Etiological Observations in 36 Patients With Hodgkin's Lymphoma

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Abstract. *Background/Aim:* Hodgkin's lymphoma (HL) accounts for 1% of cancers and is of largely unknown pathogenesis. This study intended to find clues about potential causes (etiology) of HL through observations on patients and their families. *Patients and Methods:* In 37 years of a medical oncology practice in Basel, Switzerland, 36 out of 2201 patients (1.6%) had HL. Etiological information has been obtained from the patients with the help of a German translation of the NCI Medical History Questionnaire for Cancer Etiology, and through the study of their medical charts. *Results:* Findings of etiological interest were observed in the medical history of 26 out of the 36 patients with HL; these findings were grouped as follows: benign tumors (25%), carcinogenic exposures (19%), immunologic disorders (19%), secondary malignancies (14%), infections (11%), congenital disorders (8%) and tonsillectomies (6%). Twenty-two out of 36 patients had one or more relatives with cancer. *Conclusion:* Personal and family history of patients with HL is a readily available useful tool for etiology research. The fact that HL is frequently associated with other cancers in patients and their relatives points to causal genetic factors.

Etiology is defined as the science concerned with the causes of a disease (1). Alert clinicians have played a key role in recognizing environmental and genetic influences in cancer etiology (2), since many carcinogens, teratogens, and genetic syndromes have been first described by alert observers (3). Hodgkin's lymphoma (HL) accounts for 1% of cancers. Most frequently two age groups are affected: patients aged between 15–35 years, and aged >55 years. The probability of cure has improved dramatically over the past 50 years. HL patients survive for longer, however, with more serious and lasting damage, than almost any other group of cancer patients.

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The etiology of HL is not well understood. Environmental factors are suspected to play a role (4). Epstein-Barr virus (EBV) is detected in Hodgkin and Reed-Sternberg cells in most HL specimens from the developing world, but less often in the industrialized countries (5). Immunosuppression (HIV-infection, organ transplantation, autoimmune conditions such rheumatoid arthritis, systemic lupus erythematoses and sarcoidosis) has been shown to increase the risk for HL (5). HL shows strong familial aggregation (6). No major susceptibility genes have been identified to date. A predisposing mutation has been identified in the KDR gene (7).

Patients and Methods

Patients. In a 37-year medical oncology practice (started on April 1981), 2,201 cancer patients have been examined in hospitals affiliated to the University of Basel, Switzerland or in a private office setting (by W.W.). Out of these patients, 36 had HL. Twenty patients were female (median age at diagnosis was 29 years; range=14-70; median age at death or last contact was 52 years; range=25-74) and 16 were male (median age at diagnosis was 31 years; range=15-75; median age at death or last contact was 54 years; range=25-76).

Data collection. Etiological information has been obtained from patients with the help of a German translation of the NCI Medical History Questionnaire for Cancer Etiology (8) and through the study of patients' medical charts.

Results

Fourteen out of 36 patients have died, 8 from progressive HL, 3 from a second malignancy (1 malignant schwannoma, 1 bilateral breast cancer, and 1 carcinoma of the hypopharynx), and 3 in complete remission (1 sepsis, 1 cardiac arrhythmia, and 1 cerebrovascular insult).

Personal history. Further patient characteristics are summarized in Table I. Findings of etiological interest have been found in 26 patients (Table II). These findings can be grouped as follows: i) benign tumors occurred in 9/36 patients; ii) carcinogenic exposures have been reported by 7/36 patients; iii) immunologic disorders have been reported

Table I. Characteristics of the 36 patients with Hodgkin's lymphoma.

	N	N
Gender	16 male	20 female
Stage		
I A	3	0
I B	1	0
II A	0	5
II B	0	3
III A	4	2
III B	3	3
IV A	3	1
IV B	2	4
Unknown	0	2
Histology		
Lymphocyte rich	2	1
Nodular sclerosis	7	11
Mixed cellularity	6	4
Lymphocyte poor	0	1
Unknown	1	3
Treatment		
Surgery + RT	2	1
Surgery + RT + CT	3	6
Surgery + CT	2	0
RT	2	0
RT + CT	3	8
RT + CT + Autologous bone marrow transplantation	1	0
CT	3	4
Unknown	0	1

RT, Radiotherapy; CT, chemotherapy.

by 7/36 patients; iv) secondary malignant tumors occurred in 5/36 patients; v) infections were reported by 4/36 patients; vi) congenital disorders occurred in 3/36 patients; vii) tonsillectomies were reported by 2/36 patients.

Family history. Findings of etiological interest are summarized in Table III. Twenty-two patients have a positive history of cancer. Fourteen patients have one or more first-degree relative with one or more of the following cancer types: skin (n=3), leukemia (n=3), breast (n=2), ovary (n=2) and other cancer types (n=11).

Discussion

This is a retrospective study of a medical oncology practice cohort of 36 patients with HL. The main focus is laid on aspects of potential etiological interest by submitting anamnestic and clinical patient data to the scientific community for further use. The strength of such an approach is that original data are presented; however, it is only descriptive. Dr. Robert W. Miller has promoted causal

Table II. Findings of etiological interest in the personal history of 26 patients with Hodgkin's lymphoma.

No.	Gender	Findings
1	Male	Exposure to agrochemicals. Chronic polyarthritis. Interstitial lung disease under treatment.
2	Male	Exposure to dyes. Atopic dermatitis. Infectious mononucleosis at the age of 24. Chemotherapy delays and compromises due to psyche.
3	Male	Bilateral cryptorchidism. Factor V-Leiden (heterozygote). Combined hyperlipidemia. Hypothyroidism under chemotherapy. Multiple coronary artery stenoses (diagnosed at age 45).
5	Female	Multiple allergies.
7	Male	Electrician.
8	Male	Exposure to dyes. Generalized coronary heart disease. Myocardial infarction at the age of 53. Sacral teratoma.
9	Female	Dermoid of right ovary (D28). Achalasia (D52).
11	Female	Radiation fibrosis (D27). Fibroadenoma left breast (D28).
12	Female	Sarcoidosis (D68)
13	Male	Malignant schwannoma paravertebral Th3 (D44).
14	Female	Cyst of the median anterior neck. Bilateral breast cancer at the age of 34 (premenopausal, invasive ductal, DCIS comedo type, hormone receptor positive, Her2 negative).
17	Female	Recurrent pneumonias.
19	Female	Borderline mucinous cystadenoma of the right ovary.
20	Female	Squamous cell carcinoma of the right hypopharynx (D56). Sacral dermoid, migraine (D32).
21	Female	Anorexia (D15).
22	Male	Asbestos exposure. Hypogammaglobulinemia (IGM 40MG/DL N: 70-280MG/DL).
24	Male	Celiac sprue (D45).
26	Male	Bilateral gynecomastia since puberty.
28	Female	Infectious mononucleosis (D22). Tonsillectomy (D24). Hepatitis B (D26).
29	Male	Infectious mononucleosis (D36), dental cysts (D52), trichilemmoma of the scalp (D61). Obesity. Coronary atherosclerosis. Diabetes type 2.
30	Female	Cervical carcinoma <i>in situ</i> (D30). Colorectal neoplasia (D42).
31	Female	Congenital ectopia of right kidney. Radiotherapy of both breasts because of keloids after bilateral mastoplasmy at age 22. Worked in a solarium.
32	Male	Tonsillectomy at age 39. Depressions.
33	Female	Aortic stenosis (D51). Coronary stenoses (D53). Stenosis of left subclavian artery (D53).
34	Male	Squamous cell skin carcinoma (D55). Atopic dermatitis in childhood. Psychic problems.
35	Male	Generalized lymphadenopathy (D29) lasting for 3 years.

Insulator age 16-27 (asbestos exposure). Zoo keeper age 27-63. Death at the age of 66 due to occlusions of left carotid artery and left posterior cerebral artery.

Table III. Findings of etiological interest in the family history of 22 (61%) patients with Hodgkin's lymphoma.

No.	Gender	Findings
2	M	Leukemia (F, 2°fs, +1, nv). Brain mal (M, 2°fs, +2, nv). Colorectal mal (F, 2°ms, nv). Colorectal mal (F, 3°ms, nv). Atopic dermatitis in 5 relatives.
3	M	Rectal ca (M, 1°fs, D69, +, v). Rheumatoid arthritis (f, 1°ms, D51, 86).
5	F	Prostate ca D68 + CML D72 + Squamous cell skin ca D76 (M, 1°fs, 81, v). Prostate mal + chronic leukemia (M, 2°fs, +91, nv). Prostate mal (M, 2°ms, D65, +86, nv). OMF (F, 2°ms, D68, +76, nv). OMF (F, 2°ms, D71, v). Lung mal (F, 2°fs, D68, +, nv). GI mal (M, 2°fs, D67, nv). GI mal (F, 3°fs, +, nv).
6	F	Stomach mal (M, 1°fs, +60, nv). Stomach mal (M, 2°fs, +60, nv).
10	M	Lung mal (M, 2°fs, +60, nv).
11	F	Stomach mal (M, 2°fs, +50, nv). Stomach mal (f, 2°fs, +60, nv).
12	F	Ovarian ca endometrioid type + congenital bronchiectases + Factor V-Leiden (F, 1°daughter, D34, 66, v). Ovarian ca (F, 1°mother, +74, nv). Gyn mal + skin mal (F, 1°daughter, D43, nv)
13	F	GI mal (F, 2°ms, +62, nv). Lung mal (M, 2°ms, + 69, nv). Kidney mal (F, 3°ms, +72, nv). GI mal (F, 3°ms, +73, nv).
14	F	Testicular ma (M, 1°fs, D60, nv). Testicular mal (M, 2°fs, +75, nv). Leukemia (M, 3°ms, +45, nv).
17	F	Bone marrow mal (M, 3°ms, +43, nv). Stomach mal (F, 2°ms, +70, nv).
18	F	Brain lesion (1°, D32, nv). GI mal (F, 2°fs, nv). Multiple sclerosis (M, 1°fs, D41, nv).
20	F	Skin mal (F, 2°fs, nv). Lung mal (M, 2°fs, +57, nv). Lung mal (M, 2°fs, +, nv). Gyn mal (F, 2°ms, +, nv). Malformations (F, 2°ms, +1).
21	F	Chronic myelo-monocytic leukemia (F, 1°ms, D63, +65, v). Leukemia (F, 3°fs, +40, nv). Lung mal (M, 2°fs, +, nv). Suicide (M, 1°, +25) Neurodermitis (F, 1°, D2). Pernicious anemia (M, 1°fs, D36, +78).
24	M	Gyn. mal (F, 1°ms, nv).
27	M	GI mal (F, 1°ms, D59, 63, nv). Unknown primary mal (M, 2°fs, D55, nv).
28	F	Unknown primary mal (M, 2°ms, +80, nv).
29	M	Breast ca, ductulolobular, left side, ER+PR+HER2- (F, 1°, D64, 76, v). Spindle cell lipoma of the skin (M, 1°, D75, 79, v). Squamous cell ca of the tongue (M, 1°fs, D58, +61, v). Endometrial ca (F, 1°ms, D60, +81, v). Uterine mal. (F, 2°ms, +50, nv). Breast mal (F, 3°ms, nv). Larynx mal. (M, 3°ms, +63, nv). Obesity of 2 sisters, 1 brother and both parents.
31	F	Stomach mal (M, 2°ms, +, nv). Liver mal (M, 2°ms, +, nv).
33	F	Leukemia (M, 1°fs, +82, nv).
34	M	Cutaneous T cell lymphoma (M, 2°, D14, nv). NHL (M, 1°fs, D75, +, nv).
35	M	Breast ca (F, 1°ms, D65, +81, v). Prostate mal (M, 2°ms, D67, +71, nv). Atrial myxoma (F, 1°, +19, nv). 2nd wife: FH suggestive of Lynch syndrome.
36	F	Stomach mal (F, 2°fs, +70, nv).

ca, Carcinoma; D, diagnosis; D69, age at diagnosis (69 years); ER+, estrogen receptor positive; F, female; FH, family history; Fs, father's side; GI, gastrointestinal; Gyn, gynecological; HER2-, herceptin negative; m, male; mal, malignancy; ms, mother's side; NHL, non-hodgkin lymphoma; nv, not verified; OMF, osteomyelofibrosis; PR+, progesteron receptor positive; syndr, syndrome; v, verified by autopsy/cytology/histology report; 1°, first degree relative; 2°, second degree relative; 3°, third degree relative; +, dead; +1, age at death (1 year); 86, actual age (86 years).

research by alert clinicians (3). A comprehensive review of already published data would be beyond the scope of such a small study.

The personal history of 26 out of the 36 HL patients revealed aspects of potential causal relevance, such as benign and malignant tumors, carcinogenic exposures; immunologic, infectious and congenital disorders. Out of 36 HL patients, 22 had one or more close relative with malignancies. This finding supports the conclusion of a previous report, which demonstrated that familial cancers might have a genetic basis and highlighted the importance of recording family history and survival data (9). Indeed, although HL patients survive

for longer than almost any other group of cancer patients, studies including old (>65 years old) and long-term (>5 years) survivors have lagged behind (10).

Patient registries and biobanking are increasingly recognized as crucial tools for rare disease research (11). Therefore, in this study, sera from 19 HL patients have been stored for further genetic analysis studies.

In conclusion, a detailed presentation of anamnestic and clinical data of HL patients combined with the preservation of biological material for future laboratory studies could facilitate the identification of etiological (causal) factors of the disease.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Conception and design of the study, provision of study materials or patients, data analysis and interpretation, as well as final approval of manuscript were done by Walter Weber. Both Walter Weber and Samuel S. Weber contributed to the financial support, collection and assembly of data, and writing of the manuscript.

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