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Review Article

IpiColitis: ipilimumab-induced colitis with a wide spectrum of histological features

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Abstract: CTLA-4 is a T lymphocyte receptor and immune checkpoint molecule. It blocks cytotoxic T-cell activation and proliferation through its competitive binding on CD80 and CD86 molecules on antigen-presenting cells. Ipilimumab, a CTLA-4 monoclonal antibody removes this inhibition and prolongs cytotoxic T-cells activation and action on tumor cells. Despite impressive anti-cancer benefits of the immune checkpoint antibody, its use can be hampered by serious adverse events affecting multiple organs including the skin, gastrointestinal tract, kidneys, both peripheral and central nervous systems, liver, lymph nodes, eyes, pancreas, and endocrine system. Immune-mediated colitis is a common complication in patients on ipilimumab treatment. Severe colitis can be life threatening with severe dehydration or intestinal perforation, which requires prompt and appropriate diagnosis and treatment. Histopathological features of ipilimumab-induced colitis are diverse with different injury patterns including focal or diffuse active colitis, apoptosis, chronic active colitis, and lymphocytic colitis. These findings can resemble acute graft-versus-host disease, drug toxicity, flares of inflammatory bowel disease (IBD), or infection. Clinicians and pathologists should be aware of the expanding spectrum of ipilimumab-induced colitis. The purpose of this review is to summarize pathological features of ipilimumab-induced colitis (IpiColitis) and its differential diagnosis with other conditions.

Keywords: Ipilimumab, CTLA-4, colitis

Introduction

Cancer immunotherapy field has had many promising developments in recent years. Immune checkpoint inhibitors are the best examples. Over the past two decades, immunological research has elucidated how T cell-mediated-immune responses are initiated and regulated [1-3]. The activation of T cells requires two sets of signals: a ligation of T cell receptors with an antigen bound to the major histocompatibility complex protein on the surface of antigen presenting cells and the interaction of CD28 on the T cell surface with CD80 or CD86 on antigen presenting cells inducing an enhanced and sustained T cell activation through T cell receptors [1-3]. On the other hand, inhibitory signals are also crucial to balance T cell immune responses and prevent autoimmune disorders [1-3] (**Figure 1A**). CTLA-4 is a cell surface molecule that is expressed nearly exclusively on CD4-positive and CD8-positive T cell surfaces and is important in maintaining T cell homeostasis. It acts as a counterbalance to the activity of the costimulatory receptor CD28 [1-3]. CTLA4 is homologous to CD28 and the two receptors are localized on the surface of T cells where they compete to bind to the costimulatory ligands CD80 and CD86 on antigen presenting cells. CTLA4 and CD28 are centrally important for the initial activation of naive T cells induced by the migration of activated antigen presenting cells to lymphoid organs [1-3].

The human immune system utilizes CTLA-4 as an immune checkpoint to prevent T lymphocyte overactivation and development of autoimmune disorders. Immune dysregulations with different types of autoimmune disorders have been described in patients with CTLA4 mutations. It is characterized by T cell infiltration in a number of organs, including gastrointestinal tracts, lungs, bone marrow, central nervous system, etc. Some patients exhibit severe diarrhea with autoimmune enteropathy. Other clinical presentations include thrombocytopenia,

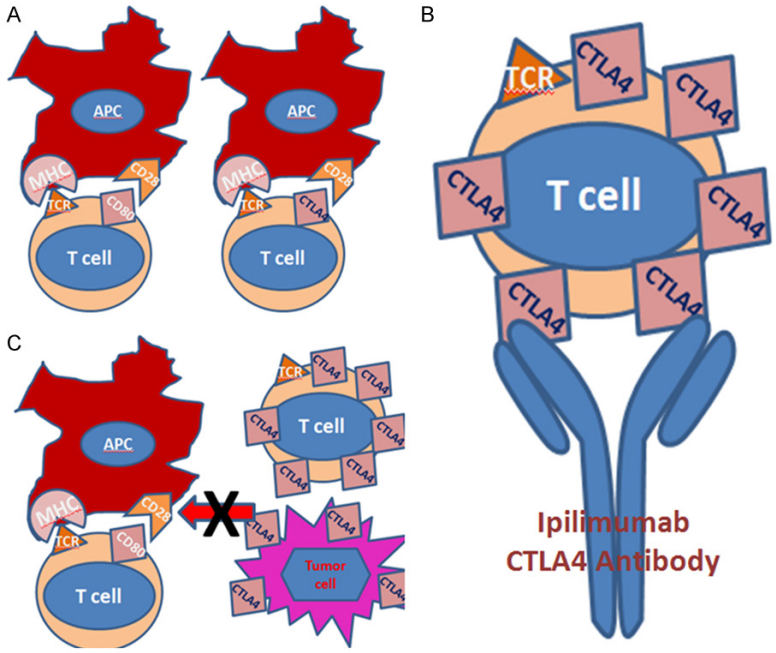

Figure 1. A. CTLA-4 negatively regulates T cell activation by blocking interaction between CD28 molecules on the T cell surface and CD80/CD86 molecules on the antigen-presenting cells. B. In the setting of malignancy, there is an increase in CTLA-4-positive T cells. Tumor cells may also express CTLA-4 molecules, leading to increased tumor immune tolerance. C. Ipilimumab binds to and blocks CTLA-4 signaling therefore enhances immune-mediated anti-tumor effect.

hemolytic anemia, thyroiditis, type I diabetes, psoriasis, and arthritis [3-6].

The immunogenicity of tumor-associated antigens spans a wide range depending on the degree of mutation in self-antigens. Most tumor-associated antigens are ubiquitously expressed, but they are not mutated or tumor specific. Therefore, a robust autoimmune response is required for successful tumor eradication [3-7]. On the other hand, cancer cells can take advantage of the negative regulatory pathway to evade monitoring by the immune system [3-7].

In the setting of malignancy, multiple mechanisms of immune suppression exist, such as indoleamine-2, 3-dioxygenase, IL-10, regulatory T cells, and myeloid-derived suppressor cells, thus preventing an effective anti-tumor immunity [8]. Multiple studies have shown an increase in CTLA4-positive T regulatory lymphocytes in the circulation and tumor microenvironment (**Figure 1B**). Constitutive expression of CTLA-4 on regulatory T lymphocytes blocks the interaction of the CD28 ligand on T lymphocytes with the CD80 and CD86 receptors on tumor antigen presenting cells, leading to the inhibition of antigen presenting cell activation, inhibition of IL-12 production, cell cycle arrest of T lymphocytes, and suppression of CD8+ cytotoxic T lymphocyte proliferation and function. CTLA-4 also causes down-regulation of T-cell response, leading to increased tumor immune tolerance [8]. Furthermore, recent studies have shown that CTLA-4 is also expressed on non-lymphoid cells of different tissues including the liver, skeletal muscle, placental fibroblasts, monocytes, leukemia cells and some solid tumor cells. CTLA-4 expressed on tumor cells is able to interact with CD80 and CD86 and induce apoptosis of antigen presenting cells [9-11] (**Figure 1B**). The concept of CTLA4 blockage to treat human cancer was first developed by James P. Allison. This has led to the development of a monoclonal antibody targeting CTLA-4 for cancer immunotherapy [12].

Ipilimumab

Ipilimumab is a fully human monoclonal immunoglobulin G_1 (IgG1) specifically binding to CTLA-4 molecules. It had been approved by US FDA (United States Food and Drug Administration) in 2011 to treat patients with late-stage melanoma and clinical studies have demonstrated favorable outcomes in patients with advanced melanoma [13].

Phase III and IV clinical trials are also ongoing for gastric cancer, gastroesophageal junction cancer, recurrent glioblastoma, renal cell carcinoma, small cell lung cancer, non-small cell lung carcinoma, squamous cell carcinomas of the head and neck, and urothelial carcinoma, besides numerous phase I and II studies for a variety of other cancers [14].

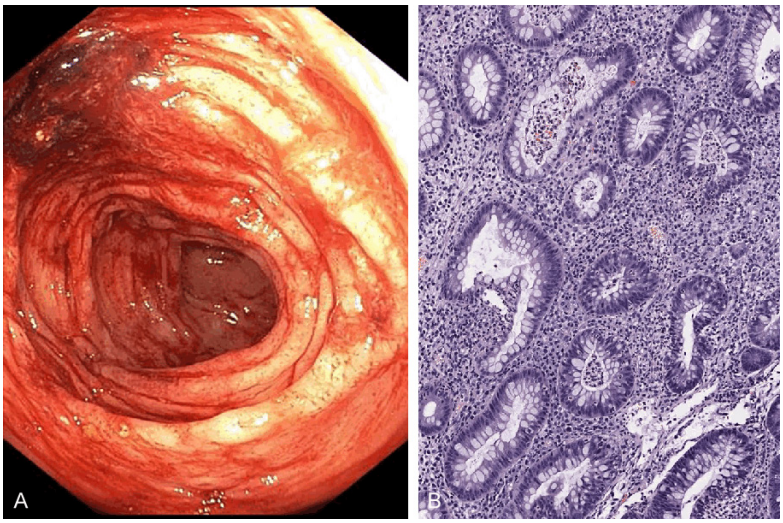

Figure 2. Ipilimumab-induced active colitis. A. Colonic mucosa with diffuse erythema and focal ulceration; B. Active colitis histologically characterized by cryptitis, crypt microabscesses, lamina propria neutrophil infiltration and slightly increased lymphoplasmacytosis without crypt architecture distortion.

Ipilimumab achieves its anti-neoplastic effect by binding to the immune inhibitory receptor CTLA-4 to block the inhibitory signal (**Figure 1C**). Therefore, ipilimumab enhances immune function and allows cytotoxic T lymphocytes to destroy tumor cells [14-16]. Although ongoing clinical trials of the targeted therapy have exhibited long-term improvement in cancer patient outcomes, immunological adverse effects are not uncommonly observed following ipilimumab treatment. Serious immunological adverse events have been described in multiple organs including the skin, gastrointestinal tract, kidneys, both peripheral and central nervous systems, liver, lymph nodes, eyes, pancreas, and endocrine system. One of the most frequent side effects is observed in gastrointestinal tract, particularly colitis, which can be severe and even fatal [17, 18]. In a recently published meta-analysis with a total of 234 patients on ipilimumab treatment, gastrointestinal adverse effects were seen in 39.7% of the cases. The incidence of ipilimumab-induced diarrhea was 34.2%, of which 5.1% developed life threatening intestinal perforation [19].

Differentiating patients with mild symptoms from those who will progress to severe and life-threatening colitis is difficult, especially because the clinical presentation can be subtle and easily confused with infection, ischemia and inflammatory bowel disease. Given the life-threatening nature of ipilimumab-induced colitis and the favorable response to steroids if started early, an accurate diagnosis is essential. Colonoscopy, including biopsy and pathologic evaluation of colonic mucosa, is currently a validated diagnostic tool to confirm immune-related colitis and used to rule out other etiologies.

There have been several excellent reviews and studies focusing on the clinical presentations and management of ipilimumab-associated side effects [19-24]. Whereas a comprehensive review on pathological patterns of ipilimumab-induced colitis has not been available so far. The histological diagnosis of IpiColitis is critical for patient's management, but can be extremely challenging because of the spectrum of diverse pathological features. With this goal in mind, we attempt to conduct a comprehensive review on the pathological features of IpiColitis and its differential diagnoses.

Ipilimumab-induced active colitis

The most common histopathologic pattern of colitis associated with ipilimumab is active colitis. In a metaanalysis including 10 studies and more than 2,000 patients treated with ipilimumab, colitis was frequently reported and ranged from 1-16% [24-27]. Active colitis is pathologically characterized by neutrophilic infiltration in the lamina propria, cryptitis, and crypt microabscesses, often with prominent distension of the crypt (**Figure 2**). It is usually associated with increased transmucosal inflammatory infiltrate in the lamina propria consisting of lymphocytes, plasma cells, and neutrophils with a varying number of eosinophils [24]. The infiltrate is not preferentially located at or under the base of the crypts but evenly distributed throughout the lamina propria. Features of chronicity such as marked mononuclear expansion of the lamina propria, basal lymphoplasmacytosis, crypt architectural distortion, or Paneth cell metaplasia in the distal

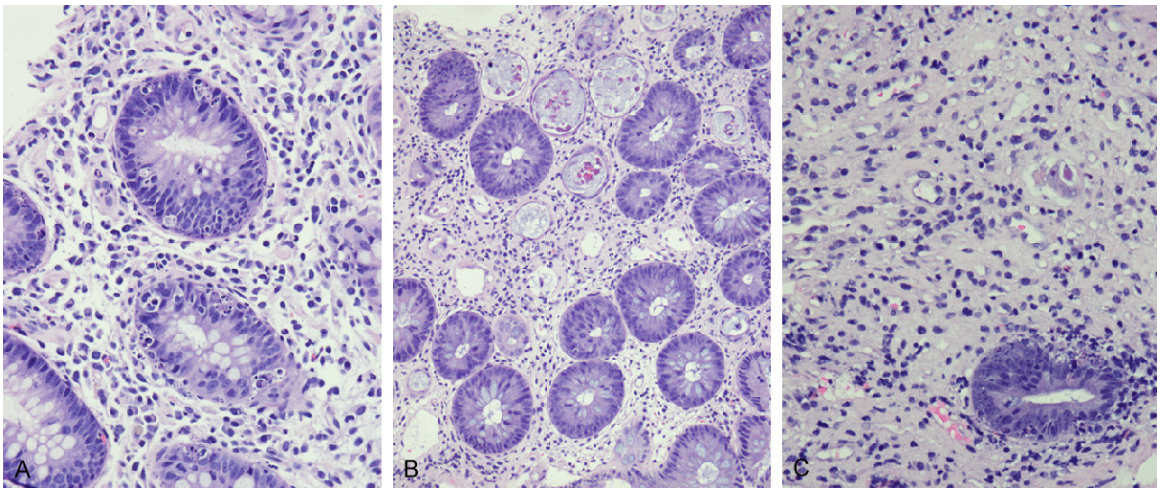

Figure 3. A. IpiColitis with numerous epithelial apoptosis; B. Crypt damage characterized by dilated crypts with flattened epithelium and eosinophilic luminal debris; C. Marked crypt dropouts with only two remaining injured crypts associated with apoptotic bodies and eosinophilic debris.

colon are generally not obvious [24]. Endoscopic presentation of ipilimumab-induced active colitis is similar to inflammatory colitis in other conditions characterized by a loss of vascular pattern, friability, spontaneous bleeding, and ulcerations [24]. However, even if these signs of inflammation are not present endoscopically, biopsies should be taken and are required to confidently rule out colitis [24]. The most common locations of endoscopic colitis are the rectum and sigmoid colon, but 66% of patients could have extensive pancolitis. 55% of patients present with patchy distribution and 20% with ileal inflammation as reported by Marthey *et al*, which poses a challenge in distinguishing from Crohn's disease endoscopically [27]. Furthermore, a study from Robert *et al* showed that ipilimumab-mediated colitis more commonly affects the left colon with sparing of the rectum, differing from ulcerative colitis which almost always involves the rectum [26]. The relationship between ipilimumab dosage and the risk of developing active colitis is controversial even though some reports appear to be dosedependent [26].

Ipilimumab has been described as a cause of severe pancolitis with colonic perforation. Shah *et al* reported a case of pancolitis with multiple colonic perforations involving the splenic flexure and the Cecum. Macroscopic and histological analysis of the total colectomy specimen demonstrated the large bowel with a cyanotic and dusky appearance and severe active colitis with ulcers and necrosis [29]. Mitchell *et al* described 3 cases of perforating colitis induced by ipilimumab with histologic findings of deep, fissuring inflammation, variably dilated crypts with small crypt abscesses, reactive epithelial changes, and multifocal crateriform ulceration with pseudopolyps [30].

Ipilimumab-induced active colitis with prominent epithelial apoptosis

Apoptotic cells are rare in normal intestinal mucosa and usually confined to the surface epithelium due to a normal cell turnover, especially status post bowel preparation prior to colonoscopy. Increased crypt apoptosis should prompt the pathologist to look for associated histologic findings and request for a detailed clinical history. In IpiColitis, it is not uncommon to see epithelial apoptotic bodies at the base of crypts [24, 27, 31]. One study showed that apoptosis is present in 40% of IpiColitis [27]. The distribution of apoptosis could be either diffuse or patchy. Apoptosis is often associated with epithelial regenerative changes, marked crypt damage characterized by dilated crypts with flattened epithelium and eosinophilic luminal debris (**Figure 3**). In addition to apoptosis, active colitis is often present with lamina propria edema, neutrophil infiltration, cryptitis, and crypt abscesses. Overall, the histological features are reminiscent of other colitides with prominent apoptosis such as acute graft-versus-host disease (GVHD), certain drug-induced

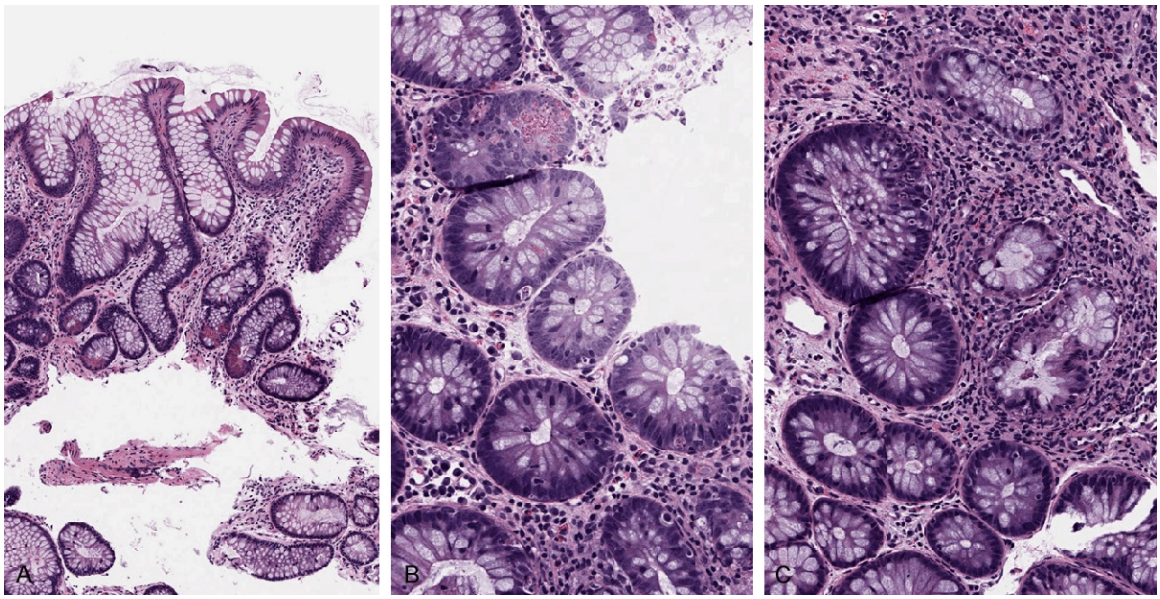

Figure 4. Ipilimumab-induced chronic colitis. A. Crypt architecture distortion and Paneth cell metaplasia in a sigmoid colon biopsy; B. A few apoptotic bodies and Paneth cell metaplasia; C. Cryptitis and lamina propria lymphoplasmacytosis.

colitis (particularly mycophenolate), and autoimmune enteropathy. Perhaps not surprisingly, this pattern also is similar to the reported histopathologic features of IPEX (Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-Linked) syndrome, which is due to a germline mutation of *FOXP3 gene*, a transcription factor critical for T regulatory cell activation [32].

Gros *et al* [33] reported a case of severe acute GVHD following administration of ipilimumab for early relapse of AML after haploidentical stem cell transplantation. Ipilimumab was used as an approach to treat AML relapse in this case. Severe acute GVHD developed shortly after the antibody application. The author speculated that the severe acute GVHD was likely related to the immune checkpoint blockade and pointed out that use of immune checkpoint inhibitors should be carefully discussed in the case of bone marrow transplant given the risk of developing severe acute GVHD.

Ipilimumab-induced chronic active colitis mimicking idiopathic inflammatory bowel diseases (IBD)

With timely diagnosis and treatment, the majority of IpiColitis can be controlled and is completely reversible by temporary immunosuppression with glucocorticoids. Infliximab or other agents are warranted only in the most severe illnesses [34]. If treatment is delayed or not effective, IpiColitis may progress to chronic colitis which may mimic inflammatory bowel diseases. Akel *et al* [35] reported a case of a 71-year-old male diagnosed with *BRAF* wild-type metastatic melanoma treated with three cycles of ipilimumab, after which he developed severe enterocolitis. The symptom improved on steroid treatment; three year later, the patient's diarrhea returned. Colonoscopy revealed active chronic colitis with multiple long shallow colon ulcers and patchy inflammatory changes throughout the entire colon. Colonic biopsies exhibited mild to moderate crypt architectural distortion associated with moderate increase in lamina propria mononuclear cells, resembling inflammatory bowel disease. We have also seen an IpiColitis patient who had developed chronic active colitis 6 months after initial onset of active colitis. Histopathologic examination showed chronic mucosal injury pattern similar to inflammatory bowel disease characterized by crypt architecture distortion, basal lymphoplasmacytosis and Paneth cell metaplasia involving the distal colon (**Figure 4**). Rastogi recently reported an IpiColitis with anal fissures and fistulas mimicking Crohn's disease [36]. Bertha *et al* [37] also described a 73-year-old man with metastatic melanoma who developed

ipilimumab-induced colitis with subsequent transformation to a Crohn's colitis-like phenotype. The patient's colitis persisted despite steroid treatment. A colonoscopy revealed deep and punched out linear ulcers in the distal half of the rectum, as well as moderate erythema and superficial ulcerations with a granular appearance in the proximal rectum and distal sigmoid colon. Skip lesions were also present. Pathology was notable for quiescent chronic colitis of the transverse colon, mildly active chronic colitis in the descending colon, and moderate to severe active chronic colitis in the rectosigmoid colon associated with a peri-rectal abscess. Arellano *et al* [38] presented a case of diffuse, non-necrotizing granulomatous lymphadenitis and granulomatous vasculitis following ipilimumab use in a patient with metastatic melanoma. Case reports of sarcoidosis and sarcoidosis-like granulomatous disease associated with ipilimumab therapy have also been described in the literature [39-42].

Ipilimumab-induced lymphocytic colitis

Lymphocytic colitis has been thought to have an immune dysregulation etiology for a long time, given its microscopic appearance of intraepithelial lymphocytes, response to steroids, and tendency to exist in a constellation with other autoimmune disorders such as celiac disease, type 1 diabetes, polyarthritis, and thyroid disorders [43]. It is therefore not entirely unexpected that it occurs following CTLA-4 blockade. Histologically, lymphocytic colitis is characterized by increased intraepithelial lymphocytes, surface epithelial injury, and mononuclear expansion of the lamina propria [43].

Classic lymphocytic colitis-like IpiColitis is only rarely described in the literature even though Foppen *et al* [31] reported that increased lamina propria cellularity with mononuclear cells is a frequent histopathological feature in IpiColitis. Lamina propria mononuclear cell expansion is often associated with cryptitis and crypt microabscesses as described in active colitis. Romain *et al* [44] reported a case of Ipilimumab-associated lymphocytic colitis with prominent intraepithelial lymphocytosis, surface epithelial injury, and expansion of the lamina propria by lymphoplasmacytic inflammation. Interestingly, increased apoptotic activity was also noted in this case. The patient's symptoms did not respond to symptomatic treatment with loperamide and lomotil but the diarrhea had a rapid improvement after administration of budesonide, a medication of the corticosteroid type. In the only other reported case to date, Garcia-Varona et *al* [45] described a 65-year-old male with stage IV ocular melanoma who developed watery diarrhea and abdominal discomfort 6 weeks after initiating ipilimumab therapy. Biopsies from the rectum, sigmoid, and descending colons showed normal crypt architecture but with markedly increased intraepithelial lymphocytes and diffuse lymphoplasmacytic infiltrate with scattered eosinophils in the lamina propria. The patient was treated with oral and systemic steroids, and symptoms resolved in two weeks despite continuation of ipilimumab therapy.

As mentioned earlier, lamina propria expansion with lymphoplasmacytosis is a common feature in IpiColitis. Some studies have further characterized lymphocytic infiltrates in the lamina propria [46-48]. Coutzac *et al* [46] analyzed lymphocytes of the colonic lamina propria from patients with ipilimumab-induced colitis and inflammatory bowel diseases by immunohistochemistry and flow cytometry. The study showed B cells were not predominant in the lamina propria in IpiColitis whereas T lymphocytes were the main component. The majority of lamina propria lymphocytes are activated CD4-positive T cells and were found in the lamina propria in anti-CTLA-4-induced colitis. Arriola *et al* [47] recently observed that CD8-positive and FoxP3-positive cells were significantly higher in patients with ipilimumab-related colitis when compared to the normal colon. Patients who required infliximab for the resolution of their colitis had a significantly higher CD8-positive/FoxP3-positive ratio than those treated with only steroids and this correlated with clinical severity. The analysis of repeat samples revealed that the resolution of the colitis was associated with a decrease in both CD8-positive and FoxP3-positive cells in patients treated with steroids and infliximab. It is apparent that further studies are needed to elucidate the underlying mechanisms of ipilimumab-induced lymphoplasmacytosis in the lamina propria.

Histopathologic differential diagnosis of IpiColitis

Differential diagnosis of IpiColitis with apoptosis should include other causes of colitis with prominent apoptosis, which include infections

(particularly CMV), GVHD, autoimmune enteropathy, and other medications. The consideration of CMV colitis is important in the context of immunotherapy, since IpiColitis patients frequently receive immunosuppressive therapy which puts patients on high risk of opportunistic infections. Colitis caused by mycophenolate may demonstrate prominent apoptosis, essentially identical to ipilimumab-induced apoptosis [49]. Chemotherapy and anti-tumor necrosis factor therapy can also induce colitis with numerous apoptotic bodies [50]. Colitis with acute inflammation, increased intraepithelial lymphocytes, and prominent apoptosis has recently been described in patients receiving the phosphoinositide 3-kinase-d inhibitor idelalisib [51]. Clinical and medication history is essential in differentiating these drug-induced colitides. In cases with lymphocytic colitis-like IpiColitis, the pathologist has to bear in mind that this pattern has been associated with a long list of medications such as nonsteroidal anti-inflammatory drugs (NSAID) and proton pump inhibitors. However, being aware that ipilimumab can cause lymphocytic colitis is very important for developing a differential diagnosis [52]. As described above, ipilimumab-induced T cell activation and subsequent colitis could mimic flares of inflammatory bowel disease. Clinical history may be helpful and crucial to distinguish idiopathic inflammatory bowel disease from IpiColitis. Even though the histologic features of IpiColitis are not specific and have overlapping features with varying phases of inflammatory bowel disease, IpiColitis often demonstrates prominent apoptosis while apoptosis usually is less obvious in inflammatory bowel disease unless a concurrent drug-induced injury is present. One most recently published multi-institutional study compared Histopathological and Immunophenotypic Features of Ipilimumab-Associated Colitis to treatment-naïve ulcerative colitis. The study shows similar colonoscopic findings in both Ipilimumab-associated-colitis and ulcerative colitis groups. However Ipilimumab-associated Colitis has several notable and distinct endoscopic and pathologic features compared to ulcerative colitis. Involvement of the gastrointestinal tract was more diffuse in IpiColitis. As compared to ulcerative colitis, a smaller proportion of IpiColitis had basal lymphoplasmacytosis and crypt architecture distortion. In contrast, IpiColitis had more apoptotic bodies in the left colon. There are no significant differences in cryptitis, ulcerations and crypt abscesses in both groups. Furthermore, IpiColitis had a lower density of CD20-positive lymphocytes than ulcerative colitis in lamina propria but CD4, CD8, CD138 and FOXP3-positive cells are similar in both groups [53].

Other causes of diarrhea beyond IpiColitis

The pathologic features of IpiColitis are not truly specific. Awareness of the clinical context is the key to arrive at a correct diagnosis. Keeping in mind of the major histological patterns should help the pathologist recognize IpiColitis, although it is often difficult to definitively prove that pathologic changes are due to a medication. The distinction between different histopathologic patterns is somewhat arbitrary due to overlapping features. For example, apoptosis is nearly a universal feature in all ipilimumab-induced colitis regardless of the predominant pattern. It is particularly important to recognize that recurrent IpiColitis may develop many months after ipilimumab treatment.

Immunosuppressive drugs are often used to manage IpiColitis, with high doses of steroids as standard treatment for severe IpiColitis. If colitis is refractory to corticosteroids, other immunosuppressive drugs such as infliximab are used. High-dose corticosteroids and infliximab increase susceptibility to infections. Franklin *et al* [54] retrospectively reviewed data of 370 patients treated with checkpoint inhibitors. Patients who did not respond to standard immunosuppressive therapy within 2 weeks were classified as refractory. Amongst these, 5 (12.2%) were refractory to standard immunomodulatory treatment with corticosteroids and infliximab. Therapy-refractory cases tended to show more severe inflammation in colonic biopsies. In all therapy-refractory cases, cytomegalovirus (CMV) was detectable. CMV-DNA in colonic biopsies and in plasma was significantly more detectable in therapy-refractory cases. This report emphasized the need of repetitive monitoring of CMV reactivation during management of refractory IpiColitis. In the same report, it appeared that Clostridium Difficile also contributes refractoriness of IpiColitis with recommenced diarrhea, which was treated with metronidazole leading to the resolution of symptoms. Koldenhof and Suijkerbuijk [55]

presented a patient with metastatic melanoma who developed an immune-related pancreatitis, uveitis, and thyroiditis shortly after starting pembrolizumab treatment. She subsequently developed diarrhea caused by pancreatic insufficiency. This case illustrated that not all ipilimumab induced-diarrhea is caused by colitis. As immune-related pancreatitis during immune checkpoint inhibition often occurred asymptomatically, it is important to also consider that ipilimumab induced diarrhea can be secondary to the pancreatic insufficiency.

Summary

Blockade of the T-cell inhibitory receptor CTLA4 with a monoclonal antibody could induce autoimmunity involving a diverse array of target tissues. Immune-related colitis is the most frequent serious toxicity and, if untreated, may lead to intestinal perforation. IpiColitis most commonly presents as an active colitis with apoptosis, reminiscent of other colitides such as acute GVHD, autoimmune colitis, and other drug-induced toxicities. Less commonly, IpiColitis exhibits chronic colitis resembling inflammatory bowel diseases or demonstrates marked intraepithelial lymphocytosis mimicking lymphocytic colitis. As the use of ipilimumab continues to increase, awareness of these pathological patterns could help with the diagnosis and promote treatment of IpiColitis. The pathological differential diagnoses of IpiColitis are broad depending on the predominant pathological pattern and thorough clinical history. The application of high-dose corticosteroids and TNF antagonists to control autoimmune toxicities substantially increases the incidence of opportunistic infections. It is also particularly important to rule out infectious colitis to avoid management pitfalls. As far as the clinical management of IpiColitis, it is not a primary focus of the current review. In brief, a therapeutic algorithm has been suggested based on severity of diarrhea and other clinical symptoms. When patients develop diarrhea, an infectious etiology such as Clostridium Difficile, other bacterial or viral infection should always be evaluated first. The mainstay of IpiColitis therapy is immunosuppression with corticosteroids. In cases of mild watery diarrhea, anti-diarrhea agents, such as loperamide can be used and might be enough to control the side effect. In severe cases, hospitalization may be necessary for intravenous fluids and electrolyte replacement plus intravenous administration of corticosteroid. For more severe and steroid-refractory cases, combined administration of tumor necrosis factor alpha antagonist and steroid is recommended and would resolve the clinical symptoms in most patients. For further details on management of IpiColitis, it is recommended to refer several recently published reviews and studies [23, 56, 57]. As regards the relationship between Ipilimumab-associated toxicity and tumor treatment outcome, the available reports were inconsistent from differential studies. Studies from Attia and Yang et al suggested a better tumor response in advanced melanoma and renal cell carcinoma patients with more severe ipilimumab-associated toxicity compared with those exhibiting minimal side effects [58, 59]. On the other hand, another melanoma study showed no differences in the outcome and overall survival between patients without any toxic effect and those of patients with ipilimumab-associated side effects [60]. In summary, the emergence of anti-CTLA4 treatment for solid tumor represents a major oncologic advance. Although ipilimumab has demonstrated promising antitumor effects in many types of cancer, it also poses a challenge to identify patients with immune-related adverse events (irAE). Its management is different from that of conventional cytotoxic anti-tumor agents. This review summarizes the pathological patterns of Ipilimumab-induced colitis.

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