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A cluster of vitreoretinal lymphoma in New York with possible link to the Chernobyl nuclear disaster

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Vitreoretinal lymphoma (VRL) is an ultra-rare disease and an unusual presentation of primary central nervous system lymphoma (PCNSL) [1]. A quarter of PCNSL patients develop VRL and upto 85% of VRL patients have or will develop another PCNSL [2,3]. VRL, if accompanied by brain lymphoma, is associated with significant morbidity and mortality [4]. The case definition for VRL has evolved. It used to be considered a subcategory of intraocular lymphoma (IOL), but the current definition is diffuse large B-Cell lymphoma (DLBCL) arising in the vitreous, retina and the optic nerve [1,4,5]. VRL is most often composed of B-cells [6]; although, rare T-cell variants are reported [7]. To date, the etiology of VRL is unknown and reliable epidemiologic data for VRL are sparse in the literature. There are no reports of population-based rates for VRL in the USA.

We diagnosed 10 subjects with VRL in our clinical practices in New York City (NYC) during 2010–2014. Intrigued by our encounter with these cases of an extremely rare malignancy, we conducted an investigation to identify potential risk factor(s) and determine population incidence rates of VRL in the USA and NYS. Study procedures were approved by the Institutional Review Board (IRB) of the New York Eye Cancer Center (IRB Approval Study #1042–2016).

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Authors' contributions

SK designed the clinical investigation. RM conducted the epidemiologic analyses. SK and RM wrote the paper with assistance from PTF and RPG. All authors contributed to the project and approved the manuscript.

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Pathologic diagnosis of VRL was made at four ophthalmology practices in NYC (by P.T.F., J.R., A.A., I.G.). Staging included physical examination, imaging studies (computed tomography [CT], positron emission tomography [PET-CT]), bone marrow examination and cerebral spinal fluid (CSF) studies. Patients were subsequently treated by medical oncologists (S.K., R.F.) and radiation therapists (J.R., W.C.). Following qualitative analysis of clinical parameters, descriptive epidemiologic analysis was performed (R.M.).

We used population-based incidence data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program to calculate rates of VRL in 13 SEER areas from 1992 to 2014 (Surveillance Epidemiology and End Results [SEER] Program, National Cancer Institute [www.seer.cancer.gov] SEER*Stat Database: Incidence – SEER 13 Regs Research Data. Nov 2015 Sub (1992–2013) <Katrina/Rita Population Adjustment> – Linked to County Attributes – Total U.S., 1969–2014 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2016, based on the Nov 2015 submission). Histology/behavior codes 9680 (DLBCL)/3 (malignant) were used in conjunction with International Classification of Diseases for Oncology, Third Edition (ICDO-3) topography codes C692 (retina), C694 (intraocular), and C723 (optic nerve) [8]. ICD-O-3 does not provide a unique topography code for vitreous, but DLBCL of vitreous is normally coded to C694. Rates were calculated per 100,000 person-years and were age-adjusted using the 2000 USA standard population. SEER*Stat was used to calculate rates (Surveillance Research Program, National Cancer Institute SEER*Stat software. Available from: www.seer.cancer.gov/seerstat, version 8.2.1). Incidence trends using 10-year intervals (1992–2002 and 2003–2014) were also analyzed. Since NYS data are not reported to SEER, we separately analyzed NYS incidence data (1992–2014) reported to the New York State Cancer Registry (NYSCR; New York State Cancer Registry Database. New York State Department of Health Registry. Based on data as of July 2016. Available from: www.health.state.ny.us/statistics/cancer).

The diagnosis in the 10 subjects was DLBCL (CD20 positive, BCL2 positive, BCL6 positive) and the presentation was bilateral in all cases (Table 1). The most common complaint was cloudy vision. The most common ophthalmologic findings were anterior chamber cells, sheets of cells within the vitreous, uveitis and sub-retinal infiltrates. Diagnoses in all patients were made by immunohistochemical analysis on retrieved tumor specimens. Tissue samples were obtained via vitreous fine needle aspiration (FNA), vitreous biopsy, and/or a stereotactic brain biopsy. When performed, the Ki-67 proliferative index was 80–90%. None of the patients had a family history of lymphoma or had taken immunosuppressive medication. We did not obtain EBV titers or perform HIV testing. Nine of the 10 patients were alive at median follow-up of 4 + years. One patient [Unique Patient Number (UPN) 9] died from a cause other than lymphoma within a year after diagnosis. The median age at diagnosis among the 10 subjects was 70.4 years (range, 60–85; Table 1).

Upon survey for potential risk factors, six patients (one man and five women) reported residence in regions proximal to the Chernobyl nuclear power facility at the time of the accident. Of those six, four reported living in Ukraine, one in Poland, and one in Moldova at the time of the Chernobyl nuclear disaster (Table 1). Median time from the accident to diagnosis was 26 years (range, 24–27 years). There were no other medical conditions unique

to this group of six patients when compared to the other four. Five were diagnosed with VRL prior to the development of brain involvement (one subsequently developed brain lymphoma) and one concurrently. Median age at diagnosis among the six subjects was 76 years (range, 63–83 years). Five of the six patients are currently alive at median follow-up of 4 + years (Table 1). The only common demographic variable among the cases was Ashkenazi Jewish ancestry in 7 of 10 subjects.

Descriptive epidemiologic analyses revealed the extreme rarity of this condition. During 1992–2014 in the 13 SEER areas, there were 20 cases of VRL, all among non-Hispanic whites and Asian/Pacific Islanders. VRL rates per 100,000 person-years for both sexes were higher (based on small numbers) among Asian/Pacific Islanders (0.0026 for males and 0.0059 for females) than whites (0.0023 for males and 0.0030 for females; Table 2). Based on small numbers, VRL rates among white females increased from 0.0021 in 1992–2002 to 0.0038 in 2003–2014, and rates among Asian/Pacific Islander females increased from 0.0050 to 0.0058 during this time period (Table 2). Rates among white males was 0.0025 in 1992–2002 and 0.0022 in 2003–2014, while rates among Asian/Pacific Islander males increased from 0.00 to 0.0043 during this time period (Table 2).

Analysis of NYSCR data revealed 18 cases (13 females and five males) of VRL diagnosed during 1992–2014. The racial/ethnic breakdown of the 18 VRL cases in NYS was as follows: 15 whites (13 non-Hispanic, two Hispanic), one black, and two Asian/Pacific Islanders. Due to small numbers, rates for NYS cannot be calculated but based on incidence data, 3.3 cases of VRL are expected in 4 years in NYS. The expected number of cases is even lower taking into account that the 18 VRL cases reported in NYS in the 22-year period included our 10 patients. Thus, our observation of 10 cases of VRL in 4 years in NYC is unanticipated and significant.

The only common environmental exposure among this cluster was proximity to Chernobyl nuclear disaster decades earlier in 6 of 10 patients. Radiation from the Chernobyl nuclear power facility accident, which occurred on 26 April 1986, contaminated large areas of Eastern Europe with the greatest impact in Ukraine, Belarus and the Russian Federation. The most common neoplastic long-term side effect after the Chernobyl accident was thyroid cancer [9]. Reported hematologic side-effects include blood count abnormalities and adult and childhood leukemia [10]. The recent report of an increased incidence of chronic lymphocytic leukemia (CLL) in Chernobyl mitigation personnel [11] suggests that some B-cell neoplasms may be radiation-related. A number of ocular abnormalities have also been reported after the Chernobyl accident including arteriosclerosis of the fundus oculi blood vessels, macular degeneration, chronic conjunctivitis and retinopathies [12].

The only common demographic factor among this cluster was Ashkenazi Jewish ethnicity. The composition of NYC with a large Ashkenazi Jewish population may explain this observation; although, increased risk of myeloproliferative disorders (MPD) among Ashkenazi Jews has been reported [13]. A study reported a cluster of MPD in northern Israel among Ashkenazi Jews originating from Romania, Poland and European USSR [13].

Population-based incidence rates of VRL and IOLs in the USA have been scarcely reported. When reported, the estimated rates are based on incidence patterns of PCNSL and the assumption that approximately 15–35% of patients with PCNSL have intraocular involvement [4,5]. Our direct analysis of population-based VRL incidence data suggests higher rates of VRL among females in the USA and among Asian/Pacific Islanders, in contrast to other extra-nodal (non-ocular) and nodal NHLs, which are more common among white males. Interestingly, a similar pattern was reported for ocular adnexal NHL [14,15]. The underlying reasons for the current observations for VRL and those reported previously for ocular adnexal NHL are not known and the influence of environmental factors and/or gene–environment interactions cannot be ruled out [16].

A Canadian study reported 22 individuals diagnosed with VRL in British Columbia (BC) in 1990–2010 with incidence estimated as 0.047 per 100,000 person-years [1]. Our incidence estimates of VRL in the USA during 1992–2014 for both genders combined (0.0044 per 100,000 person-years for Asian/Pacific Islanders and 0.0027 for whites) are lower than the estimates in this Canadian study. The lower rates may be explained by several factors, including differences in ethnic makeup of the population in BC versus the 13 SEER areas in the USA.

To our knowledge, ours is the first report of a cluster of VRL in the USA. Our analysis of population-based incidence rates of VRL provides data that are sparse in the literature. SEER rates are representative of national cancer incidence even though some states such as NYS are not represented. Another strength of our study is the analysis of NYS data, given that all our patients resided in NYS.

In conclusion, our reported cluster of 10 individuals diagnosed with VRL in our four local practices in NYC over a 4-year period is significant considering the extreme rarity of this condition (the expected number is ~3 cases in 4 years for the entire NYS). The sole environmental factor we identified was residence in regions proximal to the Chernobyl nuclear disaster decades before and a common demographic factor was Ashkenazi Jewish ethnicity. The extreme rarity of this condition and its apparent increasing trend underscores the importance of VRL registries to facilitate cluster investigations and registry-based studies to search for etiologic clues.

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Table 1.

Clinical and demographic characteristics of patients diagnosed in New York.

Unique patient number	Age at diagnosis	Sex	Residence at the time of exposure	Year of diagnosis	Pathology	Treatment	Survival (Years)
1	74	F	Ukraine	2012	DLBCL	Rad	3+
2	76	F	Poland	2012	DLBCL	Rad/Cth	3+
3	85	F	Ukraine	2013	DLBCL	Rad	2+
4	75	F	Ukraine	2012	DLBCL	Rad/Cth	3+
5	63	M	Moldova	2011	DLBCL	Rad/Cth	4+
6	83	F	Ukraine	2010	DLBCL	Cth	3
7	65	F	China	2011	DLBCL	Rad	5+
8	60	F	USA	2010	DLBCL	Rad/Cth	6+
9 ^a	61	F	USA	2014	DLBCL	Rad	1
10	62	M	USA	2011	DLBCL	Rad/Cth	5+

DLBCL: diffuse large B-cell lymphoma; Rad: radiation; Cth : chemotherapy.

^a Patient no. 9 died within a year of diagnosis from a cause other than lymphoma.

Table 2.

Incidence of vitreoretinal lymphoma by gender and ethnicity in 13 areas of the National Cancer Institute's Surveillance, Epidemiology and End Results Program^a, 1992–2014.

						Ethnicity rate ratio	
Vitreoretinal lymphoma ^b (Years)	Male count	Male rate ^c	Female count	Female rate ^c	Male/Female rate ratio	Males	Females
(1992–2014)							
White (non-Hispanic)	6	0.0023	10	0.0030	0.77	1.00 ^d	1.00 ^d
Black	0	0.0000	0	0.0000			
American Indian/Alaskan native	0	0.0000	0	0.0000			
Asian/Pacific Islander	1	0.0026	3	0.0059	0.44	1.13	1.97
(1992–2002)							
White (non-Hispanic)	3	0.0025	3	0.0021	1.19	1.00 ^d	1.00 ^d
Black	0	0.0000	0	0.0000			
American Indian/Alaskan native	0	0.0000	0	0.0000			
Asian/Pacific Islander	0	0.0000	1	0.0050			2.38
(2003–2014)							
White (non-Hispanic)	3	0.0022	7	0.0038	0.58	1.00 ^d	1.00 ^d
Black	0	0.0000	0	0.0000			
American Indian/Alaskan native	0	0.0000	0	0.0000			
Asian/Pacific Islander	1	0.0043	2	0.0058	0.74	1.95	1.53

^a Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco–Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia and the Alaska Native Tumor Registry.

^b Histologic type ICD-O-3 code 9680 (diffuse large B-cell lymphoma) and primary site codes C692 (retina), C694 (intraocular), and C723 (optic nerve).

^c Age-adjusted using 2000 USA Standard per 100,000 person-years.

^d Referent group.