Research Article

Role of Abdominal and Pelvic CT Scans in Diagnosis of Patients with Immunotherapy-Induced Colitis

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ABSTRACT

Introduction: Colitis is one of the most common immune-related adverse events in patients receiving immune checkpoint inhibitors. Although radiographic changes on computed tomography (CT), such as mild diffuse bowel thickening, mesenteric fat stranding, and mucosal enhancement, have been reported, the utility of CT in diagnosis of patients with suspected immune-related colitis is not well documented. The aim of this retrospective study was to determine the value of CT scans in diagnosis of immunotherapy-induced colitis. **Methods:** CT scans of the abdomen and pelvis of 34 patients receiving immunotherapy who had a clinical diagnosis of immunotherapy-induced colitis and 19 patients receiving immunotherapy without clinical symptoms of colitis (controls) were evaluated. Segments of the colon (rectum, sigmoid, descending, transverse, ascending, and cecum) were assessed independently by two abdominal imaging specialists, blinded to the clinical diagnosis. Each segment was assessed for radiographic signs such as mucosal enhancement, wall thickening, distension, and periserosal fat stranding. The presence of any of the signs was considered radiographic evidence of colitis. **Results:** CT findings suggestive of colitis was seen in 20 of 34 patients with symptoms of colitis and in 5 of 19 patients without symptoms of colitis. The sensitivity, specificity, positive predictive value, and negative predictive value for colitis on CT were 58.8%, 73.7%, 80%, and 50%, respectively. **Conclusions:** We found that CT had a low sensitivity, specificity, and negative predictive value for the diagnosis of immunotherapy-induced colitis. We therefore conclude that CT has a limited role in the diagnosis of patients with suspected uncomplicated immune-related colitis.

Keywords: colitis, immunotherapy, CT scans, biopsies

INTRODUCTION

The introduction of immunotherapy has resulted in a significant paradigm shift in the treatment of cancer over the past decade. Among immunotherapy agents, immune checkpoint inhibitors (ICIs) targeting programmed cell death protein (PD-1), its ligand (PD-L1), or cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) are prominently used. The increased use of these agents has also resulted in increased immune-related

adverse events (irAEs). IrAEs differ from adverse events associated with traditional cancer therapies and can involve any organ or system.[1] The most common sites of adverse events are the skin, gastrointestinal tract, lungs, endocrine system (adrenal pituitary), and musculoskeletal, renal, and central nervous systems.[2] Consequently, in patients being treated with ICIs, there should be a high level of suspicion that their symptoms or signs may be related to the therapy. Most irAEs are of low grade and are treatable, but some adverse effects can be severe, with permanent effects. Timely identification of these adverse events and management is important.[2] Management is primarily based on stopping the ICI and treating with corticosteroids and other immunomodulatory agents.[3–5]

ICI-induced colitis is a frequent adverse event and is seen in 15–25% of patients on CTLA-4 inhibitors and in up to 10% of patients treated with PD-1 and PD-L1 inhibitors.[1,6,7] Colitis typically appears between 5 and 10 weeks after initiating treatment; however, the timing can range from immediately after the first dose to more than 6 months after the last dose.[8–12]

The diagnosis is based on clinical symptoms, signs during a physical exam, stool tests, endoscopic evaluation, biopsy, and sometimes imaging examination.[6–8] The severity of the presentation of colitis and diarrhea is graded by using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Patients with grade 1 colitis are asymptomatic. Patients with grade 2 colitis present with abdominal pain and mucus or blood in stool, and these symptoms are more severe with peritoneal signs in grade 3 colitis. Patients with grade 4 colitis have severe symptoms requiring urgent intervention. Patients with a mild increase in frequency of stools but < 4 per day over baseline are considered to have grade 1 diarrhea according to CTCAE version 5.0. Patients with 4 to 5 stools per day over baseline and $\geq$ 7 stools per day over baseline are considered grade 2 and grade 3, respectively. Severe diarrhea that requires urgent intervention is considered grade 4 diarrhea.[13,14]

No specific diagnostic work-up is recommended for grade 1 adverse events. However, for colitis, which is classified as grade 2 and above, a diagnostic work-up that includes evaluation of blood, stool, and imaging with computed tomography (CT) has been recommended.[1,2,7,15–18] Endoscopy is indicated for select patients for early immunomodulatory treatment, such as infliximab or other tumor necrosis factor (TNF)–blocking agents, based on presence of ulceration.[2] Common findings seen in the colon on CT scans of the abdomen and pelvis are circumferential bowel wall thickening, mucosal thickening, mucosal enhancement, a distended fluid-filled colon, mesenteric hyperemia, and pericolic fat stranding.[17–20] Radiologists use such imaging features, either in isolation or in combination, to make a diagnosis of colitis in the context of the clinical history. The practice of synthesizing a differential diagnosis in the clinical context can also lead to errors, which may

depend on a multitude of factors, including the accuracy and completeness of the clinical history available and experience leading to occasional misattribution of imaging findings. A few reports have also shown that CT scans have a poor sensitivity, as low as 50% in these patients.[2,21,22] Thus, the role of CT in assessment of patients with immune-related colitis is not clear, and further contextual evaluation of this test would be useful.

In this institutional review board (IRB)–approved retrospective study, we evaluated ICI-treated patients with and without clinical symptoms of colitis to determine the value of routine CT scans of the abdomen and pelvis in diagnosis of immune-related colitis.

METHODS

This retrospective study (PA15-0798) was approved by the IRB at MD Anderson Cancer Center, and the requirement to obtain informed consent was waived. This retrospective study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

We reviewed the electronic medical records of patients with advanced cancer who were treated in early-phase immunotherapy clinical trials in the Department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center. In this study, we identified patients with cancer who received a treatment regimen that included an ICI, underwent endoscopy for clinical diagnosis of ICI-induced colitis, and had a concurrent CT scan of the abdomen and pelvis between Jan 1, 2010, and Dec 31, 2019. We identified 34 patients suitable for inclusion in the study. We also selected a control group of 19 patients who received an ICI and had a CT scan of the abdomen and pelvis but were without history or symptoms of colitis.

The CT scans of the study and control groups were randomly arranged and presented to two radiologists with 8 and 13 years of experience who specialized in abdominal imaging. The radiologists reviewed the CT scans of all the patients independently initially to establish a diagnosis of colitis based on CT findings. Points of discrepancy were resolved by discussion and consensus between the two radiologists. The radiologists were blinded to the diagnosis of colitis. Each anatomically distinguishable segment of the colon (cecum, ascending, transverse, descending, sigmoid, and rectum) was reviewed independently for the presence of bowel wall thickening, mucosal enhancement, luminal distension, and pericolic fat stranding.

Based on the findings from the CTs, the patients were further subclassified into those with $\geq$ 3 contiguous anatomical segments involved and those with $\leq$ 2 contiguous anatomical segments or $\geq$ 3 discontinuous segments involved.

It is not uncommon to see isolated apparent wall thickening of the sigmoid colon and rectum, which is generally due to underdistension. This can be a source of false-positive interpretations of CT. Hence, isolated involvement of the rectosigmoid colon was considered to be negative for colitis unless the degree of abnormality was compelling enough to assign such a diagnosis. Peristalsis and underdistension of the colon are also frequently encountered in CT scans. These collapsed and contracted segments can present as colonic wall thickening and can be misinterpreted as pathology. To minimize this erroneous attribution, abnormal findings had to be present in contiguous segments to be considered.

The findings were entered into a 2 × 2 contingency table. The sensitivity, specificity, and accuracy of CT with 95% confidence intervals (CI) were calculated using the exact binomial method.[23] The positive and negative predictive values with 95% CI were calculated using the standard logit method.[24] All analyses were performed in R version 4.0.4 and R package "bdpv" (version 1.3, R Foundation, Vienna, Austria).[25]

RESULTS

The study group consisted of 34 patients: 17 men (median age, 67 years; range, 25–88 years) and 17 women (median age, 65 years; range, 50–86 years). The control group consisted of 19 patients: 9 men (median age, 61 years; range, 54–71 years), 10 women (median age, 60 years; range, 49–70 years). The patient characteristics are detailed in Table 1.

Twenty-three patients in the study group had grade 3 colitis, eight patients had grade 2 colitis, and three patients had grade 1 colitis based on the CTCAE version 5.0 classification. None of the presentations was considered grade 4 colitis, which is severe and fulminant, and none of the patients had complications such as perforations, pericolic abscesses, or signs of bowel obstruction.

In the study group, 25 of 34 patients had CT scans with intravenous (IV) contrast; 9 patients did not receive IV contrast because of contraindications, including allergies and poor renal functions. In addition, 16 patients in this group received oral/GI contrast. In the control group, 17 patients had CT scans of the abdomen and pelvis with IV contrast; 2 patients did not receive IV contrast because of ordering protocols or poor renal function. In addition, 14 patients received GI contrast.

Involvement of ≥ 3 contiguous segments was observed in 20 patients in the study group and 3 patients in the control group. Involvement of ≤ 2 contiguous anatomical segments or of ≥ 3 discontinuous segments was observed in 8 patients in the study group and 11 patients in the control group. Isolated involvement of the rectum or sigmoid colon was seen in 6 patients in the study group and 10 patients in the control group (Table 2).

However, two of these patients in the control group had, in addition to wall thickening, significant mucosal

Table 1. Patient characteristics in the study and control groups

Site of Primary Cancer	No. of Patients
Study Group	34
Lung	7
Urothelium	6
Pancreas	4
Melanoma	4
Prostate	3
Head and neck	2
CNS	2
Renal	1
Colorectal	1
Esophagus	1
Anal canal	1
AML	1
Liver	1
Control group	19
Colorectal	3
Lung	3
Prostate	3
Head and neck	2
Breast	2
Pancreas	1
Urethra	1
Uterus	1
Gastric	1
Cervix	1
Ovary	1

CNS: central nervous system; AML: acute myeloid leukemia.

Table 2. Subclassification of CT findings based on segmental involvement

Segmental Involvement	Study Group (*n* = 34)	Control Group (*n* = 19)
≥ 3 contiguous segments	20	3
≤ 2 continuous segments or ≥ 3 discontinuous segments	8	11
	Rectum or sigmoid: 6	Rectum or sigmoid: 10
	Rectum or sigmoid + ascending colon: 2	Ascending colon: 1
Normal	6	5

enhancement; these results were considered highly suggestive of colitis on CT. The degree of distension and the spurious assignment of wall thickening were the most common causes for disagreement. Hence, based on CT findings alone, 20 patients in the study group and 5 patients in the control group were diagnosed with colitis (Table 3).

Table 3. Performance of routine CT scans in diagnosing colitis in patients receiving ICI

Clinical Diagnosis (Gold Standard)	CT-Based Diagnosis (Predictive)	
	CT Positive	CT Negative
Colitis present	20	14
Colitis absent	5	14

CT: computed tomography; ICI: immune checkpoint inhibitor.

The sensitivity of CT in this study for diagnosis of colitis was 58.8% (95% CI, 40.7–75.4); the specificity was 73.7% (95% CI, 48.8–90.9); the positive predictive value was 80% (95% CI, 64.2–89.9); the negative predictive value was 50% (95% CI, 38.2–61.9); and accuracy of the test was 64.2% (95% CI, 49.8–76.9).

DISCUSSION

Our study demonstrates that a CT scan suffers from poor sensitivity and specificity in the context of diagnosing ICI-associated colitis. We found that for 14 of 34 patients with clinically evident colitis, the CT scans of the abdomen and pelvis did not show any abnormalities. On the other hand, for 5 of 19 patients in the control group, the CT scans showed features that could be attributable to colitis. The high rates of false-positive and false-negative results in this carefully selected cohort suggest that CT scans have a very limited role in diagnosis or triage of patients with grades 1–3 colitis.

In general, diagnosing irAEs is challenging because some adverse events may mimic infectious, inflammatory process due to a nonimmune reaction to drugs, disease progression, or other common causes. Colitis presents clinicians with such a conundrum. In addition, colitis is a common adverse reaction encountered with ICIs. A meta-analysis involving 13 trials that compared the clinical symptoms of colitis in patients receiving ICIs found the relative risk of all grades of immune-related colitis to be 7.66 (95% CI, 4.58–12.8) and risk of high-grade colitis (grades 3–4) to be 5.85 (95% CI, 2.66–12.8).[26] Colitis is the second most common irAE and the most fatal.[27] Seventy percent of fatal irAEs associated with ipilimumab (anti-CTLA-4) monotherapy reported in the World Health Organization pharmacovigilance database were due to colitis.[28] Among patients receiving a combination regimen (ipilimumab + anti-PD-1 or anti-PD-L1), colitis was still the most common cause of fatality (37%).[29] Hence, timely recognition and management of colitis is essential. Currently, there are no serologic or fecal markers to diagnose ICI-induced colitis, and many practice guidelines, including those of the European consensus groups, require a CT scan among a battery of other tests for establishing the severity and extension of lesions.[1] Although a few small reports have described the imaging appearance of immune-related colitis in the literature, a systematic study with an appropriate control group to evaluate CT of the abdomen and pelvis as a diagnostic and screening test has not been performed in these patients. Our study is an attempt to address this gap.

We designed this study to assess systematically the appearance of the colon on CT scans in both a study group (those with clinical colitis) and a matched control group (those without clinical colitis). The reporting radiologists were presented with randomly arranged CT scans from the two groups and were blinded to the patients' history of presence of colitis. The introduction of the control group and blinding was necessary to remove the confirmation bias that can be influenced by the clinical history. Although clinical history and context are extremely important in providing accurate diagnosis, the clinical history should be withheld for accurate evaluation of CT as a freestanding testing tool. The importance of this study structure is further necessitated by the lack of universally accepted objective criteria for diagnosis of colitis based on initial features. Radiologists use a multitude of imaging features, including mucosal enhancement, circumferential wall thickening, pericolonic fat trending, pericolonic vascular engorgement, and presence of diverticula to diagnose colitis. Because the radiologists were blinded to the clinical presentation, the consensus of two experienced radiologists minimized the subjective nature of interpretation.

The incremental value of a test in improving on the information provided by history, other clinical information available, and its accuracy is a difficult attribute to measure; it would require a sophisticated study designed to account for many confounding variables.[30] However, information on the relative performance of the test may be easier to obtain. Sensitivity and specificity, unlike positive and negative predictive values, are less dependent on prevalence of the condition. For a test to be useful, sensitivity plus specificity should be at least 1.5 (halfway between 1, which means the test is useless, and 2, which means the test is perfect).[30] The sum of the sensitivity and specificity of CT scan in our study is 1.33, and hence CT is not acceptable as a high-quality diagnostic test.

The patients in the study group were selected based on clinical diagnosis of colitis, which was considered the gold standard. This is in line with standard clinical care. Almost all patients in this study group underwent endoscopy, suggesting that they had sufficient clinical signs and symptoms for a diagnosis of colitis. The diagnosis of colitis was further corroborated and confirmed in the patients' electronic health records. Hence, the selection criteria of our study group were robust.

It should be noted that these results probably represent an oversimplification and do not capture the differences in individual sensitivity and specificity demonstrated in routine interpretation of diagnostic scans among radiologists. However, we submit that consensus determination was an imperfect but partial remedy to this shortcoming.

There are a few other shortcomings in our study. It has been documented that signs of colitis may be present on CT scans for 2 to 3 months after the clinical episode of colitis. The patients in our control arm did not have any symptoms attributable to colitis or diarrhea prior to their CT scans while receiving ICIs. This was based on their electronic health records, which may be prone to incomplete documentation and underreporting by patients. However, it is probably safe to assume that any undocumented symptoms were mild or subclinical. An additional weakness of our study is that none of the patients in the study group had grade 4 colitis. Hence,

the results of this study cannot be applied to grade 4 colitis and other severe forms of colitis wherein CT is probably justified.

CONCLUSIONS

Our study demonstrates that CT is not a useful tool for diagnosing colitis in patients receiving ICIs with grades 1–3 colitis. Routine use of CT scans to diagnose colitis in such patients should be discouraged. Use of CT scans should be reserved for patients with signs of complicated colitis, such as perforation, obstruction, and abscesses.

Acknowledgment

Data Availability

The data sets used or analyzed during the current study are available from the corresponding author on reasonable request.

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