MEGA JOURNAL OF CASE REPORTS

Case Presentation

Compiled Date: January 14, 2023

Abatacept in the Treatment of Rheumatoid Arthritis in the Presence of Pulmonary Adenocarcinoma: A Case Report and Literature Review

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Abstract

Background: Rheumatoid arthritis patients are more likely than the overall population to acquire cancer, especially lung cancer, which is difficult to detect early. Treatment options for patients with both diseases have been challenging.

Case summary: We present the case of a 54-year-old lady who had moderately active rheumatoid arthritis as well as lung adenocarcinoma and chose abatacept therapy after unsatisfactory treatment with traditional synthetic disease-modifying medicines and glucocorticoids and had excellent outcomes. After nearly one year of treatment, the patient's clinical symptoms considerably improved, and the disease activity was reduced, the patient continued to achieve clinical remission, and the lung HRCT showed no progress compared with the previous one.

Conclusion: Abatacept, a biologic disease-modifying anti-rheumatoid medication, has been shown to be efficacious and safe in clinical studies in a number of conditions. The selection of immunosuppressive drugs in rheumatoid arthritis patients with tumors is a critical issue for doctors. This example indicates the feasibility of utilizing abatacept to treat rheumatoid arthritis in lung cancer patients.

Keywords: Rheumatoid arthritis; Abatacept; Lung adenocarcinoma; Therapy; Tumor necrosis factor inhibitors

Introduction

Rheumatoid Arthritis (RA) is an autoimmune illness characterized by persistent symmetric polyarthritis. Patients with RA not only have a high disease burden, but they are also more prone to acquire infections and certain malignancies, including lymphomas and lung cancer, than the general population. Biologic and Targeted Synthetic Disease-Modifying Antirheumatic Drugs (b/tsDMARDs) can successfully treat RA. The possibility of the Tumor Necrosis Factor Inhibitors (TNFi) being possibly carcinogenic has also been raised due to their ability to suppress the immune system and increase sensitivity to oncogenic agent infection **[1].** The selective T-cell stimulator Abatacept (ABA), which has been approved for the treatment of RA **[2],** operates through a fundamentally distinct mechanism from other b/tsDMARDs: by competing for the costimulatory signal on antigen-presenting cells, it lowers cellular immunity.

We present a patient with RA complicated with lung adenocarcinoma. Two years after the surgery of lung cancer, the patient with active RA accompanied by severe pain that could not be effectively treated with Conventional Synthetic Disease Modifying Antirheumatic Drugs (csDMARDs) and glucocorticoids and the symptoms improved after the treatment with ABA. This case report adds to the reference to the treatment of such diseases to clinical doctors.

Case Presentation

A 54-year-old woman was diagnosed with RA 20 years ago because of swelling and morning stiffness in the small joints of her hands after giving birth. For several years, she was treated with Sulfasalazine (SSZ), Iguratimod (IGU), and Hydroxychloroquine (HCQ). She went to the local hospital in May 2018 with complaints of worsening arthralgias and joint stiffness. Symptoms included pain in the right middle finger's proximal interphalangeal joints, the first proximal interphalangeal joint of the left hand, the second metacarpophalangeal joint, the wrists, and the right knee joint. At the time, her disease activity score derivative for 28 joints (DAS 28) was 4.21 and she was in moderate disease activity. Lung CT revealed mixed ground-glass nodules in the lower lobe of the right lung, multiple small ground-glass nodules in the middle and lower lobes of the right lung and fibrosis in the lower lobes of both lungs. The patient was diagnosed with moderately active RA, pulmonary nodules and pulmonary fibrosis. Given the lack of disease control with conventional medical therapy, she was switched to etanercept, Methotrexate (MTX), IGU and HCQ. After a period of treatment, the joint pain was relieved, and the DAS28 score showed discernible improvement.

The patient was admitted to the hospital in February 2019 with pneumonia. Symptomatic treatment included anti-inflammatory, cough relief, and phlegm removal. Therapy was halted one month later due to no discernible improvement in cough or sputum. Re-examination of lung CT revealed multiple mixed ground-glass nodules in the right lower lobe, raising the possibility of lung cancer **(Figure 1a);** PET-CT revealed small ground-glass nodules in the basal segment of the right lower lobe, with no abnormality in FDG, raising the possibility of

micro-invasive adenocarcinoma. All RA medications, including etanercept, were stopped three days before surgery. In April 2019, the patient was taken to the hospital and underwent a video-assisted thoracic surgery radical operation for right-lower lung cancer under general anesthesia. Histopathology revealed a right lower lobe peripheral minimally invasive adenocarcinoma (pT1N0M0). After 7 days of recovery, she resumed RA treatment with IGU. To control the disease, the patient was treated with SSZ, HCQ, leflunomide and thalidomide over the next two years. And leflunomide was discontinued after a generalized rash. She still had bilateral wrist pain, primarily on the left side, after almost all csDMARDs and hormone therapy, as well as swelling and mobility impairment. But we dare not use biological agents hastily after an operation.

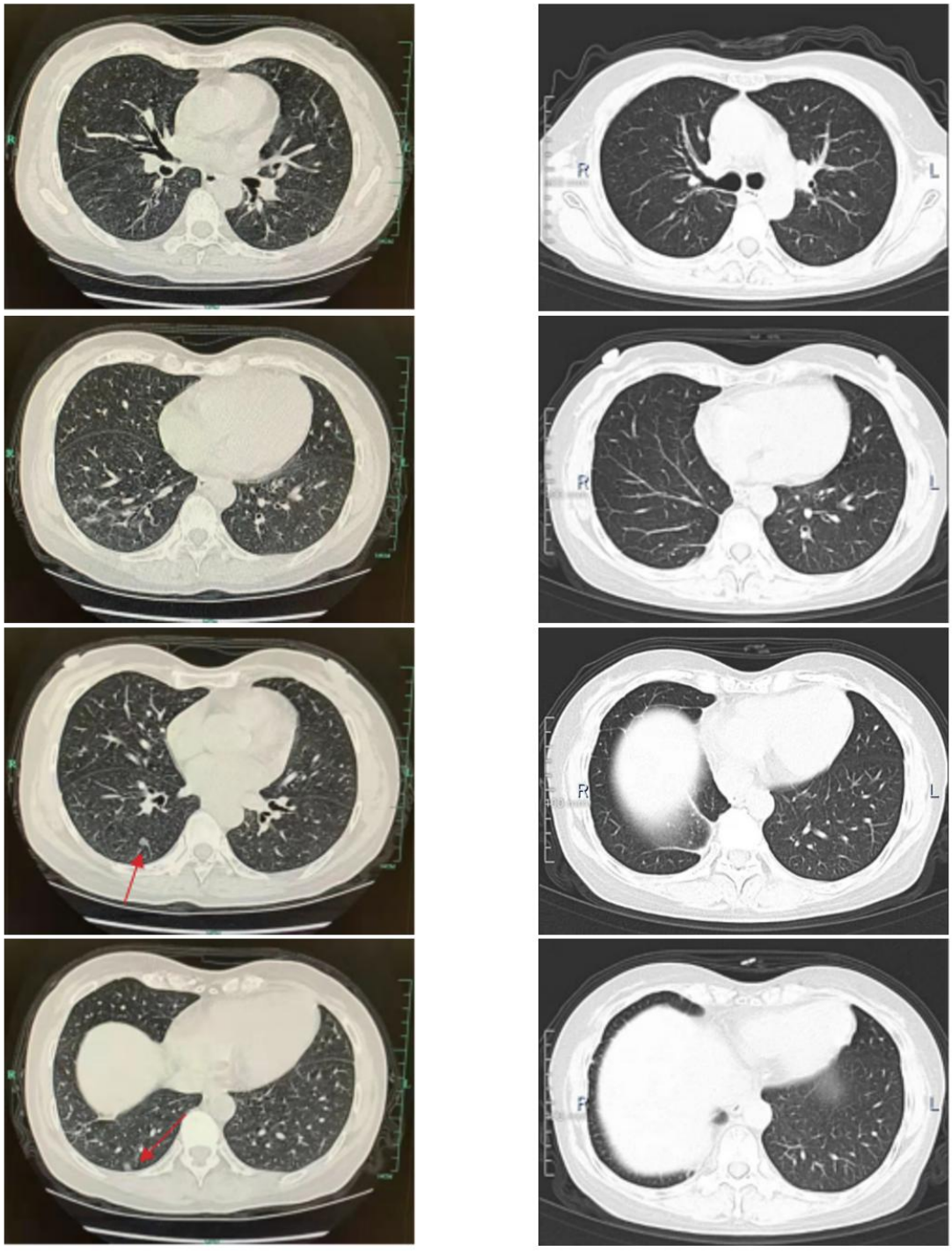

Figure 1: High-Resolution Computed tomography (HRCT) of lung. (a) Preoperative HRCT in April 2019, the ground glass nodule indicated by the red arrow. In addition, there were scattered fibrous foci and bronchiectasis in both lungs. (b) HRCT after the abatacept therapy in February 2022, no new nodules were found, fibrous foci in both lungs were significantly improved, and bronchiectasis showed no obvious progress.

Up until April 2021, she had generalized multi-joint migratory pain throughout her body, as well as mild deformation of her right wrist and restricted movement of her right knee joint. Laboratory tests revealed that the Erythrocyte Sedimentation Rate (ESR) was 23 mm/1h (0~20 mm/1h), the hypersensitive C-Reactive Protein (CRP) was 13.2 mg/L (0~10 mg/L), and the Rheumatoid Factor (RF) was 25 IU/ml (0~22 IU/ml), indicating that the patient was moderately active in RA (DAS28 4.49). The patient's ultrasound of the left wrist joint revealed extensive synovial thickening, with the thicker part measuring about 3.1 mm and blood flow signals visible inside. Because of the patient's history of lung cancer, the biological agent ABA was chosen for treatment. After 2 months of treatment, ESR and CRP were reduced to 4 mm/1 h and 0.8 mg/L, respectively **(Figure 2),** and the DAS28 was reduced to 3.51.

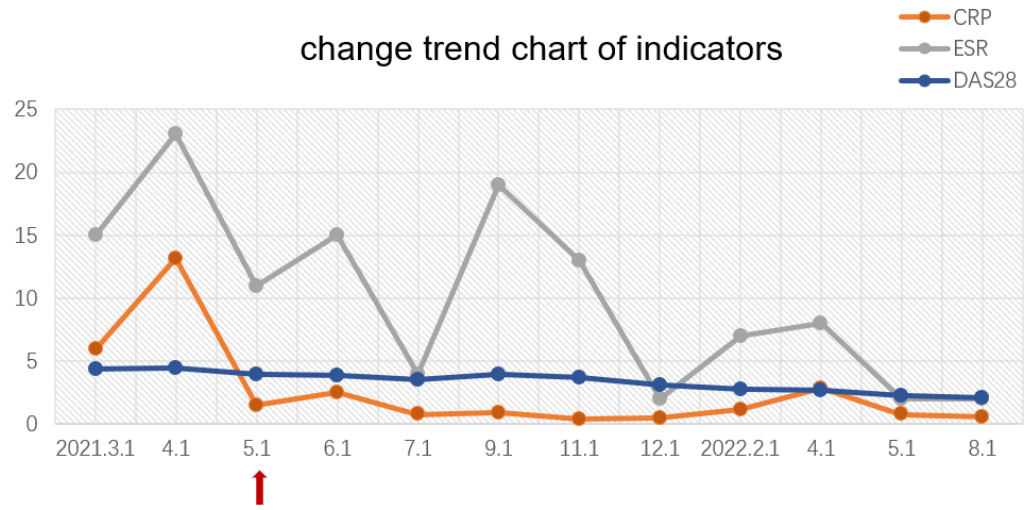

Figure 2: Trends in ESR, CRP and DAS28 scores of patients in the past year. The red arrow points to May 2021, the patient started abatacept.

Since then, the patient has been receiving ABA, IGU, SSZ, and HCQ on a regular basis. After three months, this strategy yielded a positive reaction (improvement in DAS28 of 2.3). Furthermore, her edema and soreness in bilateral wrist joints also improved significantly during this time. The re-examination of lung CT revealed no new nodules or worsening, and the fibrosis in both lungs was significantly improved compared with the previous one **(Figure 1b).** In conclusion, ABA appears to be a safe, effective, and well-tolerated treatment for individuals with RA complicated by lung cancer. And provide some advice and confidence for clinicians dealing with such patients.

Discussion

RA is an autoimmune inflammatory disease which can cause progressive joint damage, and also can involve extra-articular **[3].** In recent years, the risk of RA patients suffering from tumors has been increasing, especially lung cancer **[4].** According to a meta-analysis, RA patients had a slightly higher Standardized Incidence Rate (SIR) of overall malignancy than the general population, including lymphoma, lung cancer, and Non-Melanoma Skin Cancer (NMSC). Lung cancer risk typically increases by around twofold. Breast and colorectal cancer risks would fall, while other cancer risks, such as cervical and prostate cancer, would stay the same as in the general

population [5]. There are several factors explaining why RA patients are more likely to develop malignancies. (1) Environmental: Tobacco use raises the risk of both lung cancer and RA. Tobacco use increases the Cyclooxygenase-2/Thromboxane A2 (COX-2/TxA2) pathway, which acts as a feedback regulator in the formation of lung cancer and synoviocytes similar to RA fibroblasts [6]. (2) Disease activity: Because RA is an autoimmune disorder; persistent immunologic stimulation may raise the possibility that immune system cells could become cancer. As a result, the incidence of cancer in RA patients may grow. Patients with severe and active RA had a 2-fold greater risk of cancer, compared to those with modest RA activity, according to a prospective, case-control cohort study conducted in Germany [7]. (3) Immunosuppressive therapy: The introduction of immunotherapy improves patients' quality of life by lowering disease activity and delaying joint degeneration. Regarding the relationship between immunosuppressive therapy and the likelihood of acquiring cancer, there is, however, contradictory evidence. Tumor Necrosis Factor alpha (TNF-alpha) is a proinflammatory cytokine produced by monocytes and macrophages that is involved in normal immune and inflammatory responses in the body. Theoretically, TNFi might increase the risk of cancer [8]. 3367 patients who had never used a biological agent were compared to 11931 individuals who had received TNFi treatment in the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. For these groupings, the risk of lymphoma was not significantly different [9]. (4) Genetics: Both RA and cancer have a genetic component to them. According to some experts, both illnesses demonstrate some family aggregation [10]. By causing immune cell death, biologics can suppress the inflammatory response, improve symptom management, and reduce structural damage in RA. However, there is not enough evidence at this time to establish a link between biologic therapy and the risk of cancer. According to ECCO standards, immunosuppressants should not be administered for at least two years after the conclusion of cancer therapy. For malignancies with a moderate or high risk of recurrence, the panel suggested waiting up to 5 years [11]. Immunosuppression was more effective when administered before 6 years following the conclusion of cancer therapy [12]. Shorter time frames could be safe for those who have a lower chance of cancer recurrence, although it is uncertain if they are. According to the research by Hjalmar and Thomas et al. [13] RA patients who received TNFi, Tocilizumab, ABA, or Rituximab did not have a greater overall risk of getting cancer than the general population or RA patients who received csDMARDs. Furthermore, Pauline et al. observed that TNFi medication did not raise the probability of RA patients acquiring first malignancies or recurrences [14]. This might be related to the mechanism of TNFi. TNFi may promote death in immune cells that make TNF, in addition to lowering the downstream inflammatory factors produced by other immune cells. Long-term TNFi use can inhibit the body's immune response, resulting in immune insufficiency. Immune weakening and decreased host surveillance of early tumors may hasten cancer growth [1]. The use of TNFi in people who have cancer or a history of cancer is still a hotly debated topic right now. This patient had pulmonary ground-glass nodules as well as two foci of pulmonary fibrosis and bronchiectasis. Rituximab-treated patients showed a greater 5-year survival rate in a study on the 5-year survival of RA-related bronchiectasis patients treated with TNFi [15]. After being diagnosed with lung cancer in 2019, the patient opted to discontinue TNFi and switch to the somewhat safer antirheumatic medication ABA two years later.

ABA, a soluble recombinant fusion protein that is approved for the treatment of moderate to severe RA, suppresses T-lymphocyte costimulatory signalling. T cell activation is essential for the development of RA. Two stages are necessary for T cell activation: First, Antigen Presentation Cells (APC) must detect certain antigens,

and then CD28 on T cells must bind to CD80/68 on APC to generate a costimulatory signal. The impact of ABA on this costimulatory signal can suppress T lymphocyte activation, decrease inflammation, and postpone the disease process, relieving joint pain and decreasing disease activity. The following are the reasons why ABA therapy was chosen for RA patients with a history of lung cancer: (1) Effectiveness: Numerous clinical trials have proven that ABA treatment for RA is effective **[16,17].** This patient showed significant improvement in symptoms and indicators after using ABA. (2) Low immunogenicity: The ability to elicit an immune response is referred to as immunogenicity. Low immunogenicity, the body is not easy to produce antibodies to ABA, in vivo can play a better effect. Clinical trials have shown that the rate of immunogenic response to ABA is low **[18].** (3) Safety: In RA patients, ABA usage does not raise the risk of cancer (except NMSC). Simon et al. **[19]** reported no significant differences in the risk of certain malignancies (other than NMSC) or infection between individuals treated with ABA or other b/tsDMARDs. In contrast to other bDMARDs, ABA use was not linked to an overall increased cancer risk, according to research by Germay et al. **[20].** Lung cancer and Interstitial Lung Disease (ILD) share some physiopathological alterations **[21].** Nakashitade et al. **[22]** reported that individuals with deteriorating or new ILD were all treated with TNFi in two retrospective analyses of RA-ILD patients, but those treated with ABA exhibited no new onset or deterioration. The patient belonged to the early stage of lung adenocarcinoma, and did not receive postoperative radiotherapy and chemotherapy. For malignant tumors in other parts of the body, late stage or active cancer undergoing radiotherapy and chemotherapy, could ABA still be effective? Is ABA still safe for three, five, or even ten years in cancer patients with RA who have long survival? These need to be further explored. Because clinical trials frequently exclude these patients, information on the use of ABA in the treatment of preexisting solid tumors is still limited.

Conclusion

RA is a type of autoimmune disease that causes erosive inflammatory arthritis. For the treatment of RA, several biological agents have been approved. ABA has been shown in both domestic and international studies to significantly reduce RA symptoms, control disease activity, delay the progression of joint structural damage, and improve joint function. ABA not only effectively relieved the symptoms and disease condition of RA in this patient with RA complicated by lung cancer, but it also stabilized and improved the patient's pulmonary disease. Of course, additional long-term monitoring and cases are required to confirm this conclusion. The selection of immunosuppressive agents in RA patients with tumors is a serious issue for clinicians. This case suggests that ABA could be a viable treatment option.

References

1. Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006;295(19):2275-85.
2. Bonelli M, Lisa G, Stephan B, et al. Abatacept (CTLA-4Ig) treatment reduces T cell apoptosis and regulatory T cell suppression in patients with rheumatoid arthritis. Rheumatology (Oxford, England). 2016;55(4):710-20.

3. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet (London, England). 2016;388(10055):2023-38.
4. Wilton KM, Matteson EL. Malignancy Incidence, Management, and Prevention in Patients with Rheumatoid Arthritis. Rheumatol Ther. 2017;4(2):333-47.
5. Simon TA, Teresa AS, Marc CH, Samy S. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther. 2008;10(2):R45.
6. Huang QC, Huang RY. The cyclooxygenase-2/thromboxane A2 pathway: a bridge from rheumatoid arthritis to lung cancer? Cancer Lett. 2014;354(1):28-32.
7. Strangfeld A, Franka H, Rau R, et al. Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. Arthritis Res Ther. 2010;12(1):R5.
8. Lopez-Olivo MA, Tayar JH, Juan AM, et al. Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. JAMA. 2012;308(9):898-908.
9. Mercer LK, James BG, Lunt M, et al. Risk of lymphoma in patients exposed to antitumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Ann Rheum Dis. 2017;76(3):497-503.
10. Ekström K, Henrik H, Lena B, et al. Risk of malignant lymphomas in patients with rheumatoid arthritis and in their first-degree relatives. Arthritis Rheum. 2003;48(4):963-70.
11. Nguyen GC. First Do No Harm: Is It Safe to Use Immunosuppressants in Inflammatory Bowel Disease Patients With Prior Cancer? Gastroenterology. 2016;151(1):22-24.
12. Shelton E, David L, Frank IS, et al. Cancer Recurrence Following Immune-Suppressive Therapies in Patients With Immune-Mediated Diseases: A Systematic Review and Meta-analysis. Gastroenterology. 2016;151(1):97-109.e4.
13. Wadström H, Frisell T, Askling J. Malignant Neoplasms in Patients With Rheumatoid Arthritis Treated With Tumor Necrosis Factor Inhibitors, Tocilizumab, Abatacept, or Rituximab in Clinical Practice: A Nationwide Cohort Study From Sweden. JAMA Intern Med. 2017;177(11):1605-12.
14. Raaschou P, Jonas S, Carl T, et al. Tumor Necrosis Factor Inhibitors and Cancer Recurrence in Swedish Patients With Rheumatoid Arthritis: A Nationwide Population-Based Cohort Study. Ann Intern Med. 2018;169(5):291-9.
15. Md Yusof MY, Iqbal K, Darby M, et al. Effect of rituximab or tumour necrosis factor inhibitors on lung infection and survival in rheumatoid arthritis-associated bronchiectasis. Rheumatology (Oxford, England). 2020;59(10):2838-46.
16. Kremer JM, Charles P, Russell AS, et al. Longterm safety, efficacy, and inhibition of structural damage progression over 5 years of treatment with abatacept in patients with rheumatoid arthritis in the abatacept in inadequate responders to methotrexate trial. J Rheumatol. 2014;41(6):1077-87.
17. Blair HA, Deeks ED. Abatacept: A Review in Rheumatoid Arthritis. Drugs. 2017;77(11):1221-33.
18. Genovese MC, Tena CP, Arturo C, et al. Longterm Safety and Efficacy of Subcutaneous Abatacept in Patients with Rheumatoid Arthritis: 5-year Results from a Phase IIIb Trial. J Rheumatol. 2018;45(8):1085-92.

19. Simon TA, Boers M, Marc H, et al. Comparative risk of malignancies and infections in patients with rheumatoid arthritis initiating abatacept versus other biologics: a multi-database real-world study. Arthritis Res Ther. 2019;21(1):228.
20. de Germay S, Haleh B, Despas F, et al. Abatacept in rheumatoid arthritis and the risk of cancer: a world observational post-marketing study. Rheumatology (Oxford, England). 2020;59(9):2360-7.
21. Naccache JM, Gibiot Q, Monnet I, et al. Lung cancer and interstitial lung disease: a literature review. J Thorac Dis. 2018;10(6):3829-44.
22. Nakashita T, Ando K, Takahashi K, Shinji M. Possible effect of abatacept on the progression of interstitial lung disease in rheumatoid arthritis patients. Respir Investig. 2016;54(5):376-9.

Citation of this Article

Yixuan L, Jing W, Huan J, Jiaping Q, Ju Z, Wei H, Yuan Z, Teng W and Zhenhua Y. Abatacept in the Treatment of Rheumatoid Arthritis in the Presence of Pulmonary Adenocarcinoma: A Case Report and Literature Review. Mega J Case Rep. 2023; 6: 2001-2008.

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