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Case Report

More Than Just a Flare: Unexpected Findings of Disseminated Histoplasmosis in the Setting of TNF-α Blockade in a Patient with Ulcerative Colitis

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Abstract

Goals: To present a case report of a patient with ulcerative colitis on infliximab hospitalized with symptoms concerning for active inflammatory bowel disease who was found to have disseminated histoplasmosis involving his colon, and to discuss how this infection impacted subsequent management of his ulcerative colitis.

Background: Histoplasmosis is an infection that is often asymptomatic but can present as more severe or even disseminated disease in patients who are immunosuppressed. Tumor necrosis factor alpha (TNF-α) inhibitors can place patients at increased risk of developing disseminated histoplasmosis infections. Gastrointestinal involvement of histoplasmosis can be mistaken for inflammatory bowel disease. Identification of this infection in patients with inflammatory bowel disease is critical to providing correct treatment.

Conclusions: Providers should be vigilant for the development of opportunistic fungal infections in patients with inflammatory bowel disease and can consider alternative therapies to TNF-α inhibitors, such as vedolizumab, for management when necessary.

Key Words: Histoplasmosis, Ulcerative Colitis, Tumor Necrosis Alpha Inhibitors, Vedolizumab

Introduction

Histoplasma capsulatum is an endemic fungal organism found worldwide. It is most commonly found in central and eastern parts of the United States, with high prevalence in the Ohio and Mississippi River valley regions. Histoplasmosis, an infection that primarily affects the lungs, can occur if *Histoplasma capsulatum* spores are inhaled. These spores can often be found in bat or bird droppings [1]. Many patients with histoplasmosis are asymptomatic, and the disease tends to be self-limited. However, patients with a high inoculation burden or those who are immunosuppressed are at higher risk for more severe or even disseminated disease.

Tumor Necrosis Factor alpha (TNF-α) and interferon gamma play important roles in the body's defense mechanism against histoplasmosis. Thus, those who are immunocompromised due to underlying diseases or from taking immunosuppressive medications are at higher risk for developing disseminated histoplasmosis infections. Disseminated histoplasmosis can be life threatening, with one small review of histoplasmosis in patients on TNF-α blockers noting a 19.4% mortality rate [2]. Despite this, the clinical presentation of disseminated histoplasmosis is relatively non-specific. While pulmonary involvement of disseminated histoplasmosis has been described in as many as 70-80% of cases, hepatic, lymphatic, integumentary and intestinal involvement have been noted as well [3]. Gastrointestinal lesions can be seen in the ileum and colon.These include polypoid masses and ulcerations, which can easily be mistaken for inflammatory bowel disease [4].

We present a case of a patient with a history of ulcerative colitis (UC) on TNF-α inhibitor therapy hospitalized with UC flare symptoms and distal rectal ulceration who was incidentally found to have miliary histoplasmosis with disseminated involvement of the gastrointestinal tract.

Case

A 34-year-old immunosuppressed male with a past medical history of immunoglobulin A (IgA) vasculitis and UC, on infliximab, mercaptopurine, and mesalamine, presented with increasing frequency of bowel movements, bright red blood per rectum, and tenesmus. He also reported new intense rectal pain, which had never occurred before with previous UC flares. He was diagnosed-with UC 12 years prior to this presentation with abdominal pain and bloody diarrhea. He had previously been treated with azathioprine before initiation of infliximab, mercaptopurine, and mesalamine approximately four to five years prior to this presentation. He had not had any flares of his UC symptoms within that time period. Laboratory testing was notable for elevated c-reactive protein and erythrocyte sedimentation rate. Infectious stool studies were negative. Given concern for ulcerative colitis flare, he was then started on IV methylprednisolone. Flexible sigmoidoscopy was performed, and biopsies were obtained. Endoscopic findings were significant for Mayo score 3 (severe with spontaneous bleeding and ulcerations) in the distal 13cm of rectum and Mayo score 2 (erythematous mucosa with loss of vascularity) in the sigmoid colon (Figure 1). Given his history of IgA vasculitis, this was considered as a potential cause for inflammation as well. He was diagnosed with IgA vasculitis two years prior to this presentation with palpable purpura, abdominal pain, and polyarthritis with a steroid responsive rash. He underwent skin biopsy in the following year confirming this diagnosis with leukocytoclastic vasculitis and evidence of IgA immune deposits by direct immunofluorescence microscopy. However, he did not have evidence of polyarthritis or purpuric rash at time of this presentation and he demonstrated normal renal function at time of this presentation. Colonic biopsies obtained via flexible sigmoidoscopy revealed chronic colitis, and staining was negative for cytomegalovirus.

A day after presentation, he complained of new epigastric abdominal pain. A computerized tomography (CT) enterography study was obtained due to concern for possible proximal gastrointestinal disease activity. Imaging was limited due to technical factors but showed active inflammation in rectum and distal sigmoid colon; the rest of the bowel was unremarkable. However, there was an incidental finding of innumerable punctate pulmonary nodules visualized at lung bases captured on CT enterography (Figure 2). A subsequent CT chest was completed for further evaluation and re-demonstrated innumerable, small, 1-3mm nodules scattered throughout both lungs in a miliary pattern. Upon closer review of a prior abdominal scan done 9 months ago, nodules were al-

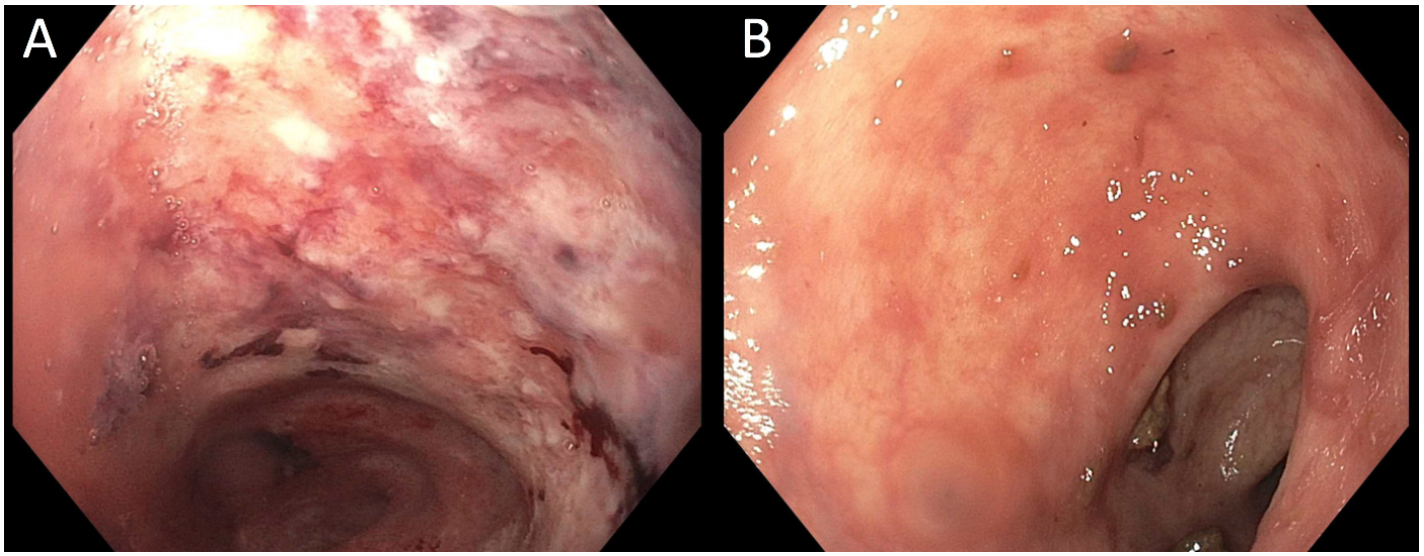

Figure 1: Sigmoidoscopy. Demonstrates significant ulceration of the distal rectum – Mayo 3 colitis (A) with relative sparing of the sigmoid – Mayo 2 colitis (B).

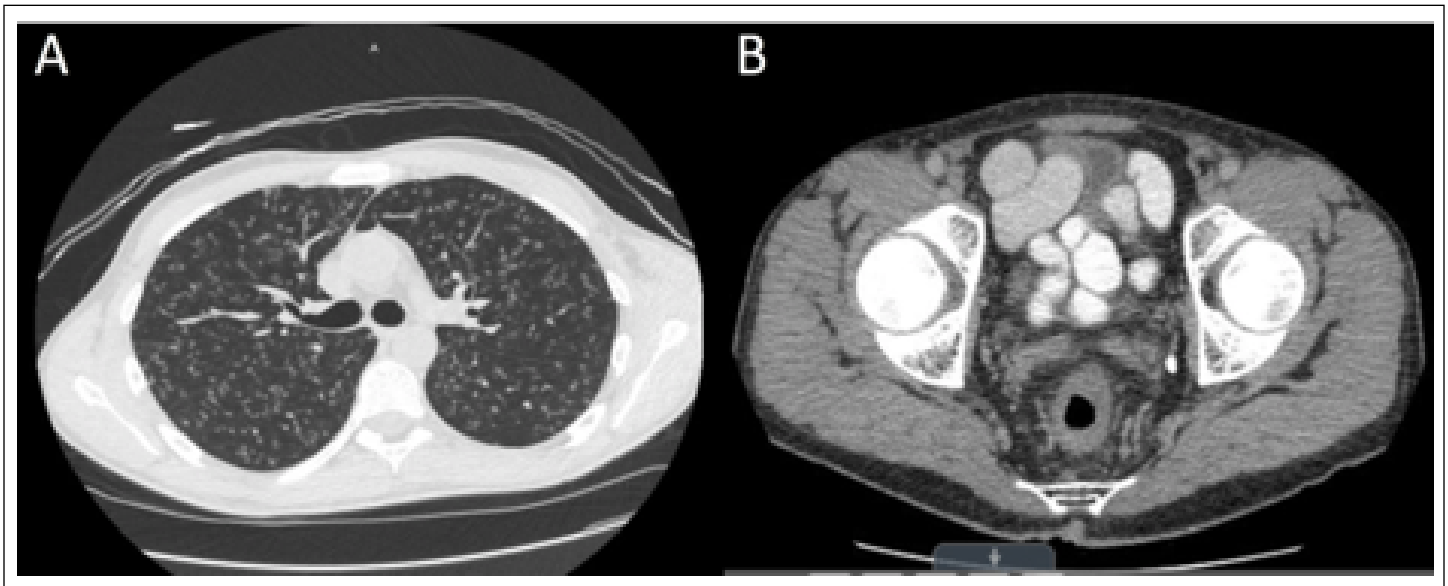

Figure 2. Axial Computerized Tomography (CT) Imaging. CT Chest non-contrast. Window Level = 550. Innumerable small pulmonary nodules (A) and Abdomen & Pelvis enterography with contrast. Window level = 40. Circumferential wall thickening with mild peri-colonic inflammation (B).

ready present; however, they had since significantly increased in number. These findings were concerning for an infectious etiology such as tuberculosis (TB) or fungal infection, or possibly a pulmonary manifestation of IgA vasculitis. The rheumatology service was consulted and stated that these radiographic findings were not consistent with vasculitis. The infectious disease team was also consulted, and the patient was started on empiric therapy for miliary TB while further infectious tests were pending. During this time, the patient experienced no respiratory symptoms and had a normal pulmonary exam. He was unable to produce sputum to be assessed for evidence of active TB infection. However, he did endorse weight loss, fatigue, and drenching night sweats for some time.

His infectious disease workup revealed a positive urine and se-

rum histoplasmosis antigen. Of note, this patient reported being an avid outdoorsman who enjoys cycling in various local state parks which are located in an endemic area of the United States. Given these findings, empiric TB treatment was stopped, and he was started on IV liposomal amphotericin B. There was concern that the patient may have disseminated histoplasmosis with gastrointestinal manifestations because he reported that symptoms of rectal pain were atypical for his UC flares, and he was having persistent symptoms despite steroid therapy and improving inflammatory markers. This suspicion was further supported by the improvement in his rectal bleeding and abdominal symptoms with initiation of amphotericin therapy. Rectal biopsy samples initially taken via flexible sigmoidoscopy at time of admission were then reexamined 10 days later to specifically evaluate for the presence of fungal organisms. These samples demonstrated ulcers with organisms within the exudate that were consistent with Histoplasma yeast forms (Figure 3). Given the patient's disseminated fungal infection, he could no longer remain on infliximab, a TNF-α inhibitor, for UC treatment and was ultimately switched to vedolizumab for continued treatment of his UC.

Discussion

Interpretation of Pulmonary Nodules on CT

The CT chest obtained for this patient demonstrated diffuse, nodular disease in a miliary pattern. Miliary patterns seen on CT imaging are described as multiple nodules that are 1 to 3 mm in size (micronodules), randomly distributed throughout bilateral lung fields. This pattern is often classically associated with tuberculosis infections. However, there are other causes to keep in mind when evaluating a patient with nodular pulmonary disease. These include fungal infections (histoplasmosis, blastomycosis, coccidiosis), hematogenous lung metastases, sarcoidosis, and silicosis [5,6]. Suspicion for fungal infection should be higher if the patient has recently travelled to or lives in an endemic region and if the patient may be immunocompromised. Diagnosis may require serological testing and bronchoscopy with biopsy.

The distribution of micronodules is crucial in distinguishing between different disease processes. Generally, involvement of the centrilobular regions can be secondary to infectious (i.e. viral or mycobacterial) or inflammatory (i.e. hypersensitivity pneumonitis) etiologies that involve small airways. Sarcoidosis, silicosis and pneumoconiosis tend to follow a peri-lymphatic distribution of micronodules. Sarcoidosis often has multiple nodules located in interlobar fissures and findings of enlarged lymph nodes and ground glass attenuations. Pneumoconiosis tends to present with calcified nodules that have upper lobe predominance, and subpleural involvement is common [6].

When evaluating a randomly distributed, nodular pattern on CT the most common considerations include infection and malignancy. The most common secondary malignancies of the lung include those from the breast, colorectal tissue, kidneys, skin (melanoma) and thyroid. Metastases to the lung can present in a random, nodular distribution. However, unlike tuberculosis, these nodules can be larger (up to 1 cm) and are not uniform in size [6].

The diagnosis of pulmonary histoplasmosis on CT can be challenging as the infection can present in a variety of ways. However, in disseminated histoplasmosis, the most common imaging manifestation is diffuse pulmonary micronodules. Other presentations include patchy consolidations with hilar and mediastinal lymphadenopathy, solitary or multiple nonspecific nodules, and calcified granulomas [7].

Clinical Presentation of Disseminated Histoplasmosis

In the case presented, the patient did not have any respiratory

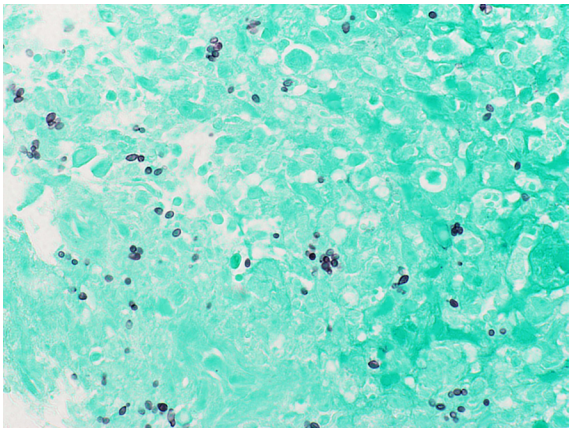

Figure 3: Rectal Biopsies. 20x magnification. Grocott-Gomori's Methenamine Silver (GMS) staining of rectal tissue. Demonstrates budding yeast bodies as seen in black.

symptoms, and findings were incidental. The clinical manifestations of histoplasmosis infections can vary broadly depending on the immune status of the host and infectious dose [1]. While some immunocompetent patients may experience a mild self-limited illness, those who are immunocompromised may develop severe progressive pulmonary disease or disseminated disease. In most cases of pulmonary histoplasmosis in an immunocompetent patient, subacute pulmonary symptoms would be expected within 3-21 days of exposure [1]. Given that the pulmonary nodules identified this admission were present several months prior on CT, it is possible that the patient did have a mild initial presentation that was not worked up further. However, given his immunocompromised status and worsening pulmonary disease by CT, it is unusual that he did not have any respiratory symptoms and was even unable to produce any sputum for respiratory culture at the time of diagnosis of disseminated infection. Overall, it is likely that his high functional capacity, otherwise stable health status and young age resulted in a clinical picture that was significantly milder than what would be expected based on the pathologic and radiographic findings of disseminated infection.

Therapy choices in patients with fungal infections - Why Vedolizumab?

Therapy for ulcerative colitis has been revolutionized by biologic therapies. These treatments target a number of proinflammatory mediators and have allowed for improved management of this chronic condition. However, these mechanisms also have the potential to interfere with the body's immune response to infection. Specifically, TNF-α blockers may place patients at risk for opportunistic infections. One 2013 meta-analysis of patients with inflammatory bowel disease on TNF-α blockers vs placebo showed a significantly increased rate of opportunistic infections [8]. A brief review of the literature regarding IBD and histoplasmosis was performed and can be reviewed in (Table 1) [9-22]. Most of these cases involved patients on TNF-α inhibitor therapy who developed histoplasmosis and were subsequently treated with antifungal medication.

Given this patient's immunocompromised status on Infliximab therapy, consideration of alternative therapy for management of his UC while being treated for disseminated histoplasmosis was necessary. We identified a few reports that discussed the continued use of or reinstitution of TNF-α inhibitor therapy in patients with histoplasmosis and demonstrated minimal recurrence of histoplasmosis [9,17,23]. However, the literature regarding this topic is sparse and thus other IBD management strategies should be considered for these patients. Vedolizumab is another therapy for ulcerative colitis that acts as a relatively gut-specific anti-integrin agent. Studies examining the risk of infection in patients on vedolizumab therapy demonstrate an increased risk of bacterial infection compared to placebo but have not demonstrated an association between vedolizumab and invasive fungal infection [24]. Thus, we opted to start therapy with vedolizumab in this patient with a plan to avoid TNF-α inhibitors for at least one year through completion of treatment for his histoplasmosis infection. Notably, while we initially viewed his presentation as potential infliximab treatment failure, it is likely that his symptoms were the result of disseminated histoplasmosis involving his distal gastrointestinal-tract rather than treatment failure.

Conclusion

Ulcerative colitis is one of numerous conditions that has benefited from the advent of immune-modulating therapy. While these treatments have offered a growing array of options for patients to help manage what can be debilitating symptoms, some come at an inherently increased risk of opportunistic infection. This patient presented with what was thought to be a flare of his UC but, through incidental findings on imaging and subsequently pathology, was found to have a disseminated histoplasmosis infection likely secondary to immunosuppression on infliximab and environmental exposures. This presentation was particularly notable for the rectal involvement of his fungal infection pointing to this as the likely cause of his rectal bleeding, weight loss, and pain as opposed to true infliximab treatment failure. This conclusion is supported by the fact that his symptoms did not significantly improve until anti-fungal therapy was initiated.This presentation was also notable for the complete lack of respiratory symptoms despite significant pulmonary disease burden. Providers should continue to be vigilant for the development of opportunistic fungal infections in this population of patients and can consider alternative therapies, such as vedolizumab, for management when necessary.

Table 1: Literature Review via Pubmed and Google Scholar using MeSH terms "histoplasma" AND "inflammatory bowel disease."

Study Details	Study Design	Cases	IBD Dx	Therapy regimen (# on therapy)	Presenting Symptoms	Type of Histoplasmosis	Imaging Findings	Treatment
Jansson-Knodell *el al.* (2020)	Retrospective Review	49	CD (41), UC (7), IBD (1)	Infliximab (35), Adalimumab (13), Certolizumab (1) AND Prednisone (12), Azathioprine (13), MTX (6), Tacrolimus (1), Budesonide (1)	Fever, weight loss, cough, night sweats, dyspnea	Disseminated (36), Pulmonary only (13)	CXR pulmonary infiltrate (23), CT chest w/pulmonary infiltrate (24), enlarged nodes (16); CT A/P: splenomegaly (9), abdominal LAD (7)	Amphotericin then itraconazole; second line antifungal used if side effect developed
Henke *et al.* (2019)	Case Report	1	UC	Infliximab	Progressive abdominal pain and distension	Disseminated	CXR unremarkable; CT multiple enlarged mesenteric lymph nodes and omental soft tissue thickening, suggestive of possible omental metastatic disease; colonoscopy, which showed a "single 2 cm discrete ulcer with heaped-up edges" in the distal ascending colon	Amphotericin then itraconazole
Krishna *et al.* (2019)	Case Report	1	UC c/b recurrent CDI	Infliximab	High grade fever, AMS, hypotension s/p fecal microbiota transplantation	Primary Colonic	CT: circumferential wall thickening of the proximal ascending colon to the cecum; sigmoidoscopy: diffuse colitis	Amphotericin then itraconazole
MacIsaac *el al.* (2019)	Case Report	1	CD	Infliximab and Azathioprine	Difficulty swallowing due to a painful, large, non-healing tongue ulcer. Fatigue, fever, chills, night sweats.	Disseminated	CT: ill defined irregular region in the left tongue, enlarged cervical lymph nodes bilaterally and focal consolidation and centrilobular nodules throughout both lungs. PET scan suspicious for primary oral cancer	Albendazole
Pabla *et al.* (2019)	Case Series	17	CD (9), UC (6), IBD (2)	Infliximab (9), Adalimumab (6), Golimumab (1), Tofacitinib (1) AND steroids (6)	n/a	Pulmonary (1), N/a (2), Disseminated (14)	n/a	Amphotericin then itraconazole (8), voriconazole to itraconazole (3), itraconazole only (6)
Bhut *et al.* (2018)	Case Report	1	CD	Azathioprine and prednisone	proximal myopathy, bleeding per rectum, and perianal ulceration, fever, and cervical lymphadenopathy	Disseminated	CT: bilateral adrenal enlargement and thickening of the ileocecal junction; Colonoscopy revealed rectosigmoid ulceration with stricture	Amphotericin then itraconazole

Bosshardt *et al.* (2018)	Case Report	1	CD	Adalimumab	abdominal pain, fatigue, fever and chills	Disseminated	CT abdomen: chronic thickening of the terminal ileum and cecum and new-onset ascites.	Amphotericin then itraconazole
Vicetti *et al.* (2018)	Case Report	1	CD	Adalimumab and 6-MP	abdominal pain, fatigue, nausea, decreased appetite, progressive abdominal distension, weight loss	Disseminated	MRI A/P: large amount of ascites with marked enhancement of the peritoneal lining	Itraconazole
Vergidis *et al.* (2015)	Retrospective Review	98	IBD	Infliximab, Adalimumab AND prednisone, MTX, 6-MP	n/a	Disseminated, pulmonary only	n/a	Amphotericin then azole step down therapy; azole only
Abou Zhar *et al.* (2013)	Case Report	1	CD	Infliximab, azathioprine, prednisone	Odynophagia, hoarseness, fever	Disseminated	Laryngoscopy: exophytic lesion arising from the edge of the epiglottis with extension to the laryngeal surface of the epiglottis and to the left aryepiglottic fold.	Amphotericin then itraconazole
Ahmad *et al.* (2012)	Case Report	1	CD	Infliximab	Fatigue, generalized weakness, cough, dyspnea	Pulmonary only	CXR: bilateral reticulonodular airspace disease	Amphotericin then itraconazole
Dotson *et al.* (2011)	Case Series	5	CD	Infliximab (4), Adalimumab (1) AND 6-MP (4), MTX (1)	Abdominal pain, mild SOB, fever, headache, fatigue, cough	Pulmonary only	CT A/P: Incidental pulmonary nodules (2); CT Chest: small round nodules in RML and RLL (1), cenrilobular nodules (1), reticular nodular pattern in lung base (1), mediastinal and hilar LN (2), lower lob interstitial process (1),	Itraconazole (3), Amphotericin (2)
Galandiuk and David (2008)	Case Report	1	CD	Infliximab and 6 MP	Bloody diarrhea and decreased stool caliber	Disseminated	CT Chest; proctoscopy	Proctocolectomy and end ileostomy THEN amphotericin and THEN itraconazole
Goulet and Iqbal (2003)	Case Report	1	CD	Infliximab and steroids	Diarrhea, Abdominal pain	Disseminated	Colonoscopy: right sided stricture with surrounding erythema, edema, and friability	Amphotericin

ABBRIEVIATIONS: 6-MP = 6 Mercaptopurine; CD = Crohn's Disease,;CDI = Clostridium difficile infections; CT A/P = Computed Tomography of Abdomen and Pelvis; CXR = Chest X-Ray; IBD = Inflammatory Bowel Disease; MeSH = Medical Subject Headings; MRI A/P = Magnetic Resonance Imaging of Abdomen and Pelvis; MTX = Methotrexate; UC = Ulcerative Colitis.

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