Govaresh/ Vol.28/ No.3/Autumn 2023; 196-200

Misdiagnosis of a Patient with Terminal Ileitis; A Case Report

Case Report

Pedram Beigvand[1], Arman Azarpour[2], Niloofar Moradi[3], Seyed Hasan Abedi[1*]

[1]Gastroenterologist, Department of Internal Medicine, School of Medicine, Babol University of Medical Sciences & Health Services, Babol, I.R.Iran
[2]Medical Student, School of Medicine, Babol University of Medical Sciences & Health Services, Babol, I.R.Iran
[3]Senior Assistant of Pediatric Diseases, School of Medicine, Babol University of Medical Sciences & Health Services, Babol, I.R.Iran

ABSTRACT

Abdominal tuberculosis is one of the most critical and life-threatening ailments affecting the digestive system. Distinguishing it from other gastrointestinal disorders is paramount due to the potential complications of treatment overlap. Therapies such as corticosteroids and anti-tumor necrotic factor (anti-TNF) agents, effective against various diseases, can unintentionally exacerbate and propagate tuberculosis.

The case in focus involves a 22-year-old man initially presented with abdominal pain. The clinical, endoscopic, and pathological assessments led to a diagnosis of Crohn's disease. Subsequently, the patient underwent treatment. However, 6 months into the treatment, the patient developed abdominal distension and ascites, necessitating hospital admission and re-evaluation.

A comprehensive series of investigations revealed a diagnosis of military tuberculosis. The patient was subsequently administered four anti-tuberculosis drugs, resulting in a complete resolution of symptoms. This case underscores a crucial point: administering anti-TNF agents can inadvertently contribute to tuberculosis dissemination. Hence, a meticulous assessment to exclude tuberculosis before initiating such treatment is paramount.

Keywords:
Tuberculosis, Crohn's disease, Terminal ileitis, Anti-TNF agents

Please cite this paper as:
Beigvand P, Azarpour A, Moradi N, Abedi SH. Misdiagnosis of a patient with terminal ileitis; a case report. *Govaresh* 2023;28: 196-200.

Corresponding author:
Seyed Hasan Abedi, MD
Department of Internal Medicine, School of Medicine,
Babol University of Medical Sciences &
Health Services, Babol, I.R.Iran
Tel :+98 1132238301
Fax :+98 1132238309
Email : h.abedi@mubabol.ac.ir

Received: 20 May 2023
Revised: 14 Aug. 2023
Accepted: 15 Aug. 2023

INTRODUCTION

Intestinal tuberculosis (TB), a rare disease in the 21st century, has unfortunately faded from the daily landscape of medical practice. Abdominal TB has increased over the last two decades, particularly in regions like the United Kingdom, Asia, and other tropical areas (1-3). A 2015 World Health Organization (WHO) report states TB affects 16 out of every 100 000 patients (4,5).

Despite advancements, it poses a significant health challenge in developing countries. Interestingly, North America has witnessed a surge in TB cases since the mid-1980s, attributed to factors such as immigration, human immunodeficiency virus (HIV) co-infection, and the emergence of multidrug-resistant TB (6).

The landscape of treatments used in inflammatory bowel diseases has also evolved. The employment of anti-tumor

necrotic factor (anti-TNF) agents, including adalimumab and infliximab, as monotherapy or in combination with other immunosuppressants has gained popularity in the management of conditions like Crohn's disease (7).

A comparative analysis against the general population reveals a well established heightened risk of active TB in individuals utilizing anti-TNF agents (8-10). Intriguingly, intracellular pathogens like TB incite a robust immune response in humans, in which TNF alpha plays a pivotal role. It orchestrates macrophage activation and ongoing cellular recruitment. This role assumes greater significance following anti-TNF therapy, particularly in rheumatoid arthritis and similar ailments (11).

In this paper, we highlight a case of intestinal TB that was initially misdiagnosed as Crohn's disease and subsequently treated with adalimumab. Our focus also underscores the critical significance of accurately distinguishing pure terminal ileitis to minimize misdiagnosis and mitigate potential complications associated with such cases.

CASE REPORT

The patient, a 22-year-old single man, presented to the Emergency Department with a gradual onset of abdominal distension and mild peri-umbilical abdominal pain that had been ongoing for about a week. The pain was constant and not radiating. Interestingly, the pain worsened after eating and improved following defecation, though it was not dependent on body position. Alongside these symptoms, he experienced bloating, sweating, and weight loss, but he did not exhibit any fever.

Regarding his medical history, the patient had a confirmed diagnosis of Crohn's disease, established 6 months prior, and had been undergoing treatment with adalimumab. Pertinently, his medical records included a colonoscopy report. This report indicated the presence of three aphthoid ulcers in the terminal ileum, while the rest of the colon displayed a normal appearance. A detailed analysis of the biopsy sample revealed significant chronic inflammation, infiltration of various immune cells such as lymphoplasma cells and polymorphonuclear neutrophils (PMN), and a notable abundance of eosinophils. Additionally, lymphoid aggregation was observed along with fibrinoleukocytic exudate. Furthermore, a small granuloma was identified within the lamina propria. The pathologist noted that these findings were indicative of Crohn's disease. Following a thorough assessment that included screening for latent TB using a negative tuberculin skin test and an evaluation for hepatitis B infection, treatment with adalimumab was started, administered at a two-week interval, a regimen initiated six months earlier.

It is worth noting that the patient was a non-smoker, and his family history did not reveal any distinctive medical conditions.

The patient's hemodynamic status remained stable, and he had no fever. During the physical examination, evident signs included abdominal distension and a pervasive dullness upon percussion. However, no tenderness or guarding was detected.

Following admission, abdominal ultrasonography showed substantial fluid with internal echogenicity within the peritoneal cavity, alongside right-sided pleural effusion.

The results of the laboratory tests were as follows: a white blood cell (WBC) count of 4,800/microliter, a hemoglobin level of 9.4 g/dL, a mean corpuscular volume of 71 fL, a red blood cell (RBC) count of 4.35×10^6/microliter, and a platelet count of 393,000/microliter. Notably, a sample of ascitic fluid was collected, and its analysis revealed a low serum-to-ascites albumin gradient (SAAG), accompanied by an ascitic protein level of 5 g/dL. The fluid's WBC count was 2,500/microliter, with lymphocytes comprising the majority (80%). Both the gram staining and cytology results were negative. Additionally, the adenosine deaminase (ADA) level was measured in the fluid, and it was elevated at 56 U/L, exceeding the normal threshold of 40 U/L. Given the characteristics of the ascitic fluid, the primary differential diagnoses considered were TB peritonitis and peritoneal carcinomatosis.

Comprehensive chest and abdominopelvic computed tomography (CT) were conducted to investigate the condition further. The lung CT revealed bilateral pleural effusion and numerous interstitial nodules in both lungs. These nodules exhibited a maximum diameter of 5.5 mm. On the other hand, the abdominopelvic CT unveiled multiple small, round foci distributed diffusely within the liver parenchyma. While these findings suggested

a metastatic process, they were less likely to represent infectious abscesses. A similar pattern of findings was observed in the upper lobe of the spleen. Moreover, massive ascites were identified within the abdominal cavity and the pelvis.

Furthermore, the abdominopelvic CTs demonstrated the presence of multiple mesenteric lymph nodes, with the largest short-axis diameter measuring up to 10 mm. Additionally, the omentum in the upper abdominal regions exhibited thickening and nodularity, displaying an appearance consistent with omental seeding. Based on the gathered findings and in consultation with the patient, a decision was made to proceed with a laparoscopy, during which a biopsy sample of the peritoneum would taken. The surgeon's observations included notable adhesions and omental seeding that bore a resemblance to carcinomatous lesions. Additionally, multiple lesions were observed on the liver's surface, indicating a potential for metastases. Both the omental lesions and liver lesions were subjected to biopsy sampling.

While awaiting the pathology report, upper gastrointestinal endoscopy and colonoscopy were performed to identify any potential source of metastasis. However, no evident lesions were detected through these procedures.

Subsequently, upon examining the biopsied liver and peritoneal tissues, a pathological assessment revealed the presence of a granulomatous inflammatory process with sporadic necrosis. These characteristics were indicative of a condition closely resembling TB. As a result, the patient was diagnosed with TB and subsequently received appropriate treatment. Throughout follow-up, the patient's condition demonstrated gradual improvement.

DISCUSSION

It is well established that individuals undergoing anti-TNF therapy are more susceptible to TB (12). Based on various studies, screening for latent TB before initiating anti-TNF therapy is considered essential (13). The WHO recommends three specific tests for this purpose: the TB skin test (TST), as well as two interferon-ϒ releasing assays (IGRAs) known as QuantiFERON-TB Gold In-Tube and T-SPOT TB (14). Notably, IGRA has shown greater sensitivity and specificity than TST in diagnosing latent TB and detecting new TB cases (15).

Indeed, many TB cases associated with TNF-alpha inhibitors are thought to arise from the reactivation of latent TB infection (LTBI). This highlights the importance of screening for LTBI before initiating therapy with TNF-alpha inhibitors. Much like TB that emerges with other forms of immunosuppression, TB linked to TNF-alpha inhibitors exhibits a heightened tendency to involve extrapulmonary sites and may present in a disseminated manner, in contrast to TB cases without immunosuppression (13). As a result, conventional TB diagnostic assays, such as chest radiography and sputum smears tailored for symptomatic pulmonary TB, do not provide substantial assistance in these scenarios (15).

A recommended course of action for patients who return a positive TB skin test is to administer chemoprophylaxis with isoniazid for 6-9 months or rifampin for 3-4 months (16). Typically, the initiation of anti-TNF therapy should be delayed until 2 months after the completion of chemoprophylaxis. During anti-TNF therapy, vigilant patient monitoring is crucial, extending up to 12 months after the conclusion of chemoprophylaxis (6).

TB infection follows a unique course within the body. Instead of being outright eradicated by the immune system, the bacterium responsible for TB is often contained within granulomas. These granulomas act as quarantine, enabling the bacterium to persist within the body for extended periods, ranging from years to decades. Importantly, TNF plays a significant role in forming and maintaining granulomas. It orchestrates the recruitment of various immune cells and contributes to the structural integrity of these granulomas. Without TNF, the granulomas may lose their ability to effectively control the TB infection, potentially leading to the reactivation of the dormant bacteria (17,18).

Furthermore, TNF's influence extends to various active TB symptoms and outcomes. It is responsible for driving some of the hallmark signs of active TB, such as weight loss, night sweats, and the destruction of tissues. These effects highlight TNF's complex role in both the containment and the manifestation of TB infection (19).

Despite advancements in diagnosis and treatment, a comprehensive guideline outlining the precise approach for diagnosing and treating symptomatic terminal ileitis has

yet to be established (1-3). A broad spectrum of potential conditions must be considered when confronted with a patient exhibiting isolated terminal ileitis. This includes but is not limited to Crohn's disease, intestinal TB, non-specific inflammatory bowel disease, drug-induced ileitis, radiation-induced ileitis, other forms of granulomatous inflammation, endometriosis, and backwash ileitis in patients with ulcerative colitis, angiodysplasia, foreign bodies, or tumors (1,2,20-28).

While TB and Crohn's disease can manifest with similar symptoms, such as diffuse abdominal pain, pain in the right iliac fossa, or peri-umbilical pain, there are distinctive characteristics that can aid in accurate diagnosis. Variables like the duration of symptoms, specific features, or the presence of extra-intestinal manifestations can provide valuable clues for arriving at the correct diagnosis (1,2,20,21,23,26,29-32). For example, lower gastrointestinal bleeding tends to be more prevalent in Crohn's disease, and its occurrence might point toward Crohn's rather than TB (1,2,20,21,23,26,29-32).

Distinguishing between Crohn's disease and TB based on endoscopic features can pose a challenge due to their similarities (33). The endoscopic patterns associated with each condition provide crucial clues for differentiation. For TB, a distinctive pattern involves ulcers arranged transversely, enveloped by diffusely inflamed and nodular mucosa, alongside a patulous ileocecal valve. On the other hand, Crohn's disease tends to exhibit features like aphthous longitudinal ulcers, deep and fissuring in nature, a cobblestone appearance, normal mucosa surrounding the ulcers, and structuring of the ileocecal valves (34).

Pathologically, TB presents multiple, large, confluent granulomas that may display caseation or central necrosis. In contrast, Crohn's disease-associated granulomas are generally smaller, less numerous, and lack necrosis. For definitive diagnosis, acid-fast bacilli can be identified in intestinal biopsies, followed by polymerase chain reaction (PCR) testing (34).

The utmost importance lies in accurately diagnosing the underlying cause of ileitis, as the treatment strategies for Crohn's disease and TB differ significantly. Incorrect diagnosis and subsequent treatment could lead to unnecessary harm, complications, and even death.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

REFERENCES

1. Burke KA, Patel A, Jayaratnam A, Thiruppathy K, Snooks SJ. Diagnosing abdominal tuberculosis in the acute abdomen. *Int J Surg* 2014;12(5):494-9. doi: 10.1016/j.ijsu.2014.02.006
2. Wijewantha HS, de Silva AP, Niriella MA, Wijesinghe N, Waraketiya P, Kumarasena RS, et al. Usefulness of routine terminal ileoscopy and biopsy during colonoscopy in a tropical setting: a retrospective record-based study. *Gastroenterol Res Pract* 2014;2014:343849. doi: 10.1155/2014/343849
3. Niriella MA, de Silva AP, Dayaratne AH, Ariyasinghe MH, Navarathne MM, Peiris RS, et al. Prevalence of inflammatory bowel disease in two districts of Sri Lanka: a hospital based survey. *BMC Gastroenterol* 2010;10:32. doi: 10.1186/1471-230x-10-32
4. World Health Organization (WHO). *World Health Organization Global Tuberculosis Report 2013*. Geneva, Switzerland: WHO; 2019.
5. World Health Organization (WHO). *Global Tuberculosis Report 2013*. WHO; 2013.
6. Allahyar Torkaman MR, Nasiri MJ, Farnia P, Shahhosseiny MH, Mozafari M, Velayati AA. Estimation of recent transmission of *Mycobacterium tuberculosis* strains among Iranian and Afghan immigrants: a cluster-based study. *J Clin Diagn Res* 2014;8(9):DC05-8. doi: 10.7860/jcdr/2014/8886.4864
7. Wang MH, Liu X, Shen B. Disseminated tuberculosis in a patient taking anti-TNF therapy for Crohn's disease. *ACG Case Rep J* 2015;3(1):45-8. doi: 10.14309/crj.2015.97
8. D'Haens GR. Top-down therapy for IBD: rationale and requisite evidence. *Nat Rev Gastroenterol Hepatol* 2010;7(2):86-92. doi: 10.1038/nrgastro.2009.222
9. Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Ann Rheum Dis* 2010;69(3):522-8. doi: 10.1136/ard.2009.118935
10. Scrivo R, Armignacco O. Tuberculosis risk and anti-tumour necrosis factor agents in rheumatoid arthritis: a critical appraisal of national registry data. *Int J Rheum Dis* 2014;17(7):716-24. doi: 10.1111/1756-185x.12375
11. Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, Montero D, Pascual-Gómez E, Mola EM, et al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum* 2005;52(6):1766-72. doi: 10.1002/art.21043
12. Wallis RS, Ehlers S. Tumor necrosis factor and granuloma biology: explaining the differential infection risk of etanercept and infliximab. *Semin Arthritis Rheum* 2005;34(5

Suppl1):34-8. doi: 10.1016/j.semarthrit.2005.01.009
13. Sartori NS, de Andrade NPB, da Silva Chakr RM. Incidence of tuberculosis in patients receiving anti-TNF therapy for rheumatic diseases: a systematic review. *Clin Rheumatol* 2020;39(5):1439-47. doi: 10.1007/s10067-019-04866-x
14. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001;345(15):1098-104. doi: 10.1056/NEJMoa011110
15. Godoy P. Guidelines on controlling latent tuberculosis infection to support tuberculosis elimination. *Rev Esp Sanid Penit* 2021;23(1):28-36. doi: 10.18176/resp.00028
16. Huang TH, Wei YC, Lan CE. QuantiFERON®-TB Gold test conversion in a psoriatic patient with pleural tuberculosis one year after adalimumab treatment. *Kaohsiung J Med Sci* 2018;34(3):179-80. doi: 10.1016/j.kjms.2017.11.001
17. Sterling TR, Njie G, Zenner D, Cohn DL, Reves R, Ahmed A, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *Am J Transplant* 2020;20(4):1196-206. doi: 10.1111/ajt.15841
18. Scott Algood HM, Lin PL, Flynn JL. Tumor necrosis factor and chemokine interactions in the formation and maintenance of granulomas in tuberculosis. *Clin Infect Dis* 2005;41 Suppl 3:S189-93. doi: 10.1086/429994
19. Gardam MA, Keystone EC, Menzies R, Manners S, Skamene E, Long R, et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. *Lancet Infect Dis* 2003;3(3):148-55. doi: 10.1016/s1473-3099(03)00545-0
20. Keane J. TNF-blocking agents and tuberculosis: new drugs illuminate an old topic. *Rheumatology (Oxford)* 2005;44(6):714-20. doi: 10.1093/rheumatology/keh567
21. Dilauro S, Crum-Cianflone NF. Ileitis: when it is not Crohn's disease. *Curr Gastroenterol Rep* 2010;12(4):249-58. doi: 10.1007/s11894-010-0112-5
22. Kedia S, Kurrey L, Pratap Mouli V, Dhingra R, Srivastava S, Pradhan R, et al. Frequency, natural course and clinical significance of symptomatic terminal ileitis. *J Dig Dis* 2016;17(1):36-43. doi: 10.1111/1751-2980.12307
23. Hermon-Taylor J, Barnes N, Clarke C, Finlayson C. *Mycobacterium paratuberculosis* cervical lymphadenitis, followed five years later by terminal ileitis similar to Crohn's disease. *BMJ* 1998;316(7129):449-53. doi: 10.1136/bmj.316.7129.449
24. Anand AC, Patnaik PK, Bhalla VP, Chaudhary R, Saha A, Rana VS. Massive lower intestinal bleeding--a decade of experience. *Trop Gastroenterol* 2001;22(3):131-4.
25. Wani RA, Parray FQ, Bhat NA, Wani MA, Bhat TH, Farzana F. Nontraumatic terminal ileal perforation. *World J Emerg Surg* 2006;1:7. doi: 10.1186/1749-7922-1-7
26. Leung VK, Law ST, Lam CW, Luk IS, Chau TN, Loke TK, et al. Intestinal tuberculosis in a regional hospital in Hong Kong: a 10-year experience. *Hong Kong Med J* 2006;12(4):264-71.
27. Kapan M, Karabicak I, Aydogan F, Kusaslan R, Kisacik B. Intestinal perforation due to miliary tuberculosis in a patient with Behcet's disease. *Mt Sinai J* Med 2006;73(5):825-7.
28. Surlin V, Georgescu E, Comănescu V, Mogoantă SS, Georgescu I. Ileal iterative spontaneous perforation from foreign body granuloma: problems of histopathologic diagnosis. *Rom J Morphol Embryol* 2009;50(4):749-52.
29. Yadav D, Garg PK. Spectrum of perforation peritonitis in Delhi: 77 cases experience. *Indian J Surg* 2013;75(2):133-7. doi: 10.1007/s12262-012-0609-2
30. Amarapurkar DN, Patel ND, Rane PS. Diagnosis of Crohn's disease in India where tuberculosis is widely prevalent. *World J Gastroenterol* 2008;14(5):741-6. doi: 10.3748/wjg.14.741
31. Park JK, Lee SH, Kim SG, Kim HY, Lee JH, Shim JH, et al. [A case of intestinal tuberculosis presenting massive hematochezia controlled by endoscopic coagulation therapy]. *Korean J Gastroenterol* 2005;45(1):60-3. [Korean].
32. Surewad G, Lobo I, Shanbag P. Pulmonary and ileal tuberculosis presenting as Fever of undetermined origin. *J Clin Diagn Res* 2014;8(10):PD01-2. doi: 10.7860/jcdr/2014/9695.4998
33. Gan H, Mely M, Zhao J, Zhu L. An analysis of the clinical, endoscopic, and pathologic features of intestinal tuberculosis. *J Clin Gastroenterol* 2016;50(6):470-5. doi: 10.1097/mcg.0000000000000514
34. Almadi MA, Ghosh S, Aljebreen AM. Differentiating intestinal tuberculosis from Crohn's disease: a diagnostic challenge. *Am J Gastroenterol* 2009;104(4):1003-12. doi: 10.1038/ajg.2008.162