Immunome Research
ISSN: 1745-7580

Allen and Kuppam, Immunome Res 2014, 10:1
DOI: 10.4172/1745-7580.1000074

Review Article Open Access

A Review on Clinicopathological Correlation between Classical Inflammatory Bowel Disease and Immunotherapy Related Inflammatory Bowel Disease

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Abstract

Blockade of various immune targets such as cytotoxic T-lymphocyte antigen-4 and Programmed cell death leads to immune-mediated tumor regression and immune-related adverse events, predominantly gastrointestinal events including diarrhea and colitis. The current review is done to understand the underlying mechanism of action and to identify potential biomarkers that could help in the prediction and management of gastrointestinal immune-related adverse events. Histological assessment of bowel biopsies and assessment of serologic markers of inflammatory bowel disease and colitis secondary to immune mediated antibodies are reviewed. Ipilimumab causes dysregulation of gastrointestinal mucosal immunity, which can be evidenced by altered antibody levels to enteric flora and inflammatory cell infiltration into gastrointestinal mucosa associated with diarrhea and clinical evidence of colitis. The pattern of drug induced antibody titers to microbial flora and the histological features and location of the inflammation were distinct from classic inflammatory bowel disease. Although classic inflammatory bowel disease and immune mediated antibodies related gastrointestinal toxicity are both immune mediated, the pattern of biomarkers and histological features suggests that the later may be a distinct clinicopathologic entity.

Keywords: Inflammatory bowel disease; Crohn's disease; ulcerative colitis; GI irAEs; Serological markers

Abbreviations: TAAs: Tumor Associated Antigens; GI: Gastrointestinal; IBD: Inflammatory Bowel Disease; CD: Crohn's Disease; UC: Ulcerative Colitis; CTLA-4: Cytotoxic T-Lymphocyte Antigen-4; IL: Interleukin; irAEs: Immune Related Adverse Events; NOD2: Nucleotide Oligomerization Binding Domain 2; ATG16L: Autophagy Related 16 like; IRGM: Immunity – related GTPase M; HLA: Human Leukocyte Antigen; ADCC: Antibody Dependent Cell-Mediated Cytotoxicity; ADL: Activities of Daily Living; pANCA: Perinuclear-staining Anti-neutrophil Cytoplasmic Antibody; ASCA: Anti-Saccharomyces Cerevisiae Antibody; Anti I2=Antibodies to Bacterial Protein which is a T cell Super Antigen; OmpC: *Escherichia coli* outer membrane porin; CBir1: CBirflagellin Antibody

Introduction

Immunotherapy treatment for cancer was first considered in practice by William Coley who proposed active immunizations (later known as Coley toxins) of cancer patients in the late 19th century [1]. Immunization strategies were followed several decades later by the discovery and clinical application of recombinant immune cell signaling proteins such as interleukin-2 [2]. Most recently, both preclinical and clinical evidence has affirmed a long held hypothesis that tumors inhibit functionality of immune infiltrate and that this process is at least partially reversible through direct blockade of negative regulatory signaling through a class of cell-surface signaling proteins known as checkpoint modulators which include Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) & Programmed Death 1 (PD-1) pathways [3,4].

Components of immunity are seen as potentially more specific weapons to direct against tumors than chemotherapy or radiation [5]. With our expanding knowledge of tumor associated antigens (TAAs), there are many different approaches being developed to direct immunity against transformed cells. Immunotherapies may involve the active generation of immunity to TAA, via vaccination with peptides or peptide-pulsed dendritic cells [6]. In addition, administration of immune modulators, such as cytokines, can boost existing antitumor immunity and target immune effector cells to sites of tumor growth [7]. Monoclonal antibodies harness both innate and adaptive immune mechanisms and direct them against tumor cells [8]. In addition, the effector functions of cytotoxic T lymphocytes have proven them to be particularly useful in targeting TAA in adoptive immunotherapeutic protocols [9].

Some TAAs are tumor specific, whose expression is entirely limited to tumors, examples of which include viral antigens expressed on cells in which viral oncogenes have contributed to cellular transformation. In these cases, immunotherapy can be used with fine specificity and very little toxicity against normal tissues [10]. However, most TAAs are expressed by some cells of normal tissues and the potential exists for on-target toxicity against these tissues. These on-target toxicities can be assigned to 2 broad categories. First, they can comprise "true" autoimmunity, involving a fundamental induction of endogenous immunity against self-antigens, and we refer to this type as "autoimmunity." Second, they can be more "drug-like" in nature, where damage is mediated directly by the immunomodulatory agent, and these toxicities are referred to as "immune-mediated".

There is much promise and excitement in the use of monoclonal antibodies for immunotherapy, with around 10 drugs approved by the Food and Drug Administration for the treatment of cancer [11]. These antibodies are specific for a variety of molecular targets expressed on a range of cancers, including lymphomas, leukemia, breast cancer,

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Received November 09, 2013; **Accepted** January 10, 2014; **Published** January 17, 2014

Citation: Allen TR, Kuppam LG (2014) A Review on Clinicopathological Correlation between Classical Inflammatory Bowel Disease and Immunotherapy Related Inflammatory Bowel Disease. Immunome Res 10: 074. doi: 10.4172/1745-7580.1000074

and colorectal cancer. A variety of effector mechanisms are used by antibodies against tumor cells, which include antagonizing growth factors and their receptors, or inducing their degradation. Alternatively, antibodies may activate antibody-dependent cell-mediated cytotoxicity (ADCC) or the complement pathway. Finally, antibodies may also be used to antagonize receptors, such as CTLA-4, which normally down-regulate immune responses. However, just as spontaneously arising tumor-specific antibodies have been shown to induce autoimmune pathologies in paraneoplastic neurologic disorders, toxicities against normal tissues have also been observed in a proportion of patients receiving exogenous antibody [12].

The blockade of CTLA-4 by monoclonal antibodies results in immune-related adverse events (irAEs), including diarrhea and colitis [13]. Examination of colonic biopsies obtained after onset of diarrhea or colitis reveals both acute and chronic inflammation [14]. The etiology of classic inflammatory bowel disease (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), results from dysregulated GI mucosal immunity, possibly related to both genetic susceptibility and an environmental component not yet known but suggested to be related to commensal bacteria [15-17]. Thus, there is an interest in exploring the relationship between GI irAEs resulting from CTLA-4 blockade and classic IBD.

In this review, we discuss the various pathogenetic mechanism, clinical presentations and serological markers associated with IBD and Immunotherapy related colitis, as well as the various differences that can be noted with biopsy and endoscopy.

Inflammatory Bowel Disease

Incidence and prevalence

The highest incidence and prevalence rates for IBD have been reported from northern Europe and North America. In North America, the incidence of UC ranges from 2.2 to 14.3/100,000 person-years and for CD, 3.1 to 14.6/100,000 person- years. The prevalence ranges from 37 to 140/100,000 persons for UC and from 26 to 200/100,000 persons for CD [18,19]. IBD is associated with earlier age of diagnosis (second–fourth decade). Men and women are at similar risk to develop IBD, and there is an increased incidence of IBD in patients those who are of Jewish descent [20].

Pathogenesis

IBD results from a combination of defects in host interactions with intestinal microbiota, intestinal epithelial dysfunction, and aberrant mucosal immune responses.

Genetics

Specific NOD2 polymorphisms confer at least a four-fold increase in CD. NOD2 encodes a protein that binds to intracellular bacterial peptidoglycans and subsequently activates NF-κB. It has been postulated that disease-associated NOD2 variants are less effective at recognizing and combating luminal microbes, which are then able to enter the lamina propria and trigger inflammatory reactions [21].

LikeNOD2, ATG16L1 and IRGM are related to recognition and response to intracellular pathogens, supporting the hypothesis that inappropriate immune reactions to luminal bacteria are an important 18 component of IBD pathogenesis [22]. Polymorphisms of the IL-23 receptor are protective in both CD and UC [23].

Mucosal immune responses

Polarization of helper T cells to the TH1 type is well-recognized in CD and in UC patients. A recent report linking polymorphisms near the IL-10 gene to UC, but not CD [24]. Overall, it is likely that some combination of derangements that activate mucosal immunity and suppress immune regulation contribute to the development of UC and CD.

Epithelial defects

Defects in intestinal epithelial tight junction barrier function are present in CD patients [25]. This barrier dysfunction is associated with NOD2 polymorphisms [26], and experimental models demonstrate that barrier dysfunction can activate innate and adaptive mucosal immunity and sensitize subjects to disease [27]. Defects in the extracellular barrier formed by secreted mucin may also contribute [28]. Interestingly, polymorphisms in ECM1 (extracellular matrix protein 1), which inhibits matrix metalloproteinase 9, are associated with UC but not CD [29]. Finally, the Paneth cell granules, which contain antibacterial peptides termed defensins, are abnormal in CD patients carrying ATG16L1 mutations [30], suggesting that defective epithelial anti-microbial function contributes to IBD.

Microbiota

Despite growing evidence that intestinal microbiota contribute to IBD pathogenesis [31], their precise role remains to be defined and is probably different in UC and CD. Antibodies against the bacterial protein flagellin are associated with NOD2 polymorphisms as well as stricture formation, perforation, and small-bowel involvement in patients with CD, but are uncommon in UC patients. In addition, some antibiotics, e.g. metronidazole, can be helpful in management of CD, and broad-spectrum antibiotics can prevent disease in some experimental models of IBD [32]. One model that unifies the roles of intestinal microbiota, epithelial function, and mucosal immunity suggests a cycle by which transepithelial flux of luminal bacterial components activates innate and adaptive immune responses [33].

Clinical presentation and Endoscopy

CD is often characterized by abdominal pain, weight loss, fatigue, diarrhea with or without gross bleeding and sometimes fever. Fistula formation between the bowel and adjacent organs may have different clinical presentations, including enteroenteric, enterovesical, enterovaginal, and enterocutaneous fistulas [34].

The clinical presentation of patients with UC usually correlates with disease extent and severity [35,36]. Distal colitis refers to colitis extending into the sigmoid colon. Left-sided colitis extends up to the splenic flexure. Pancolitis describes inflammation extending beyond the splenic flexure, even if the inflammation does not reach the caecum. Disease severity is classified as mild, moderate or severe. Mild disease usually manifests as mild diarrhea, tenesmus and intermittent bleeding; moderate disease is characterized by bloody diarrhea (<10 stools per day), abdominal pain and low-grade fever; severe disease is characterized by more significant bloody diarrhea (>10 stools per day), severe abdominal cramping, and high grade fever [37].

IBD is associated with a number of extra intestinal disease manifestations, the mechanisms of these are not completely understood, and may be related to immunologic or non-immunologic processes. The organs most commonly involved include the skin, joints, biliary tract, and eyes, as reviewed elsewhere [38].

Ulcers, ranging from small aphthous ulcers to large, deep or serpigenous ulcers, and discontinuous or skip lesions are common endoscopic findings in CDas in Figure 1. Mucosal granularity, friability and edema are seen in mild UC, with frank ulceration in moderate to severe cases as in Figure 2.

HPE

Grossly CD may occur in any area of the GI tract, but the most common sites involved at presentation are the terminal ileum, ileocecal valve, and cecum, sparing rectum. The presence of multiple, separate, sharply delineated areas of disease, resulting in skip lesions, is characteristic. Histological examination shows cryptitis, crypt abcess, chronic mucosal damage in the form of architectural distortion, atrophy, and metaplasia and non caseating granulomas. The intestinal wall is thickened as a consequence of transmural edema, inflammation, submucosal fibrosis, and hypertrophy of the muscularis propria, all of which contribute to stricture formation as in Figure 3 [39,40].

Grossly UC involves the rectum and sigmoid and may involve the entire colon. Isolated islands of regenerating mucosa bulge upward to create pseudopolyps. Histological examination shows mucosal inflammation characterized by cryptitis and crypt abcess, ulceration, and chronic mucosal damage. Diffuse, predominantly mononuclear inflammatory infiltrate with plasma cells in the lamina propria is almost universally present as in Figure 4 [41,42].

Serological markers

Atypical P-ANCAs and ASCAs are markers for UC and CD, respectively. The combined use of atypical P-ANCA and ASCA test results distinguishes UC from CD in patients with IBD. The P-ANCA+/ ASCA−combination is specific for UC, whereas the $ASCA^{+}/P\text{-}ANCA^{-}$ combination is specific for CD. There is no relationship between the presence or titer of ANCAs and UC activity [43,44]. The ANCA titer remains positive after colectomy [44]. In addition, the presence of ASCAs is stable over time and is independent of CD activity and duration [43,45]. ASCA titers most often remain stable after treatment [45]. Hence, serial measurement of ANCA and ASCA titers in IBD is not useful for follow-up of disease activity and prediction of relapses.

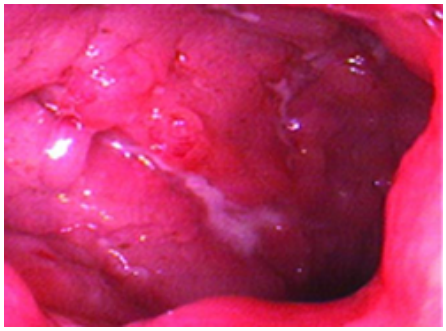

Figure 1: Serpigenous ulcers in Crohn's disease.

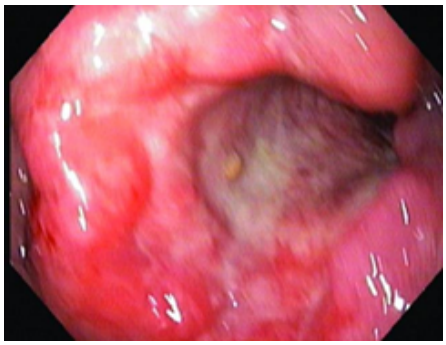

Figure 2: Diffuse ulcers in Ulcerative colitis.

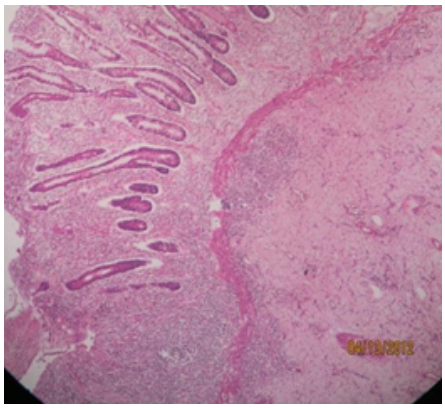

Figure 3: Crypt atrophy with granuloma in CD.

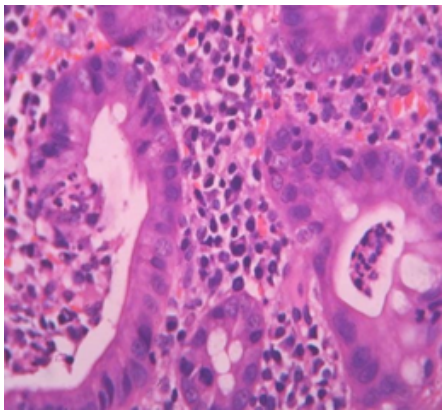

Figure 4: Cryptitis and crypt abscess in UC.

Antibodies against exocrine pancreas have been described in patients with CD, and have been reported to be specific [46,47]. Screening lysates of cultures of colonic bacteria with a monoclonal P-ANCA antibody revealed that *Escherichia coli* outer membrane porin (OmpC) is an antigen in IBD [48]. Landers et al. [49] reported anti-OmpC antibodies in 55% of CD patients. The flagellin CBir1 has been identified as a dominant antigen capable of inducing colitis in C3H/ HeJBir mice and eliciting IgG antibody responses in a subpopulation (~50%) of patients with CD [16,50].

Immunotherapy Related Colitis

Incidence and prevalence

Incidence of GI irAEs (e.g. colitis, diarrhea) with ipilimumab 3mg/ kg monotherapy was 28.2%, low grade (Grade 1-2) being 20.6% and high grade ((Grade 3-4) being 7.6%. Clinically, the average time of onset of diarrhea was at 6–8 weeks, but can occur as early as 3 days post initiation of treatment with rapid progression to colitis hence early multidisciplinary management is crucial [51].

Pathogenesis

Toxicities arising from antibody administration can occur in various ways. First, toxicity can follow the induction of potent endogenous autoimmunity against both tumor antigens and other self-antigens, resulting in both on- and off-target toxicities. Second, toxicities can involve on-target depletion of normal cell subsets, compromising normal tissue function [5]. CTLA-4 is a regulatory molecule expressed by T cells that transmits an inhibitory signal to T cells on binding to CD80 and CD86 on antigen-presenting cells. The targeting of this inhibitory receptor in immunotherapy has been used to break immune tolerance of T cells to TAAs, resulting in the expansion of T cells that elicit antitumor effects. However, in addition to tumor regression, anti–CTLA-4 antibodies, such as ipilimumab and tremelimumab, have been associated with autoimmunity affecting tissues, including the thyroid, lung, joints, gastric mucosa, and liver.

Of significant interest is that autoimmunity has been demonstrated to be associated with clinical response, suggesting that the greater the immune dysregulation mediated by anti–CTLA-4, the greater the antitumor effect [52]. The delivery of exogenous antibody specific for TAA expressed on both tumor and normal tissue can result in damage to normal tissue mediated by complement or ADCC mediated by innate immune cells, such as macrophages.

Genetic knock-out of CTLA-4 in mice results in diffuse infiltration of inflammatory immune cells into multiple organs due to peripheral T-cell proliferation especially skin and GIT (53). Not surprisingly, blockade of CTLA-4 by monoclonal antibodies results in immune-related adverse events (irAEs), including diarrhea and colitis [13].

In a study, association with worst-grade GI irAE was studied for 20 genetic polymorphisms in 10 immune-related genes. No Cancer Immunity polymorphism exhibited a statistically significant departure from Hardy-Weinberg equilibrium. No association between genotype and worst-grade GI irAE was observed for any of the 18 polymorphisms analyzed. Possible associations with GI irAEs were analyzed for each allele separately. For HLA-A and -B, four and seven alleles, respectively, were carried by at least 10% of all treated subjects with HLA data. No associations between HLA-A or HLA-B allele carrier status and worst-grade GI irAE were observed [53].

Blockade of CTLA-4 by ipilimumab induced fluctuations in the levels of one or more of enteric flora related antibodies. The levels of antibody could exhibit increases, decreases, or both during the induction phase with similar degrees of fluctuation for enteric flora related antibodies [54].

HPE

Biopsies revealed active colitis characterized by marked lamina propria mixed inflammatory cell infiltrates consisting of neutrophils, lymphocytes, plasma cells, and eosinophils. Foci of neutrophiliccryptitis, crypt abscesses, glandular destruction, and erosions of the mucosal surface were evident as in Figures 5 and 6. Ulceration was noted occasionally. Inflammatory changes were diffuse in 75% of the biopsies. There was no meaningful increase in the number of intraepithelial lymphocytes or apoptotic activity in colonocytes. Histologic evidence of chronicity, such as crypt architectural distortion, basal plasmacytosis, granuloma, Paneth cell metaplasia, or pyloric metaplasia, was not evident [55].

Clinical presentation

Most common site for immunotherapy induced GI toxicity is the lower GI tract. Most common presentation is mild to severe diarrhea or colitis with occasional bloody stools. Diarrhea can be graded based on the severity. GRADE 1 is Increase of < 4 stools per day over baseline and mild increase in ostomy output compared with baseline. GRADE 2 is increase of 4-6 stools per day over baseline; IV fluids are indicated in< 24 hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL. GRADE 3 is increase of ≥ 7 stools per day over baseline; incontinence; IV fluids ≥ 24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL. GRADE 4 is life-threatening consequences (eg. hemodynamic collapse). GRADE 5 is Death. The image from the endoscopy examination shows edema in the bowel and ulcerations in the descending colon as in Figure 7 [55].

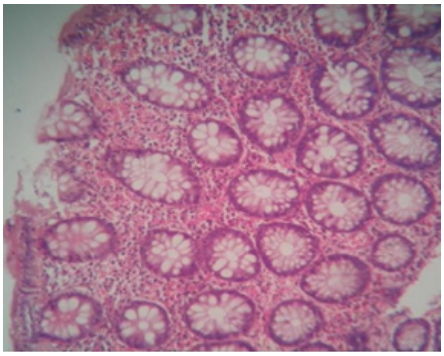

Figure 5: Erosion of mucosa, mixed inflammatory infiltrate in lamina propria and crypt abcess.

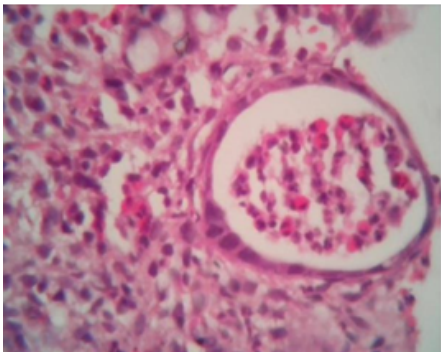

Figure 6: Erosion of mucosa, mixed inflammatory infiltrate in lamina propria and crypt abcess.

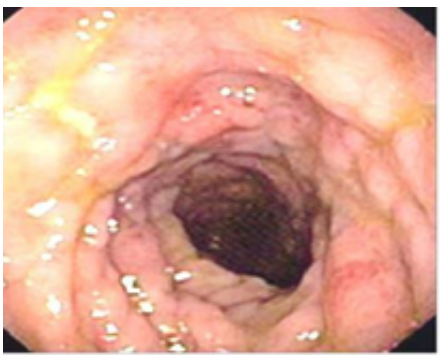

Figure 7: Bowel edema and ulcer in descending colon.

It can rarely lead to gastrointestinal perforation in less than 1% of cases. However in most of the GIirAEs were reversible using product-specific treatment guidelines including vigilant follow-up and early use of steroids when appropriate. Opiates can mask symptoms of perforation and infliximab should not be used in cases of bowel perforation.

Serological markers

In a study, the most common positive antibody titers were to the perinuclear-staining anti-neutrophil cytoplasmic antibody (pANCA) and OmpC (*E. coli*). No strong associations between a positive level and GI irAEs were observed. Most subjects who were positive for anti-I2, anti-Saccharomyces cerevisiaeantibody (ASCA), or CBir flagellin antibody (CBir1) did not have any grade GI irAE, while approximately 50% of subjects positive for pANCA or OmpC had at least a grade 1 GI irAE [56].

In subjects with grade 2 or higher GI irAEs, the highest frequency of patients with positive titers were seen with anti-pANCA (21.4%) and anti-OmpC (40.5%), with <10% of patients positive for anti-I2, anti-ASCA, and anti- CBir1.

Discussion

Immunotherapy most frequently results in GI and skin irAEs because these are the sites that are exposed to the commensal flora [57]. Blockade of CTLA-4 will result in dysregulation of GI mucosal immunity as evidenced by fluctuating antibody titers to enteric flora, increased levels of neutrophil-derived fecal calprotectin, and inflammatory infiltration into the mucosa. However, the pattern of GI-specific serological markers and histopathological changes are distinct from those observed for classic IBD.

Development of antibodies to enteric flora is an evidence of a dysregulated mucosal immune environment in IBD but not acute (diverticulitis/infection) inflammation [58]. However, antibody positivity to enteric flora is also observed in GI irAEs is not consistent with that for classic IBD. In CD, approximately half of patients are positive for ASCA, anti-CBir1, and anti-I2, anti-OmpC and less than 25% are positive for pANCA, in UC, approximately half of patients are positive for pANCA, but less than 10% are positive for ASCA, anti-CBir1, anti-I2, and anti- OmpC [59]. In GI irAEs more than half of patients wi0.th grade 2 or higher irAEs were positive to pANCA and anti- OmpC, with less than 10% of patients positive for anti-I2 and ASCA, and <15% positive for anti-CBir1. Therefore, in GI irAEs, like UC pANCA were positive in approximately 50% of cases, like CD anti-OmpC were positive in approximately 50% of cases. Antibody titers observed in GI irAEs were fluctuating, whereas titers CD are stable over time and with change in disease activity [49]. This fluctuation may reflect changes in the state of T-cell activation as drug concentrations cross an unidentified threshold.

In GI irAEs the location and histological features of the lesion were different from classical IBD [56]. The predominantly diffuse nature of the active inflammation in colonic biopsies from patients after onset of diarrhea are similar to CD, but without granulomas, fissuring ulcers, and bowel wall thickening which are characteristic of CD. Like UC distal colon is frequently involved, but features of chronicity and diffuse colonic involvement distally, which are hallmarks of UC were not observed. Even though cryptitis, crypt abscess present in GI irAEs, chronic mucosal changes like crypt architecture distortion, loss of mucosal goblet cells and paneth cell metaplasia, which is characteristic of classical IBD, is not seen in GI irAEs [60-63]. Finally, the histologic findings observed here were also distinct from graft-vs.-host disease, which is characterized by prominent epithelial apoptosis and glandular destruction [64].

Like in classical IBD biomarkers to reliably predict which patients would develop, GI irAEs were not identified. Immune cell infiltration of the bowel mucosa early in treatment is suggested to be associated with later onset of colitis but is not reliable enough for routine use. No association between abnormal endoscopic findings and colitis were observed, possibly due to the lower sensitivity. Neutrophil-derived fecal calprotectin, a biomarker of active IBD [64,65] increases upon immunotherapy, indicating active inflammation in the bowel wall but cannot be used to predict onset of any irAE. No associations between GI irAEs and any of 18 single nucleotide polymorphisms (SNPs) in 10 immune-related genes were observed, despite previously reported association of CTLA-4 polymorphisms with autoimmune disease [66].

Conclusion

Immunotherapy is now increasingly used as an effective therapy against tumors; however, it is prone to immune toxicities. Immunotherapy will result in dysregulation of GI mucosal immunity, as this is one of those sites where it is exposed to plenty of commensal flora. The pattern of GI mucosal dysregulation, in GI irAEs evidenced by histology and antibodies to enteric flora, was distinct from that observed for classical IBD, suggesting that diarrhea and colitis due to GI irAEs may represent a distinct clinicopathologic entity which can be treated by drug withdrawal, systemic steroids and infliximab.

Conflict of Interest

This paper has been written without external financial funding. There is no conflict of interest.

Acknowledgments

None declared

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