T-Cell Lymphoma of the Rectum in a Patient with AIDS and Hepatitis C: A Case Report and Discussion

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ABSTRACT
Primary T-cell non-Hodgkin’s lymphoma (NHL) occurring in the context of acquired immune deficiency syndrome (AIDS) is uncommon. Here, we report and discuss such a case presenting in the rectum, and review relevant literature. Although typical in some respects, the case is, in other ways, somewhat unusual for an AIDS-related NHL (ARL); ARL tends to be B cell and advanced stage and our case was T cell and stage IE. In addition, the patient suffered from concomitant cirrhosis related to hepatitis C. Chemotherapeutic options for ARL were limited early in the AIDS epidemic due to poor tolerability. Although this has largely been mitigated by the advent of highly active antiretroviral therapy, our patient eventually suffered complications of chemotherapy, apparently related more to his liver disease than to either his lymphoma or AIDS, that ultimately brought about his demise. The Oncologist 2005;10:292–298

INTRODUCTION
The gastrointestinal (GI) tract generally is the most common site for extranodal non-Hodgkin’s lymphoma (NHL), usually of the B-cell type. These NHLs may be Epstein-Barr virus (EBV) related and have long been known to be associated with immunodeficiency. Various immunodeficient states, including ataxia telangiectasia, Wiskott-Aldrich syndrome, and X-linked lymphoproliferative disorder, all exhibit increased incidences of NHL. NHL is 60–100 times more common in HIV-infected patients, and B-cell NHL is an AIDS-defining illness. AIDS-related lymphomas (ARLs) show a high incidence (about 95%) of extranodal involvement, and >50% may be exclusively extranodal. Most ARLs are of high grade, of B-cell lineage, advanced stage, and are associated with B symptoms. ARL is usually a late event in the course of AIDS, coming after some other AIDS-defining illness [1]. Almost all ARLs are of the B-cell type and may be related to chronic B-cell stimulation in HIV-infected patients. T-cell lymphomas are uncommonly reported in AIDS patients; this could be due to the toxic effect of HIV on T-cell survival. A registry survey of 6,788 cases of NHL with specified phenotype in AIDS patients showed that only 1.4% were T-cell lymphomas [2]. Here, we present an unusual case of extranodal T-cell lymphoma presenting in the rectum of an AIDS patient with chronic hepatitis C virus (HCV) infection. We are aware of a case

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of Hodgkin’s disease presenting in the rectum of an HIV-positive patient, but to the best of our knowledge, this is the first report of T-cell NHL presenting in the rectum of an AIDS patient as a solitary site [3].

**Case Report**

The patient was a 46-year-old gentleman who presented to our facility with a 6-week history of rectal pain and hematochezia in March 2001. His rectal pain was exacerbated by bowel movements, but he denied constipation, weight loss, fever, and chills or night sweats. His past medical history did not include surgery or infection in the anorectal region. The patient had transiently abused i.v. drugs in the 1980s and had a history of alcohol abuse. In July 2000, he had suffered a cavitary mycobacterial lung infection associated with a CD4 count of <5 cells/mm³ and an HIV viral load (VL) of >250,000 copies/ml. He was diagnosed as having AIDS and was started on highly active antiretroviral therapy (HAART), consisting of lamivudine (Epivir®; GlaxoSmithKline, Philadelphia, PA, http://www.gsk.com), stavudine (Zerit®; Bristol-Myers Squibb, Princeton, NJ, http://www.bms.com), and efavirenz (Sustiva®; Bristol-Myers Squibb). He quit using alcohol. The patient’s CD4 was 130 with an undetectable VL by October 2000 (Table 1). His HCV antibody level was repeatedly positive, and on October 31, 2000, his HCV level was measured at 63.67 copies/ml in an assay regarded as investigational. His hepatitis B virus (HBV) status was assessed repeatedly, and was consistently negative. His liver function was assessed regularly in terms of enzymes and bilirubin (Table 2). His alkaline phosphatase and albumin levels were tabulated also but are not shown, as there was less variation. The patient was a nonsmoker, was married with no children, and remained fully active in his usual work during his evaluation and treatment. Abdominal computerized tomography (CT) scanning was performed due

<table>
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<th>SGOT, U/l (10–45)a</th>
<th>Total bilirubin, mg/dl (0.2–1.2)a</th>
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<td>331</td>
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*Range of normal values shown in parentheses.

Abbreviations: CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; XRT = radiation therapy.
to a rising alpha-fetoprotein (AFP) level and abnormal liver function tests (LFTs); this revealed dilation of the rectal vault, and a rectal mass could not be excluded. Nodularity was noted on rectal exam, which was biopsied. Pathology revealed nodules of monomorphic intermediate lymphoid cells consistent with lymphoma. Polymerase chain reaction (PCR) amplification failed to show rearrangement of immunoglobulin heavy chain genes. Immunohistochemistry confirmed the majority of the lymphoid cells to be CD3+, CD43+ with only scattered CD20 elements, consistent with a peripheral T-cell lymphoma of undetermined grade. The presence of CD3 antigen qualified the lymphoma as T cell, whereas CD20 positivity would have qualified it as B cell [4].

At his initial medical oncology clinic visit in May 2001, the patient denied any B symptoms (weight loss, fever, night sweats). He was afebrile and without regional or generalized lymphadenopathy. His LFTs were abnormal, with aspartate aminotransferase and alanine aminotransferase elevations of 276 U/l (normal 10–45) and 112 U/l (normal 7–52), respectively, alkaline phosphatase of 264 U/l (normal 30–115), and a total bilirubin of 2.1 mg/dl (normal 0.2–1.2). His lactate dehydrogenase (LDH) level was 255 U/l (normal 90–270) and his AFP was 16.6 ng/ml (normal 0–10). This would be judged as mild-moderate liver dysfunction [5]. Bone marrow and cerebrospinal fluid (CSF) examinations were normal, and a gallium scan was focally positive in the rectum only. Thus, his clinical stage was IEA, with an International Prognostic Index (IPI) of 0. He was commenced on growth factor-supported combination chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) [6].

HAART increases CD4 counts, decreases opportunistic infections, and increases survival in AIDS patients [10]. Low CD4 counts have been linked to the occurrence of ARL [11]. HAART increases CD4 counts, decreases opportunistic infections, and increases survival in AIDS patients [10].

Primary intestinal lymphomas in the general population are of the T-cell type in 10%–34% of cases, and have been described as presenting as rectal bleeding [12]. In Western countries, EBV appears not to play a pivotal role in the pathogenesis of ARL, in contrast to the more direct link evidenced by higher levels of EBV RNA transcripts in tumors diagnosed in the Third World. The exact mechanism of EBV involvement is not yet known [13], although multiple related actions have been described [14].

Peripheral T-cell neoplasms by the Revised European-American Classification of Lymphoid Neoplasms/World Health Organization Classification of Lymphoid Neoplasms are a family of lymphoid neoplasms, of which peripheral T-cell lymphoma, not otherwise specified, is only one general entity but is apparently the most appropriate designation for our present case. Some of the other family members are T-cell prolymphocytic leukemia, adult T-cell lymphoma/leukemia (which is human T lymphotropic virus 1 positive), mycosis fungoides, hepatosplenic gamma-delta T-cell lymphoma, and enteropathy-type T-cell lymphoma. This last lymphoma has a GI location, but is usually found in the
jejenum and is associated with a gluten-sensitive enteropathy, and the disease generally follows a short, aggressive course, with the patient expiring with multiple perforated jejunal malignant ulcers [15].

Geographical variation has been observed in the association between HCV and B-cell lymphomas [16, 17]. A recent, large Italian series found 5 of 287 (0.31%) HCV-infected patients with liver lesions had B-cell NHL, an approximate 12-fold higher incidence than in the general population [18]. HCV is known to be lymphotropic as well as hepatotropic, and its transcripts can be detected in CD34+ stem cells. It has been hypothesized that chronic immune stimulation leads to both mixed cryoglobulinemia and an increased incidence of B-cell NHL [19].

The staging work-up of ARL should include CT scans of the chest, abdomen, and pelvis since two-thirds of ARL patients will have intra-abdominal disease in such areas as lymph nodes, the GI tract, the liver, the kidney, or the adrenals [20]. Laparotomy would rarely be used for staging today; in an earlier era its systematic employment disclosed that, in clinical stage I and II supradiaphragmatic non-AIDS related NHL, only 22.5% of diffuse lymphomas were advanced in stage at laparotomy, whereas 61% of nodular or follicular lymphomas were advanced in stage at laparotomy [21]. 67-Gallium scanning can be useful at staging or in follow-up in deciding whether a residual mass is likely to be a viable tumor or not [20]. Since CNS or leptomeningeal involvement complicates ARL in 15%–40% of cases, lumbar puncture is often included in the work-up [1].

Adverse prognostic factors for ARL include a CD4 count of <100, a Karnofsky Performance Status score of <70%, age >55 years, stage III or IV disease, an elevated LDH level, and a history of injection drug abuse, factors of which our patient had just two, age 46 and an earlier history of injection drug abuse [22]. HCV positivity has been reported to be much higher in injection drug abusers than in homosexuals [23]. Prognostic evaluations of NHL in the general population have used the IPI, which incorporates Ann Arbor stage, age, elevated LDH level, performance status, and number of extranodal sites [22, 24]. According to this measure, our patient was at moderate risk for recurrence and death from his NHL. However, survival rates for ARL have been poor relative to results in the general population [25].

Several groups published studies circa 1989–1991 comparing modest numbers of T-cell lymphomas with diffuse large B-cell lymphomas and came to the general conclusion that they were prognostically somewhat similar [26–28]. In 1997, a group from the MD Anderson Cancer Center published a study with larger patient numbers, arriving at the conclusion that the T-cell immunophenotype was an independent adverse prognostic factor, in contrast to diffuse large B-cell lymphoma [24]. Presumably, our patient’s T-cell morphology would be considered an adverse factor.

CHOP chemotherapy may be regarded as the standard regimen to use for ARL, whether of the B- or T-cell type, although several modified regimens and doses are in some use, including CDE (cyclophosphamide, doxorubicin, etoposide [Etopophos®, VePesid®, Bristol-Myers Squibb]), and EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) [1]. ARL patients should also be treated with HAART, which maximally suppresses HIV-1. The present National Comprehensive Cancer Network guidelines treat peripheral T-cell lymphomas as they do diffuse large B-cell lymphomas, that is, by a combination of CHOP chemotherapy and involved-field radiation therapy [29]. Several studies are available to support the use of combined-modality therapy for localized intermediate or high-grade NHL; the common specific entity treated is, however, diffuse large B-cell lymphoma [30–32]. Published evidence is unclear as to the necessary degree of anthracycline dose reduction in patients with advanced liver cirrhosis [33]; we employed a minor reduction. Another consideration, the vinca alkaloids, have been observed to be neurotoxic in the setting of hepatotoxicity due to reduced drug clearance [33]; our patient did experience a degree of this. Successful antiviral treatment of viral hepatitis reactivated by systemic chemotherapy has been described, although the scenario of reactivation then reported successful hepatitis treatment, is uncommon [34]. A Japanese survey suggests that chemotherapy regimens containing steroids (common in lymphoma treatment) may be associated with fatal reactivation of hepatitis [35].

By general standards, our patient received appropriate therapy, only to die from progression or reactivation of pre-existing hepatic disease. Given the advantage of hindsight, an alternative plan that might have given a better outcome for our patient would be to have given only two cycles of CHOP therapy with some reduction of anthracycline, and possibly of steroid, followed by involved field radiotherapy to control the identified disease, considering his stage I status. Two more cycles after a rest period might then be considered. This might (or might not) have altered the outcome. The hazard of reactivation of HBV with cytotoxic therapy for NHL is more clearly established. Cytotoxic and immunosuppressive therapy enhances viral replication, with a consequent increase in hepatocyte infection. When cytotoxic or immunosuppressive drugs are withdrawn, immune function becomes restored, resulting in destruction of infected hepatocytes, which appears as acute hepatitis or hepatic failure [35, 36]. NHL patients with hepatitis B surface antigen are particularly at risk, with clinical hepatitis in 20%, with perhaps 3%–4% mortality. The great majority of them, however, ultimately recovers [36].
A reported series of 33 patients who were HCV positive and were treated with cytotoxic chemotherapy for leukemias/lymphomas (26 had B-cell lymphomas) were followed and monitored with LFTs. Eighteen of them encountered increases in transaminase levels of a mild-moderate nature, occurring 2–3 weeks after withdrawal of chemotherapy. Only one of the 33 had a severe flare of hepatitis C. No patient died of liver failure, and the final post-treatment levels of transaminases did not differ significantly from the pretreatment levels [4]. Although following enzyme levels is the usual manner of gauging liver dysfunction, some patients who, at liver biopsy, have significant fibrosis or cirrhosis have fairly benign enzyme levels [37]. Stage of liver fibrosis with HCV infection has been found to be worse with heavy alcohol consumption and male gender [38]. A study of cyclic chemotherapy for NHL in patients with either HBV or HCV positivity associated a relevant number of hepatitis cases with HBV, but not with HCV [39]. An Italian study of NHL, with 37% of patients HCV positive, found that, with similar chemotherapy regimens employed, there was no difference in survival with HCV positivity [40]. In contrast to the foregoing studies, Vento et al. [41] reported that two cases of NHL patients who were HCV positive and treated with chemotherapy developed severe hepatitis after chemotherapy was withdrawn, and one of them died of liver failure; no denominator was given. High-dose chemotherapy with autologous or allogeneic transplant may, in the future, be applicable in ARL given that newer HAART regimens have improved patient tolerability of aggressive therapies [42, 43]. However, the presence of severe comorbidities, such as active liver disease, even with preserved performance status, may remain a harbinger of poor outcome for aggressive therapies. Bone marrow transplant patients have been known to be at appreciable risk for reactivation of hepatitis C, and two hepatic deaths were reported in one series of 11 patients [44]. A second report also cited two deaths related to bone marrow transplant following withdrawal of immunosuppressive therapy [45]. These were two acute leukemia patients who contracted post-transfusion hepatitis during chemotherapy for induction and consolidation. Membranoproliferative glomerulonephritis is one of the extrahepatic manifestations that has been associated with HCV infection [46].

CONCLUSIONS

When planning treatment for a particularly unusual lymphoma presentation, such as this case of stage IE T-cell lymphoma of the rectum in an HCV/HIV coinfected patient, one must apply general principles, given the absence of applicable large series. An overall management approach popular for some time for early-stage, aggressive lymphomas is involved-field radiation therapy combined with systemic chemotherapy such as CHOP [47]. In such a plan, the role of radiation therapy is to reduce the risk of failure in the area of original gross disease, while chemotherapy reduces the risk of failure at distant sites [48]. Optimal treatment of an AIDS patient also includes HAART. Despite a preserved performance status and favorable traditional prognostication scores, the outcome may still be poor when concomitant viral hepatitis and T-cell disease morphology lessen disease responsiveness and hamper tolerability of chemotherapy. A recent article suggests use of interferon-α and ribavirin (Virazole®; Valeant Pharmaceuticals, International, Costa Mesa, CA, http://www.valeant.com) to treat HCV infection, but also notes problematic ribavirin interactions with HAART drugs [49].

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

REFERENCES


