J Hematopathol (2015) 8:37–41
DOI 10.1007/s12308-015-0231-x

CASE REPORT

Clinicopathologic features of primary colonic enteropathy-associated T cell lymphoma type II in an elderly Asian male with diarrhea

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Received: 24 November 2014 / Accepted: 22 January 2015 / Published online: 4 February 2015
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Abstract A 76-year-old Asian man with a 6-month history of intractable watery diarrhea proceeded to colonoscopic examination that revealed diffusely dull-appearing colonic mucosa with focal areas of superficial ulceration. Mucosal biopsies demonstrated a neoplastic population of monomorphous small-to-intermediate-sized CD8+/CD56+ cytotoxic T cells that densely infiltrated the surface epithelium and crypts in a near pan-colonic distribution without tumor formation. Clinical staging revealed no disease elsewhere. The patient was treated aggressively with chemotherapy but died from disease five and a half months after presentation. In all likelihood, the patient had primary colonic involvement by enteropathy-associated T cell lymphoma (EATL) type II, a rare and aggressive extranodal non-Hodgkin lymphoma that occurs more commonly in Asians in whom celiac disease is infrequent. Widespread colonic disease in the absence of a mass-forming infiltrate has not been characterized in EATL type II and highlights an expanded clinical and pathological spectrum of the disease.

Keywords Enteropathy-associated T cell lymphoma (EATL) · Primary intestinal T cell lymphoma (ITL) · Monomorphic · Cytotoxic T cells · Natural killer (NK) cells

Abbreviations

EATL	Enteropathy-associated T cell lymphoma
ITL	Primary intestinal T-cell lymphoma
NK	Natural killer

Introduction

Primary intestinal T cell lymphoma (ITL) is a rare group of extranodal non-Hodgkin lymphoma of which enteropathy-associated T cell lymphoma (EATL) is the most common. Two types of EATL are currently recognized by the World Health Organization. Type I disease occurs primarily in Caucasians, is frequently associated with celiac disease and malabsorption, and is characterized by polymorphous intermediate-to-large-sized neoplastic cells. Type II disease, by contrast, is more common among Asians, is characterized by monomorphous small-to-intermediate-sized cells positive

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for cytotoxic T/natural killer (NK) cell markers, and is only infrequently associated with celiac disease or malabsorption. Herein, we describe a 76-year-old Asian man who presented with diarrhea due to a primary colonic T cell lymphoma with clinicopathologic similarities to EATL type II. The neoplasm involved the colonic mucosa in a near pan-colonic distribution with striking epitheliotropism but was without an intestinal mass-forming infiltrate which in all probability is consistent with primary colonic manifestation of EATL type II.

Clinical history

A 76-year-old Asian man presented to our facility with a 6-month history of persistent watery diarrhea that was initially diagnosed and successfully treated for Clostridium difficile, confirmed by serial negative toxin assays. A physical examination revealed an elderly slender man with a non-tender, non-distended abdomen, and no palpable lymph nodes or hepatosplenomegaly. His medical history was notable for psoriasis and inflammatory arthritis, but he had no antecedent history of celiac disease, malabsorption, or inflammatory bowel disease. The patient proceeded to colonoscopy, which was remarkable for colonic mucosa that appeared focally inflamed with patchy areas of shallow ulceration (Fig. 1). The remainder of the colonic mucosa was vaguely dull in appearance. There was no endoscopic appearance of a polyp or a mass. Biopsies of the colon from the cecum to the rectum were obtained.

Materials and methods

The biopsy samples were fixed in 10 % neutral buffered formalin and processed and stained with routine hematoxylin and eosin. Immunostains for CD3 (Ventana Medical System, 2GV6, 0.4 μg/mL), CD20 (Ventana Medical System, L26, 0.3 μg/mL), CD56 (Dako, 123C3, 1:100), CD4 (Leica Biosystems, 4B12, 1:250), CD8 (Dako, C8/144B, 1:100), CD2 (Leica Biosystems, AB75, 1:50), CD5 (Leica Biosystems, 4C7, 1:100), CD7 (Biocare Medical, 272, 1:25), CD57 (PhenoPath, HNK-1, 1:5), CD30 (Ventana Medical System, Ber-H2, 1 μg/mL), CD103 (Epitomics, EPR4166(2), 1:1000), TIA-1 (Immunotech Laboratories, 2G9A10F5, 1:1000), and TCR-βF1 (Thermo Fisher Scientific, 8A3, 1:25) following antigen retrieval were visualized using polymer-based immunoperoxidase reaction and counterstained with hematoxylin. In situ hybridization for Epstein-Barr virus-encoded small RNA using fluorescein-conjugated oligonucleotide probes (Leica Biosystems, EBER, 0.1 μg/mL) was performed in conjunction with positive and negative reagent controls. T cell receptor gamma (TCRγ) gene rearrangement studies were performed on purified genomic DNA (Qiagen, Puregene), amplified by multiplex PCR using fluorescently labeled primers for the VγI and VγII variable regions and for the Jγ1/2 and JγP1/2 joining regions of TCRγ, and size fractionated on an ABI 3130 Sequence Analyzer (Applied Biosystems).

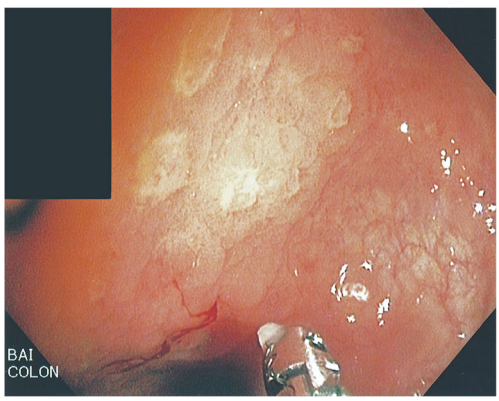

Fig. 1 Endoscopically dull-appearing colonic mucosa with foci of shallow ulceration

Results

Histopathologic examination showed a neoplastic population of lymphocytes that involved the mucosa throughout the length of the colon with relative sparing of the descending and sigmoid colon. The neoplastic cells were monomorphic, small-to-intermediate in size with round-to-irregular nuclei, condensed chromatin, indistinct-to-small nucleoli, and small-to-moderate amounts of pale or clear cytoplasm (Fig. 2). The cells infiltrated the colonic mucosa with marked epitheliotropism, densely infiltrating and obscuring the surface and crypt epithelia with extension to their apical surfaces. The lymphocytes infiltrated the epithelium singly but in a few foci aggregated to form small intraepithelial Pautrier-like microabscesses. There was no necrosis or large cell transformation of the neoplastic population. Rare mitotic figures were observed. The lamina propria was variably expanded, greater in the right than the left colon, by a small number of the neoplastic cells intermixed with reactive lymphocytes, plasma cells, eosinophils, and occasional neutrophils. The accompanying epithelial injury was characterized by apoptosis, desquamation of cells into the crypt lumen, regeneration of damaged crypts, atrophy, and focal ulceration. Also present were features of chronic mucosal injury, including mild crypt shortening, focal loss of crypts, and Paneth cell metaplasia in the left colon, but the characteristic changes associated with chronic inflammatory bowel disease such as established basal plasmacytosis and branching crypts were absent.

Immunoperoxidase studies showed that the neoplastic lymphocytes were T cells positive for CD3, CD2, CD7, CD8, CD56, CD103, TIA-1, and TCR-βF1 and negative for

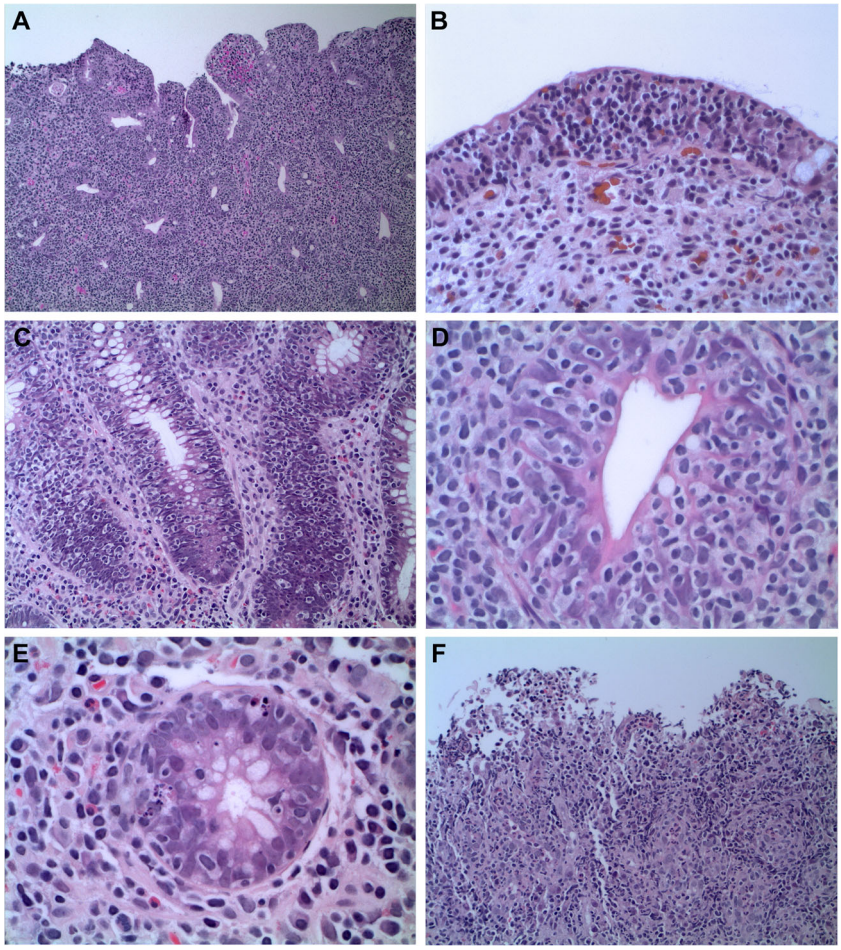

Fig. 2 Histopathologic features of primary colonic epitheliotropic CD8+/CD56+ T cell lymphoma. The neoplasm is characterized by monomorphic small-to-intermediate-sized cells that diffusely infiltrate colonic mucosa with striking epitheliotropism (**a**, ×10), obscuring the surface (**b**, ×40), and crypt (**c**, ×20) epithelia with formation of occasional small intraepithelial Pautrier-like microabscesses (**d**, ×60). The accompanying epithelial injury is characterized by scattered apoptotic bodies (**e**, ×60) and focal mucosal ulceration (**f**, ×20)

CD20, CD4, CD5, CD57, and CD30 (Fig. 3). Intermixed reactive CD4-positive T cells were located predominantly in the lamina propria. B cells, highlighted by CD20, were limited to rare basal lymphoid aggregates. An immunostain for CMV was negative, as was in situ hybridization for Epstein Barr virus-encoded small nuclear RNA (EBER). Polymerase chain reaction performed on paraffin-embedded tissue detected clonal gene rearrangement of the T cell receptor (TCR) γ-chain in the neoplastic T cell population.

Disease staging with a positron emission tomography/computed tomography (PET/CT) scan revealed increased SUV activity in the colon and rectum, but no appreciable activity elsewhere. There was no lymphadenopathy or organomegaly. His serum LDH was within normal limits. A staging bone marrow biopsy was deferred. The patient was treated with an attenuated chemotherapy regimen of cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) at 3-week intervals, resulting in symptomatic improvement including a decrease in diarrhea. Unfortunately, within 4 months following 5 cycles of CHOP therapy, the patient developed progressive fatigue, anorexia, recurrent diarrhea, and a marked decline in his performance status. A repeat colonoscopic evaluation revealed recurrent/persistent disease. The patient was transitioned to hospice care and expired five and half months following his diagnosis. An autopsy was not requested.

Discussion

Primary intestinal T cell lymphoma (ITL) is a rare, heterogeneous group of extranodal non-Hodgkin lymphoma of which the most common and best characterized is enteropathy-associated T cell lymphoma (EATL) [1, 2]. EATL is clinically aggressive, associated with 70 % mortality within 6 months of diagnosis, and typically presents as a mass-forming infiltrate in the small intestine with histological features of enteropathy in the surrounding non-tumorous mucosa. The tumor is often multifocal, involves the intestine transmurally, and exhibits a high tendency toward ulceration, bowel obstruction, and/or perforation. Based on clinical, serological, histopathologic, and genetic features, two types of enteropathy-associated T cell lymphoma are currently recognized by the World Health Organization [3–5]. Type I, or the classical form of EATL, is frequently associated with celiac disease and malabsorption and occurs primarily in the Caucasian population of northern

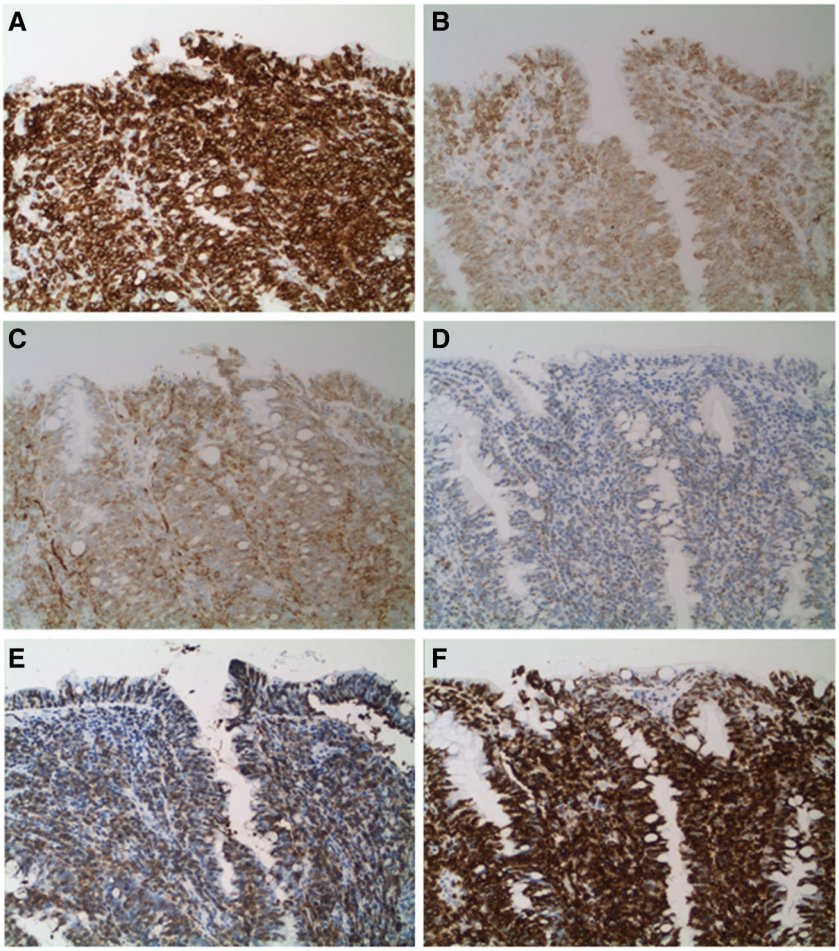

Fig. 3 Immunophenotypic features of primary colonic epitheliotropic CD8+/CD56+ T cell lymphoma (×20). **a** CD3, **b** CD8, **c** CD56, **d** TIA-1, **e** CD103, **f** TCR-βF1

European descent. It is typically limited to the small intestine, often associated with histological features of enteropathy in the adjacent mucosa, and characterized by polymorphous medium-to-large sized neoplastic cells with immunoblastic and/or high-grade features and an immunophenotypic profile that is negative for CD4, CD8, and CD56. Type II, by contrast, is less commonly associated with an enteropathy or malabsorption and has a broader geographic and ethnic distribution. It mainly involves the small intestine but can also involve the colon and is characterized by monomorphous small-to-medium-sized lymphocytes that co-express CD8 and CD56 in the majority of cases and lack high-grade histologic features or angioinvasive properties [4–10].

Since the refinement in the classification of EATL, there has been growing interest in ITL and EATL in the Asian population in whom the frequency of celiac disease is low and Epstein-Barr virus (EBV) infection and extranodal T/NK cell lymphoma are more prevalent [6–17]. In European patients, EATL comprises the majority of ITL and is composed of approximately 80–90 % type I and 10–20 % type II disease, reflecting the high prevalence of celiac disease in this population. In Asians of the Far East, in whom celiac disease has only been rarely reported, EATL comprises a smaller proportion of ITL and is composed predominantly, if not exclusively, of type II disease. Although the clinicopathologic and genetic features of EATL type II in Asian and Western patients are similar in many respects, including an absence of an etiologic association with celiac disease in most cases, there appears to be more variable clinical and/or histopathological association with an enteropathy or malabsorption, greater prevalence of colonic involvement, and a higher frequency of neoplastic T cells expressing TCR-γδ in the Asian population [4–7, 10, 12–15, 18].

This patient's ITL shares many clinicopathologic similarities with EATL type II. It was a clinically aggressive neoplasm that presented insidiously as diarrhea in an elderly Asian man who had no prior history of celiac disease or malabsorption. The neoplastic T cells were monomorphous, small-to-intermediate in size, demonstrated prominent epitheliotropism, and expressed CD103, the human mucosal lymphocyte-1 antigen that is commonly expressed in intraepithelial T lymphocytes and cytotoxic T/NK cell-associated markers CD8, CD56, and TIA-1 with loss of the pan-T cell marker CD5 and absent CD30 expression. Nevertheless, the patient's near pan-colonic disease involvement and absence of an intestinal mass-forming infiltrate are

dissimilar to the characteristic mass-forming and zonal features of EATL type II. Although EATL is defined as a neoplasm of intraepithelial T cells, the clinicopathologic studies of EATL type II have largely been focused on clinical or surgically resected small intestinal masses [5, 7–10, 13, 15, 16, 19]. While type II disease limited to the colon is uncommon, comprising at most 18 % in one study [10], the clinicopathologic colonic manifestations have not been well characterized and there has been no reported case to date of type II disease without a clinically apparent intestinal mass. Secondly, epitheliotropic neoplastic cells are typically limited to the small intestinal mucosa immediately adjacent to a central tumor-forming zone [7, 13, 16]. Although reports of discontinuous or distant intraepithelial involvement away from a mass are emerging [7, 13, 20], this disease pattern appears to be an infrequent finding.

In all likelihood, this patient had primary colonic involvement by EATL type II due to the similarities in their aggressive clinical course, monomorphic small-to-intermediate cell size, expression of cytotoxic T/NK cell immunophenotypic profile, and epitheliotropism. The clinical and endoscopic features of our patient's disease are reminiscent of primary colonic T cell lymphoma in Korean patients in whom there was a high association with diarrhea, diffuse colonic disease involvement, endoscopic impression of an ulcerative/infiltrative process, and low association with a mass-forming infiltrate [21]. In the absence of an intestinal mass, the patient's neoplasm may represent an "early" (i.e., epitheliotropic) manifestation of EATL type II; however, the patient's rapid clinical decline suggests that intraepithelial-predominant disease may be as clinically aggressive as those associated with an intestinal mass-forming neoplasm.

Conflict of interest The authors declare that they have no conflict of interest.

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