Histoplasmosis as a Complication of Inflammatory Bowel Disease Therapy: A Case Series

To the Editor:

Histoplasma capsulatum is a thermally dimorphic fungus endemic to North, Central, and South America and parts of Europe and Africa. Therapy with tumor necrosis factor (TNF)- α inhibitors has been noted to increase the risk of serious *Histoplasma* infection, with rates of infection noted to be 3 times more frequent in patients taking TNF- α inhibitors than tuberculosis.¹ Prior series of histoplasmosis infections associated with TNF- α inhibitors have included a combination of inflammatory bowel disease (IBD) and non-IBD diagnoses and have not described IBD-related outcomes. Here we report our institution's experience with this infection, with a focus on IBD management and outcomes.

Seventeen patients with IBD were identified through a retrospective chart review between November 2011 and January 2018 as having a diagnosis of disseminated or pulmonary histoplasmosis. The cases were predominately male (70.6%); 9 (52.9%) had Crohn's disease, 6 (35.3%) had ulcerative colitis, and 2 (11.8%) had indeterminate colitis. All but 1, who was on tofacitinib, were on a TNF- α inhibitors at the time of diagnosis. Ten patients completed antifungal treatment during follow-up after a mean duration (range) of 548 (92–948) days. There was no evidence of clinical recurrence of histoplasmosis in any of the 17 patients at a mean follow-up (range) of 757 (21–2229) days.

All patients initially stopped immunosuppressive therapy for IBD at histoplasmosis diagnosis. Ten (58.8%) patients required re-initiation of biologic therapy at a mean of 383 days after initiation of histoplasmosis therapy. Three patients were given intravenous immunoglobulin (IVIG) before restarting a biologic agent due to early recurrent IBD symptoms at a mean of 51 days postinfection.² Seven patients were treated with vedolizumab, 2 with anti-TNF agents, and 1 with ustekinumab after diagnosis of histoplasmosis. Complete details for each patient in the case series are in [Table 1](#).

Through preferential treatment with IVIG or the gut-specific agent vedolizumab, TNF- α inhibitor re-initiation was avoided in all but 2 patients. At the end of follow-up, 15 of 17 individuals maintained surgery-free clinical IBD remission without recurrence of histoplasmosis. Notably, this included patients with active disease at the time of infection, and only 1 ulcerative colitis patient in this series required surgery for refractory disease activity. In summary, our series supports that biologic therapy in IBD patients diagnosed with histoplasmosis can be safely re-instituted when necessary.

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TABLE 1. Case Series Detailed Overview

Age/Sex	IBD Type	Pre-histo Meds		Isolated Pulm Disease?	Histo Tx	Histo Tx Time, d	Post-histo Meds		Time to Biologic, d	IBD Clinical Remission
		Steroids	Biologic				IVIG, d to IVIG	Biologic		
21M	IC	N	ADA	N	Itra	354	N	-	-	Y
51F	UC	N	IFX	N	Itra	630	Y [39]	VDZ -> Sx	219	N -> Colectomy
42F	UC	N	IFX	N	Ampho -> Itra	557	N	-	-	Y
27M	CD	N	IFX	N	Ampho -> Itra	385	N	IFX	769	Y
21M	IC	Y	ADA	N/A	Itra	67	Y [5]	USK	60	Y
40M	CD	Y	ADA	Y	Itra -> Vori	116	N	-	-	Y
26M	CD	Y	IFX	N	Ampho -> Itra	327	N	-	-	Y
50F	CD	Y	ADA	N	Itra -> Vori -> Itra	346	Y [110]	VDZ -> IVIG	643	Y
32M	CD	N	IFX	N	Ampho -> Itra	792	N	ADA -> CZP -> VDZ	761	Y
35F	UC	N	TOF	Y	Ampho -> Itra	92	N	VDZ	637	Y
27M	CD	N	IFX	N	Itra	914	N	VDZ	165	Y
26M	UC	N	ADA	N	Ampho -> Itra	276	N	VDZ	297	Y
37M	CD	Y	ADA	N	Vori -> Itra	948	N	-	-	Y
44M	UC	Y	GOL	Y	Itra	61	N	-	-	Y
44M	UC	N	IFX	N/A	Itra	365	N	VDZ	147	Y
51F	CD	N	IFX	Y	Ampho -> Itra	730	N	VDZ -> Sx	135	N -> ICR
21M	CD	N	IFX	N	Ampho -> Itra	20	N	-	-	Y

Overview of all cases of IBD and histoplasmosis. Each row details the IBD characteristics and histoplasmosis treatment course of each included case (n = 17).

Abbreviations: ADA, adalimumab; Ampho, amphotericin; CD, Crohn's disease; CZP, certolizumab; GOL, golimumab; histo, histoplasmosis; IC, indeterminate colitis; ICR, ileocolic resection; IFX, infliximab; Itra, itraconazole; N/A, patients were diagnosed by urinary antigen alone; Sx, surgery; TOF, tofacitinib; UC, ulcerative colitis; VDZ, vedolizumab; Vori, voriconazole.