Tuberculosis under anti-TNF therapy: case series of a center (reporting the experience from the period 2006-2019)

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ABSTRACT

Patients with inflammatory rheumatic diseases refractory to conventional disease modifying antirheumatic drugs (DMARDs)have been treated with biologics for the last two decades. It is also known that patients under biologics present a higher risk of developing Tuberculosis (TB). Portugal has now a TB incidence classified as low. National recommendations advise on latent TB screening before starting biologic treatment. This screening consists in the detection of risk factors and/or signs and symptoms of latent TB through clinical history, physical examination, chest X-ray, tuberculin skin test and Interferon Gamma Release Assay (IGRA) test. We describe five clinical cases of patients who underwent biologic treatment at our Hospital and developed TB.

Keywords: Biologic therapy; Tuberculosis; Anti-tumor necrosis factor therapy.

INTRODUCTION

Patients with inflammatory rheumatic diseases refractory to conventional disease modifying antirheumatic drugs (DMARDs) have been treated with biologics for the last two decades. This has changed dramatically the prognosis of these diseases. Nevertheless, it is also known that patients on biologics present a higher risk of developing Tuberculosis (TB), either by reactivation of latent TB or by primary infection. This risk is higher for patients on biologics therapy with anti-tumor necrosis factor (anti-TNF), and it is even higher (approximately twice) with monoclonal antibodies Against, such as anti TNF infliximab (IFX) or adalimumab (ADA), as opposed to Etanercept[1]. TNF is an important cytokine for granuloma formation and maintenance which is the central defense mechanism against *Mycobacterium tuberculosis* infection[2]. Therefore, anti-TNF therapy increases the risk of developing active TB[2].

Portugal has now a TB incidence classified as low (estimated incidence in 2018 of 17.5 per 100000 inhabitants) but was up to recently a TB intermediate incidence geographical area[9,10]. Despite the progress, incidence rate is still higher than the European Union (EU) incidence (10.7 per 100000 inhabitants) and only 4 other EU members have higher TB incidence (Bulgaria, Latvia, Lithuania and Romania)[9,10]. BCG vaccination was recommended for Portuguese children born between 1965 and 2016. National recommendations published initially in 2006, and subsequently updated in 2012, advise on latent TB screening before the beginning of biologics[2]. This screening consists in the detection of risk factors and/or signs and symptoms of latent TB through clinical history, physical examination, chest X-ray, tuberculin skin test (this test is considered positive when ≥ 5mm in immunocompromised patients, and ≥ 10mm in immunocompetent patients; when negative a second test is recommended) and Interferon Gamma Release Assay (IGRA) test[3]. IGRA test was only introduced as a screening method in 2008, and its accuracy has improved progressively. For patients with immune-mediated inflammatory diseases and patients on immunosuppressive therapy, this is a more sensitive test compared to tuberculin skin test. It is also more specific than the tuberculin skin test as it is not influenced by BCG vaccination nor by other strains of mycobacteria[4].

National recommendations advise also on an annual assessment while patients are on biologics if they had a negative screening on baseline. Patients who have undergone a latent TB therapy do not need this annual assessment. These patients should only attend regular appointments with their rheumatologist in order to identify possible contacts with individuals suffering from TB[2].

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Patients with high probability of having latent TB should undergo isoniazid therapy for 9 months and can start biologics after 1 month of isoniazid treatment[5]. In case of intolerance or toxicity other treatment regimens are available. Several observational and retrospective studies documented that this treatment effectively prevents the reactivation of latent TB in patients on biologics[3,6].

TB screening before the beginning of biologics is a mandatory procedure at our centre. Patients are assessed by a TB expert at one of the centres of the national network for TB diagnosis and treatment (Centro Diagnóstico Pneumológico, CDP) where the need for latent TB therapy is verified. The treatment regime with isoniazid during 9 months has an effectiveness of approximately 90%[3]. Nevertheless, cases of TB have occurred despite this treatment, especially in those undergoing therapy with IFX and ADA[5].

In this manuscript we describe five clinical cases of patients who were treated with biologics at our Hospital (Hospital de Santa Maria, CHULN, in Lisbon, Portugal) since 2006 and developed TB.

CASE REPORTS

CASE 1

A 26 years-old male patient of romani ethnicity, street market worker, had a diagnosis of Psoriatic arthritis (PsA) when he was 20 years old, with recurring oligoarthritis affecting the knees. The patient was proposed for therapy with IFX (5mg/kg every 8 weeks) in 2009 and underwent prior latent TB screening in the local CDP with chest X-ray, which was normal, two tuberculin skin tests, which were negative (0 mm), and an IGRA test, which was negative. No risk factors for latent TB were identified and therefore the patient did not undergo isoniazid therapy. IFX was started on December 2009 and after two drug administrations, the patient developed severe respiratory symptoms and was admitted to our hospital. A diagnosis of milliary TB was made based on chest imaging and *Mycobacterium tuberculosis* isolated in sputum. The patient underwent quadruple anti-TB therapy (isoniazid, ethambutol, pyrazinamide and rifampicin), as an outpatient with good response. The patient is now on treatment with ustekinumab.

CASE 2

A 17 years-old female patient, student, was diagnosed with Juvenile Idiopathic Arthritis (JIA) – enthesitis-related arthritis – when she was 14 years old, with axial inflammatory pain and peripheral oligoarthritis. The patient was proposed for ADA therapy in 2010. She underwent latent TB screening in the local CDP prior to starting ADA. The chest X-ray was normal, the two tuberculin tests were 0 mm and 3mm and the IGRA test was negative. The patient did not have any epidemiological risk factors, therefore she did not undergo therapy for latent TB. The patient began ADA and

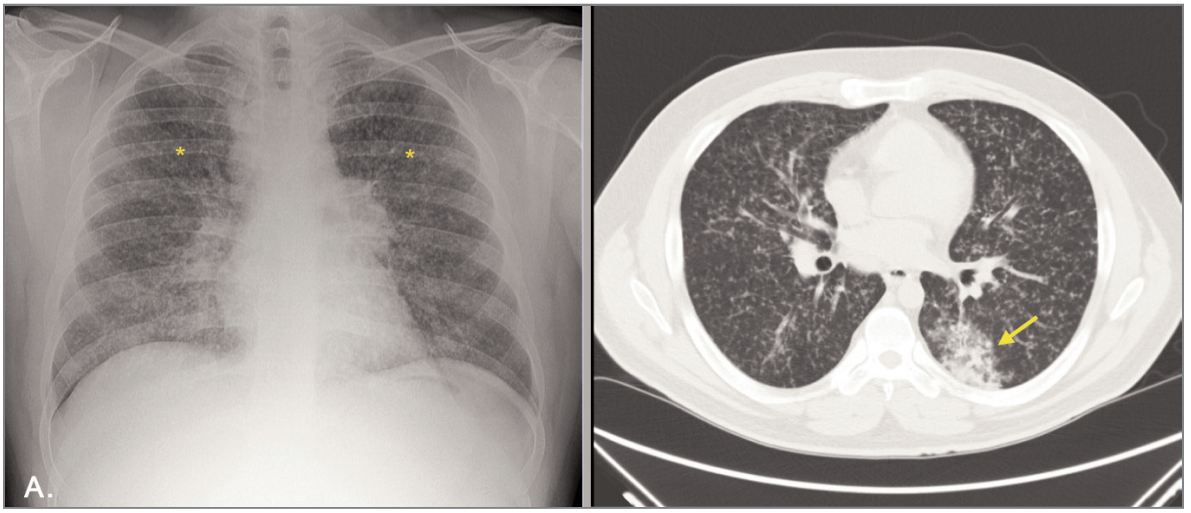

FIGURE 1. Case 1 patient A. PA chest x-rays demonstrate wide spread small nodular opacities distributed throughout both lungs (*); B. Best CT showed dispersed mocronodular pattern, with presence of small consolidation in air bronchogram in the upper segment of the left lower lobe (arrow)

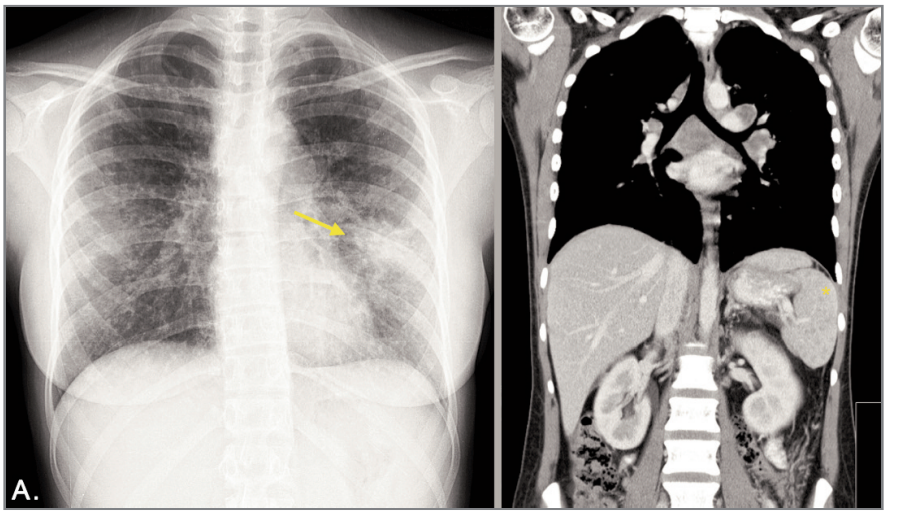

FIGURE 2. Case 2. PA chest x-rays demonstrate wide spread small nodular opacities distributed throughout both lung and air space opacification of the left lung (arrow); B. Thoraco-abdominal CT scan with normal dimensioned spleen, presenting several nodular images (*)

one year later developed respiratory symptoms. A military TB diagnosis was made, based on lesions identified on the spleen and lymph nodes (Figure 2) and on the isolation of *Mycobacterium tuberculosis* in the sputum and in the bronchoalveolar lavage. The patient underwent quadruple anti-TB treatment (isoniazid, ethambutol, pyrazinamide and rifampicin) with favourable evolution. As her disease remained in remission on DMARDs therapy, there was no reintroduction of a biological drug. Retrospectively it was possible to identify an active TB case with whom the patient had contacted with. Despite all close contacts were submitted to a diagnostic workout for active TB and received latent TB treatment by the local CDP; the patient was not invited for this screening, as she was not identified as a close contact.

CASE 3

A 36 years-old male patient, physical education teacher, was diagnosed with PsA at the age of 18, with peripheral and axial involvement. The patient was proposed for treatment with golimumab (GOL) in 2010. He underwent latent TB screening in the local CDP with chest X-ray, which was normal, two negative tuberculin tests and a negative IGRA test. The patient began GOL therapy, however, due to secondary failure, he was switched to ADA in 2014. He had no further evaluation in the CDP at this time. In 2016, two years af-

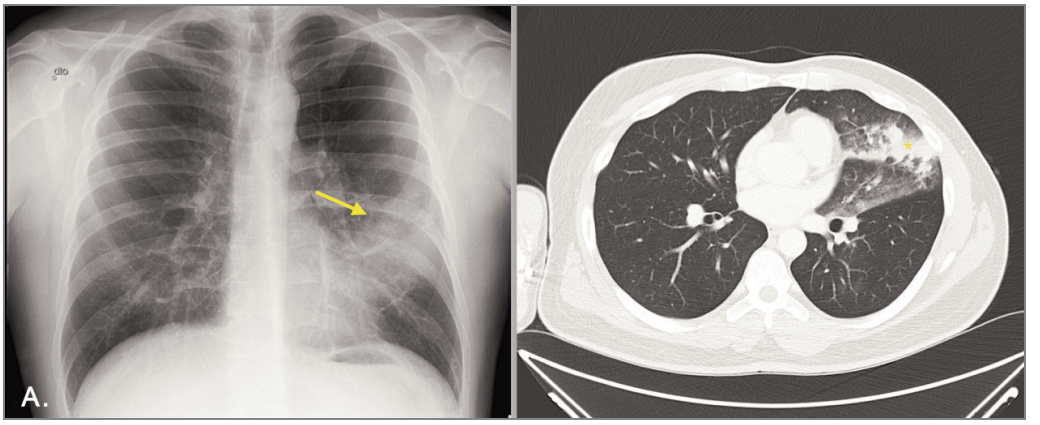

FIGURE 3. Case 3. A. Chest x-rays showing air space opacification of the left lung (arrow); B. CT scan showing lingual interstitial infiltrate (*).

ter beginning ADA, the patient developed a respiratory infection. A bronchial TB diagnosis was made, with acid-alcohol-resistant bacilli present in the bronchoalveolar lavage and necrotizing granuloma in the bronchial biopsy. The patient underwent quadruple anti-TB therapy (isoniazid, ethambutol, pyrazinamide and rifampicin), resulting in the resolution of the infectious condition. The patient is currently being treated with secukinumab.

CASE 4

A 58 years-old male patient, diagnosed with adult-onset Still disease in 1988 was proposed for biologics in 2001. This patient was one of the first patients starting anti-TNF therapy at our centre, prior to the implementation of a mandatory TB screening before starting biologics. Therefore, there are no clinical records of latent TB screening of this patient in the CDP and he did not undergo latent TB therapy. The patient began IFX in 2001, without subsequent assessment in the CDP. The patient underwent therapy for 18 years always on remission (dose reduced to 3mg/kg every 9 weeks). In January 2019, the patient developed milliary TB, with pulmonary, hepatic, splenic, testicular, oropharyngeal, ganglionar and periarticular involvement. There was a *Mycobacterium tuberculosis* isolation in the bronchoalveolar lavage culture test, in the oropharynx exudate and in synovial fluid of an olecranon bursitis. The

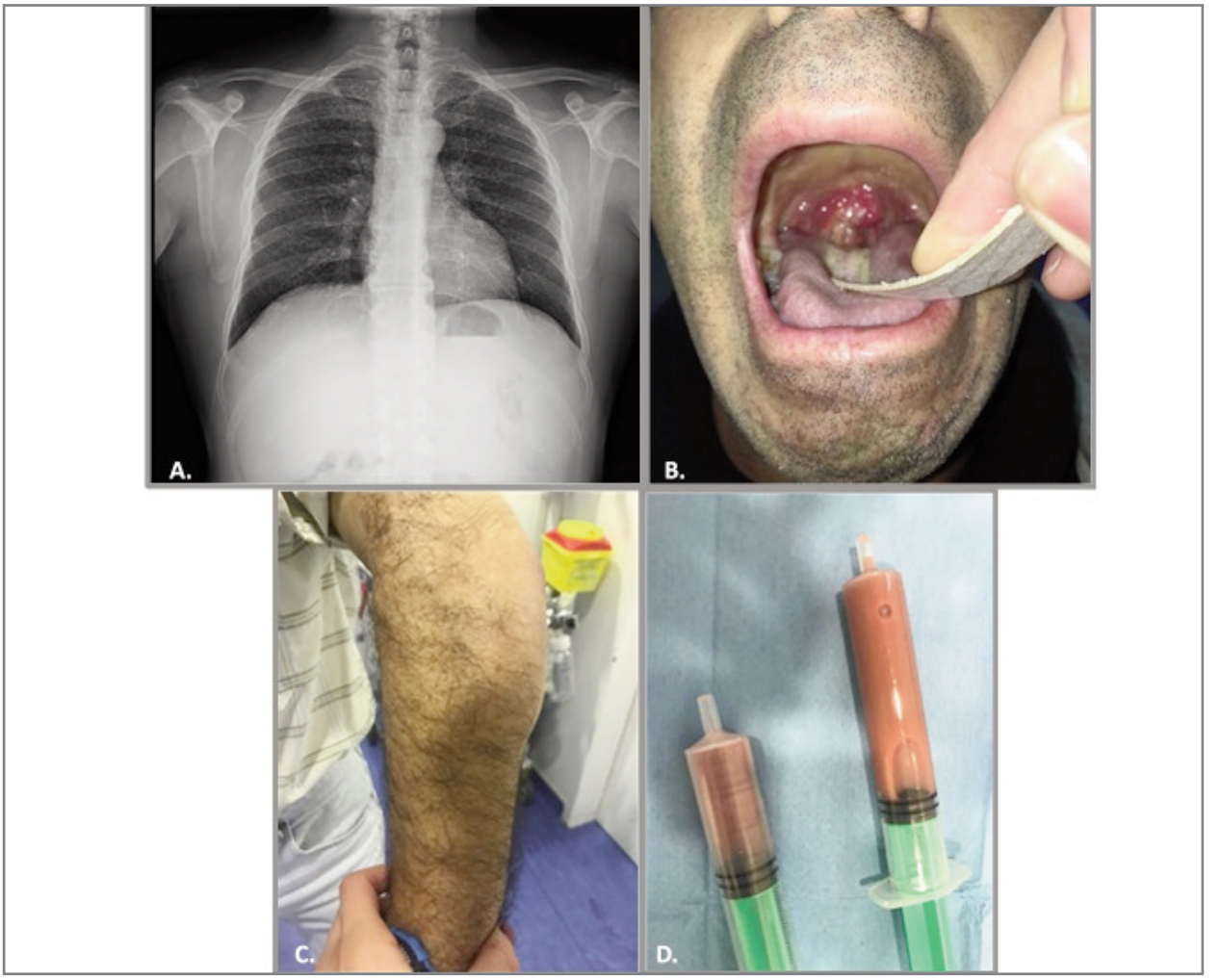

FIGURE 4. Case 4. A. PA chest x-rays demonstrate wide spread small nodular opacities distributed throughout both lungs; B. Tonsillar hypertrophy and exudate (with isolation of *M. tuberculosis* in oropharynx exudate); C. Olecranon bursitis (*M. tuberculosis* isolation in synovial fluid); D. Synovial fluid of olecranon bursitis.

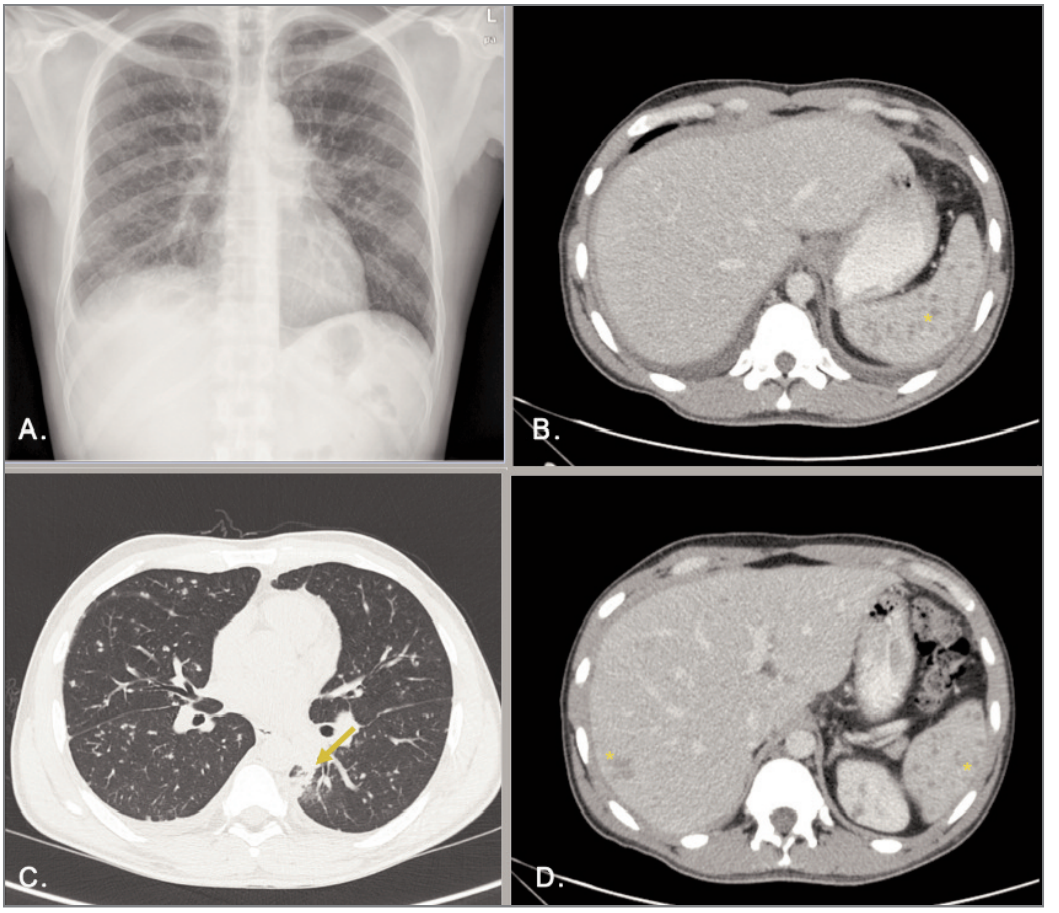

FIGURE 5. Case 5. A. PA chest x-rays demonstrate wide spread small nodular opacities distributed throughout both lungs; B and D. Slight hepatomegaly wuth a regular contour, with several scattered hypoden de nodules of irregular control, coexistence of several hypodense splenic micronodules (*); C. Consolidation with air bronchogram of the upper left lower lobe segment-arrow limited by the fissurem in addition to multiple grossly nodular and centrilobular opacities with multilobar involvement.

patient had a positive IGRA test. This patient was started on quadruple anti-TB therapy (isoniazid, ethambutol, pyrazinamide and rifampicin), however, subsequent results showed strain resistance to isoniazid, ethambutol and pyrazinamide. For this reason and due to worsening of his condition, the patient had to be hospitalized in the infectious diseases department. Antibiotics were changed to levofloxacin, linezolid, amikacin, cycloserin and rifampicin. The patient was subsequently discharged with indication for follow-up at a TB resistance centre.

CASE 5

A 37 years-old male patient, engineer, born in Angola and living in Portugal since 2000, with frequent visits to his country of origin was diagnosed with Ankylosing Spondylitis when he was 20 years old. He was proposed for IFX therapy in 2004 and underwent latent TB screening at the local CDP. He had a normal chest X-ray and a tuberculin skin test of 15 mm. IGRA was not part of the screening tests performed in 2004. Due to a positive tuberculin skin test, the patient was treated with isoniazid for 6 months. No subsequent assessment in the CDP was made. The patient underwent IFX for 15 years with good disease control (dose reduced to 5mg/kg every 9 weeks). In November 2018, the patient developed respiratory symptoms, weight loss and fever. A milliary TB diagnosis was made based on pulmonary, hepatic and splenic involvement (Figure 5). *Mycobacterium tuberculosis* was isolated in the bronchoalveolar lavage and on hepatic microgranulomas. The patient underwent quadruple anti-TNF treatment (isoniazid, ethambutol, pyrazinamide and rifampicin) with good response.

DISCUSSION

From the 942 patients registered in Reuma.pt who visited our day-care unit to undergo treatment with biologics, 5 developed TB between 2006 and 2019 (the 5 cases here reported) and 3 developed TB between 1999 and 2006 (reported elsewhere[7]), corresponding to 0.85% of the exposed patients.

We would like to emphasize that only one case (patient number 1) can be classified as a reactivation of latent TB, as it occurred immediately after starting of the biotechnological therapy However, this patient was of romani ethnicity and this population group has a higher incidence of TB all-over Europe.8 In the context of the Portuguese recommendations probably this patient could have been regarded as a high-risk patient and should have received treatment for latent TB before starting biologics.Of interest, all cases were observed in patients treated with anti-TNF monoclonal antibodies, specifically ADA and IFX, suggesting a higher frequency of TB in the context of treatment with these drugs.

The other 4 cases probably represent new TB infections and highlight the relevance of a high degree of suspicion for TB that has to be present in all appointments for patients on anti-TNF.

One of these patients (patient number 5) received a 6-months isoniazid treatment regime, which is recognized as effective but offers a lower degree of protection (65-69%) as compared to the first line 9 months' treatment (90%).3 It is unclear why the patient received this shorter treatment option. Issues related to compliance, traveling to his home country or drug tolerance/toxicity might have played a role in the decision by the TB expert. It is likely that this case corresponds to a new TB infection. Despite this, patients who are not treated with the standard 9 months' isoniazid regime should probably be considered for yearly surveillance by a TB expert.

Patient number 4 represents a special situation as he began biological therapy in 2001, when latent TB screening was not routinely performed. Nevertheless, this patient should have been subsequently referred to a TB expert at a CDP, as was recommended for all patients after the first guidelines published in 2006. It is unclear why there is no written reference of this patient being reviewed by a TB expert, an error in the clinical charts, a non-compliance with internal procedures or miscommunication are possibilities. Nevertheless, this was clearly a new TB infection and not a reactivation and the reference to a TB expert would have not prevented this infection. However, it could have provided an early diagnosis.

Case number 2 illustrates the increased susceptibility for acquiring a TB infection by patients treated with a TNF antagonist. These patients whenever they have contact with active TB cases should be immediately screened for active TB and if active infection is excluded they should at least receive latent TB treatment.

Patient number 3 was on anti-TNF for a long period of time and developed TB 2 years after a switch to ADA, highlighting the relevance of TB screening when a patient switches drugs.

In summary these 5 cases emphasise the role of rheumatologist's awareness towards the development of active TB that might occur at any time during biologic treatment and also the relevance of routine surveillance by TB experts of patients on long term biologic therapy, particularly with anti-TNF drugs. It is also relevant to better use Reuma.pt as a tool to clinically monitor safety procedures regarding the prevention and early diagnosis of TB in the context of biologic treatment.

A review of the initial screening procedures does not seem to be necessary, as all cases here reported were not related to any hypothetical issue in the local recommendations.

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