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Diagnosis of systemic metastatic retinal lymphoma

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Abstract

Purpose—Systemic metastatic retinal lymphoma (SMRL) is exceptionally rare, as systemic lymphomas most often metastasize to the uvea. We have evaluated a series of SMRL cases to elucidate the clinical and pathological features of SMRL.

Methods—The pathologic specimens of intraocular lymphomas (IOLs) at the National Eye Institute from 1991–2009 were retrospectively reviewed. These cases were diagnosed by cytology, cytokine measurement (ELISA for interleukin (IL)-10 and IL-6 levels), and *Immunoglobulin-Heavy (IgH)* and *T-cell-receptor (TCR)* gene analyses.

Results—There were 9 B-SMRLs among 96 B-cell retina lymphomas (9.4%) and 3 T-SMRLs among 5 T-cell retinal lymphomas (60%) from a total of 116 IOLs. The original sites were nasopharynx (3), testis (2), skin (2), breast (1), blood (1), retroperitoneum (1), ileo-cecum (1) and stomach (1). Cytology of vitreous samples illustrated atypical lymphoma cells with either B- or T-monoclonality. More B-SMRLs had a high ratio of vitreal IL-10 to IL-6 than T-SMRLs. Molecular pathology demonstrated lymphoma cells with gene rearrangements of *IgH* in all B-SMRLs and *TCR* in all T-SMRLs.

Conclusions—SMRL and primary retinal lymphoma present with similar clinical manifestations. Systemic T-cell lymphoma invades the retina and vitreous more aggressively than systemic B-cell lymphoma. A diagnosis of SMRL is made when there is a clinical history of systemic lymphoma (particularly from nasopharynx, testis, and skin) and lymphoma cells are identified in the vitreous or retina. Molecular analysis is more useful than vitreal cytokine measurement for SMRL diagnosis.

Keywords

Systemic Metastatic Retinal Lymphoma; Intraocular Lymphoma; Cytokine; *IgH* gene rearrangement; *TCR* gene rearrangement

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Introduction

Lymphomas are derived from a monoclonal proliferation of B- or T-lymphocytes. Lymphomas inside the eye are relatively uncommon and account for 1% of non-Hodgkin's lymphomas and less than 1% of all intraocular tumors (Bardenstein 1998). The term intraocular lymphoma (IOL) describes a lymphoma located inside the eye, which arises from the central nervous system (CNS), including the retina, the uvea (extremely rare), or a metastatic systemic lymphoma. The former, primary intraocular lymphoma (PIOL) is a subset of primary CNS lymphoma (PCNSL) and is also called primary retinal lymphoma (PRL). PIOL and has a significantly higher prevalence than the other forms of IOLs (Chan 2007; Coupland et al. 2009). Primary uveal lymphoma is extremely rare and has a much lower prevalence than the above two IOLs. Primary choroidal lymphoma is an extranodal marginal zone B-cell lymphoma (EMZL). Only few cases of primary choroidal MALT (mucosa-associated lymphoid tissue) lymphoma have been studied (Coupland & Damato 2008). Primary iridal or ciliary lymphomas are extremely rare, and few cases have been documented (Chan et al. 2008). Systemic lymphomas usually metastatize though blood into the uveal tissues.

The incidence rate of PIOL is estimated to be approximately 21 per 100,000 patients with ocular disorders who present in a referral eye center per year (Mochizuki & Singh 2009). Among the IOLs, PCNS/PIOL is most common (61%), followed by PIOL alone (17%), IOL secondary to metastatic systemic lymphoma (17%), and IOL secondary to both metastatic systemic and CNS lymphoma (5%) (Singh et al. 2007).

PIOL may initially present in the eye with or without simultaneous CNS involvement. Most PIOLs/PCNSLs are extranodal, non-Hodgkin, diffuse large B-cell lymphomas (DLBCLs). PIOL cells are located in the retina, vitreous and optic nerve (Chan 2007). In contrast, metastatic systemic lymphoma is a lymphoma that metastasizes into the eye via hematogenous spread. Typically, small B-cell IOLs present with advanced systemic disease. In general, intraocular T-cell lymphomas are rare and can be secondary to metastatic systemic T-cell lymphomas, including primary cutaneous peripheral T-cell lymphoma and occasionally adult T-cell leukemia/lymphoma (Kumar et al. 1994; Shibata et al. 1997; Levy-Clarke et al. 2002; Buggage 2003). The uvea is the most common site for metastatic systemic lymphomas, and metastatic systemic lymphoma to the retina and vitreous without clinical uveal or conjunctival involvement is exceedingly rare, making the diagnosis of systemic metastatic retinal lymphoma (SMRL) very difficult and challenging (Levy-Clarke et al. 2005; Calfa et al. 2007). No study has fully investigated the clinical features and pathological diagnosis of SMRL as compared to PIOL. Herein we report a small series of SMRL cases to elucidate the clinical and pathological features of SMRL.

Material and Methods

The study was approved by the National Eye Institute Institutional Review Board for human subjects, and informed consent was obtained from all patients.

The medical records of IOL cases that were diagnosed at the National Eye Institute (NEI), National Institutes of Health, from January 1991 to April 2009 were reviewed retrospectively. These cases were diagnosed by cytology, cytokine measurement (ELISA for interleukin (IL)-10 and IL-6 levels), and *Immunoglobulin-Heavy (IgH)* and *T-cell-receptor (TCR)* gene analyses as reported previously (Shen et al. 1998; Chan & Wallace 2004; Levy-Clarke et al. 2005; Gonzales & Chan 2007). The detailed protocol of processing the vitreous sample has been documented (Gonzales & Chan 2007). Briefly, the vitreous specimens were centrifuged at 1,000 rpm. The supernatant was collected and IL-10 and IL-6 levels were

measured by enzyme-linked immunosorbent assay (ELISA). The sediment in the original tube was then resuspended and cytocentrifuged (7620 CYTOCENTRIFUGE, Wescor Inc., Logan, Utah). The slides were processed for cytology and molecular analyses.

A minimum of 15 atypical cells was microdissected from the cytospin slides for DNA extraction. Polymerase chain reaction (PCR) was used to detect monoclonality of malignant B-, or rarely, T- cells. The three primer pairs for the malignant B-cells were: the second framework region (*FR2A* sense 5'-TGG RTC CGM CAG SCV YCN GG-3' and anti-sense 5'- GGA TGG TAC CAA GCT TTG AGG AGA CGG TGA CCA-3'), the third framework region (*FR3A* sense 5'-ACA CGG CYS TGT ATT ACT GT-3' and anti-sense 5'-GGA TGG TAC CAA GCT TTG AGG AGA CGG TGA CCA-3'), and *CDR3* (sense 5'-CCG GRA ARR GTC TGG AGT GG-3' and anti-sense 5'-ATC CTG AGG AGA CGG TGA CC-3'). These primers were used to detect monoclonality within the variable region of the third complementary determining region (*CDR3*) in the *IgH* gene of the malignant B-cells. The primer pairs used to detect the gene rearrangement in the *TCR* gene for the malignant T-cells were *TCR*-γ (sense 5'-AGG GAT GTG TTG GAA TCA GG-3' and antisense 5'-CGT CGA CAA CAA GTG TTG TTC CAC-3') and *TCR-CDR3* (sense 5'-GAA AGG AAT CTG GCA TTC CGT CAG-3' and antisense 5'-GAA GTT ACT ATG AGC YTA GTC CCT T-3').

The data is presented with the mean ± S.E. The chi-square analysis and *t*-tests were performed with SPSS version 17.0 (SPSS Inc., Chicago, Illinois). Statistical significance was accepted for p values less than 0.05.

Results

Between January 1991 and April 2009, 116 patients were diagnosed with IOL at the NEI, including 101 retinal lymphomas and 15 uveal lymphomas. The 101 retinal lymphomas consisted of 89 PIOLs (88%) and 12 SMRLs (12%). All 12 SMRLs were diagnosed based on the vitreous samples. Among the 12 SMRLs, there are 9 B-cell SMRLs (B-SMRL) and 3 T-cell SMRLs (T-SMRL). Thus, of the IOLs, PIOL was over 7 times more prevalent than SMRL (89/12=7.4). A summary of the demography of these 101 retinal lymphoma cases is in Table 1. The demographic data of the 12 SMRL cases is given in Table 2. Eighty-three percent of the SMRL patients (10/12) were older than 50 years of age at the time of the diagnosis.

Of the 96 B-cell retinal lymphomas, 9.4% (9/96) were secondary to systemic B-cell lymphoma. Of the 5 T-cell retinal lymphomas, 60% (3/5) were secondary to systemic T-cell lymphoma. There is a significantly higher chance of metastasis in T-SMRL compared to B-SMRL, given the total occurrences of T-PIOL and B-PIOL (p=0.001, chi-square test). The median time from diagnosis of systemic lymphoma to the onset of ocular involvement was 60.86 ± 18.35 months and 4.62 ± 4.38 months for B-SMRL and T-SMRL, respectively (p= 0.163, independent samples t-test).

Clinical features

Ocular symptoms and manifestations of the SMRL patients were similar to the PIOL patients. All patients complained of blurry vision. Anterior "uveitis" (with neoplastic cells mimicking intraocular inflammation) was seen in 3 patients. On fundus examination, all 12 SMRL patients had features of chronic vitritis. Retinal or subretinal yellowish infiltrations were found in 5 patients. Retinal vasculitis was noted in one patient. Five patients had severe vitritis such that chorioretinal lesions were not visible, and one patient did not have a chorioretinal lesion. There were no abnormal clinical findings in the uvea, conjunctiva or orbit in any of the patients. These patients were first treated with, and did not respond to,

anti-inflammatory and/or immunosuppressive therapy including corticosteroids. Diagnostic vitrectomy was performed to rule out malignancy in all 12 patients.

Cytology

Cytology of vitreous samples illustrated atypical lymphoid cells, which harbored either B- or T- cell monoclonality. These cells have large irregular nuclear, prominent nucleoli, and scanty basophilic cytoplasm. In general, B-SMRL cells were large and T-SMRL cells were variable in size (Figure 1).

Vitreal IL-10 and IL-6 levels

Table 3 summarizes cytokine data. Cytokine levels were measured in 10 of the 12 vitreous samples (7 B-SMRLs and 3 T-SMRLs). Among the 7 B-SMRL cases, 4 (57.1%) showed a ratio of IL-10: IL-6 levels greater than 1.00, compared to only 1 of 3 T-SMRL specimens (33%, p=0.48, chi-square test).

Molecular pathology

In all 9 B-SMRLs, *IgH* gene rearrangements were detected, and all 3 T-SMRLs had *TCR* gene rearrangements (Figure 2). The consistency of lymphoma cell monoclonality in Case 1, Case 2 and Case 6 (B-SMRL), and Case 10 and Case 11 (T-SMRL) were established by PCR results of tumor cells from the original site.

Discussion

The incidence of PIOL is estimated to range from 30 to 200 people annually in the United States (Chan 2003; Baehring et al. 2005; Chan 2007). Our retrospective study shows that PIOL has a much higher prevalence than SMRL. Overall, the incidence of SMRL is extremely low (Chan 2003; Baehring et al. 2005; Levy-Clarke et al. 2005). Our center is a tertiary referral center for diagnostic vitrectomy to differentiate between lymphoma and uveitis; therefore, the incidence of SMRL we present is subject to referral bias and is likely skewed when compared to other populations.

Secondary, or metastatic, intraocular lymphoma is usually located in the uvea without involvement of the neurosensory retina; however, rare cases of retinal involvement have been reported (Coupland et al. 1999; Parikh et al. 2005). Multicentricity has been documented in PCNSL/PIOL (Coupland et al. 2005). There is a possibility that the patients may have developed two different lymphomas: one outside the eye and one in the retina. The limited number of malignant cells in the vitreous prevented us from performing clonal analysis of the 12 SMRL cells to rule out this possibility. However, we suggest that these 12 SMRLs are likely from metastatic lymphomas outside the eye based on their clinical presentation and the morphologic and molecular similarities of the primary and secondary lymphoma cells in these cases.

SMRL patients, like PIOL patients, tend to be older. These patients frequently present with clinical features of PIOL, masquerade as uveitis, and elude diagnosis. Often, patients are misdiagnosed as having intractable ocular inflammation and die from dissemination of their disease (Sen et al. 2009). Most commonly, PIOL involves the posterior segment, and patients present with worsening vision due to vitritis (66% of patients), anterior chamber involvement (43%), and/or retinochoroidal involvement (41%) (Freeman et al. 1987; Char et al. 1988; Whitcup et al. 1993; Velez et al. 2000), findings comparable to our current study of SMRL.

Of the 12 SMRLs, 9 SMRLs are of B-cell origin and 3 SMRLs are of T-cell origin. However, there is a significantly higher ratio of T-cell IOLs to T-SMRLs compared with B-cell IOLs to B-SMRLs. T-SMRLs have a much shorter duration from time of the diagnosis of systemic lymphoma to the time of ocular disease. Compared to systemic B-cell lymphoma, systemic T-cell lymphomas appear more aggressive and invade the retina and vitreous (Levy-Clarke et al. 2008). Approximately 85–90% of all non-Hodgkin lymphoma (NHL) in the USA are B-cell lymphomas (Harris et al. 1994). Some B-cell NHLs are indolent, or slow-growing, yet incurable. In contrast, others are very aggressive, may be rapidly fatal, and are often curable. T-cell lymphomas represent a group of malignancies for which there has been remarkably little progress over the past several years. These diseases have a prognosis that is worse than their B-cell counterparts. Because they are extremely rare cancers, there is little consensus regarding management and treatment of the disease because of the difficulties in finding enough patients to enroll in clinical studies. Several informative clinical series of patients have reported a poor prognosis for patients with T-cell neoplasms; the 5-year survival rate is less than 30% with a median survival of less than 2 years (Campo et al. 1998; Lopez-Guillermo et al. 1998). Incredibly, the failure-free survival for patients with high-risk or intermediate-high-risk disease ranges from 0 to less than 10%, with virtually no long-term survivors (Campo et al. 1998; Lopez-Guillermo et al. 1998; Rudiger et al. 2002).

The eye, brain and testis are considered to be immunoprivileged sites (Streilein 2003). In these sites, strong blood-tissue barriers and an altered immune response allow cells, including certain malignant cells expressing non-self antigens, to escape destruction by the immune system (Filippini et al. 2001; Ferguson et al. 2002; Streilein 2003). Immunoprivilege in these specific sites may account for the appearance and metastases of lymphomas to the eye, brain and testis (Wallace et al. 2006). Testicular lymphoma accounts for only 1–8% of all testicular tumors and 1% of all NHLs (Freeman et al. 1972; Doll & Weiss 1986). Primary testicular lymphoma (PTL) is usually a B-cell lymphoma, of which 68% are of the intermediate-grade DLBCL subtype (Woolley et al. 1976; Turner et al. 1981; Ferry et al. 1994). PTL has a proclivity to spread to unusual extranodal sites and generally has a poor prognosis (Doll & Weiss 1986; Shahab & Doll 1999). Of the 12 SMRLs, 2 (17% of total SMRLs and 22% of B-SMRLs) were from testicular metastases.

Nasal lymphomas affecting the nose and nasopharyngeal region occur much more frequently in Asian countries than in Western countries and constitute 7.2% of extranodal lymphomas in Hong Kong (Ho et al. 1984). Sinonasal lymphomas are rare in the USA and Europe and represent only 2.2% of NHL (Murphy et al. 1998; Gaal et al. 2000; Rudiger et al. 2002). Many lymphomas in the sinonasal region are of NK/T-cell origin (Yamanaka et al. 1985). More than 70% of nasal NK/T-cell lymphomas (NKTL) localize in the nasopharyngeal region, although extranasal and disseminated disease can occur. Nasal NKTL is closely associated with Epstein–Barr virus (EBV) positivity. Although the prognosis of sinonasal lymphomas is variable and difficult to evaluate, the clinical course of patients with nasal NKTL is usually a rapid decline (Aozasa et al. 2008). The prognosis is far worse than for their B-cell counterparts (Cheung et al. 1998). Of the 12 SMRLs, 3 (25% of total SMRLs, 22% of B-SMRLs and 33% of T-SMRLs) are from nasopharyngeal lymphoma.

The skin is the most common extranodal site of NHL, with a yearly incidence approaching 3000 (1 case per 100,000 individuals) in the US (Smith et al. 2007). Cutaneous lymphomas represent a broad spectrum of approximately 20 distinct clinical-pathologic entities with multiple clinical presentations, natural histories, and treatment options. Cutaneous T-cell and/or NK-cell lymphomas is the most common category of cutaneous lymphoma, with a yearly incidence of 6 cases per million (Criscione & Weinstock 2007). Cutaneous B-cell lymphomas have a yearly incidence of 4 cases per million, and precursor hematologic

neoplasms are extremely rare (Smith et al. 2005). Cutaneous lymphomas rarely metastasize to the eye (Chong DY in press). Of our 12 SMRLs, 2 cases (17% of total SMRLs, 11% of B-SMRLs and 33% of T-SMRLs) are from skin metastasis.

In addition to clinical history, vitreal cytokine levels and molecular pathology of the lymphoma cells are valuable for the diagnosis of SMRL. B lymphoma cells can secrete high levels of IL-10 (Blay et al. 1993), an anti-inflammatory and immunosuppressive cytokine, while inflammatory conditions like uveitis (Murray et al. 1990) are associated with high levels of IL-6 (Bogdan et al. 1991; de Waal Malefyt et al. 1991; D'Andrea et al. 1993), a proinflammatory cytokine (Horn et al. 2000; Hodge et al. 2005). Studies have shown that PIOL can exhibit high IL-10 levels, and an IL-10/IL-6 ratio greater than 1.0 is suggestive of PIOL (Chan et al. 1995; Whitcup et al. 1997; Shen et al. 1998; Whitcup et al. 2000; Wolf et al. 2003; Chan & Wallace 2004; Merle-Beral et al. 2004; Levy-Clarke et al. 2005; Cassoux et al. 2007; Gonzales & Chan 2007). The current study also confirms a high vitreal IL-10/IL-6 ratio in 57% of B-SMRLs and 33% of T-SMRLs. The cytokine levels of IL-10 and IL-6 and the IL-10/IL-6 ratio are by no means diagnostic of SMRL, nor do they differentiate SMRL from PIOL. However, they can be useful adjunctive tests in corroborating a clinical suspicion of malignant lymphocytes in the eye. Elevated serum IL-10 levels have been also reported in NHL (Cortes & Kurzrock 1997) and nasal NKTL (Harabuchi et al. 2009). This study has detected *IgH* gene rearrangements in all B-SMRLs and *TCR* gene rearrangements in all T-SMRL. Molecular data is much more reliable than intraocular cytokine levels for the diagnosis of SMRLs.

In summary, SMRLs are extremely rare. Clinical features of SMRL and primary retinal lymphoma are similar, and both diseases may masquerade as uveitis. T-SMRL is more aggressive than B-SMRL. The key to diagnose SMRL is presence of a clinical history of systemic lymphoma (particularly from testis, skin, and nasopharynx) and identification of atypical lymphoid cells in the vitreous or retina. Molecular analysis is also helpful in making the diagnosis of SMRL.

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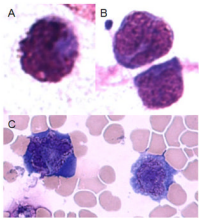

Figure 1.
Atypical B-cells and T-cells of systemic metastatic retinal lymphoma (SMRL) in the vitreous. A & B, atypical B-lymphoid cells; C, atypical T-lymphoid cells. (Giemsa, original magnification, ×640)

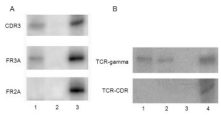

Figure 2.

PCR of gene rearrangement in two cases with SMRL. A, The PCR result of case No. 4 showing *IgH* gene rearrangement was detected using primer pairs of *FR3A* and *CDR3* and not *FR2A*; B, The PCR result of case No. 11 showing *TCR* gene rearrangement was detected using primer pair of *TCR-γ* and not *TCR-CDR*. (Lane 1, vitreous specimen; Lane 2, nasopharyngeal lymphoma; Lane 3, negative control; Lane 4, positive control)

Table 1

Categories of retinal lymphoma

Category		Case (Percent)
PIOL		89 (100.0%)
	B-cell lymphoma	87 (97.75%)
	T-cell lymphoma	2 (2.25%)
SMRL		12 (100.0%)
	B-cell lymphoma	9 (75.00%)
	T-cell lymphoma	3 (25.00%)
Total Retinal lymphoma (IOL)		101 (100.0%)
	B-cell lymphoma	96 (95.05%)
	T-cell lymphoma	5 (4.95%)

PIOL, primary intraocular lymphoma; SMRL, systemic metastatic retinal lymphoma; IOL, intraocular lymphoma

Table 2

Demographics of systemic metastatic retinal lymphoma (SMRL)patients

Case No.	Age (year)	Gender	Type	Primary location of lymphoma	WHO Classification
1	81	Female	B-cell	Skin	Primary cutaneous Diffuse Large B-Cell Lymphoma(DLBCL) – leg type
2	63	Male	B-cell	Retroperitoneum	Follicular Lymphoma
3	64	Female	B-cell	Nasopharynx	DLBCL – paranasal sinus
4	38	Female	B-cell	Breast	DLBCL – breast
5	87	Male	B-cell	Nasopharynx	DLBCL – paranasal sinus
6	72	Male	B-cell	Testis	DLBCL – testis
7	70	Male	B-cell	Testis	DLBCL – testis
8	32	Male	B-cell	Ileo-cecum	Burkitt's lymphoma
9	72	Female	B-cell	Stomach	Mucosa-associated lymphoid tissue (MALT) lymphoma – gastric
10 (Levy-Clarke et al. 2008)	78	Male	T-cell	Skin	Primary cutaneous peripheral T-cell lymphoma (PCPTCL)
11 (Cimino et al. 2009)	54	Female	T-cell	Nasopharynx	Extranodal NK/T-cell lymphoma, nasal type
12	54	Female	T-cell	Blood	Adult T-cell lymphoma/leukemia (HTLV 1-positive)

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Table 3

Vitreal IL-10 and IL-6 levels of metastatic systemic retinal lymphoma

Case No.	Type	IL-10 (pg/ml)	IL-6 (pg/ml)	Ratio of IL-10/IL-6
1	B-cell	77	<15.6	>1.00
2	B-cell	NA	NA	
3	B-cell	<23.4	<15.6	
4	B-cell	470	15	>1.00
5	B-cell	380	250	>1.00
6	B-cell	NA	NA	
7	B-cell	624	<15.6	>1.00
8	B-cell	<23.4	<15.6	
9	B-cell	<46.8	<31.2	
10	T-cell	137	143	<1.00
11	T-cell	743	311	>1.00
12	T-cell	203	843	<1.00

NA: not measured