

Miliary tuberculosis as a severe adverse reaction to the use of adalimumab in Crohn's disease: a case report

Tuberculose miliar como reação adversa grave ao uso do adalimumab na doença de Crohn: um relato de caso

João Eugênio Loureiro Lopes¹, Helena Demuner Vallandro¹, Marina Dadalto Scarpati¹,
Bruna Barcellos Chaia¹, Vitor Lorencini Belloti¹, Felipe Bertollo Ferreira¹

Abstract

Introduction: Crohn's disease is an inflammatory bowel disease (IBD) that initiates a chronic idiopathic intestinal inflammatory process, leading to a variety of clinical symptoms with chronic diarrhea as the main one. Diagnosis is built from a combination of clinical, laboratory and endoscopic data. The treatment involves immunobiological drugs, such as adalimumab and due to its immunosuppressive effect, it must be administered with caution, because it is able to activate latent foci of infection, such as tuberculosis (TB), in susceptible individuals. **Objective:** To report a miliary tuberculosis case originated as an adverse reaction to the use of adalimumab and to make the medical community aware of the risks of administering immunobiological therapy. **Case report:** A 31-year-old male, diagnosed with Crohn's Disease, undergoing immunobiological treatment with adalimumab, is admitted in the emergency department with acute respiratory and systemic symptoms. During hospitalization, despite the investigation of alcohol-acid resistant bacillus (BAAR) in sputum showing three different samples with negative results, the computerized tomography (CT) of the chest showed a pattern suggestive of miliary tuberculosis, in addition to a bronchoalveolar lavage with a positive test for *Mycobacterium tuberculosis*. After the diagnosis of miliary TB was confirmed, treatment with rifampicin, isoniazid, pyrazinamide and ethambutol was started. **Conclusion:** Considering the high mortality and negative impacts of miliary tuberculosis, it is essential that all patients with IBD on immunobiological treatment are screened for latent infection through chest radiography and PPD. However, even with regular screening and registration of previous vaccinations, the possibility of miliary

tuberculosis cannot be ruled out in this profile of patients with unspecific clinical conditions.

Keywords: Adalimumab, Tuberculosis, Drug-related side effects and adverse reactions

Resumo

Introdução: A doença de Crohn é uma doença inflamatória intestinal (DII) que inicia um processo inflamatório crônico idiopático intestinal, levando a um quadro clínico variável cujo principal sintoma é a diarreia crônica. O diagnóstico é feito a partir da combinação de dados clínicos, laboratoriais e exames endoscópicos. Após confirmado o diagnóstico, o tratamento pode envolver classes medicamentosas como imunobiológicos. Em relação ao uso de imunobiológicos, como o adalimumabe, deve-se ter cautela pelo seu efeito imunossupressor, que pode, em indivíduos susceptíveis, ativar focos latentes de infecção, como os de tuberculose (TB). **Objetivo:** Relatar um caso de tuberculose miliar como reação adversa ao uso de adalimumabe e conscientizar a comunidade médica quanto aos riscos da administração de terapia imunobiológica. **Relato de caso:** Paciente do sexo masculino, 31 anos, com diagnóstico de Doença de Crohn em acompanhamento ambulatorial com terapia imunobiológica com adalimumab, é admitido na emergência com quadro agudo de sintomas respiratórios e sistêmicos. Durante a investigação hospitalar, apesar de pesquisa do bacilo álcool-ácido resistente (BAAR) no escarro ter apresentado três amostras negativas, a tomografia computadorizada (TC) de tórax apresentava padrão sugestivo de tuberculose miliar, além de um lavado broncoalveolar com pesquisa positiva para *Mycobacterium tuberculosis*. Confirmado o diagnóstico de TB miliar, o tratamento foi iniciado com rifampicina, isoniazida, pirazinamida e etambutol. **Conclusão:** Levando em consideração a alta mortalidade e os impactos negativos da tuberculose miliar, é imprescindível que todos os pacientes com DII em uso de imunobiológicos sejam rastreados para infecção latente, através da radiografia de tórax e teste tuberculínico (PPD). Entretanto, mesmo com o rastreamento regular e registro de vacinação prévia, a possibilidade de tuberculose

1. Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória (EMESCAM). Curso de Medicina. Vitória – ES – Brasil
Intitution: Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória (EMESCAM). Curso de Medicina. Vitória – ES – Brasil

Correspondence address: João Eugênio Loureiro Lopes. Av. Nossa Sra. da Penha, 2190 - Bela Vista – 29027-502 - Vitória – ES – Brasil. E-mail: joao.eugenioll@hotmail.com

miliar ainda não pode ser descartada em quadros clínicos inespecíficos neste perfil de pacientes.

Palavras chave: *Adalimumab, Tuberculose, Efeitos colaterais e reações adversas relacionados a medicamentos*

Introduction

The inflammatory bowel disease (IBD) corresponds to an idiopathic chronic inflammatory intestinal process, represented by Crohn's disease (CD) and ulcerative colitis (UC). The aggressive mechanism occurs through the interaction between genetic, autoimmune, environmental, and infectious factors that triggers the appearance of lesions with varying characteristics in the intestine, that distinguish the CD from UC⁽¹⁻²⁾.

The clinical condition varies with the activity and remission periods of the disease, as well as its involvement pattern, manifesting itself usually as chronic diarrhea, which is present in 70% of the cases, that could be associate with other symptoms such as abdominal pain and weight loss, in addition to extraintestinal manifestations in 20% of the cases⁽³⁻⁴⁾. The diagnosis is based on the combination of these clinical data, associated with laboratorial and endoscopic data, through a colonoscopy and histopathologic study that can distinguish the inflammatory bowel disease⁽⁵⁻⁶⁾.

The inflammatory bowel diseases treatment aims its remissions, through clinical and laboratorial criteria that includes the C-reactive protein (PCR) and fecal calprotectin, endoscopic and histopathologic data as inflammatory proof⁽⁷⁾. Therefore, the remission is achieved through medication therapy, that includes classes such as aminosalicylates, corticosteroids, immune modifiers and immunobiological⁽⁸⁾.

Regarding to immunobiological therapy, the medication choice must be personalized and in accordance with the primary presentation of the IBD. Another factor that must be considered is the immunobiological safety profile, analyzed from the construction of the safety pyramid, which top is represented by drugs such as vedolizumab and ustekinumab followed by anti-TNF alpha agents⁽⁸⁻⁹⁾.

The anti-TNF alpha agents act by blocking the alpha factor of the tumor necrosis (TNF-a), that has an important role in bowel inflammatory process⁽¹⁰⁾. Besides, they interfere in the expression of the inflammatory proteins, acting as well in the cells migration, such as macrophages, and on the bowel mucosa cicatrization. Among these immunobiological agents, infliximab and adalimumab stand out from the others⁽¹⁰⁾.

The adalimumab corresponds to a human monoclonal immunoglobulin that is used in its subcutaneous form in patients, with the recommendation of 160mg at the first dose followed by 80mg at the second

dose in the two following weeks⁽¹¹⁾. Due to the immune modulation and immune suppression effect, one of the risks during its administration in inflammatory bowel disease treatment it's the appearance of opportunistic inflammations⁽¹²⁾. Among these, the reactivation of latent foci of tuberculosis stands out, which makes it essential to perform a screening in these patients, with chest X-ray and tuberculin test (PPD) prior to immunobiological therapy⁽¹³⁾.

Amidst the tuberculosis presentation forms, in those patients who are on immunobiological therapy, it is included the miliary tuberculosis, a very severe form of the disease. This corresponds to a hematogenous lymphogenic dissemination of *Mycobacterium tuberculosis*, which the diagnosis can be hampered by the unspecific clinical condition and X-ray findings that, in some cases, does not show a classic pattern for miliary tuberculosis, delaying the beginning of the treatment, and consequently rising the mortality of the disease. Therefore, the factors combination such as clinical history, in an attempt to identify risk factors, physical exams, laboratorial exams and screen exams, such as chest computerized tomography (CT), are capable of crossing the barriers that hampered the diagnosis⁽¹⁴⁻¹⁵⁾.

Case description

This is a case study approved by the Research Ethics Committee (CEP) of Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória – Espírito Santo/ES. CAAE: 48946921.5.0000.5065 and approved under the number 4.870.287.

Male patient, 31 years old, nursing technician, diagnosed with Crohn's disease with terminal ileum, sigmoiditis, and rectum for 11 years, without any other comorbidity. A previous drug treatment was undergoing with a combination of sulfasalazine and azathioprine when, in 2016, due to the difficulty to control the symptoms and adverse effects to these medications, the combination was substituted by the immunobiological adalimumab (one ampoule every 14 days).

Since then, the patient has kept regular follow up consults, with attention to the vaccination calendar, including the bacilli Calmette-Guerin (BCG) and screening exams for latent infections, such as, for example, non-reactor tuberculin test (0 mm) in December of 2019 and the chest X-ray taken in November of 2019 as well with no alterations. Recent laboratorial exams requested for a follow up of the disease did not show any sign of alarm.

In August of 2020 the dyspnea, asthenia, myalgia, and fever temperature of 39 °C started, and after a period of 8 days he went to an ambulatory care. The

physical exam showed tachypnea, respiratory effort, and vesicular murmur present bilaterally without adventitious noises. Other systems without alternations. There was a recent infection history of COVID-19 (RT-PCR positive in May of 2020), that has manifested itself softly, without the necessity of hospitalization.

After the case was analyzed as a fever syndrome and taking in consideration the immunosuppression of the patient due to the chronic use of immunobiological, it was requested a hospitalization for further evaluation. The investigation was started with a PCR request for COVID-19, hemoculture, urinalysis and computerized tomography (CT), and further laboratorial tests, as shown in Table 1. Besides, an empirical treatment was started for community pneumonia with ceftriaxone and azithromycin.

Table 1

Laboratorial exams requested in hospitalization admission

Hemoglobin	12.2 g/L
Hematocrit	37.4%
Leukocytes	3.930/ μ L
Immature Neutrophils	16%
Platelets	131.000/ mm ³
PCR	83mg/dl
Urea	13 mg/dL
Creatinine	0.6 mg/dL
Sodium	138 mEq/L
Potassium	4.4 mEq/L
Magnesium	1.7 mEq/L
RT- PCR COVID-19	Negative

Source: Research data.

The possibility of a new clinical picture of COVID-19 was dismissed, turning the main diagnosis hypothesis to be opportunistic infections. The chest CT revealed a consolidation with centrilobular micronodules at the apical segment of the left lower lobe, unspecific, however suggestive of active infectious pneumonia. It has also evidenced diffuse micronodular infiltrate, some of which is rare, that was touching the pleura (perilymphatic), and others, centrilobular, which if putted together with clinical data could be suggestive of infectious process by miliary tuberculosis (Figure 1).

Pathologies related to immune suppression were not considered (namely cytomegalovirus, cryptococcosis, paracoccidioidomycosis, and histoplasmosis), besides the negative result of the BAAR research done on 3 samples of sputum.

During the hospitalization, among the many com-

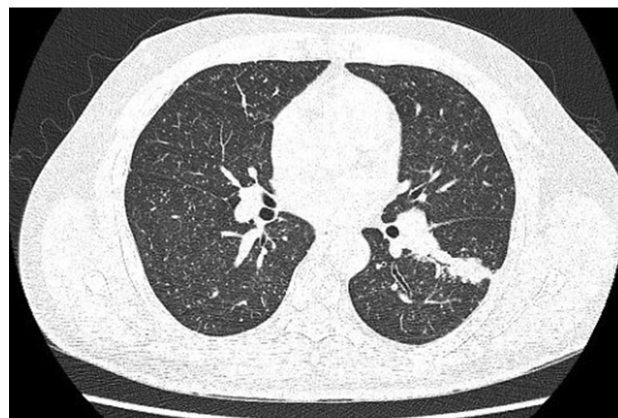


Figure 1. Chest computerized tomography showing diffuse pulmonary infiltrate with micro reticulonodular pattern.

plications followed by the severe medical situation of the patient, the hypoxemic acute respiratory failure was the main one. After it was needed an orotracheal intubation, the patient was taken to an Intensive Care Unit (ICU). While he was under intensive care, the investigation of his clinical condition was continued through collection and analysis of the bronchoalveolar lavage, which revealed a positive RT-PCR for *Mycobacterium tuberculosis*. Thus, along with the radiological and laboratorial clinical findings, it was confirmed the diagnosis of miliary tuberculosis. The antibiotics were suspended, and a treatment based on rifampicin, isoniazid, pyrazinamide, and ethambutol was started. After two months, as the clinical condition was stabilized, the patient returned to infirmary care.

After a long-term hospitalization, the patient received a hospital discharged with orientations, prescriptions for the maintenance of the RIPE therapy and referrals to ambulatory care centers for inflammatory bowel disease and infectiology. The replacement of adalimumab for ustekinumab was preferred based on the highest safety profile for infectious adverse effects.

Discussion

The CD is part of the IBD spectrum that, when diagnosed, must have its treatment started immediately, in order to retard the disease progression and prevent complications, such as strictures and fistulas⁽⁵⁾. Among the currently most recommended drugs, some of them are immunobiological, such as anti-TNF- α , represented by infliximab and adalimumab⁽⁶⁾.

Despite the great therapeutic effectiveness of immunobiological, the anti-TNF, among many possible adverse effects, could cause the reactivation of latent foci of tuberculosis, either pulmonary or extrapulmonary, such as the miliary form, which is 20 times more common in patients that are using immunobiological

then in general population⁽¹⁶⁾. Regardless of being a very rare event, it must always be considered a situation to be suspected, specially in patients with slow evolution of the clinical condition and with unspecific presentation of general symptoms^(9,15).

The miliary tuberculosis is commonly diagnosed very lately due to its unspecified signals and symptoms such as weight loss, fever of unknown origin (FUO), night sweats, anorexia, visceromegaly, and respiratory symptoms, namely dyspnea, in 8-100% of the cases, and cough, in 27-82% of the cases⁽¹⁴⁾. Some of the more suggestive signals can be obtained through screening exams, such as chest X-ray, which shows diffuse reticular micronodules opacities, or even a chest CT, that can reveal nodules of 1-3mm sparse in the pulmonary parenchyma, normally associated with pleural effusion, hilar lymphadenopathy, or mediastinal⁽¹⁷⁾.

This information set obtained through clinical exams and complementary methods makes plausible the hypothesis of miliary tuberculosis, which must be considered to proceed the investigation with more specific exams⁽¹⁴⁾. The sputum, for example, has positive sputum smear in 41,6% of the cases, followed by a bronchoscopy with bronchoalveolar lavage (BAL) collection which has a yield of 46,8%⁽¹⁴⁾. More invasive methods, such as liver biopsy or a lymph node biopsy, can be useful, even with negative previous exams, when the diagnostic suspicion maintains itself strong⁽¹⁴⁾.

The treatment for miliary tuberculosis, when there is no involvement in the central nervous system nor the osteoarticular, consists in a daily use, for 2 months, of the RIPE scheme, fixed doses pills combined with rifamycin (R), isoniazid (I), pyrazinamide (P) and ethambutol (E). When the scheme is completed, a maintenance treatment is kept for four more months, consisting only in the administration of rifamycin and isoniazid⁽¹⁵⁾.

In relation to the high mortality (25-30%) and the negative impacts of miliary tuberculosis, it is indispensable that all patients with IBD which need an immunobiological therapy must be checked for latent infection⁽¹³⁾. This checking is made through the chest X-ray and the PPD before starting the treatment and, ideally, is maintained annually. Besides, the patient must be orientated about the update of its vaccination status, considering that, once started the immunobiological therapy, the attenuated microorganisms' vaccines, such as BCG, must be avoid⁽⁹⁾.

Another determinant factor on the evolution of the clinical condition described can be associated to a previous COVID-19 infection in the last three months that preceded the hospitalization due to miliary tuberculosis. Recent studies detected that the SARS-CoV-2

virus infection can lead to an immunological dysfunction, through the depletion of T cells and reduction of its functionality, favoring the immunosuppression clinical condition and being also used as a facilitating tool for reactivation of tuberculosis⁽¹⁸⁾.

As described in the present study case, even in patients with non-reactive PPD, a previous chest X-ray with no alternations and an updated vaccine card, the possibility of miliary tuberculosis still can not be disregarded when it comes to an unspecified clinical condition. Therefore, this pulmonary opportunistic complication must always be considered in order to avoid losing the diagnoses, which must be done in its early form to stablish a direct and effective treatment, with a possibility of completely clinical recover and with no permanent sequela⁽¹⁴⁾.

Furthermore, the temporary interruption of IBD treatment can be considered in severe cases, taking into consideration the risk-benefit regarding of maintain it and until it has reached the stabilization of the miliary tuberculosis condition. The change of the immunobiological medicine must be discussed in order to avoid new adverse reactions, and a new immunobiological must be indicated, with a different drug action from the one implying the reactivation of latent foci and considering its safety profile. One of these immunobiological is ustekinumab, monoclonal antibody and anti-interleukin 12 and 23, with a better safety profile and less commonly associated with reactivation of tuberculosis^(9,19).

Final Comments

In Immunobiological therapy handling, which includes pharmaceutical such as adalimumab, either for Crohn's disease or any other affection that has a recommendation for it, opportunistic infections must always be considered. Among them, the reactivation of tuberculosis foci, with hematogenous dissemination potential and systemic compromising (miliary tuberculosis), must be remembered so that the treatment can be initiated as early as possible. Besides, the secondary prevention strategy with annuals PPD and X-ray are part of the handling regarding this kind of patients, and even if there is a negative screening for mycobacterial infection, it's risks for reactivation still exists.

References

1. Dias AK, Guedes ALV, Leite AZA. Doenças Inflamatórias Intestinais: quadro clínico e diagnóstico. In: Zaterka S, Eisig JN. *Tratado de gastroenterologia: da graduação à pós-graduação*. 2ª ed. São Paulo: Atheneu; 2016. p.763-72.
2. Arantes JAV, Santos CHM, Delfino BM, Silva BA, Souza RMM, Souza TMM, et al. Epidemiological profile and clinical

- characteristics of patients with intestinal inflammatory disease. *J Coloproctol*. [Internet]. 2017 [citado 2021 Mai 10]; 37(4):273-8. Disponível em: <https://www.scielo.br/j/jcol/a/ydkjFRqrkdBZDCdWbMxQbHg/?lang=en>
3. Quaresma AB, Kaplan GG, Kotze PG. The globalization of inflammatory bowel disease: the incidence and prevalence of inflammatory bowel disease in Brazil. *Curr Opin Gastroenterol*. [Internet]. 2019 [citado 2021 Jun 2]; 35(4):259-64. Disponível em: <https://doi.org/10.1097/MOG.0000000000000534>
 4. Greuter T, Rieder F, Kucharzik T, Peyrin-Biroulet L, Schoepfer AM, Rubin DT, et al. Emerging treatment options for extraintestinal manifestations in IBD. *Gut*. 2021;70(4):796-802.
 5. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: Management of Crohn's disease in adults. *Am J Gastroenterol*. [Internet]. 2018 [citado 2021 Jun 23]; 113(4):481-517. Disponível em: <https://doi.org/10.1038/ajg.2018.27>
 6. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. [Internet]. 2019 [citado 2021 Jun 2]; 114(3):384-413. Disponível em: <https://doi.org/10.14309/ajg.0000000000000152>
 7. Wehkamp J, Götz M, Herrlinger K, Steurer W, Stange EF. Inflammatory bowel disease: Crohn's disease and ulcerative colitis. *Dtsch Arztebl Int*. [Internet]. 2016 [citado 2021 Jun 23]; 113(5):72-82. Disponível em: <https://www.aerzteblatt.de/10.3238/arztebl.2016.0072>
 8. Abraham BP, Ahmed T, Ali T. Inflammatory bowel disease: pathophysiology and current therapeutic approaches. In: Meerveld BGV. *Gastrointestinal pharmacology. Handbook of experimental pharmacology*. Cham: Springer; 2017. p.115-46. (HEP, volume 239).
 9. Click B, Regueiro M. A practical guide to the safety and monitoring of new IBD therapies. *Inflamm Bowel Dis*. [Internet] 2019 [citado 2021 Jun 6]; 11;25(5):831-42. Disponível em: <https://doi.org/10.1093/ibd/izy313>
 10. Levin AD, Wildenberg ME, van den Brink GR. Mechanism of action of anti-tnf therapy in inflammatory bowel disease. *J Crohns Colitis*. 2016; 10(8):989-97.
 11. Abbass M, Cepek J, Parker CE, Nguyen TM, MacDonald JK, Feagan BG, et al. Adalimumab for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2019; 2019(11):CD012878.
 12. Malutta EF, Matos C, Bella CBL, Scolaro B, Souza MCC, May BM. Tuberculose (TB) miliar após o uso de adalimumabe na doença de Crohn (DC): um relato de caso. *ACM Arq Catarin Med*. [Internet] 2016 [citado 2021 Jun 23]; 45(4):84-90. Disponível em: <http://www.acm.org.br/acm/seer/index.php/arquivos/article/view/140/117>
 13. Milenković B, Dudvarski-Ilić A, Janković G, Martinović L, Mijač D. Anti-TNF treatment and miliary tuberculosis in Crohn's disease. *Srp Arh Celok Lek*. 2011; 139(7-8):514-7.
 14. Sharma SK, Mohan A. Miliary tuberculosis. *Microbiol Spectr*. [Internet]. 2017 [citado Jun 23 2021]; 5(2). Disponível em: <https://journals.asm.org/doi/10.1128/microbiolspec.TNMI7-0013-2016>
 15. Sharma SK, Mohan A, Sharma A. Challenges in the diagnosis & treatment of miliary tuberculosis. *Indian J Med Res*. 2012; 135(5):703-30.
 16. Thomson ABR, Gupta M, Freeman HJ. Use of the tumor necrosis factor-blockers for Crohn's disease. *World J Gastroenterol*. 2012; 18(35):4823-54.
 17. Nachiappan AC, Rahbar K, Shi X, Guy ES, Mortani Barbosa EJ, Shroff GS, et al. Pulmonary tuberculosis: role of radiology in diagnosis and management. *RadioGraphics*. 2017; 37(1):52-72.
 18. Elziny MM, Ghazy A, Elfert KA, Aboukamar M. Case report: development of miliary pulmonary tuberculosis in a patient with peritoneal tuberculosis after covid-19 upper respiratory tract infection. *Am J Trop Med Hyg*. [Internet]. 2021 [citado 2021 Set 6]; 104(5):1792-5. Disponível em: <https://doi.org/10.4269/ajtmh.20-1156>
 19. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as induction and maintenance therapy for Crohn's Disease. *N Engl J Med*. [Internet] 2016 [citado 2021 Set 6]; 375(20):1946-60. Disponível em: <https://doi.org/10.1056/NEJMoa1602773>

Article received: September 10, 2021

Article approved: November 29, 2021

Article published: November 30, 2021

Responsible Editor: Prof. Dr. Eitan Naaman Berezin (Editor-in-Chief)