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REVIEW ARTICLE

Hepatosplenic T-cell lymphoma and inflammatory bowel disease

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Abstract

Objective: This article reviews the current literature and knowledge about hepatosplenic T-cell lymphoma (HSTCL), providing an overview of the clinical features, a description of its pathology and immunophenotypic traits in relation to other lymphomas. In addition, we explore the history of reported cases of hepatosplenic T-cell lymphoma in relation to the possible existence of a causal relationship between infliximab use and HSTCL. The treatments for HSTCL will be briefly addressed.
Methods: A comprehensive literature search using multiple databases was performed. Keyword search phrases including "lymphoma," "hepatosplenic T-cell lymphoma," "Inflammatory bowel disease," "6-mercaptopurine," and "infliximab" were used in various combinations. In addition references from published papers were reviewed as well.
Results: There are over 200 reported cases of HSTCL. Only 22 cases of hepatosplenic T-cell lymphoma are associated with IBD treatment. Clinicians usually reserve immunomodulators and biologics for moderate to severe IBD cases. The ultimate goal of therapy is to control inflammation and therefore allow mucosal healing. IBD patients demonstrating mucosal healing are less likely to undergo surgery and experience complications related to their disease. We manipulate the immune system with corticosteroids, immunomodulators, and biologics, therefore causing bone marrow suppression. With bone marrow suppression, malignant degeneration may begin through selective uncontrolled cell proliferation, initiating HSTCL development in the genetically susceptible.
Conclusion: Hepatosplenic T-cell lymphoma is a rare disease, often with a poor outcome. With the increasing number of reported cases of HSTCL linked to the use of infliximab, adalimumab, and AZA/6-MP, there appears to be an undeniable association of HSTCL development with the use of these agents. This risk is unquantifiable. When considering the rarity of cases and the multiple complications with uncontrolled disease, however, the benefit of treatment far outweighs the risk.

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Contents

1. Introduction

For the last decade, hepatosplenic T-cell lymphoma (HSTCL) was a relatively unknown disease. In fact, although it was in 1981 that Kadin and colleagues first recognized it as a distinct entity from other peripheral T-cell lymphomas, the medical world did not quite catch on to the significance of what HSTCL entails.[1] With the tantalizing hope of control and of relief for patients suffering from inflammatory bowel disease (IBD) with immunomodulating and biological agents, the rare disease of HSTCL began to gain worldwide recognition. There are studies that suggest an increased malignancy and lymphoma risk in patients with IBD.[2–4] But perhaps, a more specific question would be whether lymphoma, including HSTCL, displays a higher incidence in IBD patients who received immunomodulating agents and/or biological agents. If so, are clinicians putting their IBD patients at increased risk for HSTCL with the use of these medications?

Between the years 2001 and 2005, 70,214 new cases of non-Hodgkin's lymphoma (NHL) were diagnosed. In the general population, the incidence of NHL is 17.2 per 100,000 individuals per year. Non-Hodgkin's lymphoma is usually a diagnosis of the older population, with a peak in the 6th to 7th decade. The incidence of extranodal NHL is 5.0 per 100,000.[5] In the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Database, there are a total of 34 reported cases between 1973 and 2005 of HSTCL, a subtype of extranodal NHL. This equates to an incidence of only 0.046 per 100,000 individuals or 1 case per 1088 patient years. Among the 34 cases, 24 were men, and 10 were women. The age breakdown is as follows: 4 patients were less than the age of 19, 6 patients were in their 20s, 12 patients were in their 30s, 5 patients in their 40s, 2 patients in their 50s, and 5 patients older than 60 years old.[5]

Hepatosplenic T-cell lymphoma is a rare and aggressive extranodal form of non-Hodgkin's lymphoma that affects predominantly men. In addition to hepatosplenic involvement as its name suggests, HSTCL is also characterized by a lack of lymphadenopathy, the presence of cytopenias, and sinusoidal infiltration of the splenic red pulp, liver, and bone marrow.[6–8] HSTCL has a rapidly progressive course. The mean time of diagnosis to death is less than 16 months.[8–10] Since Farcet et al. proposed HSTCL as a separate entity from other peripheral T-cell lymphomas, there has been approximately 238 cases of HSTCL reported worldwide through literature search.[7,8,10–102]

Among the medical community, especially the pediatricians, there is a growing concern that HSTCL is an emerging disease of the young, especially of pediatric patients treated with biologic agents. This fear may not be warranted. Of all the reported cases (not including the SEER Database), only 25 cases of hepatosplenic T-cell lymphoma are associated with IBD treatment. An overwhelming 73% of HSTCL were de novo. The de novo group includes patients that were explicitly stated as healthy, which entails lack of autoimmune diseases, treatment with immunosuppressants, history of transplant, or any other primary malignancies. Characteristics of patients who developed HSTCL de novo, including mean age, sex prevalence, presentation, histopathology, and prognosis did not differ from the patients with some degree of immunosuppression.[10,16,17,20] The second largest incidence (18%) is found in immunocompromised patients. This group consists of patients with renal and heart transplant, chronic steroid use, systemic lupus erythromatosis, recurrent malarial infections, sickle cell anemia, dermatomyositis, autoimmune hepatitis, and primary malignancies such as Hodgkin's lymphoma, acute myelogenous leukemia, and multiple myeloma. The third largest group of HSTCL (10%) was found in IBD patients exposed to treatment with immunomodulators and/or biologics (Fig. 1).

Other inflammatory and autoimmune diseases such as peripheral and axial arthritis, Sjogren's disease, polymyositis, systemic sclerosis, dermatitis herpetiformis associated with celiac disease, psoriasis, Hashimoto's thyroiditis have not been linked to the development of HSTCL. But these diseases have all been shown to have a higher risk of developing non-Hodgkin's lymphoma compared to the general population.[103]

The lack of association with HSTCL in these inflammatory diseases may be explained by the fact that B lymphocytes, not gamma–delta T cells, play a predominant role in immunity in the periphery and joint space. The chronic inflammation may be a factor in precipitating the malignant degeneration of the B cells involved. Some studies suggest a 100-fold risk with developing diffuse large B-cell lymphoma in individuals with the highest rheumatoid arthritis disease severity when compared to patients with low global disease activity.[103] Sjogren's disease, systemic lupus erythematosus, and celiac disease are also associated with large B-cell lymphoma development.[103] The specific associations with each specific inflammatory disease have been review elsewhere.[103]