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Case Report

Rare Form of Miliary Tuberculoma/Parenchymal Tuberculosis of the Central Nervous System after Rescue Therapy with Anti-TNF for Acute Severe Ulcerative Colitis

Atanassova A[1,3,4] and Georgieva A[1,2,4]*

[1]Clinic of Gastroenterology, "St. Marina "University Hospital of Varna, Bulgaria

[2]Second Department of Internal Diseases, Bulgaria

[3]Department of Anatomy and Cell Biology, Bulgaria

[4]Medical University, Varna, Bulgaria

***Corresponding author:** Avgustina Georgieva, Varna, 1 Hristo Smirnenski Bul., Floor 11, Clinic of Gastroenterology, Multiprofile University Hospital for Active Treatment "Sveta Marina", City of Varna, Bulgaria

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Abstract

A patient with a 10-year history of severe ulcerative pancolitis, nine years of treatment with 5-aminosalicylic acid (5 ASA) and azathioprine (AZA). When the disease had another flare up of acute severe ulcerative colitis (UC), the patent received a screening for preventable infectious diseases and began a rescue therapy with anti-TNF antibody- Infliximab. Following induction therapy, the patient developed hematogenously disseminated pulmonary tuberculosis (TB), cold abscess, TB lymphadenitis.

Five years after the successful completion of an anti-TB therapy, the patient has had a single episode of loss consciousness with pelvic incontinence. Magnetic resonance imaging (MRI) proved disseminated/miliary central nervous system (CNS) tuberculoma - parenchymal tuberculosis. The therapeutic challenge of the need for treatment of CNS tuberculosis and severe UC with disease progression were discussed.

Keywords: Tuberculosis; Extrapulmonary; Central nervous system; IBD; Anti TNFα antibody

Introduction

Patients with inflammatory bowel disease (IBD) who have undergone immunosuppressive treatment run the risk of developing tuberculosis infection despite receiving a screening for preventable infectious diseases before starting a biological treatment [1-3].

Case Presentation

The patient is a 41-year-old woman with ulcerative colitis (UC) – E2S2, with a disease onset at age 24, without comorbidities, non-smoker. Due to the development of corticosteroid dependence, azathioprine (AZA), 2.5mg/kg daily, was added to the 5-aminosalicylic acid (5 ASA). Within nine years, despite the treatment, the disease has progressed to pancolitis-E3S3.

During a flare up of acute severe UC, following a screening for preventable infectious diseases (tuberculin skin test (TST) - negative; IGRA (T-SPOT. TB®) negative; chest-X ray normal) the patient began biological treatment. After the induction phase at week six of the anti-TNFα antibody treatment (Infliximab), the patient developed hematogenously disseminated tuberculosis (TB) of the lung and pleura. Against the background of 6 months tubeculostatic treatment (Rifampicin 600mg daily, Isoniazid 300mg daily, Ethambutol 1500mg daily, Pyrazinamide 2000mg daily) she was operated due to a cold abscess in the right gluteal region. The treatment for TB infection after abscess drainage was continued for a total of 12 months, after which Positron-emission tomography-computer tomography (PET/CT) was performed. Multiple metabolically active lymph nodes in the cervical, thoracic and abdominal regions were discovered; multiple metabolically active lesions in the spleen; the presence of bilateral miliary changes in the lungs with low glucose metabolism; brain without pathological changes.

Two years later she underwent surgery for tuberculous lymphadenitis with cervical abscess. Tuberculostatic treatment (Isoniazid 300mg daily + Ethambutol 750mg daily + Rifampicin 600mg daily) was resumed for 9 more months. Within five years after the treatment for hematogenous tuberculosis, in the absence of active TB infection, she had a seizure with incontinence and consecutive relapse of UC. The MRI discovered TB of the central nervous system (CNS) - parenchymal form - miliary tuberculoma. Renewed TB therapy for another 9 months.

The UC flare-up caused the IBD consulting team to consider whether to perform proctocolectomy or to continue the drug treatment of UC.

Discussion

Following the introduction of TNF inhibitors used for many autoimmune diseases such as: rheumatoid arthritis, ankylosing spondylitis, psoriasis, IBD, an increase in the incidence of TB has been observed in these patients.

The immunosuppressive therapy alters the patient's response to opportunistic infections.

TNF increases the phagocytic capacity of macrophages, regulates the expression of adhesion molecules on the surface of endothelial cells and thus determines the movement of mononuclear cells and the

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formation of granulomas [4,5].

Data from the existing literature indicates that the risk of developing TB increases from 1.6 to 25 times after initiation of anti-TNFα therapy and depends on the type of drug used [6]. If among the general population the incidence of TB infection in Spain is 21/100,000, then among patients treated with INF, incidence rate (IR) is 383/100,000 [7].

Currently, we do not have data on the incidence of TB infections among patients in Bulgaria receiving anti-TNFα therapy. Nevertheless, there have been many reported cases of pulmonary and non-pulmonary TB in patients being treated with anti-TNFα therapy. Therefore, screening for active and latent tuberculosis (LTBI) before starting the biological treatment is mandatory, according to national, European Crohn's and Colitis Organization (ECCO) and National Institute for Health and Care Excellence (NICE) guidelines.

According to these recommendations, the screening includes: tuberculin skin test (TST), chest X-ray or interferon gamma release assays (IGRAs) test [3].

Many years of experience have shown that TST has low sensitivity and low specificity. There is a high rate of false negative results in otherwise healthy individuals (up to 1/4 of those infected with Micobacterium tuberculosis) [8].

In the presented case, long-term immunosuppressive therapy with AZA contributes to the false negative TST and IGRA (T-SPOT. TB®). The lack of changes seen with a chest X-ray proves insufficient to rule out LTBI.

The widespread use of IGRAs tests revealed their high specificity and sensitivity, which were not affected by a previous immunosuppressive treatment. Therefore, in the following years the use of IGRAs became mandatory in national and ECCO consensus, especially for those undergoing immunosuppressive therapy who will receive anti-TNFα treatment, as well as for BCG (Bacille Calmette-Guerin) vaccinated individuals [9].

In fact, there is no gold standard for proving LTBI. Until 2010, standard screening for active and LTBI prior to the initiation of biological treatment included the following studies: a detailed medical history of tuberculosis exposure, a chest X-ray and a TST, and it was always noted if the patient is vaccinated against BCG tuberculosis.

IBD patients receiving biological treatment are immunosuppressed due to the frequent use of corticosteroids and/or immunosuppressants. Despite their sensitivity and specificity, both TST and IGRA tests can be false positive or false negative. The combination of several methods is the best strategy for detecting latent or active tuberculosis infection [10].

In the presented case, the involvement of CNS by tuberculosis infection after a five-and-a-half-year period of clinical remission reveals that, in a haematogenously-disseminated form of tuberculosis, manifestations of reactivation of TB infection in any organ and system can be expected. CNS involvement is 1% of all forms of TB and may occur with a variety of neurological symptoms from classic meningitis symptoms (fever, headache, vomiting, neck stiffness along with focal neurological deficits, behavioural changes, and alterations in consciousness, seizures) to an absence of symptoms [11]. In this clinical case, oligosymptomatic manifestation is observed. The immediate anti-TB treatment given, despite the low threshold of passage through the blood-brain barrier of these drugs, resulted in the absence of new miliary lesions in the brain parenchyma (monitored by a control MRI at 6 months of therapy), and the absence of any CNS symptoms. The subsequent UC flare up led to other issues that had to be resolved. Can this patient be maintained in remission through medication or should a planned proctocolectomy be considered.

Conclusion

Tuberculosis is preventable and treatable, but is still one of the main causes of morbidity and mortality [12].

Despite mandatory screening for preventable infectious diseases, among candidates for biological treatment, there is a risk of LTBI reactivation or a new onset of TB infection. None of the tests gives reliable enough results to rule out LTBI. The combined use of several screening methods, as well as the systematic monitoring of patients during the course of therapy itself, is mandatory. In case of suspected tuberculosis infection (new-onset or reactivation of LTBI), a systematic assessment of the condition is necessary. The biological treatment has to be ended immediately and appropriate treatment for TB has to start. In patients who have already suffered from a pulmonary, extra-pulmonary or hematogenous disseminated form of TB, the decision to treat and follow-up should be made by a multidisciplinary team that takes under consideration the individual needs and the necessity to control the underlying disease.

Author's Contributions

Antonia Atanassova: Wrote the paper.

Avgustina Georgieva: Performed the literature search, discussed the publication with the patient.

Ethical Approval

No need for local ethical approval.

We obtained permission from the patient to publish her data.

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