Colonic in situ mantle cell lymphoma☆

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Abstract

This report describes the first case, to our knowledge, of in situ mantle cell lymphoma (MCL) in the gastrointestinal tract identified retrospectively by immunostains and fluorescence in situ hybridization (FISH) analysis after progression to disseminated disease with pleomorphic morphology several years later. A 45-year-old man with blood per rectum underwent colonoscopy and had random biopsies interpreted as benign colonic mucosa. Two years later, he presented with ileocolic intussusception related to enlarged lymph nodes. Biopsies on the second presentation demonstrated widespread MCL. Reevaluation of the original colonic biopsies showed cyclin D1–positive cells within small lymphoid aggregates, confirmed by FISH for t(11;14). Postchemotherapy, lymphoid aggregates in colonic biopsies showed scattered cyclin D1– and FISH t(11;14)–positive cells, similar to the original in situ lymphoma. We discuss this case in the context of the current understanding of the evolution of MCL and the difficulties associated with detecting primary GI lymphoma.

Keywords: In situ lymphoma; Mantle cell lymphoma; GI lymphoma; In situ mantle cell lymphoma

1. Introduction

Mantle cell lymphoma (MCL) is recognized as an aggressive B-cell lymphoma derived from a subset of naive pregerminal center cells with a propensity to involve extranodal sites, including colon. Its molecular signature is an overexpression of cyclin D1 as a result of the chromosomal translocation t(11;14)(q13;q32) that juxtaposes the protooncogene CCND1 to the immunoglobulin heavy-chain promoter. Despite the high rate of secondary colonic involvement by MCL, primary gastrointestinal (GI) lymphomas are infrequently reported. Difficulty in the diagnosis of primary GI lymphoma arises in part from the nonspecific and often benign gross endoscopic appearance [1]. Microscopically, recognition of GI lymphomas also often poses problems because (1) the sampling size is typically small, (2) intense hyperplastic responses may mimic lymphoma, and (3) differentiation into neoplasia may be incomplete in early phase biopsies. In addition, although MCL usually has a distinctive histologic appearance, the range of morphology in MCL is broad. The spectrum of morphologic presentation has been recently expanded to include several reports of an indolent in situ type of MCL, which may mimic marginal zone lymphoma or reactive follicular hyperplasia and is characterized by only scattered cells with increased cyclin D1 expression [2-5]. This putative low-grade form of MCL has been described in patients with lymphadenopathy where mantle zone cells possess the t(11;14) molecular abnormality and concomitant high cyclin D1 expression. In this article, we report a unique case of MCL that presented with a benign-appearing colonic lymphoglandular complex consistent with an in situ MCL of the colon identified retrospectively after evolution to disseminated MCL. The present case is one of only a few in
situ cases reported and the first one, to our knowledge, described in the colon.

2. Case report

A 45-year-old man underwent a colonoscopy in 2007 to workup symptoms of bright red blood per rectum. No polyps or masses were noted. A small amount of erythema in the rectum was deemed to represent bowel-prep artifact. Random biopsies were taken from this area (Fig. 1A, B). These biopsies were interpreted under microscopy as benign rectal mucosa, focally associated with lymphoid aggregates.

Rectal bleeding did not resolve, and 2 years later, the patient was admitted to the hospital for increased frequency of bright red blood per rectum with mucous discharge. On admission, he complained of lower abdominal discomfort, increasing fatigue, and a diffuse pruritic rash. He had experienced a 10-lb weight loss over a 2-month period and reported new-onset soaking night sweats. Physical examination revealed a pale, chronically ill looking man with diffuse bulky nodes in his neck, axillae, and bilateral groins. Computed tomography scan showed ileocolic intussusception associated with enlarged mesenteric lymph nodes. Colonoscopy revealed mucosal edema in a cobblestone pattern with erythema, ulcerations, and folds with a masslike appearance (Fig. 2A). The ileal mucosa and masslike colonic fold were biopsied. Histology demonstrated dense lymphocytic infiltrates (Fig. 2B), strongly positive for CD20, BCL1 (cyclin D1), and CD5, consistent with MCL. A mantle pattern of involvement of the BCL1-positive lymphomatous cells was seen (Fig. 3). A significant percentage of lymphoid nuclei (50%) were positive for Ki-67, indicating a high rate of cell cycling. Bone marrow biopsy showed a kappa-restricted CD19+ CD20+ CD5dim+ CD10− CD23− population of B cells by flow cytometry corresponding to lymphoid aggregates. Cyclin D1 messenger RNA expression as determined by reverse transcriptase polymerase chain

Fig. 1. (A) Random colonic biopsies from 2007 colonoscopy showing relatively unremarkable lymphoglandular complexes (hematoxylin and eosin, low power). (B) No mucosal invasion by lymphocytes was seen (hematoxylin and eosin, medium power). (C) Retrospective analysis of original 2007 colonic biopsy showed cyclin D1–positive cells in the mantle region of vague lymphoid follicles (low power). (D) High-power view of same section demonstrating clear nuclear staining. Rare cells were FISH positive for t(11;14) (inset).
reaction was at a level typically seen only in MCL [6]. A positron emission tomography/computed tomography scan showed involvement of bilateral axillary, hilar, and inguinal lymph nodes in addition to the spine and gastric body. Biopsy of the left inguinal lymph node showed pleomorphic histologic features of the MCL with blastic forms and a positive fluorescence in situ hybridization (FISH) study for t(11;14) (Fig. 4).

Having established the diagnosis of stage IVb aggressive MCL, the patient was treated with an intensive chemotherapy regimen of rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone (maxi-CHOP), alternating with...
rituximab and high-dose cytarabine. The patient also received consolidation with bortezomib and intrathecal methotrexate and hydrocortisone, following a standard protocol [7]. Follow-up colon and bone marrow biopsies were performed after treatment, approximately 6 months from the date of diagnosis. The bone marrow morphology and flow cytometry showed no evidence of residual MCL. The terminal ileum showed multiple superficial nodules, whereas the colonic mucosa was predominantly normal. However, both biopsies showed lymphoid aggregates, which included cells staining positive for BCL-1, consistent with residual MCL (Fig. 5). Notably, the flow cytometry performed on the intestinal posttherapy biopsies was inconclusive, while FISH showed fusion of CCDN1/IGH t(11;14) at a low frequency, again confirming the presence of abnormal cells (Fig. 5B, inset). Reevaluation of the earlier biopsy from 2007 confirmed that the lymphoid aggregates in the colonic mucosa predominantly had preserved germinal centers with normal mantle zones. Cytologically, lymphocytes were small with minimally irregular, unfolded nuclei, and smooth chromatin. In retrospect, some lymphoid follicles appeared expanded, and some mantle zones were minimally enlarged. Immunohistochemical staining for cyclin D1 was performed on the original biopsy and

Fig. 4. (A) Inguinal node biopsy showed diffuse and mantle-like (arrow) proliferation of lymphocytes (hematoxylin and eosin, low power). (B) Pleomorphic morphology of MCL in inguinal node with irregular nuclei and multiple nucleoli (hematoxylin and eosin, high power). Fluorescence in situ hybridization was positive for t(11;14) (inset).

Fig. 5. (A) Low-power view of postchemotherapy colonic biopsy on follow-up. Small lymphoid aggregates were noted on multiple biopsies (hematoxylin and eosin, low power). (B) Cyclin D1 nuclear staining was evident on most lymphocytes (medium power), and scattered cells were FISH positive for t(11;14) (inset).
highlighted the nuclei of scattered cells within the mantle zone (Fig. 1C, D). These cells are not readily distinguishable by morphology from the surrounding cyclin D1–negative lymphocytes. Fluorescence in situ hybridization for t(11;14) showed rare cells positive for CCDN1/IGH fusion signal (Fig. 1D, inset).

The patient subsequently underwent autologous stem cell transplantation and is in clinical and radiologic complete remission.

3. Discussion

Although investigators have recently described an 88% rate of secondary colonic involvement by MCL [8], primary GI lymphomas are thought to be infrequent, representing 1% to 4% of malignant tumors of the GI tract [9]. Gastrointestinal tract involvement is recognized occasionally as being the presenting sign of lymphoma, and early recognition is important for staging, prognosis, and selection of appropriate treatment. The diagnosis of primary GI lymphoma is normally made if the lymphoma mainly involves the GI tract and when lymph node involvement, if present, is confined to the drainage area of the primary tumor site with no involvement of the liver, spleen, or other lymph nodes. Lymphomas in patients who exhibit primarily GI symptoms or show predominance of lesions in the GI tract, including the pancreas and the esophagus, may also be designated as primary GI lymphomas. However, the gross and histologic pattern is often nonspecific, difficult to recognize, and easily missed.

The main challenge in establishing the diagnosis of lymphoma on colonoscopy specimens is the small sample size that limits pattern recognition and the number of ancillary studies that can be performed. Other difficulties arise from the frequency of intense benign hyperplastic responses in the GI tract as well as the lack of recognizable diagnostic features in early lymphomas [8]. The gross endoscopic appearance of GI lymphomas is also nonspecific: the lesions can be polypoid, nodular, ulcerated, infiltrative, or mixed and at times can be indistinguishable from carcinoma. Furthermore, unlike many other organ systems in which the dysplasia-carcinoma-invasive carcinoma progression is a well-recognized phenomenon, lymphomas are not traditionally associated with characteristic and detectable evolutions from prelymphoma.

In the context of clinical outcome, Majlis et al [10] have reported on the biologic features of 3 histologic variants of MCL. The 3 variants/growth patterns were as follows: (1) mantle zone—lymphocytes proliferate as collars about reactive or atrophic germinal centers; (2) nodular—frankly nodular growth resulting from centripetal as well centrifugal expansion of the follicular mantle zone; central germinal centers are effaced, with at least 90% of nodules showing a loss of mantle zone configuration; and (3) diffuse—confluent growth obliterates lymph node architecture and any residual nodularity [10]. The clinical behavior becomes correspondingly more aggressive in these variants, and it is reasonable to consider that they represent progressive genetic evolution with the acquisition of additional mutations that render the disease more resistant to defense mechanisms and therapy.

In MCL, a pattern of progression from early acquisition of the t(11;14) chromosomal abnormality and in situ morphology to eventual blastoid MCL has been proposed [11,12]. The concept of in situ MCL is relatively new with early reports dating back fewer than 10 years [2-5]. The World Health Organization refers to in situ MCL in its latest classification and describes it as a case that shows scattered cyclin D1–positive cells restricted to the inner mantle zones or to narrow mantles in otherwise reactive-appearing lymphoid tissue [5]. The few cases that have been reported in the English literature are in lymph nodes. These cases were characterized by reactive follicles (follicular hyperplasia) with minimally expanded mantle zones resulting in mild multifocal lymphadenopathy. Some authors prefer to restrict the title in situ MCL to clinically stable disease without generalized lymphadenopathy [13,14]. The limited experience has been that patients with this type of in situ presentation have a course that is more indolent than typical MCL.

Other features associated with favorable prognosis and protracted progression are hypermutated immunoglobulin heavy-chain region, fewer chromosomal abnormalities, and absence of SOX11 expression [14,15]. In particular, high SOX11 expression has been identified as a marker relatively specific to more evolved MCL. Immunohistochemical detection of SOX11 remains predominantly a research tool at this point but is likely to see increased use. Nonetheless, the relationship between these markers of indolent MCL and in situ mantle cell has not been fully established. There has been debate as to whether some cases characterized as indolent MCL may actually represent a subset of chronic lymphocytic leukemia or other lymphoma rather than MCL [16]. The presence of increased cyclin D1 and t(11;14) noted in situ eventually maturing to aggressive MCL would argue against this interpretation, although the issue becomes one of how to define a disease entity. Regardless, specific genetic abnormalities have proven to individually correlate with blastoid transformation [17], and in situ presentation is still postulated to represent an early neoplastic condition that progresses through various forms of MCL corresponding to gain of additional genetic abnormalities and with different morphologic characteristics as suggested by the case presented here.

Although reports suggest that indolent/in situ mantle pattern MCL is associated with a latency period of up to 15 years before progression to more aggressive disease [2], it remains unknown whether early intervention can help prolong or prevent the transition to aggressive MCL forms. Some advocate conservative treatment in these patients, but it is possible that early recognition and
treatment could improve outcomes in patients with MCL. Unfortunately, we are limited by the difficulty in establishing the diagnosis of early lesions. The diagnosis of MCL with a mantle zone pattern is difficult to make in a lymph node and even more so in the GI tract, particularly when incomplete obliteration of the normal lymph node follicles is present. In addition, because few or only 1 follicle may be present in a limited sample, it may be impossible to detect in situ disease. The case presented here showed subtle features that are reminiscent of that described in the mantle zone variant with overall retained architecture, minimal expansion of the mantle zone, and few or no mitotic figures, but cyclin D1–positive cells in the mantle region.

The initial colonic lesion is felt to be an in situ GI MCL on the basis of several observations. Unlike other reported descriptions of mantle cell in situ, at presentation, this patient had no other organ involvement or palpable lymph nodes, and his symptoms were exclusively GI, suggesting that the GI tract was the primary site. There was progression to diffuse aggressive MCL several years after the initial biopsy. The time interval between the initial biopsy and subsequent diagnosis of MCL with colonic involvement is consistent with progression of an in situ lesion to a full-blown malignancy, particularly because the natural history of untreated MCL is typically rapid (median survival, 3-5 years) [5]. The observation of pleomorphic morphology in the lymph node obtained in 2009, typically associated with more aggressive behavior and advanced disease, is consistent with evolution of the lymphoma over time. In addition, the presence of residual disease with in situ characteristics in the posttherapy colon biopsies further supports our hypothesis that the colon was the site of origin. The similarity between the posttherapy colon biopsy histology and the original biopsy also supports the theory that the original biopsy represented in situ disease. The cyclin D1 staining, particularly in scattered cells in the mantle region, along with positivity for t(11;14) by FISH in selected cells, is very strong evidence as well. By comparison, in our laboratory, a small sampling of cyclin D1 staining on lymphoglandular complexes of the colon shows essentially no cyclin D1–positive lymphoid cells (data not shown).

Proposed cells of origin for MCL include memory and naïve splenic marginal zone cells, peripheral blood memory B cells, and lymphoid follicle mantle cells [18]. Observations that point to the GI lymphoid tissue as a site of origin of MCL include frequency of colonic involvement, the large amount of lymphoid tissue in the GI tract, and the difficulty noted in identifying early or in situ disease. This patient’s history of persistent blood per rectum indicated that the continuation of symptoms probably paralleled the progression of “small lymphoid aggregates” to widespread colonic disease within 2 years. Histologically, the initial diagnosis was difficult to establish because lymphoid aggregates are ubiquitous in the GI tract and because the lymphoid follicle architecture within the colonic mucosa was predominantly preserved or only minimally altered. However, cytologic monotonoy in lymphoid cell size and irregularity of nuclear shape might prompt consideration of immunohistochemical studies in patients with clinical symptoms and signs associated with lymphoma. The high index of suspicion from the gastroenterologists is also crucial. A lack of suspicion on both parts (pathologists and gastroenterologists) or a total lack of endoscopy findings and clinical symptoms reduces significantly the probability of finding such a lesion.

References


