only extranodal site of involvement. Secondary orbital lymphomas are those in which the orbit is a secondary extranodal site of involvement. [6] Clinical appearance does not allow a distinction between benign and malignant lymphoproliferative disease. Exophthalmos and decreased retropulsion of the globe may be the only clinical signs. Secondary ptosis may also occur. Involvement of the nasolacrimal drainage system can occur . In rare cases, compression or invasion of the optic nerve can lead to vision loss. It includes benign lymphoproliferative lesions, epithelial tumors, melanocytic tumors, inflammatory lesions, infectious lesions, and lacrimal gland lesions of the conjunctiva. In the orbit and lid any mass, including metastases, dacryoadenitis, inflammations, and other benign and malignant tumors, must be considered as differential diagnosis.

During orbital biopsy appears as a white to pink mass, reflecting its leukocytic and vascular characteristics.

No exact cause is still identified but lymphomas arise from germinal center cells (follicular lymphoma), mantle cells (mantle cell lymphoma), or memory B cells (extranodal marginal zone lymphoma), all of which have undergone antigen exposure. These antigens may be infection, inflammation or mutation in the gene. With the recent understanding that most orbital lymphoma are also extranodal marginal zone lymphoma/MALT lymphomas, studies have appeared that show evidence of DNA from infectious agents, including Clostridium psittaci and H. pylori in orbital lymphoma.[8,9]

Orbital lymphomas are hyperdense relative to fat on computerised tomography scan, hypodense on T1-weighted MRI, Isodense to extraocular muscle on T1 and T2 weighted MRI. It moulds surrounding structures but with no osseous destruction except rarely for some malignant tumours. Imaging cannot differentiate well between orbital lymphoma and inflammatory pseudotumor. 75% patients with lymphoma in the orbits will also have lymphoma at other sites so these must be imaged following presentation (e.g., the neck, chest and abdomen). Paranasal sinus involvement is not uncommon.

Spiral computed tomography (CT) using a dual-phasecontrast-enhancement protocol report that lymphomas have a decrease in density on delayed images, as opposed to orbital pseudotumours, whose density increases on delayed images [10]. Moreover, low values in the apparent diffusion coefficient on diffusion-weighted magnetic resonance imaging (MRI) have been found helpful to discriminate lymphoma from other expansive orbital lesions.[11]

The typical location consists of the involvement of superior quadrants; specifically, the superior-lateral one. The most commonly infiltrated structures are found within the superior-lateral quadrant, such as the superior rectus muscle, lateral rectus muscle, lacrimal gland and eyelid. Involvement of intra-conal space is usually associated with the extra-conal one, and is related with large size of the tumour.[12] Orbital lymphomas are Gallium and FDG avid.[13]

Histo-pathological evaluation of the orbital mass obtained after incisional biopsy or fine needle aspiration cytology is the most critical step in diagnosis and management of orbital lymphoma. Tissue should arrive fresh without preservative to the pathology department and care should be taken to avoid excessive crushing.[14,15]

The Revised European-American Classification of Lymphoid Neoplasms (REAL) is the most recently and widely used pathology classification system based on morphology, immune-phenotype, genotype, and clinical features of lymphoma.[16] Orbital lymphoma is termed solitary if it is the only site involved, secondary when contiguous sites are involved, and systemic if remote sites are involved. According to REAL classification lymphoma divided into 3 main subgroups:

Indolent lymphoma
Follicular lymphoma
B-chronic lymphocytic leukemia/ small lymphocytic lymphoma
Lymphoplasmacytic lymphoma
Marginal zone lymphoma (nodal, extranodal, splenic)
T-cell/ natural killer large cell granular lymphocyte leukemia
T-chronic lymphocytic leukemia/ prolymphocytic leukemia
Aggressive lymphomas
Mantle cell lymphoma
Diffuse large B-cell lymphoma
Peripheral T-cell lymphoma (unspecified)
Peripheral T-cell lymphoma (angioimmunoblastic, angiocentric)
T-cell/ natural killer cell , hepatosplenic, intestinal T-cell lymphoma
Anaplatic large cell lymphoma
Highly aggressive lymphomas
Precursor T or B lymphoblastic leukemia/ lymphoma
Burkitt's and Burkitt's like lymphoma
Adult T-cell leukemia/lymphoma

World Health Organization Classification of hematopoietic and lymphoid tissue tumours.[17]Histological subtypes:

Follicular lymphoma, grade 1 of 3
Follicular lymphoma grade 2 of 3
Diffuse follicle center lymphoma
Marginal zone B cell lymphoma, MALT type
Chronic lymphocytic leukemia
Low grade lymphoma , not subclassified
Diffuse large B cell lymphoma
Mantle cell lymphoma
Burkitt's lymphoma
Other

Primary Vs Secondary Orbital lymphomas		
	Primary lymphomas	Secondary lymphomas
Characteristics	Isolated, extranodal, orbit is often the first site of lymphoma involvement	Disseminated, systemic involvement, may appear late as part of generalized relapse
Location	Usually unilateral	Usually unilateral
Age	Most common in 50 to 70 year old age group	Most common in 50- 70 years age group but younger patients more likely to have high

		grade lymphomas
Sex	M=F	M=F
Histology	Low grade, indolent, small lymphocytic, follicular or MALT	More often intermediate or high grade (diffuse, mixed or large cell type) but low grade secondary orbital lymphoma also common

Recommended staging Workup for Orbital Lymphoma:

Thorough history and physical examination
Dilated eye examination
Complete blood count and biochemistry profile
Liver function tests
Chest radiography
Computed tomography or magnetic resonance imaging of orbit
Computed tomography of abdomen, thorax and pelvis
Bone marrow aspiration
Open or fine needle biopsy of orbital mass
Upper endoscopy and barium studies
Whole body positron emission tomography

Staging is important for planning treatment and follow up the patient.

Ann Arbor Staging System for Lymphoma:[18]

Stage	Description
I	Involvement of single lymph node region or lymphoid structure (e.g. spleen or Waldeyer ring
II	Involvement of two or more lymph node regions on same side of the diaphragm or localized involvement of an extranodal lymphoid structure and of one or more lymph node region on same side of diaphragm
III	Involvement of lymph nodes on both sides of the diaphragm +- extranodal sites
IV	Involvement of two or more extranodal sites or liver or bone marrow

Management: External beam radiotherapy may be successful in controlling local orbital disease in the majority of patients with low grade indolent orbital lymphoma, the risk of distant relapse is not significant with radiotherapy alone. For more aggressive histological subtypes of orbital lymphoma in which widespread systemic involvement is likely, systemic chemotherapy or systemic immunotherapy may be more appropriate. Therapeutic approach chosen for each patient varies according to the stage and histological classification of lymphoma.[19]

Radiotherapy:

Lymphomas are markedly radiosensitive. Primary radiotherapy for stage I indolent orbital lymphoma can achieve local control in more than 90% of patients, but the rate of distant relapse may be as high as 40% with external beam radiotherapy alone.[19,20] Low grade lesions usually treated with a 30 Gray dose, intermediate grade lymphomas treated with higher doses but less than 40 gray. Distant relapse rates have been observed in 20 to 25% of patients with low grade lymphoma and 40-60 % in higher grade lymphomas.[19,21] Minimal ocular toxicity occurs as short term side effect and dry eye syndrome, ocular surface irritation, cataract occur as long term side effects. Adequate shielding can prevent cataract formation but not ocular surface problems, so newer approaches like intensity modulated conformal therapy which provides isodose delivery to tumours while sparing the uninvolved neighbouring structures , may minimize the ocular toxicity due to radiotherapy.[22]

Systemic chemotherapy or combined modality therapy:

Chemotherapy is usually indicated for the more aggressive histologic subtypes of orbital lymphoma with potential for future systemic involvement or with existing disseminated disease. Indolent lymphomas are very sensitive to single agent and combination chemotherapy.

Single agent chemotherapy is carried out with alkylating agents such as cyclophosphamide. For intermediate to high grade lymphomas, initial combination chemotherapy is usually with a doxorubicin containing regimen such as cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) or cyclophosphamide, vincristine, doxorubicin and dexamethasone (CVAD).[23]

Combined chemotherapy and radiation therapy may be an appropriate option for intermediate to high grade lymphomas. Rationale for combined modality therapy originates from observations that systemic extranodal sites of relapse are common following radiation therapy alone. Single institution and cooperative group series, reported 5 year rates of relapse free survival of 94-100% for stage I lymphomas and 72-78% for stage II lymphomas.[23,24,25]

Immunotherapy and Radioimmunotherapy :

Monoclonal antibody therapy (immunotherapy) may be effective in treatment of low grade NHL's as suggested in recent reports.[26,27,28] CD20 is a surface antigen, which is a hydrophobic phosphoprotein that is expressed on mature B cells and most B cell malignancies but not on stem cells, pre-B cells or plasma cells.

Rituximab is a genetically engineered chimeric mouse/ human antibody discovered in 1990 by IDEC Pharmaceuticals; it binds with high affinity to cells expressing the CD20 antigen and causes tumour lysis via both complement dependent and antibody dependent cellular cytotoxicity.[29] It is the first monoclonal antibody approved for treatment of cancer and first single agent approved specifically for therapy of lymphoma.

Radioimmunotherapy refers to administration of a monoclonal antibody in combination with a radioactive ligand. Beta particles emitted by commonly used radioisotopes are tumoricidal over a distance of many cell diameters, allowing eradication of antigen negative tumor cells by radioactive cross fire from neighboring antigen positive antibody coated cells. This additional mechanism for tumor lysis leads to a more dramatic treatment effect than the nonradioactive antibody.[30]

IDEC-Y2B8 (Zevalin) is a murine IgG1 k monoclonal antibody directed against the CD20 antigen that is conjugated to MX-DTPA and bound to the beta emitting radioisotope yttrium-90. Zevalin is usually given as a single dose following an infusion of rituximab. Radioimmunotherapy with Zevalin in combination with rituximab has shown greater efficacy for treatment of low grade lymphomas than rituximab alone.[31]

Prognosis

The International Prognostic Index (IPI) was developed by 16 institutions and cooperative groups in the United States, Europe and Canada as a prognostic factor model for aggressive NHL. This includes the age (<60 or >60), performance status by (Eastern Cooperative Oncology Group (0 to 1 vs. 2 to 4), Ann -Arbor stage (I-II vs. II-IV), extra-nodal sites (<1 vs. >1), and LDH level (normal or above normal).[32]

III. Discussion

The site of presentation of orbital lymphoma has been associated with prognosis with 20% of conjunctival, 35% of orbital, and 67% of eyelid orbital lymphoma developing systemic lymphoma after 4 years. Among the common orbital lymphoma tumor types, Extramarginal zone lymphomas, Follicular lymphoma, and lymphoplastic lymphoma are considered low grade or indolent, whereas diffuse large B-cell lymphoma and mantle cell lymphoma are considered high grade. Mortality for Extramarginal zone lymphomas ranges from 0-20%, Follicular lymphoma 20-37%, mantle cell lymphoma 38-100% and lymphoplastic lymphoma 14-100%. The mean time to relapse was over 5 years, suggesting that longer follow-up than typically recommended is needed.

IV. Conclusion

Every case of orbital lymphoma presents as different entity and each case requires meticulous examination and management.

CLINICAL SIGNIFICANCE

Orbital lymphoma has better prognosis compared to other lymphomas. They respond better to radiotherapy.

Bibliography

[1]. Ellis JH, Banks PM, Campbell RJ, liesegang TJ. Lymphoid tumors of the ocular adnexa: clinical correlation with the working formulation classification and immunoperoxidase staining of paraffin sections. Ophthalmology 1985;92:1311-1324

[2]. Hornblass A, Jakobeic FA, Reifler DM, et al. Orbital lymphoid tumors located predominantly within extraocular muscles. Ophthalmology 1987;94:688-697

[3]. Margo CE, Mulla ZD. Malignant tumors of the eyelid: a population-based study of non-basal cell and non-squamous cell malignant neoplasms. Arch Ophthalmol 1998; 116: 195–198

[4]. Knowles DM, Jakobiec FA, McNally L et al. Lymphoid hyperplasia and malignant lymphoma occurring in the ocular adnexa (orbit, conjunctiva, and eyelids): a prospective multiparametric analysis of 108 cases during 1977 to 1987. Hum Pathol 1990; 21: 959–973.

[5]. Coupland SE, Hellmich M, Auw-Haedrich C et al. Prognostic value of cell-cycle markers in ocular adnexal lymphoma: an assessment of 230 cases. Graefes Arch Clin Exp Ophthalmol 2004; 242: 130–145

[6]. Esmaeli B, Ahmadi MA, Manning J et al. Clinical presentation and treatment of secondary orbital lymphoma. Ophtahlmic Plast Reconstr Surg 2002;18:247-2537.

[7]. Eckardt AM, Lemound J, Rana M, Gellrich NC. Orbital lymphoma: diagnostic approach and treatment outcome. World J Surg Oncol. 2013 Mar18;11:73

[8]. Ferreri AJ, Guidoboni M, De Conciliis C et al. Evidence for an association between Chlamydia psittaci and ocular adnexal lymphomas. J Natl Cancer Inst 2004; 96: 586–594.

[9]. Chan CC, Smith JA, Shen DF et al. Helicobacter pylori (H. pylori) molecular signature in conjunctival mucosa-associated lymphoid tissue (MALT) lymphoma.Histopathol 2004; 19: 1219–1226

[10]. Moon WJ, Na DG, Ryoo JW, Kim MJ, Kim YD, Lim DH, Byun HS (2003) Orbi tal lymphoma and subacute or chroni c inflammatory pseudotumor: di fferentiation wi th two-phase helical computed tomography. J Comput Assi st Tomogr 27:510–516

[11]. Politi LS, Forghani R, Godi C, Resti AG, Ponzoni M, Bianchi S, Iadanza A, Ambrosi A, Falini A, Ferreri AJ, Curtin HD, Scotti G (2010) Ocular adnexal lymphoma: di ffusion-weighted MR imaging for differential diagnosis and therapeutic monitoring.

[12]. Radiology 256:565–574Orbi tal lymphoma: imaging features and differential diagnosis Gema Priego,Carles Majos,Fina Climent and Amadeo MuntaneDepar tment of Radiology, Hospital Universitaride Bellvitge, Feixa Llar ga, s/n, 08907 Hospitaletde Llobegat, Barcelona, Spain

[13]. Curtin H.D, Som P.M. Head and Neck Imaging, 4th ed. 2003.

[14]. Syed NA, Albert DM. Surgical pathology of ophthalmic plastic surgery. In: Albert DM, ed. Ophthalmic Surgery: Principles and Techniques. Edinburg: Blackwell Science; 1999:1648-1658.
[15]. Rosai J. In: Rosai J, ed. Ackerman's Surgical Pathology. 8th ed. St Louis: CV Mosby; 1996;1-12, 29-62.
[16]. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994,84:1361-1392
[17]. Jaffe ES, Harris NL, Stein H, Vardiman JW: World Health Organization Classification of tumours. Tumours of Haematopoietic and Lymphoid Tissues. Pathology and Genetics. Lyon: IARC Press, 2001
[18]. Bennett CL, Putterman A, Bitran JD, et al. Staging and therapy of orbital lymphomas. Cancer 1986;57:1204-1208
[19]. Smith MC, Donaldson SS. Radiotherapy is successful treatment for orbital ymphoma. Int J Radiat Oncol Biol Phys 1993,26:59-66
[20]. Esik O, Ikeda H, Mukai K, Kancko A. A retrospective analysis of different modalities for treatment of primary orbital non-Hodgkin's lymphomas. Radither Oncol 1996,38:13-18
[21]. Bolck TW, Moyses HM, Marcus RB, et al. Radiotherapy in management of orbital lymphoma. Int J Radiat Oncol Biol Phys. 1999,44:31-36
[22]. Dearnaly DF, Khoo VS, Norman AR, et al. Comparison of radiation side effects of conformal and conventional radiotherapy in prostate cancer: a randomized trial. Lancet 1999,353:267-272
[23]. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized, intermediate and high grade non-Hodgkin's lymphoma. N Engl J Med 1998,339:21-26
[24]. Cabanillas F, Rodriguez- Diaz PJ, Hagemeister FB, et al. Alternating triple therapy for the treatment of intermediate grade and immunoblastic lymphoma. Ann Oncol 1998;9:511-518
[25]. Longo DL, Glatstien E, Duffey PL, et al. Treatment of localized aggressive lymphomas with combination chemotherapy followed by involved field radiation therapy. J Chin Oncol 1989;7:1295-1302
[26]. McLaughlin P, Grillo-Lopez AJ, White CA, et al. IDEC-C2B8 (rituximab) anti CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four dose treatment program. J Clin Oncol 1998,16:2825-2833
[27]. Maloney DG, Grillo-Lopez AJ, White CA , et al. IDEC-C2B8 (rituximab) anti CD20 monoclonal antibody therapy in patients with relapsed low grade non-Hodgkin's lymphoma. Blood 1997;90:2188-2195
[28]. Maloney D, Smith B, Appelbaum F. The anti-tumor effect of monoclonal anti-CD20 antibody 9Mab) therapy includes direct antiproliferative activity and induction of apoptosis in CD20 positive non-Hodgkin's lymphoma cell lines. Blood 1996;88(suppl):637
[29]. Leget GA, Czuczman MS. Use of rituximab, the new FDA approve d antibody. Curr Opin Oncol 1998;10:548-551
[30]. Knox SJ, Goris ML, Trisler K, et al. Yttrium- 90 labeled anti CD20 monoclonal antibody therapy of recurrent B cell lymphoma. Clin Cancer Res 1996;2:457-470
[31]. Wiserman GA, White CA, Stabin M et al. Phase I/II 90Y Zevalin (yttrium-90 ibritumomab tiuxetan, IDEC-Y2B8)radioimmunotherapy dosimetry results in relapsed or refractory non-Hodgkin's lymphoma. Eur J Nucl Med 2000;27:766-777
[32]. A predictive model for aggressive non-Hodgkin's lymphoma: The International Non-Hodgkin's Lymphoma Prognostic Factors. Project. N Eng J Med. 1993;329:987–94.

Dr Rakesh Kumar MS. "Orbital Lymphoma Review of Literature." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 4, 2019, pp 05-09.