Hepatosplenic T-Cell Lymphoma: A Population-Based Study Assessing Incidence and Association With Immune-Mediated Disease

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Abstract: Hepatosplenic T-cell lymphoma (HSTCL) is a rare malignancy of unknown incidence that has been associated with immune-mediated disease. This study explored the incidence and patient characteristics of HSTCL in a population of 15.5 million over a 13-year period using a comprehensive national pathology database in The Netherlands (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief) with 100% capture. Twelve cases of HSTCL were identified during this period. The overall incidence of HSTCL in the Dutch population over this period was estimated at 0.06 per million inhabitant-years. All but 2 of the patients were adults at the time of diagnosis (median age, 34.5 years), and most patients died within a year of diagnosis. Three patients had a history of immune-mediated disease, 1 of whom was receiving azathioprine at the time of HSTCL diagnosis. Azathioprine as well as anti–tumor necrosis factor-α agents have been reported as possibly being associated with HSTCL. None of the 12 HSTCL patients had been treated with an anti–tumor necrosis factor-α agent.

Hepatosplenic T-cell lymphoma (HSTCL) is a rare form of non-Hodgkin lymphoma recognized as a distinct subtype in the Revised European-American Lymphoma and World Health Organization classification systems since 1994.[1] HSTCL typically results in death within 2 years of diagnosis even with intensive chemotherapy and bone marrow transplantation. In most of the cases described, the neoplastic cells express a γδ T-cell receptor (TCR),[2] but there have been reported cases with an αβ TCR phenotype.[3] There is very limited information on the epidemiology and pathogenesis of HSTCL, with data mainly from case reports or small retrospective studies.[4] These studies suggest that HSTCL is associated with immunodeficiency or immune-mediated disease, and anecdotal reports have linked HSTCL to biologic therapy with anti–tumor necrosis factor-α agents and to treatment with azathioprine.[4-6]

The Dutch National Database of Pathology (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief [PALGA]), a nationwide network and registry of histopathology and cytopa-

Table. Incidence Rate for HSTCL in The Netherlands From 1995 to 2008 Based on the PALGA Database

Incidence	Number of Patients	Number of Years	Dutch Population, Millions	Rate	
				Per Million Inhabitant-Years	Per 100 Million Inhabitant-Years
	12	13	15.424	0.0598	5.9846

Summary of Patients Identified With HSTCL[a]								
Age at Diagnosis/ Gender	**Year of Diagnosis**	**Diagnosis Confirmed**	**Age at Death**	**Immune-Mediated Disease**	**Prior CS or Immuno-modulator Use**	**TCR Type**	**Cytogenetic Abnormality**	**History of Cancer**
36/M	2005	Yes	NA[b]	Hodgkin lymphoma	CS[c]	αβ	NA	Hodgkin lymphoma
56/F	2005	Yes	57	No	No	γ□	NA	No
52/M	2002	Yes	54	No	No	γ□	Isochromo-some 7Q	No
63/M	2005	Yes	64	No	No	Unknown	NA	No
41/F	2002	Yes	NA[b]	No	No	Unknown	NA	No
16/M	1996	Yes	16	No	No	γ□	NA	No
51/F	2005	Yes	51	Psoriasis and polymyositis	MTX + CS	γ□	No	No
13/M	2007	Yes	13	No	CS for tick bite/FUO	γ□	No	No
19/F	2001	Yes	19	No	No	γ□	No	No
21/M	2000	Yes	NA	Crohn's disease	AZA + CS	αβ	No	No
23/M	2005	Yes	25	No	No	γ□	No	No
33/F	1995	Yes	33	No	No	γ□	Trisomy 7	No

AZA, azathioprine; CS, corticosteroid; F, female; FUO, fever of unknown origin; HSTCL, hepatosplenic T-cell lymphoma; M, male; MTX, methotrexate; NA, not available; PALGA, Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief (Dutch National Database of Pathology); TCR, T-cell receptor.

[a] None of the patients had a history of anti–tumor necrosis factor-α use, HIV infection, or transplantation.

[b] The patient was alive at the end of the study.

[c] The patient also received treatment with vinblastine, vincristine, bleomycin, doxorubicin, etoposide, cyclophosphamide, procarbazine, dacarbazine, and radiotherapy for Hodgkin lymphoma.

thology, contains standardized abstracts of all pathology reports for biopsies obtained in hospitals in The Netherlands. The PALGA database was used in this study to estimate the incidence of HSTCL in a well-described population of approximately 15.5 million in The Netherlands over a defined period of time and to assess the association of HSTCL with immune-mediated disease and immunomodulatory treatment.

Materials and Methods

This study was designed as a noninterventional, retrospective review of all reports of HSTCL cases entered into the PALGA database during the 13-year period from January 1, 1995 through April 30, 2008. HSTCL was included in the PALGA dictionary around 1995, and the first case of HSTCL was also identified in this database in 1995. The search criteria for identifying such cases used the PALGA code of M96783 for HSTCL, spelling variants of *hepato-splena/hepato-spleni*, *cytotoxic*, and/or *gamma*, and/or *delta*, along with a manual review of all cases of peripheral T-cell lymphomas and non-Hodgkin lymphomas for evidence of hepatic localization.

Follow-up information for each identified case came from the pathologist and treating physician and included diagnosis, course, prior or current treatment with corticosteroids and/or immunomodulators (including biologics) at the time of diagnosis, comorbidities (including history of cancer, transplantation, and HIV infection), cytogenet-

ics, and demographic data. Informed consent was obtained from patients who were alive at the time of the study, and care was taken to safeguard the privacy of all patients.

Descriptive statistics were used to summarize data for age at diagnosis and history of immune-mediated diseases or cancer. Population figures for The Netherlands, obtained from the Centraal Bureau voor de Statistiek, were used to calculate the incidence of HSTCL; overall rates were calculated using the number of Dutch inhabitants in 1995. Nonresidents of The Netherlands with HSTCL were excluded from incidence rate calculations. Calculation of prevalence rates was considered inappropriate because the prevalence of this malignancy was unknown for the initial year of the study period, and HSTCL is often rapidly fatal.

Results

Across the 13-year observation period, 12 patients in The Netherlands were diagnosed with HSTCL and had the diagnosis confirmed by pathology review (Table). As PALGA is an automated database, there is a high degree of assurance that this figure is an accurate reflection of the total number of HSTCL cases during this period in the population of approximately 15.5 million. The overall incidence of HSTCL was approximately 0.06 per million inhabitant-years, based on the 1995 population size for The Netherlands (Table). These data suggest that there are fewer than 413 cases of HSTCL worldwide per year (based on the 2010 total population statistic of 6.9 billion).[7] The overall incidence rate for HSTCL is less than the rate for this malignancy (0.3 per million person-years) that was recently reported using data for a 7-year period (2000 through 2006) from a large managed care organization in the United States.[8] Data from the PALGA database confirm that HSTCL is a very rare form of T-cell malignancy.[4,8,9]

The demographic characteristics of the 12 patients with HSTCL identified in the PALGA database, as well as the phenotypic, molecular, and clinical characteristics of the disease, are in general agreement with those reported by Rosh and colleagues[4] as well as Falchook and colleagues.[10] Patients ranged in age at diagnosis from 13 to 63 years (median, 34.5 years). Over half (7/12, 58%) were male. Of the patients from whom immunophenotypic data were available, the γδ TCR phenotype predominated (8/10, 80%; Table). While not all HSTCL tumors express γδ TCR,[9] this is still the most common phenotype.[4] Among the 7 patients with cytogenetic studies performed, trisomy 7 and isochromosome 7q were each identified in 1 patient. Isochromosome 7q has been strongly associated with HSTCL, and trisomy 8 has also been found in patients with this disease.[2,11]

Data from the PALGA database are consistent with the observation that HSTCL is aggressive and usually fatal. Ten of the 12 patients were known to have died during the study period (Table), with most dying within a year of diagnosis; 2 patients were alive at the end of the study.

Discussion

It has been suggested that HSTCL is associated with immunodeficiency or immune-mediated disease. In their review of published cases of HSTCL, Rosh and colleagues[4] reported that approximately one-third occurred in patients with a history of organ transplantation or other conditions requiring use of immunomodulatory therapies. None of the 12 HSTCL patients in the PALGA database cohort had undergone organ transplantation or had evidence of HIV infection. Three patients had a history of immune-mediated disease (Table). Two patients were diagnosed at least 4 years prior to HSTCL diagnosis (17% [1 with Crohn's disease and 1 with psoriasis and polymyositis]). One patient had been treated for Hodgkin lymphoma, resulting in a complete remission, 18 months before the diagnosis of HSTCL. These 3 patients had been treated with corticosteroids and/or immunomodulators, including methotrexate and azathioprine, for an unknown duration before the diagnosis of HSTCL (Table). None of the 12 patients had received therapy with anti–tumor necrosis factor-α agents (which have been available in The Netherlands beginning in 1999). Thus, data from the PALGA database over the 13-year observation period are not consistent with the reports suggesting that HSTCL primarily occurs in patients with underlying immune disorders receiving immunomodulatory therapies.[4,5,6,12]

Conclusion

HSTCL is an extremely rare and deadly disease. It is difficult, but important, to establish the background rate of such a disease to determine the contribution of environmental elements to its causation. No clear associations were identified between HSTCL and either the presence of an immune-mediated disease or biologic therapies.

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