2 Epidemiological Aspects of Intraocular Lymphoma

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Introduction

Lymphomas are malignant lymphoid tumors arising as clonal proliferation of either B-lymphocytes, T-lymphocytes, or natural killer cells. Lymphomas are divided into two major categories, namely Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) [1]. NHL is the most common type of ocular lymphoma [2]. Depending on the site of involvement ocular lymphoma can be either ocular adnexal or intraocular lymphoma.

Ocular Adnexal Lymphoma

Anatomic Location

Ocular adnexal lymphoma (OAL) was first reported in 1952 [3]. OAL can arise from the conjunctiva, eyelids, orbit, extraocular muscles, and lacrimal apparatus [4]. The frequency of involvement has been reported as 46–74% in the orbit, 20–33% in the conjunctiva, 25% in the lacrimal gland, and 5–20% in the eyelid [5–8]. OAL arising from extraocular muscles is extremely rare with few biopsy-proven cases reported in literature with rectus muscle being most commonly affected (73%) followed by obliques (17%) and levator (11%) [9].

Pathological Subtypes

Extranodal marginal zone B-cell lymphoma (EMZL) of mucosa-associated lymphoid tissue (MALT) type constitutes about 38–100% of OAL [10]. MALT is considered the third most common form of NHL accounting for about 6–7% of extranodal non-ophthalmic NHL. An extensive review of literature of 2211 cases of orbital lymphoma by Olsen TG et al. [11] showed 97% to be of B-cell origin and 3% of T-cell origin. Out of the B-cell lymphomas 59% were extranodal marginal zone lymphoma (EMZL), followed by diffuse large B-cell lymphoma (DLBCL) (23%), follicular lymphoma (FL) (9%), and mantle cell lymphoma (MCL) (5%). Uncommon OAL variants include plasmablastic lymphoma, NK/T-cell lymphoma, small-lymphocytic lymphoma, Burkitt lymphoma (BL), lymphoplasmacytic lymphoma, plasmacytoma, and peripheral T-cell lymphoma [12–14]. Out of the T-cell lymphomas 64% were mixed T/NK-cell origin. These results are consistent with other studies where EMZL was found to be the most common type of lymphoma [6, 15–18]. Woog et al. [19] reported eight cases with natural killer/T-cell lymphomas of the

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orbit from multicenter, and they found that ocular involvement was mostly secondary to invasion from adjacent nasal or paranasal involvement with mortality of 87.5%. In a large retrospective series including SEER data from 1973 to 2015 EMZL was the most common subtype in pediatric population (45.5%) followed by DLBCL (9.1%), B lymphoblastic lymphoma (7.3%), follicular lymphoma (5.5%), Burkitt lymphoma (5.5%), and T-cell lymphoma (1.8%) [20].

Incidence

NHL is the sixth and seventh most common malignancy among females and males, respectively, in the USA with an estimated 81,560 new cases and 20,720 deaths in 2021 [21]. NHL can develop from lymphatic nodal or extranodal (outside lymph nodes, thymus, spleen, and Waldeyer's ring) sites [10]. Non-Hodgkin's lymphoma (NHL) is comprised of 4.3% of all new cancer cases and 3.4% of all cancer deaths in the USA in 2021 [22]. Primary NHL of the ocular region represents 1–2% of all NHL and 5–15% of all extranodal sites [23, 24]. Ocular adnexal lymphoma (OAL) accounts for approximately 10% of all orbital tumors [25]. Epidemiological data on ocular and ocular adnexal lymphoma are sparse in literature. In Asian countries like Japan, Korea, and also in Europe lymphoma is the most common type of malignant orbital tumor [26–29]. The overall incidence of lymphoma has been increasing annually by 3–4% [30]. From 1975 to 2001 the incidence of ocular lymphoma saw a rapid and steady rise of 6.2% and 6.5% among white males and females, respectively [10]. Similarly, the incidence of OAL has been increasing at a rate of 3.4% in the Danish population from 1980 to 2005 [31].

Age

Ocular adnexal lymphoma is a disease seen most commonly in elderly [2, 10] with a median age of 65 years [32]. In Korean population the median age of OAL was found to be 46 years at the time of diagnosis [17, 18]. However, age distribution has also been reported to vary with lymphoma subtypes. In patients older than 50 years B-cell lymphomas (73%) are more common than T-cell Lymphomas (38%) [11]. A retrospective case series studied individuals with OAL in less than 18 years of age diagnosed between 1973 and 2015 from the database of the surveillance, epidemiology and end results where the incidence of pediatric OAL was found to be 0.12 (95% CI 0.08–0.16) per 1,000,000. Males and Blacks had higher tendency for OAL [20]. Burkitt's lymphoma, B-cell lymphoblastic lymphoma, and Hodgkin's lymphoma although rare have a high incidence among young patients [10].

Gender

Incidence data from 13 surveillance, epidemiology, and end results (SEER) areas in the USA from 1992 to 2007 showed near equal gender distribution in 1604 ophthalmic and 1565 patients with OAL with higher rates of incidence in Asians and Pacific Islanders [21]. However, overall there is a slight male predominance for OAL [2]. The gender distribution depends on the specific lymphoma subtype. High grade OAL was found to have male predominance [31]. A female predominance is found among patients with EMZL (53%) and follicular lymphoma (75%). A significant male predominance is found among patients with MCL (80%) and T-cell Lymphoma (67%) [11]. A study from Denmark showed both genders being equally affected by ophthalmic NHL, with male predominance for high grade tumors [31]. International data pertaining to racial and ethnic variation of OAL is sparse.

Laterality

A majority (90%) of OALs present as a unilateral tumor [11]. A retrospective study by Kirkegaard et al. [33, 34] has reported unilateral involvement in 90% of B-cell lymphomas, while bilateral involvement was seen in mantel cell lymphoma of conjunctiva and eyelid [35]. Bilateral disease presentation is associated with poor prognosis [11, 36, 37]. A review of literature by Olsen et al. [11] reported a total of 2211 cases of OAL out of which 92% of the T-cell lymphomas had unilateral involvement, while three cases of NKTL and one case of ATCL showed bilateral involvement.

Risk Factors

Infectious Agents

Several studies have established the relationship between microorganism infection and the possibility of lymphoma arising as a result of chronic antigenic stimulation. The common organisms isolated from MALT (or marginal zone) lymphomas of various body sites are *Helicobacter pylori* (gastric), *Borrelia burgdorferi* (skin), *Chlamydia psittaci* (ocular adnexa), *Campylobacter jejuni* (small intestine), *Achromobacter xylosoxidans* (lung), and hepatitis C virus (spleen) [38, 39]. However, possibly due to geographic variations these associations have been discordant and not confirmatory [40].

H. pylori infection association with gastric-MALT lymphoma has been documented in 90% of the cases [41]. Similar association was found in OAL most commonly associated with marginal zone B-cell lymphoma with an indolent course [42–44]. Helicobacter pylori DNA was found in four of the five conjunctival MALT lymphoma cells using PCR amplification and southern blot hybridization [43]. A recent study from Taiwan showed the prevalence rate of *H. pylori* to be 53.9% [8].

Chlamydia psitacci is the next microorganism thoroughly studied in association with OAL. Ferreri et al. [45] first studied this association and reported that the DNA of chlamydia was detected by immunochemistry and PCR analysis in 87% of the 40 specimens of MALT OAL. Similar association was found in 79% of cases in Korea by Yoo et al. [46]. A study by Chanudet et al. [47] demonstrated the association of chlamydia to be significantly higher in MALT lymphoma (22%) than in non-lymphoproliferative disorder (10%) and non-marginal zone lymphomas (9%). A study by Chan CC et al. [48] reported higher prevalence of *Chlamydia pneumoniae* in non-mucosa-associated lymphoid tissues (nMALTs) as compared with MALTs in Chinese population. Thus, the prevalence varied with different geographical locations as demonstrated by Chanudet et al. [47] who demonstrated the prevalence in different countries as follows—Germany (47%) followed by the East Coast of the USA (35%) and the Netherlands (29%), but relatively low in Italy (13%), the UK (12%), and Southern China (11%).

HCV is also suspected to play a role in the etiology of B-cell NHL [49]. One study reports nine HCV-positive patients (36%) out of 25 patients with orbital EMZL [50]. A study by Ferreri AJ et al. [51] demonstrated presence of HCV in 13% patients of OAL of MALT type associated with more disseminated disease and aggressive behavior of OAL. In Taiwan the incidence of hepatitis C infection was found to be 6.2% [8].

Other studies have reported an association of human herpesvirus-6 (HHV-6) with ophthalmic MALT lymphoma in Japan and Epstein-Barr virus (EBV) has been associated with conjunctival NK/T-cell lymphomas, orbital Burkitt lymphoma, and plasmablastic lymphoma of the orbit, and human T-cell leukemia virus type 1 (HTLV-1) has also been demonstrated in patients with orbital lymphoma [2, 11].

The association of hepatitis B virus infection in EMZL was found to be more common in Chinese than Caucasian patients due to the higher incidence of genetic abnormalities like chromosome translocation and abnormal activation of innate and adaptive immunity in Asian population as compared to Western population. A study in Taiwan demonstrated HCV association in 70% of the cases [8, 52, 53].

Autoimmune Disorders and Immunodeficiency Disorders

An increased risk of NHL is reported in patients suffering from autoimmune disorders such as Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, Hashimoto's thyroiditis. In these patients B-cell lymphomas, especially DLBCL and extranodal marginal zone lymphomas are the most commonly seen, whereas gastrointestinal/cutaneous autoimmune conditions are found to be associated with T-cell lymphomas [54]. In patients with human immunodeficiency virus (HIV) infection lymphoma is found to be more common than in general population and DLBCL and BL type is seen more often [55]. The mechanism of lymphoma

development in HIV was postulated to be due to the higher rate of Epstein-Barr virus infection in these patients leading to activation or genomic insertion of oncogenes from the pathogen, as well as chronic antigenic stimulation [2, 11]. Thus lymphomas in immunodeficiency conditions are usually aggressive high grade B-cell in nature involving extensive extranodal sites with typically poor prognosis.

Intraocular Lymphoma

Intraocular lymphoma is a rare malignant lymphocytic neoplasm which has two main distinct forms. Primary lymphoma can be only ocular or involving the primary central nervous system and secondary or metastatic intraocular lymphoma from systemic (visceral) lymphoma [56–59]. Primary intraocular lymphoma can also be classified based on the anatomic location primarily affected—vitreoretinal lymphoma or uveal lymphoma [60]. Primary lymphoma with or without central nervous system lymphoma is an ocular subset of primary central nervous system lymphoma (PCNSL-O) predominantly affecting the subretinal space, retina, and vitreous. Patients of PCNSL-O have CNS involvement in 60–80% of cases, while 15–25% of PCNSL patients develop ocular manifestation of lymphoma and 56–90% of primary intraocular lymphoma will develop CNS manifestations of lymphoma [61–64]. Organ involvement in intraocular lymphoma can be of four types: (1) ocular-central nervous system lymphoma (most common type—(61%)), (2) intraocular lymphoma alone (17%), (3) ocular-visceral lymphoma (17%), and (4) ocular-visceral-CNS lymphoma (5%) [57]. Intraocular lymphoma has been reported as 2% of all uveitis and 33% of masquerade syndromes [65]. Primary vitreoretinal lymphoma (PVRL) represents 1.86% of ocular malignant tumors, 4–6% of all brain tumors, and less than 1% of extranodal lymphomas [66, 67]. The incidence has been found to be 0.0047 cases per 100,000 people per year which has been decreasing in immunocompromised patients with increase in HAART therapy but there is raise in incidence in immunocompetent patients [56]. PVRLs are mostly large B-cell lymphomas, very few cases of primary T-cell PVRL have been described [68, 69]. Uveal lymphomas can be further divided into those which start as a primary disease in the uveal tract or those which occur as an ocular manifestation of systemic non-Hodgkin lymphoma [70, 71].

Incidence

The incidence of PCNSL in the USA has increased more than 30 folds in three decades with an incidence rate of 0.27 per million in 1973 to 10 per million in early 1900s as documented in National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database [72, 73]. The incidence started declining to 0.43 per 100,000 person-years between 1990 and 1994 [74] and remained stable since then at 0.46 per 100,000 person-years in 2004–2007 as documented in The Central Brain Tumor Registry of the USA. This rise and subsequent stabilization of incidence is attributed to the increased incidence of human immunodeficiency virus (HIV)/AIDS and the subsequent development of highly active antiretroviral therapies (HAART). The incidence of PCNSL declined from 5.33 per 1000 person-years between 1991 and 1994 (pre-HAART) to 0.32 per 1000 person-years after 1999 (post-HAART) [75, 76]. However, this increased incidence has not been consistently observed in all geographic locations [77–79].

Risk Factors

Age

Primary intraocular lymphoma is usually seen in elderly age group. Reduced immunity and increase in number of somatic mutations can make the advancing age one of the risk factors for intraocular lymphoma [80]. The peak incidence of PCNSL is seen between 75 and 84 years, while PVRL is seen in elderly patients with a median

age of 50–60 years with a range between 15 and 85 years [71, 72]. A recent case series from Singapore showed the mean age of presentation as 60.3 years [60]. While immunocompromised people at the age of 30 were also found to be affected by PCNSL [72].

Gender

PCNSL shows a male predominance with a male:female ratio of 1.38, while a female predominance is seen in PVRL with a ratio of 2:1 [71, 72]. A recent case series also reported the same female predominance of PVRL where out of nine patients five patients were females [60].

Ethnicity

Few studies state that there is no racial preference for intraocular lymphoma, while few studies show that blacks of age less than 50 years and elderly whites age more than 50 years showed higher incidence of PCNSL [72, 81]. This difference is thought to be due to more incidence of HIV/AIDS in young adults and blacks more than any other race groups in the USA [82]. In Asian population the Chinese have higher incidence of intraocular lymphoma as compared to others as reported in a case series by Hah et al. [60].

Immunodeficiency

Immunodeficiency and immunosuppression are the highest risk factors for the development of intraocular lymphoma [83]. PCNSL is commonly seen in younger age groups who suffer from skin cancer and the incidence increases with the intensive immunosuppressive treatment in these patients [72]. PCNSL is reported in 2% of patients who underwent organ transplantation and 4% in patients who have congenital immune disorders [84].

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