Case Report

Rare Complication During Anti-TNF-α Treatment in a Patient with Crohn's Disease: A Case Report and Review of the Literature

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ABSTRACT: Crohn's disease represents an inflammatory bowel disease of unknown etiology, with chronic evolution, which may affect any segment of the digestive tract. The main classes of drugs used in patients with inflammatory bowel disease include: aminosalicylates, corticosteroids, immunosuppressants, biological agents and antibiotics. Biological therapy with anti-TNF-α agents offers significant therapeutic benefits, but their use requires caution, as they can also be associated with numerous side effects. We present the case of a female patient known with Crohn's disease, under going biological therapy with adalimumab, who developed a complication, quite rarely described in the literature, possibly as a result of treatment with anti-TNF-α agents.

KEYWORDS: *Crohn's disease; anti-TNF-α agents; adalimumab; side effects; tuberculosis.*

Introduction

Crohn's disease represents an inflammatory bowel disease of etiology still unknown, with a long and unpredictable evolution, characterized by periods of activity and remission, which may affect any segment of the digestive tract, most commonly affecting the terminal ileum and colon [1].

In Romania, the prevalence of Crohn's disease is low, but recent epidemiological data show an increasing trend in the number of new cases in this area [2].

The pathogenesis of the disease is incompletely elucidated. Crohn's disease is thought to be the result of the interaction between certain environmental factors and the intestinal microbiota in subjects with a genetic predisposition, resulting in damaged intestinal barrier function and impaired immune response [1].

The most common clinical features are abdominal pain, chronic diarrhea, fatigue, anorexia and weight loss.

Patients may also present with extraintestinal manifestations, usually cutaneous, articular or ocular [1,3].

Therapeutic options, in the case of Crohn's disease, have benefited from constant improvements.

The main classes of drugs used include aminosalicylates, corticosteroids, immune-suppressants, biological agents and antibiotics [1,4].

Although biological agents offer significant therapeutic benefits, their use requires caution, as they can also be associated with many side effects, such as an increased risk of infection, special attention requiring tuberculosis infection, or increased risk of developing lymphomas [5].

Case Report

We present the case of a 37-year-old female patient hospitalized in the Gastroenterology Department of the Craiova County Emergency Clinical Hospital in September 2020 for high dysphagia, odynophagia and weight loss (approximately 5kg in the last 2 months before presentation).

From the personal medical history, we noted that the patient has been known to have ileo-colonic Crohn's disease since 2007, currently in clinical remission, associating extraintestinal manifestations such as spondylitis and sacroiliitis, for which she underwent biological treatment with Infliximab combined with Azathioprine, discontinued on her own initiative about 5 years ago, subsequently treatment with Mesalazine 3g/day and Azathioprine 100mg/day, and in October 2019 was initiated biological therapy with Adalimumab, discontinued one month before the presentation due to recurrent pharyngitis.

The patient's family medical history was insignificant.

The patient complained of the onset of symptoms approximately two months before the presentation, by odynophagia, symptoms that did not yield to symptomatic medication, which is why she went to the ENT Department, where, following investigations, the diagnosis of acute erythematous angina was established, for which

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she subsequently received antibiotic treatment (Amoxicillin+Clavulanic Acid), with no clinical response.

Other medical examinations were performed, initially throat cultures were achieved, which highlighted the presence of *Enterobacter cloacae*, following antibiotic treatment with Ceftriaxone; however, the symptoms did not improve significantly.

Subsequently, tonsillar biopsies were performed, which ruled out malignancy.

In evolution, the patient's symptoms worsened, from progressive difficulty in swallowing to total high dysphagia, both for solid and liquid foods, accompanied by sialorrhea, marked physical asthenia and weight loss (approximately 5kg). The patient also stated night sweats.

At physical examination, the patient was with an affected general condition, temperature 36.9^{o}C, underweight (Weight of 48kg, Height 164cm, body mass index of 17.85), pale and dehydrated skin and mucous membranes, morphologically intact osteo-articular system, with pain when mobilizing the pelvis and lumbar spine, positive Eriksen sign, positive Volkman sign; examination of the superficial lymph nodes system, highlights at the level of the right latero-cervical region, two oval structures, of firm consistency, immobile on deep and superficial planes, without sensitivity to palpation, with a long axis of about 1cm.

No significant pathological changes were observed on chest auscultation.

ENT examination found congested and hypertrophied palatine tonsils bilaterally and the presence of multiple gray-whitish granules, small in size, diffusely disseminated in the pharynx and larynx.

Several differential diagnoses were discussed: viral pharyngotonsillitis, bacterial pharyngotonsillitis, herpetic pharyngotonsillitis, pharyngotonsillitis in acute retro-viral syndrome, oropharyngeal candidiasis, periamygdalian abscess, retropharyngeal abscess, pharyngeal syphilis, acute or chronic laryngitis, tonsillar neoplasm, haematological diseases (agranulocytosis, acute leukemias, lymphomas).

Laboratory tests showed mild hypo-albuminemia, moderate microcytic hypochromic anemia, lymphopenia, ESR=120mm/h (N: 2-12mm/h), C-reactive protein=88.24mg/L (N: 0-5mg/L), prothrombin index=61% (N: 79-146%), INR=1.38 (Normal range between 0.8 and 1.16), the rest of the blood tests being within normal limits.

Additional biological investigations were performed: microbiological examination of pharyngeal exudate (negative for *Candida spp*, *Staphylococcus aureus*, *Streptococcus pyogenes*), anti-HIV antibodies 1/2 (absent), venereal disease research laboratory (VDRL) (negative); however, we found a positive result for the Koch *Bacillus* in the patient's sputum.

Following the changes encountered in the physical examination and the results of biological tests, it was decided to perform a computed tomography examination of the neck and chest region.

At the level of the neck we distinguished a diffuse thickening of the epiglottis, of ariepiglottic folds bilaterally, of vocal cords bilaterally, without obvious asymmetries andhomogeneous, non-specific jugular latero-cervical lymph nodes at the right postero-superior level with dimensions up to 12/7mm and up to 10/6mm at the level of the left postero-inferior triangle with the same characteristics (Figure 1).

Computed tomography of the thoracic region showed pulmonary condensation with massive cavitation at the level of the apical segment of the right upper lobe and the segments of the middle lobe; multiple nodular focal condensation areas, disseminated in both lung areas except the basal segments of the left lower lobe, with a tendency to confluence; micronodular lesions with the same arrangement; nonspecific right lower para-tracheal mediastinal adenopathy 14/7mm; without pleuro-pericardial fluid; the described appearance may argue for hematogenous disseminated tuberculous lesion (Figure 2).

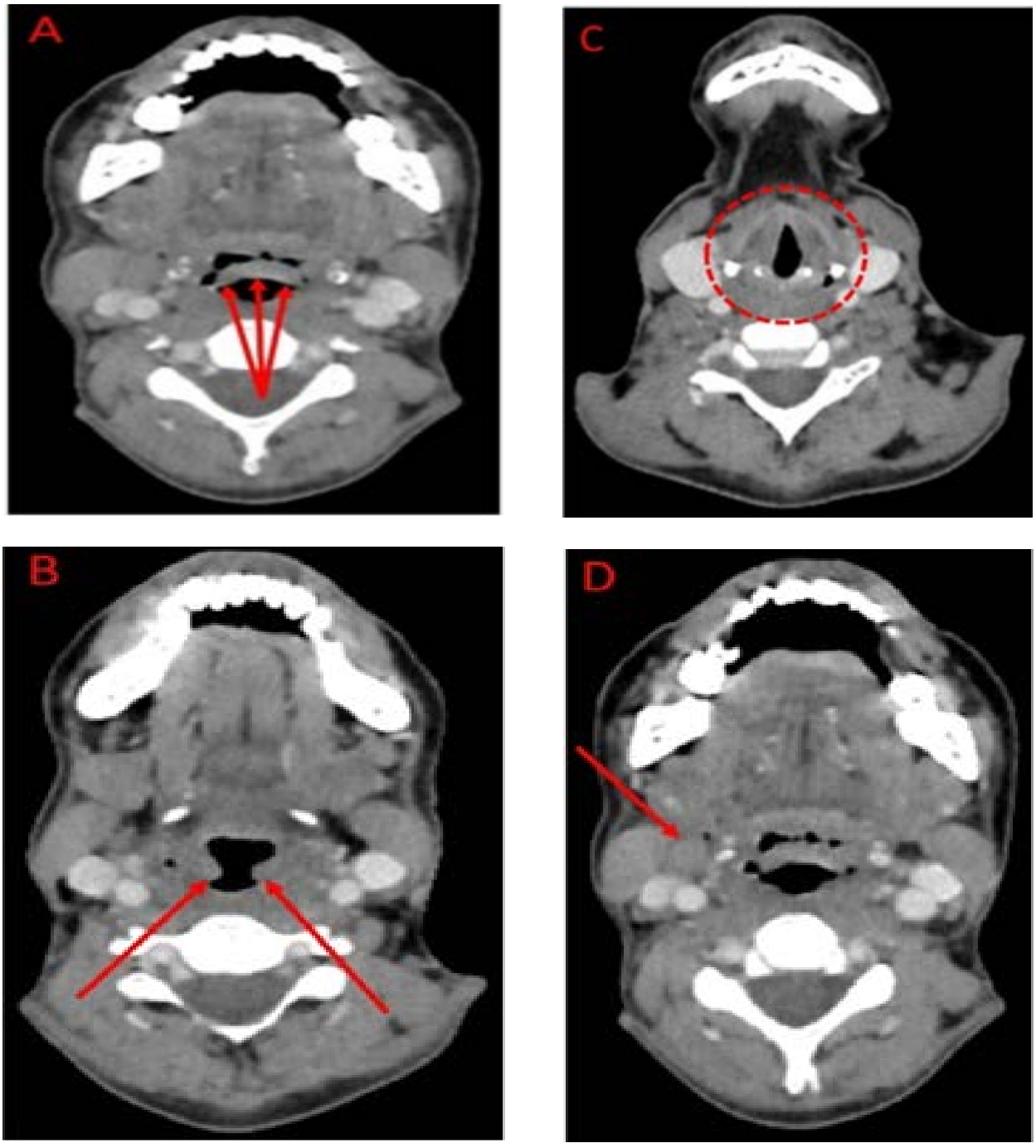

Figure 1. CT neck region, postcontrast: A-diffuse thickening of the epiglottis; B-diffuse thickening of the ariepiglottic folds bilaterally; C-diffuse thickening of the vocal cords bilaterally, without noticeable asymmetries; D-right upper carotid jugular lymphadenopathy.

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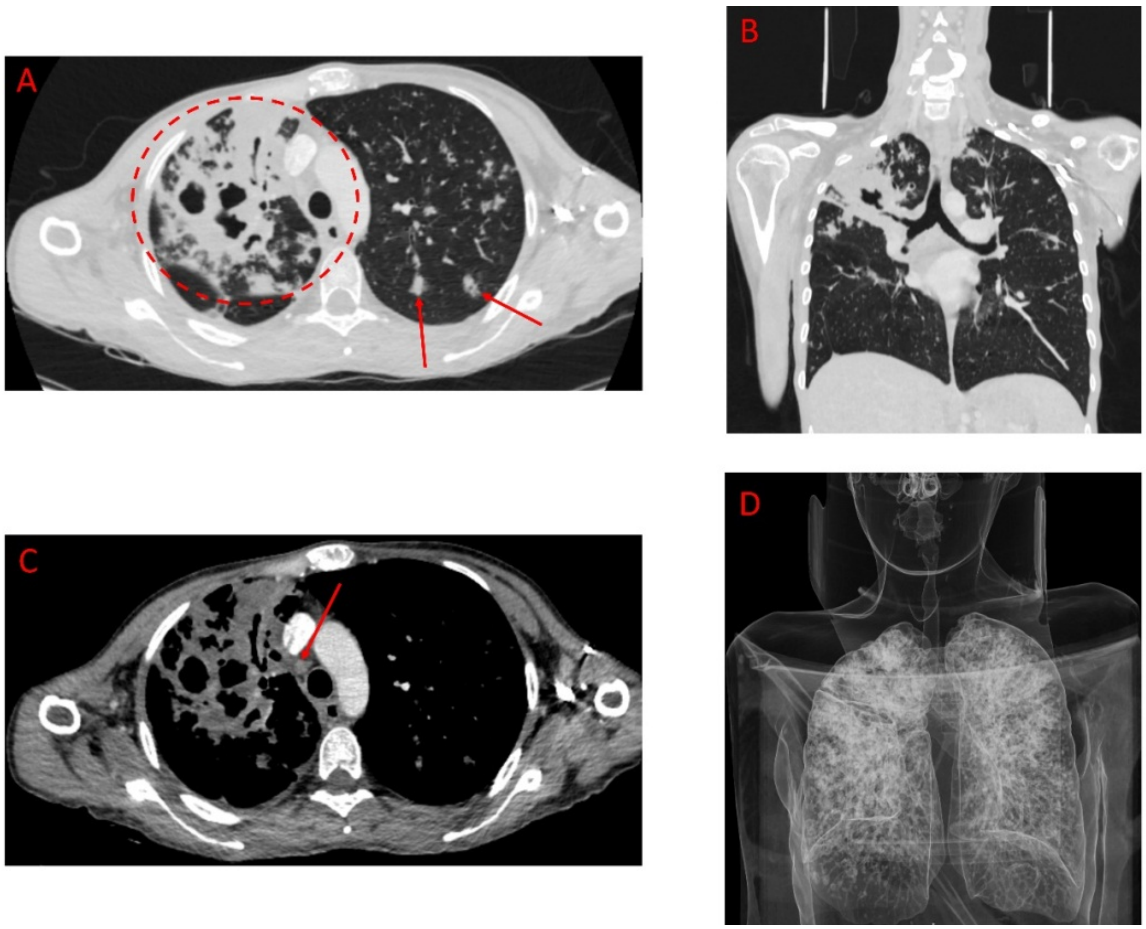

Figure 2. CT thoracic region: A-pulmonary window, encircled area →right upper lobe condensation area with massive cavitation, arrows →focal pulmonary condensation areas bilaterally;
B-coronal plane, pulmonary window →pulmonary damage predominantly at the apical portions;
C-postcontrast, mediastinal window →right inferior para-tracheal adenopathy;
D-3D reconstruction after CT examination →there is a noticeable damage to the lungs predominantly in the upper two thirds, with minimal damage to the basal regions.

Based on the information obtained from the anamnesis, physical examination and paraclinical investigations, we established the diagnosis of pulmonary tuberculosis with extrapulmonary, pharyngeal and laryngeal foci, most likely developed in the context of biological therapy with Adalimumab for Crohn's disease.

Therefore, therapy with Adalimumab was discontinued, and the patient was referred to a specialized medical unit to initiate the specific treatment.

The patient's evolution was favorable with the beginning of the tuberculostatic treatment, being discharged from the Leamna Pneumophthisiology Hospital with good general condition and improved symptoms.

Regarding the gastrointestinal pathology, the patient is still in clinical remission (one-two stools of normal consistency per day, without blood in stool), and will return for follow-up control visits, after the completion of tuberculosis-specific treatment.

Also, a clinico-biological and imaging re-evaluation of Crohn's disease will be needed in order to establish the new therapeutic approach.

Discussions

Being a pathology with a long evolution, the objectives of the treatment of Crohn's disease aim at the rapid induction of remission and its long-term maintenance [6].

Biological therapy has revolutionized the treatment of inflammatory bowel disease, but their use must take into account certain circumstances, due to possible side effects, but also the high costs of these substances [5].

The guidelines recommend the use of biological agents to induce remission in patients with moderate-severe forms of Crohn's disease who do not respond to conventional

corticosteroid and immunosuppressive therapy [6].

Biological therapy is mainly represented by anti-TNF-α monoclonal antibodies. TNF-α is a cytokine involved in the acute phase reaction and systemic inflammation, thus helping to reduce tissue damage [7].

The following anti-TNF-α agents are approved for the treatment of Crohn's disease: infliximab, adalimumab and certolizumab pegol. Infliximab is a chimeric IgG1 monoclonal antibody, while adalimumab is a fully humanized IgG1 monoclonal antibody [6].

Adalimumab appears to have an infliximab-like mechanism of action [8,9], but studies show that it is associated with a lower rate of developing antibodies directed against the biological agent [9,10].

Among the side effects of therapy with anti-TNF-α agents, we mention: increased risk of infections, significant attention requiring tuberculosis infection, given that TNF-α is considered to play a key role in antituberculous defense, [8] the risk of developing neoplasms, such as lymphoma, melanoma, but also solid organ tumors, cardiac side effects, current guidelines recommending avoiding the use of this therapy in patients with NYHA class III/IV heart failure, hypersensitivity reactions, dermatological side effects (psoriasis), haematological side effects (leukopenia, neutropenia, thrombocytopenia, anemia), autoimmune syndromes, neurological side effects (demyelination disorders) [7].

The ACCENT I trial studied the efficacy and long-term safety of infliximab treatment in a group of 573 patients with Crohn's disease.

Of these, only one patient developed tuberculosis four weeks after the dose given at week 14 and was successfully treated, 6 patients developed neoplastic pathologies and although 34% developed anti-dsDNA antibodies, only two patients developed lupus-like syndrome [11,12].

The CLASSIC-I trial, which evaluated the efficacy of adalimumab as induction therapy in patients with Crohn's disease, did not report any cases of tuberculosis or opportunistic infections [11,13].

Additionally, the percentage of patients who developed antibodies against the biological agent was low (one in 225 patients-0.04%) [13].

Also, the CLASSIC II trial, which provided data over a longer period of up to 56 weeks, did not report any cases of tuberculosis, demyelination disorders, lymphoma, neoplasia or death in the adalimumab group of patients [11,14].

The CHARM trial, which studied the efficacy and safety of adalimumab treatment as a maintenance therapy for remission in patients with moderate to severe Crohn's disease, reported two cases of tuberculosis, although at the time of therapy initiation, patients had negative tuberculin skin test and normal appearance on chest X-ray.

It should be noted that one of the patients was receiving concomitant treatment with prednisone and azathioprine [11,15].

Osterman et al conducted a review of several clinical trials involving patients known with Crohn's disease and treated with adalimumab, and concluded that the combination therapy of an immunomodulator and adalimumab increases the risk of developing non-melanoma skin cancer, but also the risk of other types of cancer [11,16].

It is assumed that the early onset of tuberculosis after initiation of therapy with biological anti-TNF-α agents would suggest the reactivation of latent infection, rather than a primary infection [17].

Interestingly, in the present case, it is the fact that the patient performed, prior to initiating biological therapy, the QuantiFERON®-TB Gold Plus test associated with chest radiography, the data obtained from these paraclinical investigations not being suggestive for the latent form of tuberculosis infection.

However, the question remains whether the infection was contracted after initiating biological therapy or could be an erroneous result of the QuantiFERON®-TB Gold Plus test, given that some studies have shown that false negative results may occur in immunocompromised patients [18].

Another issue that needs to be addressed is the identification of the appropriate therapy for inflammatory bowel disease, if patients develop a complication such as tuberculosis as a result of treatment with anti-TNF-α agents.

In this case it is recommended to stop the administration of biological therapy and treat the tuberculosis infection.

If absolutely necessary, anti-TNF-α therapy may be resumed at least two months after the initiation of anti-tuberculosis therapy, if a satisfactory response to treatment is obtained; alternatively, other monoclonal antibody therapies, such as ustekinumab or vedolizumab, may be considered [7].

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Ustekinumab is an IgG1 monoclonal antibody that binds the p40 subunit of the pro-inflammatory interleukins IL-12 and IL-23 [6,19].

The guidelines recommend ustekinumab to induce remission in patients with moderate to severe Crohn's disease with inadequate response to conventional therapy and/or anti-TNF therapy [6].

Four studies [20-23] reported side effects in 2024 patients and severe side effects in 1947 patients after induction therapy, but there was no significant difference compared to the placebo group [6].

Also, the rate of antibodies development against the biological agent appears to be low (less than 5%) [6,24].

Among the severe side effects encountered we can mention nonmelanoma skin cancer, carcinoid tumors, opportunistic infections, pulmonary tuberculosis [22].

Vedolizumab is an IgG1 monoclonal antibody that acts by blocking the α4β7 integrin, thus having a selective anti-inflammatory activity in the intestine [6,25].

The guidelines recommend vedolizumab for induction of response and remission in patients with moderate to severe Crohn's disease, with inadequate response to conventional therapy and/or anti-TNF therapy [6].

Also, in the case of vedolizumab, the results of three studies [25-27] did not show significant differences compared to the placebo group in terms of side effects [6].

The results obtained after the administration of the therapy in order to maintain remission, described severe side effects such as tuberculosis, carcinoid tumors, basal cell skin cancer [25].

Comparing the results of four studies [20,22,25,27], which included a total of 1541 patients treated with ustekinumab or vedolizumab, no significant differences were observed between the two treatment options, regarding the occurrence of side effects [6].

Conclusions

Although biological agents have opened a new era in the treatment of patients with inflammatory bowel disease, there is a need for rigorous screening of the patient prior to initiating biological therapy, as studies show that, although quite rare, severe side effects may occur, which endanger the patient's life.

Conflict of interests

None to declare.

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