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The incidence of hepatosplenic T-cell lymphoma in a large managed care organization, with reference to anti-tumor necrosis factor therapy, Northern California, 2000–2006

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Abstract

Background—Hepatosplenic T-cell lymphoma (HSTCL), a rare and rapidly progressive subtype of peripheral T-cell lymphoma, has been reported following TNF-α-blocker therapy. To better understand this relationship, we conducted an epidemiologic study in the Kaiser Permanente membership.

Methods—The retrospective cohort study was conducted among Northern California members of all ages. The Kaiser Permanente Cancer Registry, supplemented with review of medical charts and pathology slides, was used to identify and confirm cases of HSTCL. Medical histories were obtained, and we computed the standardized incidence rate for the 7-year period 2000–2006, when immunohistochemical staining was fully established throughout the health plan for diagnosing lymphoma.

Results—Six cases were diagnosed during 2000–2006, for an annual age-standardized incidence rate of 0.3 (95%CI, 0.11–0.65) per million person-years. One case had a prior diagnosis of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS); another had a prior diagnosis of Crohn's disease treated with steroids, thiopurine and infliximab.

Conclusion—Prior cases of HIV/AIDS-linked HSTCL are uncommon in the existing literature. Multiple case reports of HSTCL in the setting of Crohn's disease treated with anti-TNF plus thiopurine have been published, but HSTCL is rare, making epidemiologic assessments difficult.

Keywords

hepatosplenic T-cell lymphoma; Crohn's disease; HIV/AIDS; incidence; epidemiology; autoimmunity

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INTRODUCTION

Hepatosplenic T-cell lymphoma (HSTCL) is a rare and fatal subtype of peripheral T-cell lymphoma.[1] HSTCL is characterized by malignant T-cell proliferation in the sinusoids of the liver or spleen without apparent lymph node enlargement, characteristic cytogenetic abnormalities, and expression of the $\gamma\delta$ or $\alpha\beta$ T-cell receptor.[2,3] It has been proposed that immune-mediated conditions and related drugs may predispose to HSTCL.[4–9] We determined the incidence rate of HSTCL in a community population and explored the etiologic role of immune-related factors.

MATERIALS AND METHODS

The study included Kaiser Permanente Northern California members of all ages. Data sources included the Kaiser Permanente Cancer Registry, computerized pharmacy data, pathology reports, and pathology slides. The pathology report includes results of immunohistochemical testing, which was routine by 2000 and was performed at a centralized laboratory. Before then, some cases were referred out for immunohistochemical diagnosis, but many were not evaluated in this way.

We restricted the incidence calculation to 2000–2006, when immunohistochemical staining was routine. The cancer registry was used to identify patients coded with HSTCL (both $\gamma\delta$ and $\alpha\beta$ International Classification of Diseases for Oncology (ICD-O) code 9716) or with "mature T-cell lymphoma, not otherwise specified" (ICD-O code 9702) or with "NK/T-cell lymphoma, nasal and nasal-type" (ICD-O code 9719). All available diagnostic pathology reports were reviewed by the first author (L.J.H.) to confirm the diagnosis of HSTCL for those given code 9716 and to identify possible HSTCL cases from among those who had been given the less specific codes of 9702 or 9719. Other possible cases were identified based on clinical and pathological descriptions noting massive splenic involvement, involvement of the sinuses in liver or spleen, and an immunophenotype on flow cytometry or immunohistochemistry that was suggestive of the diagnosis. For these cases, the pathology reports and, for one case, the pathology slide, were provided to Dr Jaffe, whose opinion was taken as definitive. Cases with $\alpha\beta$-HSTCL were retained in the study, consistent with World Health Organization criteria.[3]

For confirmed cases, we reviewed the medical record from the start of the patient's first enrollment date through the date of diagnosis of HSTCL. Thirty-one immune-mediated conditions (Appendix), identified *a priori*, were ascertained, together with information on TNF-α blockers, other biologicals, salicylates, sulfasalazine, corticosteroids, azathioprine/6-mercaptopurine (thiopurine), cyclosporine A, leflunamide, and methotrexate. We did not record therapies used to treat human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS).

The age-specific and sex-specific incidence rate of HSTCL and its 95%CI was calculated using as the denominator the general Kaiser Permanente population, including all ages. The age-standardized incidence rate was estimated using the direct method of standardization, with the 2000 US Census population providing weights. This calculation was restricted to

the years 2000–2006. The 95%CI for the rate was computed assuming a Poisson distribution [10]. We further estimated the incidence rate of HSTCL among persons with HIV/AIDS or with Crohn's disease. Person-years of follow-up with HIV/ AIDS was obtained from a report of the annual prevalence of HIV/AIDS in the health plan, with cases determined through chart review and adjudication [unpublished data]. For Crohn's disease, person-years of follow-up began on the second diagnosis of Crohn's disease and ended at the earliest of the HSTCL diagnosis or the end of follow-up. For Crohn's disease, person-years were estimated for combination therapy with anti-TNF and thiopurine; for anti-TNF monotherapy; for thiopurine monotherapy, and for neither. This was accomplished using the pharmacy variables dispensing date and days-supply.

RESULTS

Three patients were coded with HSTCL (ICD-O code 9716) and 148 patients with the less specific codes "mature T-cell lymphoma, not otherwise specified" (ICD-O code 9702) or with "NK/T-cell lymphoma, nasal and nasal-type" (ICD-O code 9719). Among the latter, three had a final diagnosis of $\gamma\delta$-HSTCL and one a final diagnosis of $\alpha\beta$-HSTCL, in the pathology report. Three other potential cases were identified for Dr Jaffe's review on the basis of clinical and pathological descriptions, and for one case, she was provided the pathology slide. Dr Jaffe judged two of the three to be $\gamma\delta$-HSTCL. She judged the third (male patient, age 54years, no history of immune-related disease) to be a possible case of HSTCL; the patient was diagnosed in the late 1980s, had a clinical presentation consistent with the disease, but refused a pathologic diagnosis. Thus, the study included one case of $\alpha\beta$-HSTLC lymphoma, eight definite cases of $\gamma\delta$-HSTCL, and one possible case of HSTCL.

Among the nine definite cases, the median age was 56 years (range 19–75years), and seven were male patients. Three (male patient aged 56years, male patient aged 75 years, and female patient aged 35years) were diagnosed before 2000, and none had a history of immune-mediated disease. During the period 2000–2006, the Kaiser Permanente Northern California population accrued 20.6 million person-years of observation, during which 6 cases were diagnosed. The annual age-standardized incidence rate was 0.3 (95%CI, 0.11–0.65) per million person-years overall, 0.4 (95%CI, 0.13–0.93) per million person-years in men, and 0.1 (95%CI, 0.03–0.56) per million person-years in women (Table 1). The incidence of HSTCL did not appear to increase with age, although the number of cases was small.

Two patients had histories of immune-mediated disease preceding their cancer diagnosis. One was a 19-year-old male patient with Crohn's disease who was treated with azathioprine and infliximab. This case emerged from 20704person-years of follow-up of Crohn's disease (all ages, both sexes) during 2000– 2006, of which, 372person-years included exposure to anti-TNF–thiopurine combination therapy, 364 exposure to anti-TNF monotherapy, 3280 exposure to thiopurine monotherapy, and 16688 exposure to neither of the two drug classes. The crude incidence rate was 48 (95%CI, 1.2–269) per million person-years. The other was a 35-year-old woman with HIV/AIDS who developed from 35052 person-years of follow-up

of HIV/ AIDS (all ages, both sexes) during 2000–2006; the crude incidence rate was 29 (95%CI, 0.7–159 per million person-years.

DISCUSSION

We observed an age-standardized incidence rate of HSTCL of 0.3 (95%CI, 0.11–0.65) per million person-years in a well-characterized community population.[11] The incidence was higher in men than in women and did not vary in relation to age. The age-incidence curves of various lymphoma subtypes differ substantially, with some predominating in children, others in midlife, and others in old age, with etiologic factors being as yet being poorly understood for many subtypes.[12]

With only one case of HSTCL each in persons with prior Crohn's disease and HIV/AIDS, the respective estimated incidence rates of 48 and 29 per million person-years (both sexes, all ages) for these two conditions are quite imprecise. After our study had begun, an additional case of $\gamma\delta$-HSTCL was diagnosed in our population in 2007, in a 20-year-old man with ulcerative colitis who received 17 infusions of infliximab beginning in 2002 followed by four dispensings of adalimumab, throughout with concomitant 6-MP. He was not included in our analysis because his cancer was not diagnosed during the study period. Including this case, post hoc, in the analysis, and evaluating risk among inflammatory bowel disease as a single concept comprising both Crohn's disease and ulcerative colitis would not have appreciably changed our estimate of the risk of HSTCL in patients with inflammatory bowel disease because the denominator in the incidence calculation would have approximately doubled with the inclusion of person-years for patients with ulcerative colitis as well as Crohn's disease.

In 2009, the FDA [7] reported 15 cases of $\gamma\delta$-HSTCL among patients with inflammatory bowel disease who had been treated with anti-TNF and a concomitant thiopurine ("combination therapy"). The two cases in our population constitute two of the 15 in the FDA report. Spontaneous reports to the FDA cannot be used to estimate the relative risk of HSTCL because the denominator is unspecified. Nonetheless, these spontaneous reports motivated the present study. No report similar to the FDA report [7] has been published for persons with HIV/AIDS, and we could locate only a single case report of this association that provided detailed information on the case.[13]

Use of anti-TNF combination versus monotherapy is an important clinical decision, and clear articulation of the relative benefits and risks is essential. Regarding the benefits, recently, it was reported that combination therapy in Crohn's disease patients naïve to thiopurine was more effective in maintaining remission for 26 weeks than use of infliximab alone (remission, 56.8% versus 44.4%, p=0.02).[14] Regarding the risk, we observed a case of HSTCL with a history of exposure to both anti-TNF and thiopurine who developed from a community-based Crohn's disease cohort. The case came out of a cohort in which 2% of person-years involved combination anti-TNF/thiopurine therapy, 2% anti-TNF monotherapy, 16% thiopurine monotherapy, and 80% neither. With only one case, we cannot make a clear inference about differences in risk resulting from combination therapy in contrast to monotherapy.

The FDA report states “It has not been established that infliximab or adalimumab had an exclusive or primary role in the pathogenesis of each reported case of HSTCL”.[7] At present, anti-TNF prescribing information warns on the potential risk of HSTCL and other potential adverse effects of combination therapy but does not contraindicate combination use. Additional evidence to quantify the relative benefits and risks of anti-TNF monotherapy against combination therapy is needed.

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APPENDIX

Immune-mediated conditions identified *a priori* as potential etiologic factors.

Addison disease	Pemphigus vulgaris
Adult Still disease	Pernicious anemia
Alopecia areata	Polymyositis/dermatomyositis
Ankylosing spondylitis	Primary biliary cirrhosis
Asthma	Sjogren syndrome
Autoimmune hepatitis	Psoriasis
Behcet syndrome	Raynaud disease
CREST syndrome	Reiter syndrome (reactive arthritis)
Diabetes (type I)	Rheumatoid arthritis
Graves disease	Sarcoidosis
Guillain-Barre syndrome	Systemic lupus erythematosus
Idiopathic thrombocytopenic purpura	Systemic sclerosis (scleroderma)
Meniere disease	Hashimoto thyroiditis
Mixed connective tissue disease	Inflammatory bowel disease
Myasthenia gravis	Uveitis/iritis
Organ transplantation	Vasculitis

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Table 1.

Annual age-specific and sex-specific incidence rate of hepatosplenic T-cell lymphoma, per million person-years, Kaiser Permanente Northern California, 2000–2006

	Men			Women			Overall		
Age, years	**No. of cases**	**Population at risk, millions**	**Incidence rate (95%CI)****	**No. of cases**	**Population at risk, millions**	**Incidence rate million (95%CI)****	**No. of cases**	**Population at risk, millions**	**Incidence rate (95%CI)****
0–9	0	1.326	—	0	1.276	—	0	2.602	—
10–19	1	1.545	0.6	0	1.493	—	1	3.038	0.3
20–29	0	1.204	—	0	1.327	—	0	2.531	—
30–39	0	1.511	—	0	1.555	—	0	3.066	—
40–49	1	1.648	0.6	1	1.740	0.6	2	3.388	0.6
50–59	2	1.408	1.4	0	1.554	—	2	2.962	0.7
60–69	1	0.866	1.2	0	0.968	—	1	1.834	0.5
70–79	0	0.547	—	0	0.668	—	0	1.214	—
Total*	5	10.055	0.4 (0.13–0.93)	1	10.581	0.1 (0.03–0.56)	6	20.635	0.3 (0.11–0.65)

*Standardized to the US population, 2000.

**Per million person-years.

Cases included a 19-year-old male patient with Crohn's disease with a history of steroid for 22months, azathioprine for 65months, and infliximab for 40 months; a 42-year old female patient with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) who had a history of use of HIV/AIDS medications; and 4 men, aged 47–66years, without histories of immune-mediated disease or drug use. The case with $\alpha\beta$-hepatosplenic T-cell lymphoma (HSTLC) was a 47year-old man. All other cases were diagnosed with $\gamma\delta$-HSTCL.