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## Persistent indolent pancolonic marginal zone lymphoma of MALT-type with plasmacytic differentiation – A rare post-transplant lymphoma?

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### Abstract

Marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is associated with chronic inflammatory disorders. We present an indolent pancolonic MALT lymphoma occurring in a 39-year-old female with history of autoimmune hepatitis requiring liver transplant in 1997 and ulcerative colitis diagnosed in 2004. Random biopsies from a grossly unremarkable surveillance colonoscopy in 2015 revealed a dense monomorphic plasmacytoid infiltrate causing expansion of lamina propria without significant crypt infiltration or destruction. These cells were positive for CD79a and CD138 and showed lambda restriction; however, CD20, CD43, CD56, HHV8, and EBER were negative. A similar pancolonic infiltrate was identified in all prior colorectal biopsies from 2010 and 2012 upon retrospective review. Subsequent computed tomography of the abdomen revealed no bowel wall thickening nor enlarged lymph nodes. Bone marrow revealed involvement consistent with stage IV disease. Biopsies from 2010 and 2015 demonstrated clonal immunoglobulin gene rearrangement. *MYD88* mutation was not detected. The overall features were indicative of MALT lymphoma. Although low-grade B-cell lymphomas are not considered part of the post-transplant lymphoproliferative disorder spectrum, such cases have been reported, and are typically EBV-negative. Patient underwent treatment with pentostatin for her MALT lymphoma reaching a sustained remission despite additional immunosuppression for resurgent hepatic dysfunction. To our knowledge, this is the first reported case of EBV-negative pancolonic MALT lymphoma with plasmacytic differentiation post liver transplant presenting in an indolent, asymptomatic fashion with persistence for greater than five years successfully managed without compromising the patient's liver transplant.

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Conflict of interest

The authors declare no conflict of interests.

## 1. Introduction

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) is an extranodal lymphoma most commonly found in the gastrointestinal tract [1]. Most cases present as an ulcerated or polypoid lesion in the stomach [2]. Patients typically present with abdominal pain, dyspepsia, weight loss, and anorexia [3]. Colonic MALT lymphoma is rare. A history of diseases causing chronic inflammation is associated with development of MALT lymphoma [1]. Additionally, immunosuppression is also a (seemingly competing) risk factor for development of hematologic malignancy. We present a rare case of pancolonic, indolent, asymptomatic MALT lymphoma in a patient with a history of liver transplant discovered incidentally on surveillance colonoscopy.

## 2. Case study

In 2015, a 39-year-old African American woman presented for surveillance colonoscopy. Her past medical history was complicated and included autoimmune hepatitis requiring a liver transplant in 1997. She was subsequently diagnosed with inflammatory bowel disease (ulcerative colitis) diagnosed in 2004 and prolonged iron deficiency anemia. Her medications included prednisone 5 mg daily and tacrolimus 5 mg twice daily. Her gastrointestinal (GI) symptoms were well controlled, and her only complaint was mild fatigue.

On surveillance colonoscopy, mild erythema and friability were noted in the rectum; the ascending, transverse, and descending colon all appeared normal (Fig. 1). Multiple random biopsies were obtained.

Hematoxylin and eosin-stained sections of the ascending, transverse, and descending colonic biopsies revealed a dense, monomorphic, predominantly plasmacytoid infiltrate, causing expansion of lamina propria and some crypt architectural distortion, but without significant crypt infiltration, branching or destruction (Fig. 2). The plasmacytoid cells had relatively pale cytoplasm but were without significant nuclear atypia or mitosis (Fig. 3). There was no evidence of significant neutrophil infiltrate, cryptitis, crypt abscess, or dysplasia. On immunohistochemical staining, the cells were positive for CD79a and CD138 (Fig. 4). CD20, CD43, and CD56 were all negative. The cells demonstrated overt lambda restriction by immunohistochemical analysis, with only rare kappa positive cells (Fig. 5a and b). HHV8 and EBER were both negative (Fig. 6a and b). Prior colorectal biopsies were retrospectively reviewed. A similar infiltrate was identified in all colonic biopsies obtained in 2010 and 2012 (Fig. 7), but not in biopsies preceding those years (2004–2007).

DNA was extracted from representative formalin-fixed paraffin-embedded tissue blocks from both the 2015 biopsies and from 2010 biopsies. PCR amplification for detection of immunoglobulin gene (*IGH* and *IGk* loci) rearrangement was performed. For the *IGk* locus, two peaks with increased intensity, consistent with significant clonal rearrangements, were detected in both blocks; these peaks were identical in size for both 2010 and 2015 samples. For the *IGH* locus, by contrast, an intense peak was detected only in the 2015 sample. It is worth noting that the DNA extracted from the 2010 sample was of poorer quality, which

may have precluded detection of a significant peak at the IGH locus. Alternatively, these findings may have indicated a clonally related process with evidence of clonal evolution. Additionally, *MYD88* mutation was not detected in either sample.

The overall morphologic features, indolent clinical behavior, and absence of EBV were deemed most indicative of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma).

The patient underwent staging evaluation for her MALT lymphoma. An M-protein was identified of 0.97 g/dL, also IgG-lambda. Computed tomography (CT) of the chest, abdomen, and pelvis revealed no bowel wall thickening or mass lesions. A right inguinal lymph node at the upper limits of normal was identified and an excisional biopsy performed. Pathologic analysis of the lymph node revealed numerous plasma cells with abundant pale, eosinophilic cytoplasm in a sheetlike infiltrate resulting in complete effacement of the normal nodal architecture, which extended out into the attached adipose tissue (Fig. 8). This infiltrate showed similar immunohistochemical findings to the GI biopsies, with overt lambda restriction (Fig. 9a and b). Additionally, there was a distinct subpopulation of CD20 positive plasma cells also identified.

The patient underwent bone marrow biopsy for staging purposes. Plasma cells were increased (Fig. 10), comprising 15–20% of the cellularity, and demonstrated some atypical morphology, again with lambda restriction. She was confirmed to have stage IV MALT lymphoma with GI, lymph, and bone marrow involvement.

### 3. Discussion

#### 3.1. Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

MALT lymphoma is an extranodal lymphoma composed of heterogeneous small B-cells including marginal zone (centrocyte-like) cells, cells resembling monocytoid cells, other small lymphocytes, scattered immunoblasts, and centroblast-like cells, such as those found in the marginal zone [1]. Plasmacytic differentiation is present in about a third of cases, such as our case, and may even have a detectable M-protein by serum protein electrophoresis [1]. MALT lymphoma comprises 7–8% of B-cell lymphomas and is most commonly found in the GI tract (50% of cases) [1]. A majority of those in the GI tract are gastric representing 85% of cases [1]. However, unlike gastric MALTs, which tend to be confined, non-gastric MALTs of the GI tract are disseminated in up to 47% of cases at presentation [1,4]. In many cases, a history of chronic inflammation is present, be it due to infection, autoimmunity, or antigen stimulus [1].

#### 3.2. Differential diagnosis

One major diagnostic consideration in this case was post-transplant lymphoproliferative disorder (PTLD). PTLD is a lymphoid or plasmacytic proliferation developing as result of immunosuppression [1]. The majority of PTLDs are reportedly EBV positive [1,5]. EBV positive cases are more likely to present within the first year of transplant [1,5]. However, EBV negative cases do occur and tend to happen later (four to five years following

transplant) and may be HHV8 positive [1,5]. PTLN comprises a wide range of histologic and immunophenotypic presentations resembling many hematopoietic B-cell or T-cell neoplasms seen outside of a transplant setting, with categories including polymorphic, monomorphic, and classical Hodgkin lymphoma-type [1]. Of note, indolent B-cell lymphomas, such as follicular lymphoma and MALT lymphoma, although described in post-transplant setting, are not generally considered in the PTLN spectrum [1,6].

The majority of MALT lymphomas in the post-transplant setting are of gastric origin and associated with *Helicobacter pylori* infection, although non-gastric sites have rarely been described [6]. These include rare cases of MALT lymphomas in the post-transplant setting localized to the colon [7]. The non-gastric MALT lymphomas in the post-transplant setting appear to behave more like MALT lymphomas arising in immunocompetent patients than PTLN, have an indolent clinical course (similar to our patient), and are usually considered coincidental [6]. Additionally, the majority of these cases are EBV negative [6]. Gibson et al. did describe a series of four solid organ recipients who presented with EBV positive B-cell neoplasms resembling MALT lymphoma [6]. By definition, our patient's history of liver transplant portends an increased risk of developing lymphoma, namely PTLN. More interesting is her history of autoimmune hepatitis (AIH). One German study found that patients with AIH or long-term immunosuppression prior to liver transplant (both of which apply to our patient) are more likely to develop the late form of PTLN [5].

Lymphoplasmacytic lymphoma (LPL) also entered the differential diagnosis. A neoplasm of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells, LPL when associated with a monoclonal IgM spike is termed Waldenström's macroglobulinemia [1]. Unlike most LPL which is associated with a monoclonal IgM spike, our patient possessed an IgG spike [1]. Likewise, *MYD88*, which is mutated in ~90% of LPL cases, was negative in our case [1].

### 3.3. Special considerations

This patient's past medical history had a complex set of possible risk factors for developing a hematologic malignancy. It has been debated extensively whether or not inflammatory bowel disease (IBD) confers a risk of lymphoma. Studies on large patient registries of IBD have shown no conclusive evidence of correlation [8,9]. Any increased risk that may exist is fairly low and affects mainly men with Crohn's disease for greater than 8 years [10]. Even then, the increased risk of lymphoma may be iatrogenic due to treatment with immunosuppressive drugs (such as azathioprine, 6-mercaptopurine, anti-tumor necrosis factor) rather than the disease itself [9,10]. Our patient was diagnosed with ulcerative colitis (UC) for eleven years prior to the time her MALT lymphoma was discovered. During that period, her UC was largely treated coincidentally by her anti-rejection immunosuppression, which included prednisone and tacrolimus.

### 3.4. Interesting aspects

There were a number of interesting aspects to this case. First, the location is unusual, as colorectal lymphoma makes up less than 3% of all GI lymphomas [11]. Secondly, MALT lymphomas tend to present as a visible lesion on colonoscopy, such as a polypoid mass,

ulceration, or hypertrophic appearance with enlarged folds or nodularity [2]. Our case, by contrast, was a diffuse, cryptic infiltration not visualized by endoscopy. It is also important to note that correct histologic diagnosis was obscured for a long time in this patient due to histologic overlap between the plasmacytoid nature of the malignancy and the basal plasmacytosis that is associated with IBD. It is remarkable that she has been asymptomatic for such an extended period, with no significant malabsorptive symptoms. Finally, her complex past medical history presents a quandary as to what event(s) contributed most to developing this malignancy including chronic inflammation, immune suppression, or just coincidence [1,5,10].

#### 4. Treatment and follow up

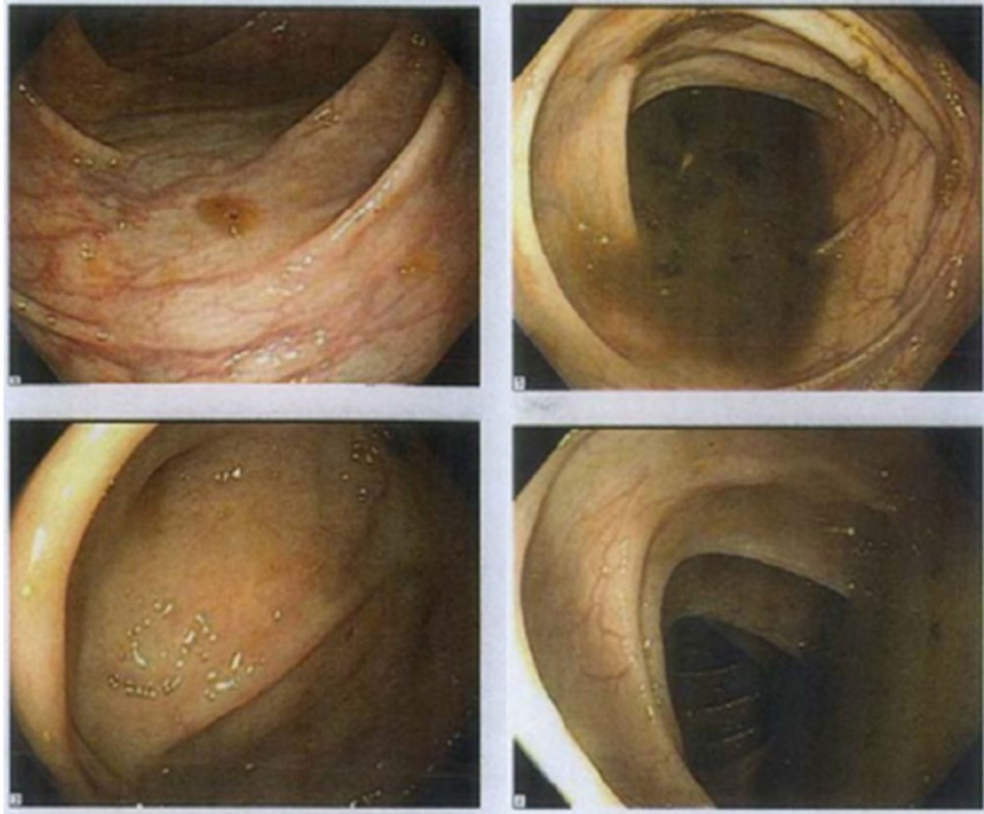
Due to the clinical concern for PTLTD, her tacrolimus dose was reduced to 0.5 mg twice daily while she continued prednisone 5 mg daily. After case review, consensus opinion was to treat with pentostatin given lack of CD20 expression and concern for limited response with rituximab-based regimens. Following 6 cycles of pentostatin 4 mg/m<sup>2</sup> every 2 weeks with good tolerance, colon biopsies demonstrated morphologic remission with only mild chronic active colitis. Bone marrow biopsies five months following completion of therapy showed no evidence of residual disease. Her aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase later increased from 28 U/L, 28 U/L, and 166 U/L, to as high as 478 U/L, 270 U/L, and 1647 U/L, respectively. She subsequently had multiple hospitalizations for hyperbilirubinemia, as high as 13.0 mg/dL, with concern for liver transplant rejection. Mycophenolate mofetil was initiated at 1000 mg twice daily and bilirubin decreased to 1.3 mg/dL. Likewise, AST, ALT, and alkaline phosphatase decreased to 109 U/L, 90 U/L, and 591 U/L, respectively and have remained stable. Colon biopsies were again negative for disease one year after completion of pentostatin.

#### 5. Summary

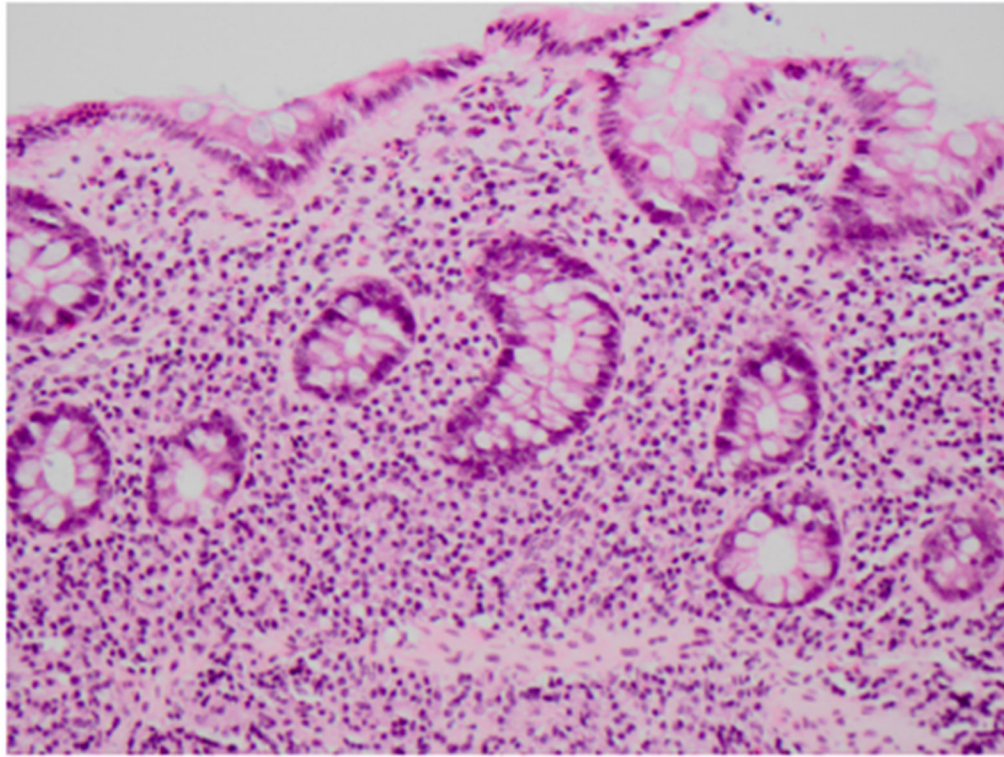
In summary, we present a rare case of pancolonic, indolent, long-standing, asymptomatic MALT lymphoma with marked plasmacytoid differentiation, which was EBV and *MYD88* negative, and discovered incidentally on surveillance colonoscopy. She was found to have stage IV disease with GI, lymph node, and bone marrow involvement. It is unclear if and to what extent potential risk factors including autoimmune hepatitis requiring liver transplant, inflammatory bowel disease, and chronic immunosuppressive therapy may have contributed to the development of her hematologic malignancy. Following reduction in her immunosuppression and 6 cycles of pentostatin she reached a complete remission. The recurrence of hepatic dysfunction with liver transplant rejection was successfully managed with addition of mycophenolate mofetil to tacrolimus and prednisone without relapse of MALT lymphoma. The case emphasizes the need to correctly diagnose and understand the potential for progression of clinically indolent EBV-negative non-gastric MALT lymphoma in the post-transplant setting. The case is also a lesson in balancing chemotherapy with immunosuppression to effectively treat MALT lymphoma while preserving organ transplant.

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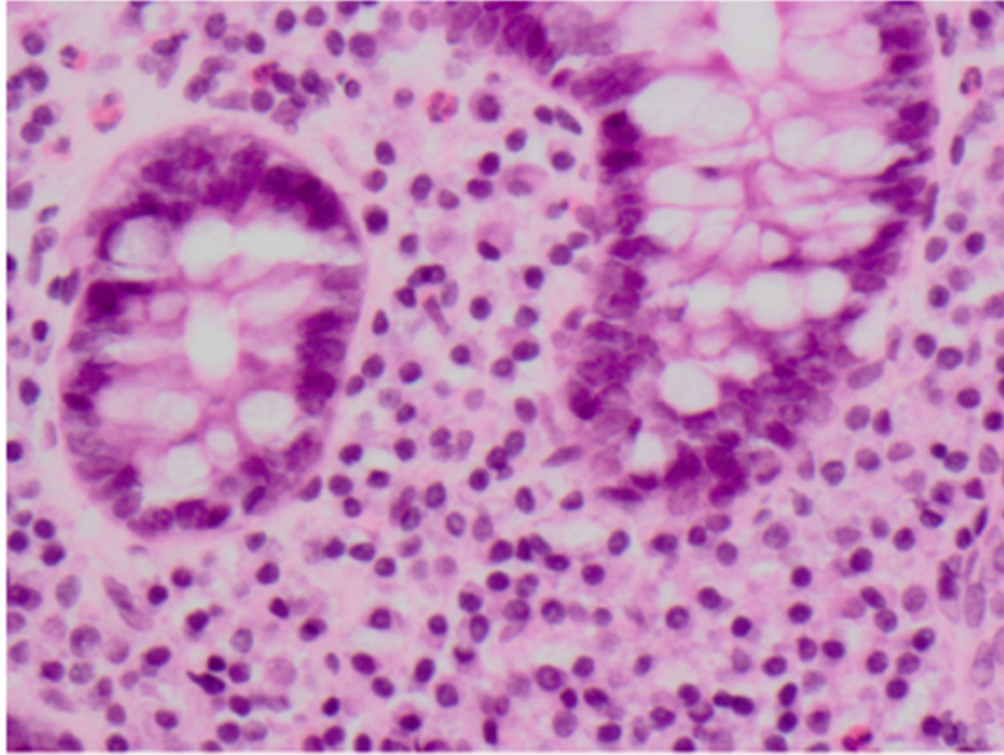


**Fig. 1.** Endoscopic visualization of the ascending, transverse, and descending colon appeared normal. Mild erythema and friability were noted in the rectum. No masses, erosions, nodularity, nor enlarged folds are noted.

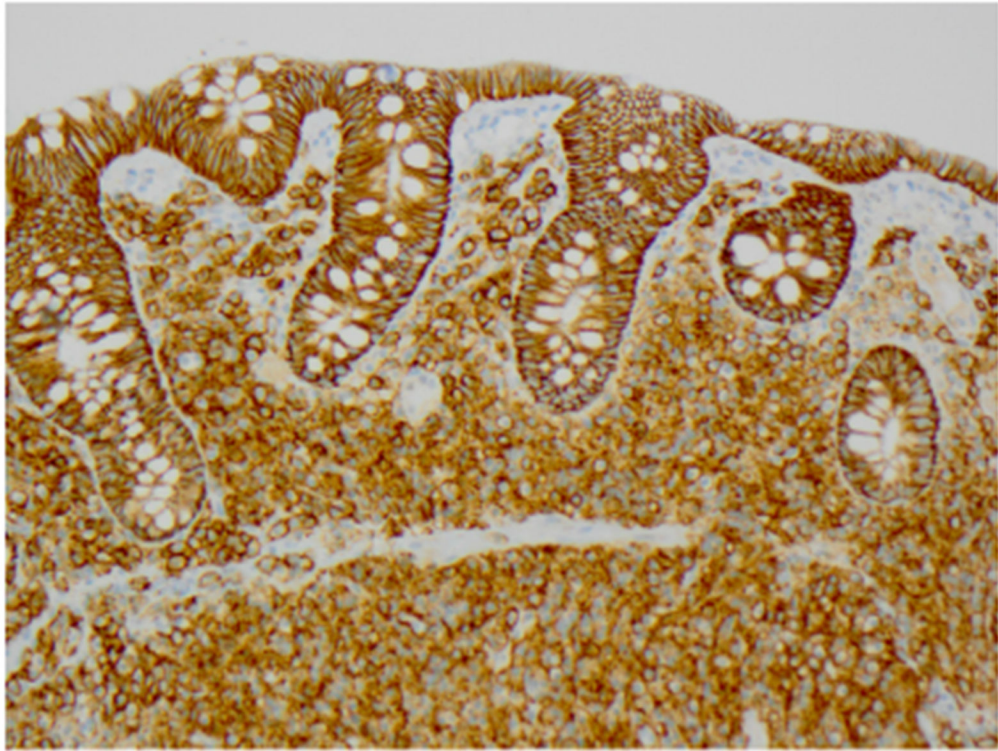


**Fig. 2.** Hematoxylin and eosin-stained section, 20×. Biopsies reveal expansion of lamina propria by a dense, predominantly plasmacytoid infiltrate.

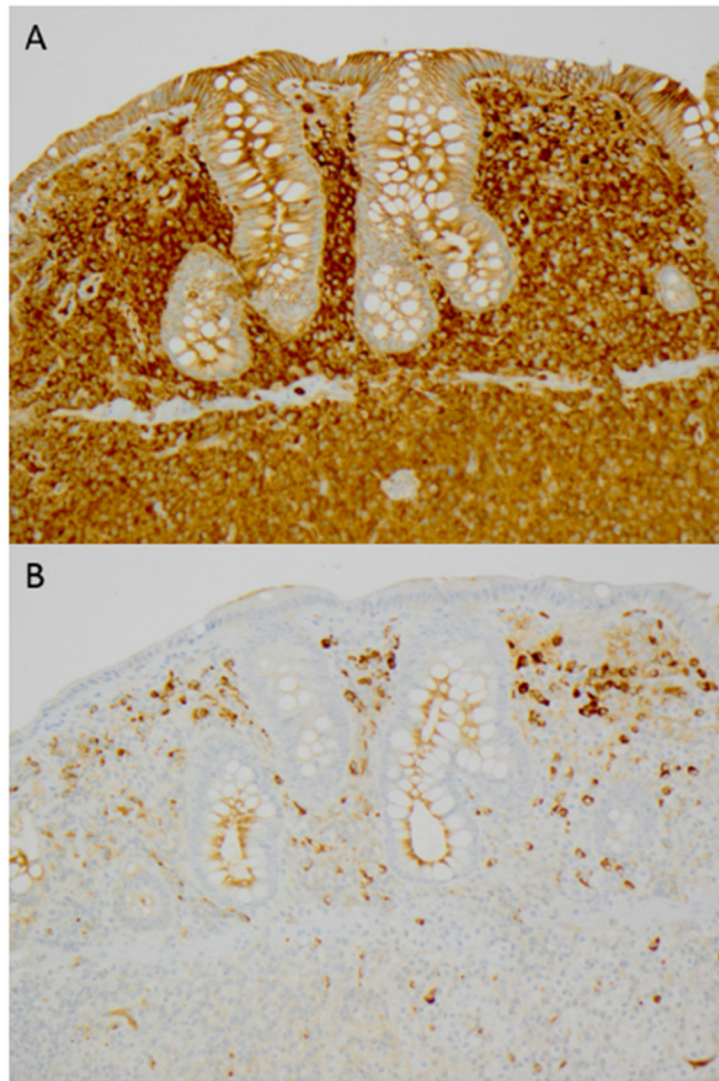




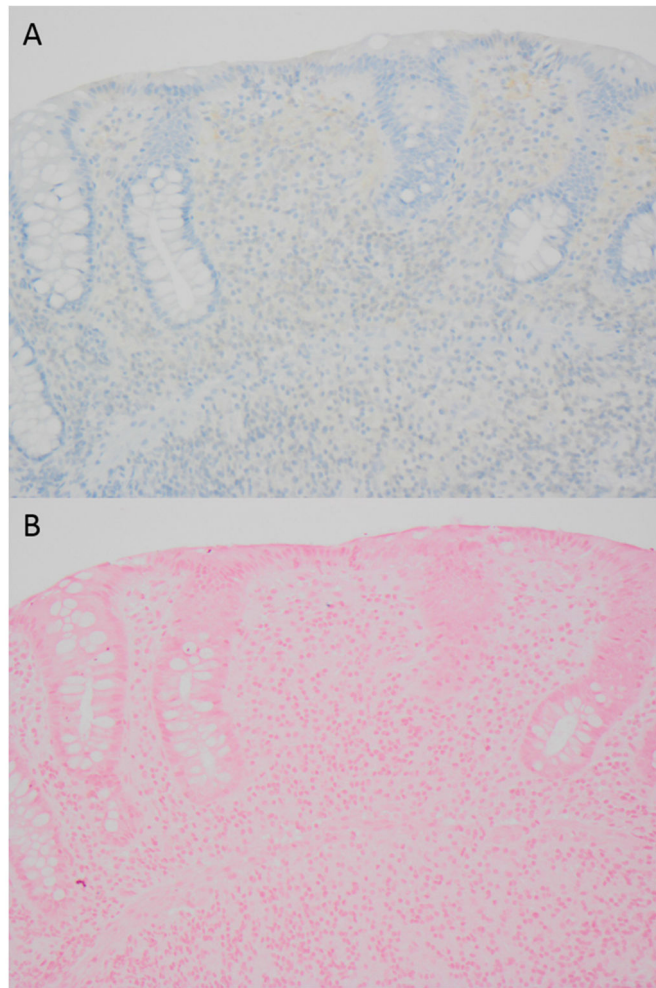
**Fig. 3.** Hematoxylin and eosin-stained section, 40×. The plasmacytoid cells are without significant atypia. No glandular destruction by the infiltrate is noted.



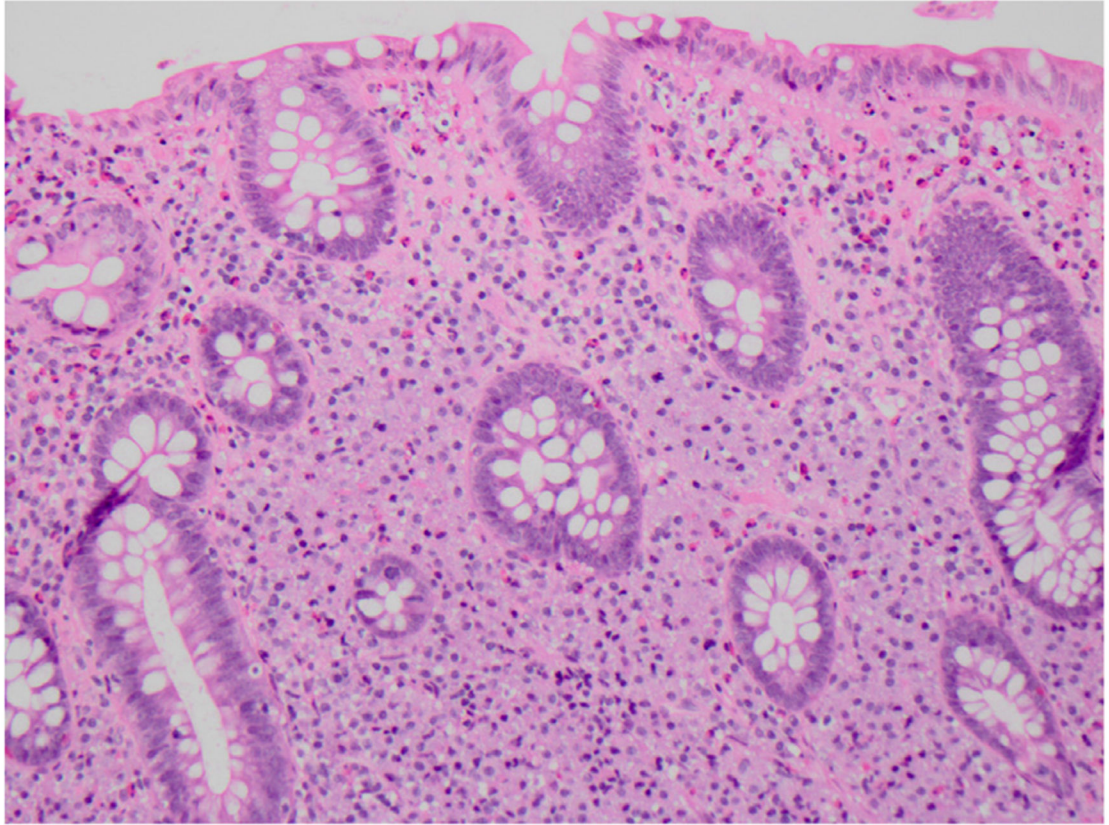
**Fig. 4.**  
CD138 immunohistochemical stain, 20 $\times$ .



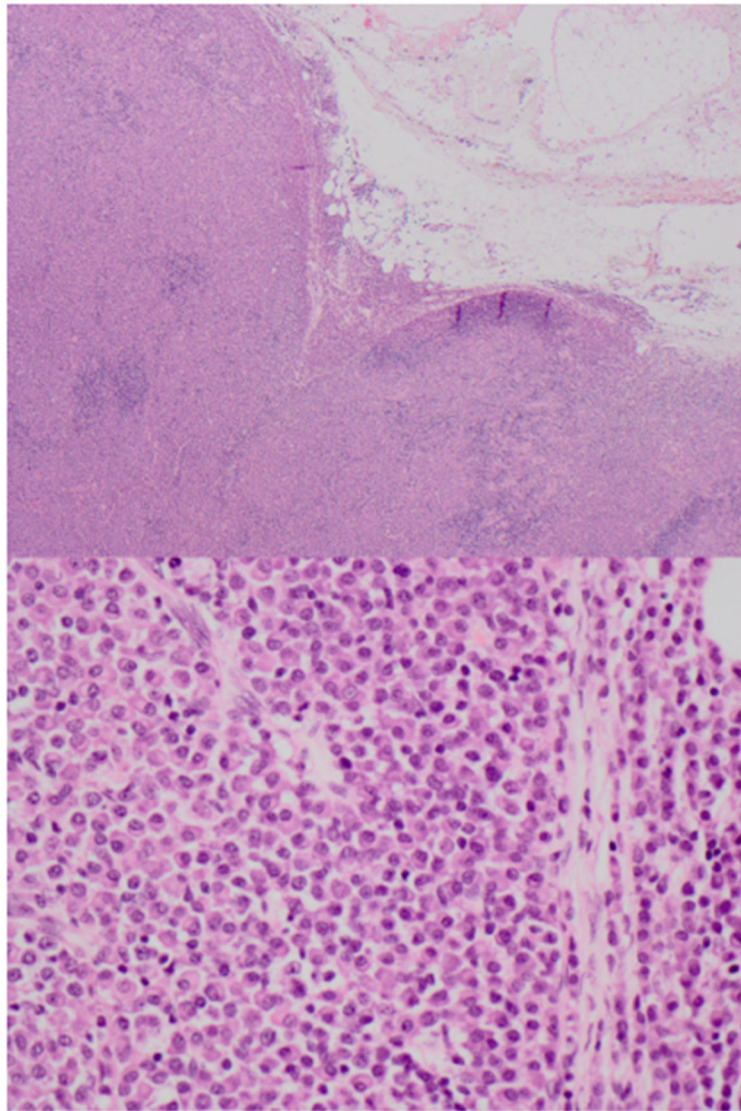
**Fig. 5.** Kappa/lambda, 20 $\times$ . The infiltrate demonstrated marked lambda restriction (A) with only scattered cells kappa positive, mostly in the superficial lamina propria (B).



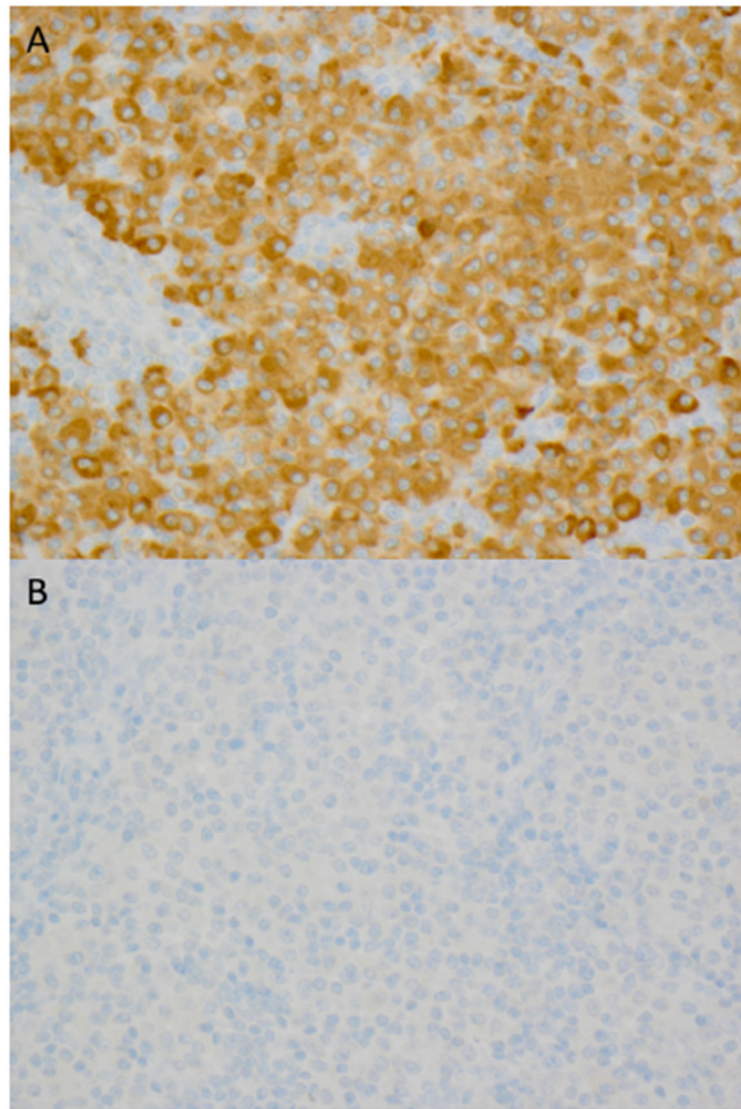
**Fig. 6.** HHV (A) and EBV in-situ hybridization (B), 20×.



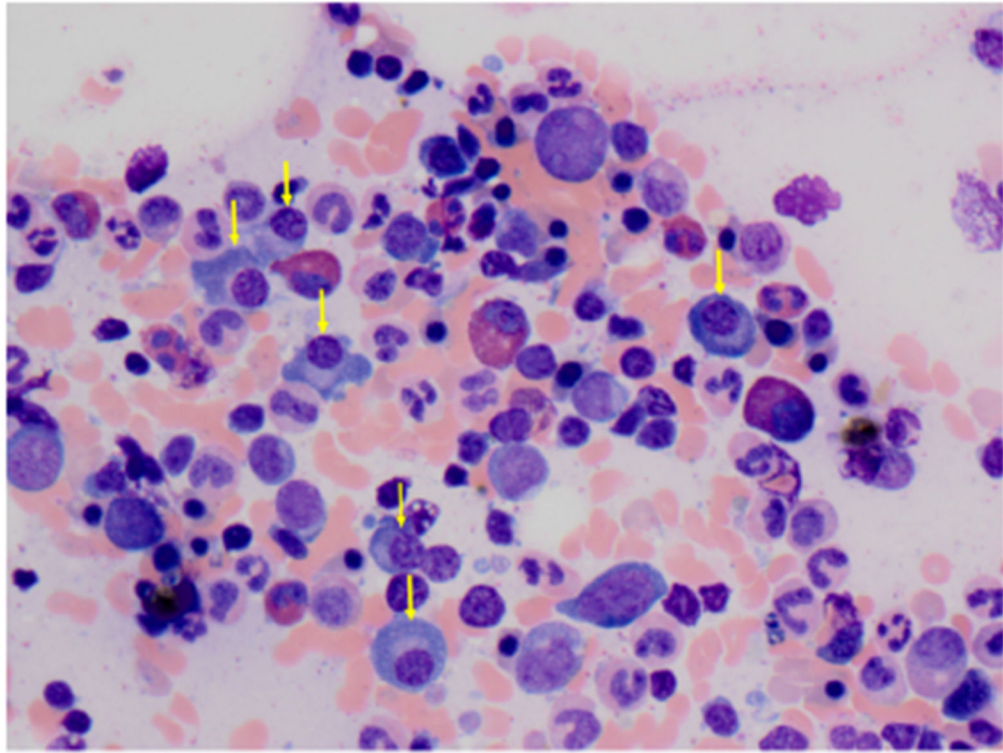
**Fig. 7.** Hematoxylin and eosin-stained section, 20×. Biopsies from 2010 showed a similar plasmacytoid infiltrate involving all sampled areas of colon.



**Fig. 8.** Hematoxylin and eosin-stained section, 4× and 40×. The inguinal lymph node demonstrates complete architectural effacement by a plasmacytoid infiltrate.



**Fig. 9.** Kappa/lambda, 20 $\times$ . The lymph node infiltrate demonstrated predominantly lambda positive cells (A) with virtually no kappa expression (B).



**Fig. 10.** Wright Giemsa, 60 $\times$ . Plasma cells were increased (arrows) within the bone marrow, as demonstrated by aspirate smear.