

# Fever of Unknown Origin in an Immunosuppressed Patient with Crohn's Disease: An Unusual Cause

by Leyla J. Ghazi, Raymond K. Cross

**Chronic immunosuppressive exposure, including conventional and biologic agents have been shown to increase the risk of infection especially in individuals with inflammatory bowel disease (IBD) receiving combination therapies. Practitioners should be cognizant of these risks in order to provide best available care. We illustrate a case of an immunosuppressed patient with Crohn's disease who did not have an identifiable organic cause for fever of unknown origin (FUO). Our patient presented with high fevers, positive blood cultures, and a variety of normal imaging studies. An unexpected diagnosis of Munchausen syndrome was brought to light after an extensive evaluation proved to be unrevealing. This case underscores the importance of formulating a broad differential diagnosis in IBD patients who develop fevers while on chronic immunosuppressants.**

## CASE REPORT

**A** 33-year-old female with perforating ileal Crohn's disease (CD) with two prior intestinal resections secondary to symptomatic stenoses was hospitalized at our institution for evaluation of abdominal pain and fever of unknown origin (FUO). She was taking adalimumab 40 mg subcutaneously weekly for treatment of her Crohn's disease. She presented with a chief complaint of acute severe epigastric abdominal pain and watery diarrhea, associated with shortness of breath, diaphoresis, and palpitations. She described the pain as episodic and short-lived, resolving within minutes of onset. Temperatures ranged from 99 to 102 degrees Fahrenheit (F) with no clear pattern. On exam-

ination, she was noted to have marked epigastric tenderness. Initial laboratory studies were unrevealing. Her adalimumab was held upon admission to the hospital and broad spectrum antibiotics (piperacillin-tazobactam and vancomycin) were started.

An abdominal ultrasound showed a hypoechoic mildly enlarged liver without evidence of gallstones or acute cholecystitis; however a sonographic Murphy's sign was noted. Blood cultures grew *Pseudomonas* species, not aeruginosa and *Candida guilliermondii*. A hepatobiliary scan (HIDA) was normal with a gallbladder ejection fraction of 79%.

Multiple stool studies for typical and atypical organisms were negative. Endoscopic evaluation including a colonoscopy to the terminal ileum showed no evidence of active Crohn's disease. Upper endoscopy revealed *Candida* Esophagitis for which intravenous fluconazole was started. Biopsies taken for *Herpes simplex virus* (HSV) and *Cytomegalovirus* (CMV) were negative. CT enterography with oral and

---

Leyla J. Ghazi, M.D. and Raymond K. Cross, M.D., M.S., University of Maryland School of Medicine, Department of Medicine, Division of Gastroenterology and Hepatology, Veteran's Affairs Maryland Health Care System Baltimore, Baltimore, MD.

intravenous contrast showed no active Crohn's jejunitis, ileitis or stricture.

Because of intermittent, sporadic spiking fevers as high as 103°F, her pre-existing Port-A-Cath was removed. Alternative central venous access was obtained to continue antibiotics for the aforementioned bacteremia. An echocardiogram did not reveal endocarditis, and a tuberculin skin test (PPD) was negative. As fevers persisted despite negative successive blood cultures, a work-up for occult malignancy was initiated. A positron emission test/computed tomography (PET/CT) of the chest revealed diffuse and abnormal prominence of interstitial markings throughout both lungs, and borderline enlarged prevascular, pretracheal, and subcarinal lymph nodes, without 18-fluorodeoxyglucose (FDG) avidity. Bronchoscopy with bronchial cultures for bacterial and fungal organisms and malignant cells was negative. To complete the patient's malignancy evaluation, hematology performed a bone marrow biopsy which showed normocellular marrow with trilineage hematopoiesis.

As her evaluation progressed, several unexpected issues were brought to light. On several instances, the patient's roommate expressed concern about the patient's prolonged bathroom trips. Also, several normal saline and heparin syringes were found in the patient's possession. She admitted to using her home supply to flush her Medi-Port and was explicitly asked to stop this behavior. Psychiatry was consulted to evaluate the possibility of factitious disorder, but felt that it was unlikely. After three inpatient weeks of persistent fever with negative blood cultures, gram-negative rods speciated as *Sphingomonas paucimobilis* and *Pseudomonas fluorescens* grew simultaneously from blood drawn from her central venous catheter and a peripheral site. Shortly after, the patient was found in her room asleep with a syringe hanging from her triple lumen port. She was confronted and admitted to continued self-injecting heparin and saline; she denied contamination with hospital toilet water or outside plant species. Her central access was removed after which her fevers abated.

## DISCUSSION

Immunosuppressants and biologics are commonly used for the treatment of moderate to severely active

IBD. IBD patients who have been exposed to immunosuppressants are at a greater risk of infection and malignancy in comparison to IBD patients not taking immunosuppressants. Azathioprine and 6-mercaptopurine are associated with an increased risk of bone marrow suppression, neutropenic infections/sepsis, and lymphoproliferative disorders (1–3). Anti-tumor necrosis factor (anti-TNF) therapy is associated with an increased risk of opportunistic infections including tuberculosis, *Pneumocystis pneumonia*, and fungal infections, such as *Histoplasmosis*, *Aspergillosis*, and *Cryptococcus* (2,4–5). Data from the Crohn's Therapy, Resource, Evaluation, and Assessment Tool Registry (TREAT) registry does not demonstrate a significant increased risk of infection in infliximab-treated patients when adjusting for confounding variables such as concomitant steroid use; however the most recent analysis reported a strong trend towards a higher risk of serious infection in patients exposed to infliximab (6). Drug regimens which employ multiple immunosuppressants have been associated with an even higher risk of opportunistic infections (OI). Marehbian *et al.* found that CD patients exposed to combination immunosuppressant therapy had a 7-fold increased risk of tuberculosis than CD patients on no therapy. Further, the overall risk of OI was higher in the group of patients on combination therapy compared to patients on monotherapy (2). Given the above data, providers of patients with IBD must be aware of the risks of infection associated with immunosuppression (especially multiple drugs) and become vigilant in evaluating for opportunistic infections when suspicious symptoms occur (7).

We present the case of an immunosuppressed patient with Crohn's disease who did not have an identifiable organic cause for FUO; an alternative diagnosis was brought to light. Munchausen syndrome is the most severe type of factitious disorder. It is a disorder in which a person repeatedly acts as if he or she has a physical or mental problem when, in truth, they have deliberately produced or exaggerated their symptoms. They might lie about symptoms, hurt themselves to bring on symptoms, or alter diagnostic tests (such as contaminating blood or urine samples). Both biological and psychological factors may play a role in the development of this syndrome. Red flags for Mun-

### A CASE REPORT

chausen syndrome include inconsistencies in medical history, symptoms that are not controllable and that worsen once treatment is begun, extensive knowledge of medical terminology and textbook description of illnesses, presence of symptoms only when the patient is alone or not being observed, and reluctance by the patient to allow health care professionals to meet with family members or conduct certain procedures (i.e. remove access).

In our case, the organisms that grew from our patient's blood cultures were known to be isolated from land, water, and soil habitats; further these organisms are associated with heparin flushes suggesting deliberate contamination by our patient. Diagnosing Munchausen syndrome is very difficult. Health care providers must rule out physical illnesses before entertaining a psychiatric disorder such as Munchausen syndrome. This may require conducting a number of diagnostic tests and procedures which not only place the patient at risk, but also result in substantial health

care costs. Patients can deceive the most experienced psychiatric specialist (8). Our patient exhibited several red flags for Munchausen syndrome; nonetheless an extensive evaluation for fever and abdominal pain was indicated in a patient with Crohn's disease being treated with biologic drug therapy.

Chronic immunosuppressive therapies, including conventional and biologic agents have been shown to increase the risk of infection especially in individuals receiving combination therapies. Whether there is an additional risk associated with greater disease severity or other co-morbidities is unclear. However, it is apparent that IBD practitioners should be cognizant of such risks, and provide appropriate pre-drug counseling and education, as well as employ routine preventative screening for high-risk patients. Suspected post-treatment infectious complications require urgent attention. We suggest temporary discontinuation of the inciting agent, evaluation for the causative organism, and consultation with appropriate specialist services. Our case illustrates a classic case of Munchausen's syndrome after meticulous pursuit of a source of infection was unrevealing. ■

## PRACTICAL GASTROENTEROLOGY

### R E P R I N T S

*Practical Gastroenterology* reprints are valuable, authoritative, and informative. Special rates are available for quantities of 100 or more.

For further details on rates or to place an order:

*Practical Gastroenterology*

99B Main Street

Westhampton Beach, NY 11978

Phone: 631-288-4404, Fax: 631-288-4435

Or visit our website at:

[www.practicalgastro.com](http://www.practicalgastro.com)

#### References

1. Connell WR, Kamm MA, Ritchie JK et al. Bone marrow toxicity caused by azathioprine in inflammatory bowel disease: 27 years of experience. *Gut* 1993;34:1081-5.
2. Marebian J, Arright M, Haas S, Tian H, Sandborn WJ. Adverse events associated with common therapy regimens for moderate-to-severe Crohn's disease. *Am J of Gastroenterology* 2009
3. Dayharsh GA, Loftus EV Jr, Sandborn WJ et al. Epstein-Barr virus-positive lymphoma in patients with inflammatory bowel disease treated with azathioprine or 6-mercaptopurine. *Gastroenterology* 2002;122:72-7.
4. Beaugerie L, Brousse N, Bouvier AM, Colombel JF, Lémann M, Cosnes J, Hébuterne X, Cortot A, Bouhnik Y, Gendre JP, Simon T, Maynadié M, Hermine O, Faivre J, Carrat F; for the CESAME Study Group. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet*. 2009 7;374(9701):1617-25.
5. Kaur N, Mahl TC. Pneumocystis jiroveci (carinii) pneumonia after infliximab therapy: a review of 84 cases. *Dig Dis Sci* 2007; 52:1481-4.
6. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Chen DM, Pritchard ML, Sandborn WJ. Safety of Infliximab and Other Crohn's Disease Therapies: TREAT Registry Data. *Clin Gastroenterol Hepatol*. 2006;4(5):621-30.
7. Toruner M, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Orenstein R, Sandborn WJ, Colombel JF, Egan LJ. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology*. 2008;134(4):929-36.
8. Stern T. Massachusetts General Hospital Comprehensive Clinical Psychiatry, 1st ed. URL: <http://www.mdconsult.com.proxyhs.researchport.umd.edu/das/book/0/view/1657/235.html>.