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Case Report

A CASE REPORT OF CHRONIC NECROTISING ASPERGILLOSIS ON TOCILIZUMAB THERAPY

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Abstract
A case report of 64 years old gentleman with underlying Rheumatoid arthritis (RA) which was resistant to disease modifying antirheumatic drugs (DMARD); prednisolone, methotrexate, sulfasalazine and hydroxychloroquine required adalimumab. He did not respond to adalimumab and tocilizumab was subsequently given. He however developed pulmonary symptoms of which further investigations revealed high suspicious of Chronic necrotizing aspergillosis. We discuss our challenges in managing this case.

Keywords: Rheumatoid arthritis, adalimumab, tocilizumab, chronic necrotizing aspergillosis

Introduction

Biologics therapy was introduced in 1998 which consist of anti-TNF, IL-1 inhibitor, and IL-6 inhibitor and anti CD20 antibody for Rheumatoid arthritis which is resistant to maximum DMARD[1]. These biologics agent has been proven to be potent drugs to treat resistant RA and to prevent RA related articular damage especially if given earlier[2]. Although these agents are safe and effective to treat RA, meta-analysis, post marketing surveillance and case reports revealed serious adverse event in particular infections includes tuberculosis reactivation, opportunistic infections and interstitial pneumonitis[3].

Aspergillosis sp is a ubiquitous organism which may cause serious infection in immunosuppressed state individuals. *Aspergillosis sp* may cause pulmonary infection ; Allergic bronchopulmonary aspergillosis (ABPA) , Aspergilloma, Chronic necrotizing aspergillosis and Invasive aspergillosis depending on the host immune state[4]. We are reporting a case of Invasive pulmonary aspergillosis after adalimumab and ongoing tocilizumab therapy for RA.

Case report

A 64 years old Malay gentleman, who was diagnosed with Rheumatoid arthritis 7 years ago. At diagnosis his rheumatoid factor is positive and clinically diagnosed base on American College of Rheumatology (ACR) criteria being fulfilled; early morning stiffness and joint pain involving both hand he was initially treated with prednisolone, methotrexate and addition of sulfasalazine. He could not tolerate Leflunomide. He was later put on prednisolone 15 mg, methotrexate 20 mg/week, sulfasalazine 1g BD and Hydroxychloroquine 200mg OD however clinically his DAS 28 was more than 5.1. His TB Quantiferon test was positive and he was treated as latent tuberculosis prior to biologic initiation. He was first started on adalimumab which he responded immediately till cycle 8th where he failed to respond. Adalimumab was stopped and substituted with Tocilizumab. He was on Tocilizumab for 1 year and 6 months before he presented with fever and cough with minimal hemoptysis for 2 weeks with loss appetite and loss of weight 2.5 kg within 2 months. On admission he was afebrile and no crepitations or bronchial breathing was detected. His WBC was normal at 8 x10 ^{9} /L with no eosinophilia and biochemistry results; CRP was elevated at 1.93 mg/dL and ESR was 106 mm/hour. Procalcitonin was mildly elevated at 1.29 ng/ml. Chest radiograph was unremarkable however his CT thorax revealed multiple small nodules seen in bilateral upper lobe and lower lobe and lingula with surrounding fibrotic and bronchiectatic changes. More nodules at the left upper lobe with consolidative changes at the right lower lobe. No fungal ball or tree in bud in the initial CT thorax. Thus correlating with bronchoscopy finding which revealed mild left upper lobe inflammation. Bronchoalveolar lavage (BAL) Culture and sensitivity (C&S) was negative, tuberculosis C&S was negative from BAL samples and fungal C&S was negative. However the Aspergillus antigen from BAL samples was positive from two separate BAL procedures. He was initially treated as Health care associated pneumonia (HCAP) and symptoms improved with minimal productive cough. He had a repeat CT thorax which showed increase amount of small nodules with tree in bud appearance at the left upper lobe and lingula region which raised the suspicion of Invasive pulmonary aspergillosis. He was treated with intravenous Amphotericin B (AMB) initially which was complicated with acute kidney injury as the creatinine from 70 mmol/l increase to 170 mmol/l which subsequently normalized after stopping AMB. As clinically patient is well and did not complained of dyspnea and hemoptysis medication was changed to tablet Itraconazole 400 mg daily. He was discharge and closely reviewed under our respiratory follow up. Despite Itraconazole treatment for 4 months, his CT thorax finding worsening on left lung with increment of pulmonary nodules with tree in bud and some of the nodule has become cavity and new nodules over the right lower lobe. BAL was repeated and he was treated as Pulmonary tuberculosis concurrently as his Mycobacterium Tuberculosis PCR from recent BAL sample turn out to be positive. His ESR was elevated ranging from 79-114 mm/hour however his Procalcitonin level was low 0.02 ng/ml. He tolerated the current therapy with evidence of weight gain and no worsening of symptoms.

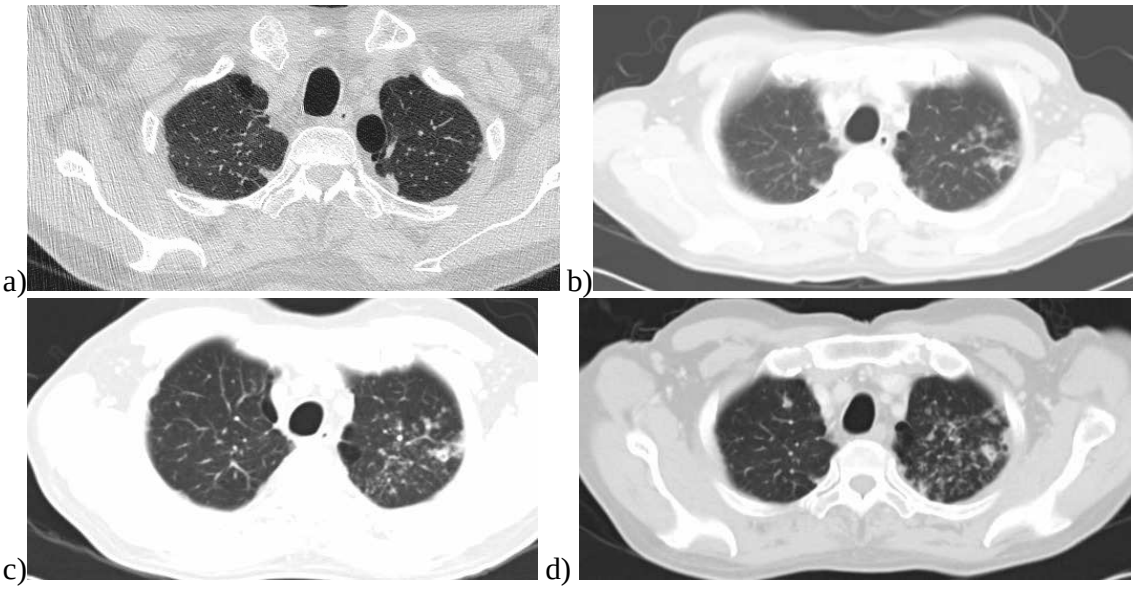

Figure 1: a) Baseline CT thorax during investigation for latent tuberculosis prior commencement of biologic agent b) initial CT Thorax which showed nodular lesions more over the left apical region c) follow up CT thorax due to the nodular lesion with positive aspergillus antigen which revealed increase nodular lesion and tree in bud lesion d) after 4 months of anti-fungal itraconazole 400 mg/day noted more cavitatory lesion over previous area.

Discussion

We report a case of high suspicious of Chronic Invasive Aspergillosis in a patient who is known to have Rheumatoid arthritis who was previously on Adalimumab and recent Tocilizumab. The patient was treated as latent tuberculosis infection due to positive TB quantiferon at baseline prior to introduction of biologics. He was also known to have bilateral apical bullae with fibrosis and traction bronchiectasis anterior segment of right upper lobe. Thus, he had the risk factor for Aspergillus infection with present of cavity and he is immunosuppresed due to the prednisolone, DMARDs and biologics agent. Both TNF-α and IL-6 are important for self-defense against fungal infection and risk of tuberculosis infection is higher in patients treated with TNF-α[5]. The risk of infection secondary to immunosuppressed state in Tocilizumab (IL-6 inhibitor) treated patients is similar if compared to TNF-α treated group. Tocilizumab was introduce to our patient as she loss respond to TNF-α inhibitor [6].

Aspergillus sp. is an ubiquitous fungal which may cause spectrum of disease from Invasive aspergillosis (Invasive pulmonary aspergillosis, sinus aspergillosis, disseminated aspergillosis, and single organ invasive aspergillosis) , chronic cavitatory aspergillosis, aspergilloma and allergic bronchopulmonary aspergillosis [7]. In this case the diagnosis of Chronic necrotizing pulmonary aspergillosis was made as the constitutional symptoms is within 2 months with aspergillus antigen test (galactomannan antigen) was positive from 2 consecutive BAL procedures. Chronic necrotizing pulmonary aspergillosis presented as insidious progression as it is associated with low grade immunosuppressions and may worsened

underlying pulmonary disease. Fungal culture are very rarely positive, thus Galactomannan test has been well proven to be highly sensitive and specific especially well studied in haematological malignancy subset and immunosupprressed post transplant patients in diagnosis of aspergillus infection [8]. The sensitivity improve if interpretation is assisted with CT Thorax imaging which support the diagnosis of aspergillus infection and allow earlier diagnosis with commencement of treatment [7]. CT Thorax is sensitive but more specific compared to MRI Thorax with may present with nodular lesion, target lesion, air crescent sign and halo sign in the early phase of the disease. MRI Thorax although was found to have higher sensitivity but has poor specificity as compared to CT Thorax[9]. Voriconazole is the anti-fungal of choice in invasive aspergillosis compared to AMB especially in haematological and immunosuppressed transplant group[10]. According to IDSA guideline 2008 for Chronic invasive pulmonary aspergillosis itraconazole is the anti-fungal of choice although voriconazole and posaconazole maybe effective. The need for lifelong treatment may need to be considered as the patient is on ongoing immunosuppressive therapy and associated with better outcome[7]. In our case we continue the therapy and close clinical and radiological assessment was done. Our search from Pubmed revealed only one case report regarding recurrent allergic bronchopulmonary aspergillosis in rheumatoid arthritis patient treated with etarnercept and tocilizumab. We suggest more study to determine the association of aspergillus infection and its temporal correlation with imaging improvement as in our case the imaging worsen although we note the possibility of concomitant new onset pulmonary tuberculosis despite tocilizumab was stopped.

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