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Gorski Kotar – An Endemic Region for Primary Gastric Non-Hodgkin Lymphoma?

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A B S T R A C T

Primary gastric non Hodgkin lymphoma (PGNHL) is a distinct group of extranodal lymphomas with interesting geographical distribution and variable prevalence in different countries. We analysed epidemyological data of our patients with PGNHL in Primorsko-goranska County. Clinical data of 30 patients with PGNHL diagnosed and treated in Clinical Hospital Center of Rijeka, Croatia between January 1995 and December 2005 were prospectively analyzed. We used statistical analysis (t-test, χ^2-test) for small groups. Out of 30 pts with PGNHL, 19 were born in Primorsko-goranska County, part of Croatia situated by the Adriatic sea which consists of three regions: City of Rijeka, Islands and Gorski Kotar. 6 of 19 patients (31.6%) were originally from Gorski Kotar which made incidence rate of PGNHL in Gorski Kotar 7 times higher than in other two regions. Many authors emphasized that relative frequency of PGNHL is very variable in various countries and regions. Geographical distribution of our patients was very surprising because Gorski Kotar is the region with lowest number of citizens, rural area without any known pollutants, and ecologically one of the most preserved microsystem in this part of Croatia. Gorski Kotar is known to be an endemic region for multiple sclerosis and lyme borreliosis. Is it for PGNHL too?

Key words: *epidemiology, Croatia, Gorski Kotar, extranodal lymphoma,* Lyme boreliosis*, multiple sclerosis, primary gastric non-Hodgkin's lymphoma*

Introduction

Primary gastric non Hodgkin lymphoma (PGNHL) is a rare tumor accounting for 30–69% of all extra nodal lymphomas and 1–10% of gastric malignant neoplasm. They form a distinct group of tumors with interesting geographical distribution and variable prevalence in different countries[1,2].

While the clinical and experimental knowledge concerning PGNHL is increasing, there is a scarcity of epidemiological data in that field. In the past two decades, there has been a sharp rise in the incidence of nodal and esspecially of extranodal primary lymphomas, representing 33% of all incident lymphomas in the US in 2000. Fisher et al. stated that the incidence of non-Hodgkin's lymphoma (NHL) has doubled over the past two decades in the US and most other westernized countries. Some of the reasons for that observation is improved cancer reporting, changes in lymphoma classification, and increases in AIDS-associated lymphomas but more than a half cases with NHL could not be contribute to that reasons.

Non-Hodgkin's lymphoma rates have steadily increased 30% each year in the US from 1970s to the mid 1990s. Most other Westernized countries in which registry data are available have reported similar trends. These increases in NHL have been observed in males and females, whites and nonwhites, and all age groups except the very young. With the exception of skin malignancies, such temporal increases in cancer incidence are unprecedented[2,3].

Since 1980, NHL incidence in males, aged 25–54, has undergone dramatic escalation, mostly related to the HIV epidemic, but other, HIV negative lymphomas have

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been in dramaticall escalation too. Current evidence suggests that factors or conditions that precipitate either chronic antigenic stimulation or immunosuppression may provide a preferential milieu for development of NHL.

High rates of lymphoma have been observed among individuals with autoimmune disease, organ transplants, and primary or acquired immunodeficiency[4–7]. Several pathogens have been linked to the risk of lymphoma, including *Helicobacter pylori*, Epstein-Barr virus, human immunodeficiency virus, human T-cell lymphotropic virus-1, hepatitis C virus, simian virus 40, and human herpes virus 8 which infections is described in patients with primary effusion lymphomas[8–10]. Whether these microbes are responsible for specific genetic mutations that initiate tumor growth, antigenic stimulation leading to B-cell proliferation and increased potential of random cell replication errors or immunosuppression, which thereby promotes tumor growth, has not been clearly delineated.

Other exogenous factors as chemicals, agricultural exposures, hair dyes, and blood transfusions[11–14], as well as genetic factors[15] have been implicated in lymphomagenesis.

Many authors showed conection of PGNHL with possible ethyological agents. We wanted to analyse geographic distribution of PGNHL and analyse their connection with possible parameters previously described in the literature.

Patients and Methods

A population-based sample of patients diagnosed and treated in Clinical Hospital Center of Rijeka, Croatia between January 1995 and December 2005 was prospectively analyzed.

Hospital archives have been collected by standardized questionnaires prepared previously for a registry. Clinical data of 30 patients with PGNHL has been collected.

For statistics and incidence rate we used data from Goverment population registry and the Department of Epidemiology and Medical Statistics, University of Rijeka, Croatia.

Statistical analysis (t-test, χ^2-test) for small groups, percentage, tabular and cartography analysis has been made16.

All data has been analyzed by Statistica (ANOVAe) program in Windows XP operational system.

Results

Over a period of 10 years, 30 patients with primary gastric non Hodgkin lymphoma (PGNHL) were recorded in UniversityHospital Center Rijeka, Rijeka, Croatia. Out of 30 pts with PGNHL, 19 (10 men, 9 women, mean age 62.1 y) were born in Primorsko-goranska County. A total population of Primorsko-goranska County is 331,090 citizens which mean that incidence of PGNHL in our population is 0.574/100.000 *per* year.

Primorsko-goranska County is a part of Croatia situated by the Adriatic Sea which consists of three regions: City of Rijeka, Islands and Gorski Kotar. 6 of 19 patients (31.6%) were originally from Gorski Kotar which made incidence rate of PGNHL in Gorski Kotar 4 to 9 times higher than compared with whole region or other two regions respectively (Table 1). The higher concentration of the patients with gastric lymphoma in Gortski Kotar is also seen on the map (Figure 1).

We compared clinical data of patients from Gorski Kotar with other patients with PGNHL seen at our clinic and there were no significant differences among those two groups in age, sex, clinical presentation, laboratory

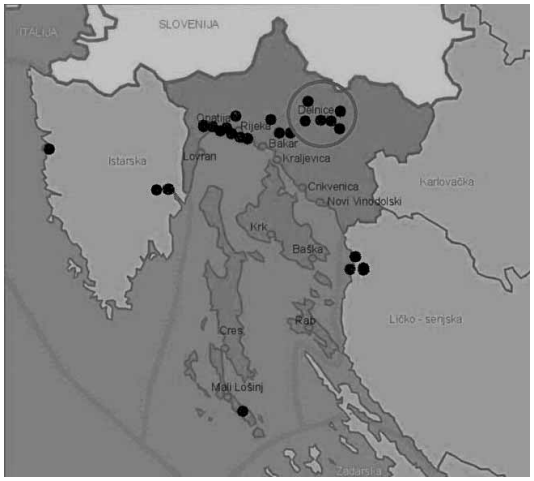

Fig. 1. Geographic distribution of patients with primary gastric non-Hodgkin lymphoma in County of Primorje-Gorski Kotar. Part inside the circle represents Gorski Kotar.

TABLE 1
DEMOGRAPHYC CHARACTERISTICS AND INCIDENCE RATE OF PRIMARY GASTRIC NON HODGKIN LYMPHOMA (PGNHL) IN COUNTY OF PRIMORJE-GORSKI KOTAR

	Surface area (km^2)	Population	Regional density (Residents/km^2)	Patients with PGNHL	Incidence rate
County of Primorje-Gorski Kotar	3893	331,090	85	19	0.57
Rijeka and coast (Crikvenica Opatija)	1279	255,182	200	12	0.47
Islands	1342	45,372	34	1	0.22
Gorski kotar	1272	30,536	24	6	1.96

parameters, histological type of lymphoma, remission and survival rate.

Patients from whole region were predominantly from higher age groups (mean age 62,1 years). The distribution of histological subtypes was as follows: marginal zone B-cell lymphomas (MZBL), 65%; diffuse large-cell B-cell lymphoma (DLBL), 29%; and mixed forms, 6%. *H. pylori* could be detected histologically in 79% of all cases, 91% of MZBL cases and 62% of DLBL cases.

Discussion

Primary gastric non Hodgkin lymphoma (PGNHL) is one of the major sites of extra nodal NHL. Previous researches tried to analyze its epidemiological and etiological characteristics and concluded that PGNHL had variable geographic distribution.

In the United States NHL represents 4% of all cancers. The majority of NHL cases arise in lymph nodes, but primary extra nodal disease accounts for 20–30% of all cases. The most frequent primary extranodal sites are the stomach. The incidence of non-Hodgkin's lymphoma (NHL), particularly at certain extra nodal sites is rising rapidly. Leukemia Research Fund Data Collection Survey which covers many parts of England and Wales reported Age-standardized incidence rates of gastrointestinal NHL at all sites ($0.58/10^5$ *per* year),and gastric lymphoma ($0.24/10^5$ *per* year). It was the lowest rate gastric NHL in Europe. Analysis showed that the incidence of gastrointestinal NHL significantly increased by 2.7% *per* annum. Time-trend analyses showed annual increases in incidence rates for gastric (6.3%) and small bowel (5.9%). The reasons for these increases are poorly understood. After accounting for the impact of changes in diagnosis and well-established risk factors, there remains an unexplained increase in incidence of more than 40% over the past 40 years. Incidence differ according sex (50% higher for males), age (elderly) and race (35% higher among whites). Rates of NHL historically have been about 40% higher in urban counties than in rural counties, but the excess has become smaller (about 15–25%) in recent years and is attributed to a more rapid increase in the incidence of NHL in rural areas.

The incidence rates among various countries are very variable. NHL in the United States tends to exceed those of most other countries. The difference is particularly striking for follicular lymphoma, which constitutes 20% of cases in Western countries but is relatively rare in developing countries, China, and Japan. Geographical differences in etiologic or host factors may play a role in these international differences. The increase in incidence has been more rapid in rural than urban regions of the United States and might be associated with exposures to pesticides[17–19].

Non Hodgkin lymphoma occurs worldwide and is strongly correlated with socioeconomic status. The disease is most common in developed countries, with US rates exceeding those of most other countries in the world. Notable are the unusually low rates of NHL reported in Thailand and China (2–3/100,000). The occurrence of NHL subtypes varies by geographic area. For instance, Burkitt's lymphoma is most common in tropical Africa; the highest rates of adult T-cell lymphoma occur in southwest Japan and the Caribbean; and follicular lymphomas are extremely rare in Latin America[20].

Extranodal lymphomas especially primary gastric non Hodgkin lymphoma (PGNHL) also has variable incidence rates. Higher incidence has been noticed in northern Italy[21] especially in Feltre[22] where were 13 times more cases of PGL in 1986–91 than in the UK communities, and in USA[23] where compared with whites, Asians/Pacific Islanders had higher rates of NHL of the stomach. In Germany were similar to that in other European countries, except England where rates were lower[24].

The annual incidence rate of NHL in 1995–1999, estimated from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, was 19.1 cases per 100,000 persons, while crude incidence for NHL in Primorsko-goranska County is 14.5/100,000 citizens *per* year[25].

We noticed unusually high incidence of PGNHL in Gorski Kotar which was not explainable to us at this point and we would like to share our results and compare them to other studies. Gorski Kotar is the region with lowest number of citizens, rural area, without any known pollutants, and ecologically one of the most preserved microsystems in this part of Croatia. In the same time Gorski Kotar has been known for years to be endemic region for multiple sclerosis (MS)[26] and Lyme borreliosis. We speculate a possibility that those two illnesses could be in some way connected with extranodal lymphomas. Is it possible that certain cytogenetic sussceptibility, immunodeficiency, in combination with some environmental agents, esspecially some viral or microorganism material in certain geographic area in certain moment lead to either lymphomagenensis or multiple sclerosis? Are they only sharing the same factors? Are they the similar diseases in different clinical presentation?

The challenge in the future would be to research the connection among those diseases and conduct a prospective study on the larger number of examiniees.

Conclusion

Incidence rate of gastric lymphoma in Primorsko-goranska County was similar to incidence rate in other European countries, but it was very unusually concentrated in Gorski Kotar. Geographical distribution of our patients was very surprising because Gorski Kotar is also known to be an endemic region for multiple sclerosis and Lyme borreliosis. Is it for PGNHL too? Our results arouse questions of the possible conection of those three illnesses known to be endemic for the same region. Our future researches focused on NHL risks and causal factors are ongoing in that direction.

REFERENCES

1. FISHER SG, FISHER RI, Oncogene, 23 (2004) 6524. — 2. GURNEY KA, CARTWRIGHT RA, GILMAN EA, Br J Cancer, 79 (1999) 1929. — 3. PALACKDHARRY CS, Oncology (Williston Park), 8 (1994) 67. — 4. GRULICH AE, VAJDIC CM, Pathology, 37 (2005) 409. — 5. KNOWLES DM, Mod Pathol, 12 (1999) 200. — 6. OERTEL SH, RIESS H, Recent Results Cancer Res, 159 (2002) 1. — 7. ANDREWS CN, JOHN GILL M, URBANSKI SJ, STEWART D, PERINI R, BECK P, Am J Gastroenterol, 103 (2008) 1762. — 8. ENGELS EA, Cancer Epidemiol Biomarkers Prev, 16 (2007) 401. — 9. GISBERT JP, GARCIA-BUEY L, ARRANZ R, BLAS C, PINILLA I, KHORRAMI S, ACEVEDO A, BORQUE MJ, PAJARES JM, FERNANDEZ-RANADA JM, MORENO-OTERO R, Eur J Gastroenterol Hepatol, 16 (2004) 135. — 10. PSYRRI A, PAPAGEORGIU S, ECONOMOPOULOS T, Ann Oncol, 19 (2008) 1992 — 11. WEISENBURGER DD, Ann Oncol, 5 (1994) 19. — 12. BOFFETTA P, DE VOCHT F, Cancer Epidemiol Biomarkers Prev, 16 (2007) 369. — 13. BARIS D, ZAHM SH, Curr Opin Oncol, 12 (2000) 383. — 14. HARTGE P, DEVESA SS, Cancer Res, 52 (1992) 5566s. — 15. WEISENBURGER DD, Am J Ind Med, 18 (1990) 303. — 16. PETZ B, Osnovne statističke metode za nematematičare (Naklada Slap, Jastrebarsko, 2007). — 17.CHIU BC, DAVE BJ, BLAIR A, GAPSTUR SM, ZAHM SH, WEISENBURGER DD, Blood, 108 (2006) 1363. — 18. T MANNETJE A, DRYSON E, WALLS C, MCLEAN D, MCKENZIE F, MAULE M, CHENG S, CUNNINGHAM C, KROMHOUT H, BOFFETTA P, BLAIR A, PEARCE N, Occup Environ Med, 65 (2008) 354. — 19. CHANG ET, SMEDBY KE, HJALGRIM H, PORWIT-MACDONALD A, ROOS G, GLIMELIUS B, ADAMI HO, J Natl Cancer Inst, 97 (2005) 1466. — 20. MÜLLER AM, IHORST G, MERTELSMANN R, ENGELHARDT M, Ann Hematol, 84 (2005) 1. — 21. MILANI M, TRICOMI P, ZUCCOLI E, ROSSI G, PEZZOTA MG, LARI C, CRISTOFORI E, Patologica, 88 (1996) 478. — 22. DOGLIONI C, WOTHERSPOON AC, MOSCHINI A, DE BONI M, ISAACSON PG, Lancet, 340 (1992) 186. — 23. WU XC, ANDREWS P, CHEN VW, GROVES FD, Cancer epidemiol, 33 (2009) 337 — 24. ULLIRCH A, FISCHBACH W, BLETTNER M, Ann Oncol, 13 (2002) 1120 — 25. PETRANOVIC D, SEVER-PREBILIĆ M, DULETIĆ-NAČINOVIĆ A, VALKOVIĆ T, JONJIĆ N, LUČIN K, SEILI'BEKAFIGO I, HOST I, Medicina, 42 (2006) 31. — 26. MATERLJAN E, MATERLJAN M, MATERLJAN B, VLACIĆ H, BARIĆEV-NOVAKOVIĆ Z, SEPČIĆ J, Coll Antropol, 33 (2009) 539.

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GORSKI KOTAR – ENDEMSKO PODRUČJE ZA PRIMARNI LIMFOM ŽELUCA?

SAŽETAK

Primarni gastrični non Hodgkin limfom (PGNHL) rijedak je tumor (30–69% svih ekstranodalnih limfoma i 1–10% malignih neoplazmi želuca) s interesantnom geografskom distribucijom i različitom prevalencijom u raznim zemljama. Prospektivnom analizom kliničkih podataka 30 pacijenata liječenih zbog PGNHL u KBC Rijeka, uočili smo da je od 30 pacijenata s PGNHL 19 rođeno u Primorsko goranskoj županiji (PGŽ) koja se sastoji od tri regije: Grad Rijeka, Otoci i Gorski Kotar. 6 of 19 pacijenata (31,6%) rođeni su u Gorskom Kotaru što obzirom na površinu tih područja, broj stanovnika i gustoću naseljenosti čini incidenciju PGNHL 7 puta većom nego u ostale dvije regije. Gorski Kotar je ruralno, ekološki očuvano područje s najmanjim brojem stanovnika i gustoćom naseljenosti u PGŽ, poznato kao endemsko područje za multiplu sklerozu i Lyme boreliozu. Prospektivna studija na većem broju bolesnika pokazat će radi li se o endemskom području i za PGNHL ili druge limfome.