

Pulmonary aspergillosis after treatment with infliximab in Still's disease and a literature review of Still's disease and pulmonary aspergillosis

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Abstract

The use of anti-tumor necrosis factor alpha (anti-TNF- α) agents has increased during the past decade in rheumatology practice. Opportunistic infections have been reported with anti-TNF- α agents in clinical trials and post-marketing usage. *Aspergillus* infection is a rare opportunistic infection that is associated with immunosuppression, and there are reported cases of pulmonary aspergillosis in various rheumatic diseases treated with anti-TNF- α agents. Here, we present the first case of pulmonary aspergillosis associated with infliximab treatment in a patient with Still's disease.

Keywords: Still's disease, pulmonary aspergillosis, tumor necrosis factor-alpha inhibitors, infliximab

Introduction

The use of anti-tumor necrosis factor alpha (anti-TNF- α) agents has increased in the past decade in rheumatology practice. As a result, the number of reported side effects has also increased (1). Non-tuberculous opportunistic infections, such as *Aspergillus* infections, are rare fungal opportunistic infections that are associated with anti-TNF- α agents (2, 3). Infliximab is an anti-TNF- α agent, which is a chimeric monoclonal antibody (1). Infliximab can almost completely neutralize TNF- α activity by blocking both its soluble and membrane-bound forms (3). Several case series and case reports have demonstrated the efficacy of infliximab in patients with resistant adult onset Still's disease (AOSD) (4, 5).

The first invasive pulmonary aspergillosis associated with infliximab therapy was reported in a patient with fistulizing Crohn's disease (6). Since then, several *Aspergillus* infections that are associated with infliximab therapy have been reported in various autoimmune diseases (2, 3, 7). We report the first case of pulmonary aspergillosis after infliximab therapy in a patient with AOSD, which was refractory to conventional therapies.

Case Presentation

A 45-year-old male patient was diagnosed with juvenile rheumatoid arthritis in a university hospital with complaints of fever and swelling of joints when he was 4 years old. He was treated with corticosteroids and received the benefits of treatment for 10 years.

However, his complaints re-emerged in 1984. Methotrexate was added to the corticosteroid therapy. After that, he was hospitalized many times because of flare-ups of the disease. He could not clearly remember the doses and names of the treatments he received during these hospitalizations. Moreover, he had a history of schizophrenia, which was diagnosed in 1998.

In 2004, when he was 35 years old, the patient was admitted to the outpatient rheumatology clinic of Hacettepe University Hospital; with fever (exceeding 39°C), arthralgia, swelling and stiffness of knee joints, sore throat, and maculopapular skin rashes involving the trunk and extremities. Laboratory tests revealed leukocytosis and thrombocytosis with values of $23.0 \times 10^3/\mu\text{L}$ ($4.3\text{--}10.3 \times 10^3/\mu\text{L}$) and $827 \times 10^3/\mu\text{L}$ ($156\text{--}373 \times 10^3/\mu\text{L}$), respectively. His erythrocyte sedimentation rate (ESR) was 98 mm/h (0–20 mm/h), C-reactive protein (CRP) level was 29.4 mg/dL (0–0.8 mg/dL), and procalcitonin level was normal. The patient's ferritin level was 6048 ng/mL (24–336 ng/mL). After excluding probable infectious, neoplastic, and other autoimmune diseases, the patient was diagnosed with AOSD. His bone marrow biopsy was consistent with reactive hemophagocytic syndrome (RHS). After treatment with pulse steroids, he was discharged with an oral prednisolone, methotrexate, and hydroxy-



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chloroquine regimen. In the same year, in outpatient visits, methotrexate was replaced with oral azathioprine because of low adherence. He was in remission, and his oral prednisolone dose was tapered. However, the patient's adherence to treatment and outpatient controls were too low, and the patient could not be evaluated for a long time. In January 2014, he was hospitalized with fever, swelling of knee joints, and maculopapular skin rashes. On admission, he was taking only azathioprine and hydroxychloroquine. The laboratory tests revealed leukocytosis and thrombocytosis with values of $20.9 \times 10^3/\mu\text{L}$ ($4.3\text{-}10.3 \times 10^3/\mu\text{L}$) and $650 \times 10^3/\mu\text{L}$ ($156\text{-}373 \times 10^3/\mu\text{L}$), respectively. ESR was 56 mm/h (0-20 mm/h), CRP level was 34.5 mg/dL (0-0.8 mg/dL), and procalcitonin level was normal. His ferritin level was 8147 ng/mL (24-336 ng/mL). Only his cholestatic liver enzyme levels were elevated; alkaline phosphatase level was 160 U/L (30-120 U/L) and gamma-glutamyl transferase level was 133 U/L (0-55 U/L). The patient's hepatitis B, C, and human immunodeficiency virus serologies were negative. Anti-nuclear antibody, rheumatoid factor, and antibody to cyclic citrullinated peptides tests were all negative. Tuberculin skin test and QuantiFERON-TB Gold In-Tube (QFT-GIT; Cellestis Ltd.; Chadstone, Vic., Australia) test results were negative. The blood cultures revealed no microorganisms. Malignancy and infection were not detected using thoracoabdominal computed tomography (CT). Because of hyperferritinemia and elevated liver enzyme levels, a bone marrow aspiration and biopsy were performed. The pathology revealed hemophagocytosis, increased megakaryocytes, and an increased myeloid to erythroid ratio. The overall clinical picture was evaluated as RHS and a flare-up of Still's disease. After 1000 mg/day-pulse steroid treatment for 3 days under isoniazid prophylaxis, per oral 2×100 mg cyclosporine and 1×40 mg methylprednisolone were administered as maintenance therapy. On the first outpatient visit, the patient's disease was evaluated as refractory to disease-modifying anti-rheumatic drugs (DMARDs). In February 2014, the patient was administered 5 mg/kg infliximab twice at a 2-week interval under isoniazid prophylaxis.

At 2 weeks after the patient received the last dose of infliximab, i.e., 1 month after the first dose, he was admitted to the emergency department with a poorly productive cough and fever exceeding 38°C . On physical examination, rhonchus was heard on the left middle and left lower part of the chest. Laboratory tests revealed the patient's hemoglobin level was 13.6 gr/dL (13.6-17.2 gr/dL), leukocytocyte count was $8 \times 10^3/\mu\text{L}$ ($4.3\text{-}10.3 \times 10^3/\mu\text{L}$), and platelet count was $309 \times 10^3/\mu\text{L}$ ($156\text{-}373 \times 10^3/\mu\text{L}$). The patient's ESR was 79 mm/h (0-20 mm/hour), CRP level was 29 mg/dL (0-0.8 mg/dL),

and procalcitonin level was normal. Galactomannan level in the serum sample and QFT-GIT (Cellestis Ltd.) test results were negative. Chest radiography demonstrated a left lower infiltration (Figure 1). All immunosuppressive medications were discontinued, and ampicillin/sulbactam+clarithromycin+oseltamivir anti-biotherapy was initiated. Thorax CT revealed no pulmonary thromboembolism but demonstrated bilateral pulmonary infiltrates and ground-glass opacifications (Figure 2). Bronchoscopy revealed no endobronchial lesion, and bronchoalveolar lavage (BAL) fluid was obtained for culture. Because of high suspicion of a fungal infection, voriconazole was added to antibiotherapy. On the 4th day of admission, acute deterioration and hypoxia occurred. The patient's antibiotherapy was extended, and the patient was transferred to the intensive care unit. At that time, repeated blood and sputum cultures, galactomannan serum levels, and viral load of cytomegalovirus tests were negative. However, a culture of BAL fluid revealed the growth of a mold, which was identified as *Aspergillus fumigatus* complex on the basis of macroscopic and microscopic morphological features (8, 9). Despite the intensive care and treatment, deterioration could not be reversed. Hypotension, septic shock, and respiratory insufficiency followed each other. On the 15th day of admission, the patient died from septic shock and respiratory failure because of pulmonary aspergillosis.

Discussion

The increased use of anti-TNF- α agents has been related to the increased opportunistic infections in rheumatology practice. TNF- α

also plays a central role in host defense mechanisms against mycobacterium tuberculosis, fungi, and viruses (10). Therefore, blocking this molecule has resulted in an increased risk of some opportunistic infections, including aspergillosis, as expected (2, 3).

In a 3-year prospective multi-center French RATIO registry it was found that tuberculosis was the most frequent opportunistic infection among patients using TNF blockers (3). During this period, 45 cases (in 43 patients) of non-tuberculosis opportunistic infections were detected. Ten of 45 cases were fungal (five pneumocystosis, three invasive aspergillosis, and two cryptococcosis). Although in total these cases were rare, their mortalities were very high (9%).

In a study by Tsiodras et al. (2), reports of invasive fungal infections between 1966 and 2007 were reviewed. Of 281 cases, which were associated with TNF blockers, 226 (80%) were associated with infliximab, 44 (16%) with etanercept, and 11 (4%) with adalimumab. In this review, histoplasmosis (n=84), candidiasis (n=64), and aspergillosis (n=64) were the most common fungal infections associated with TNF blockers. Of the 64 reported cases of aspergillosis, 44 (75%) occurred after infliximab therapy, 14 (22%) after etanercept therapy, and two (3%) after adalimumab therapy. Infliximab seems to be more associated with fungal infections. However, the low percentages for adalimumab and etanercept may be due to the rarity of their use at that time (2, 3).

Pulmonary aspergillosis is a spectrum of diseases, limited to the lungs, caused by *Asper-*

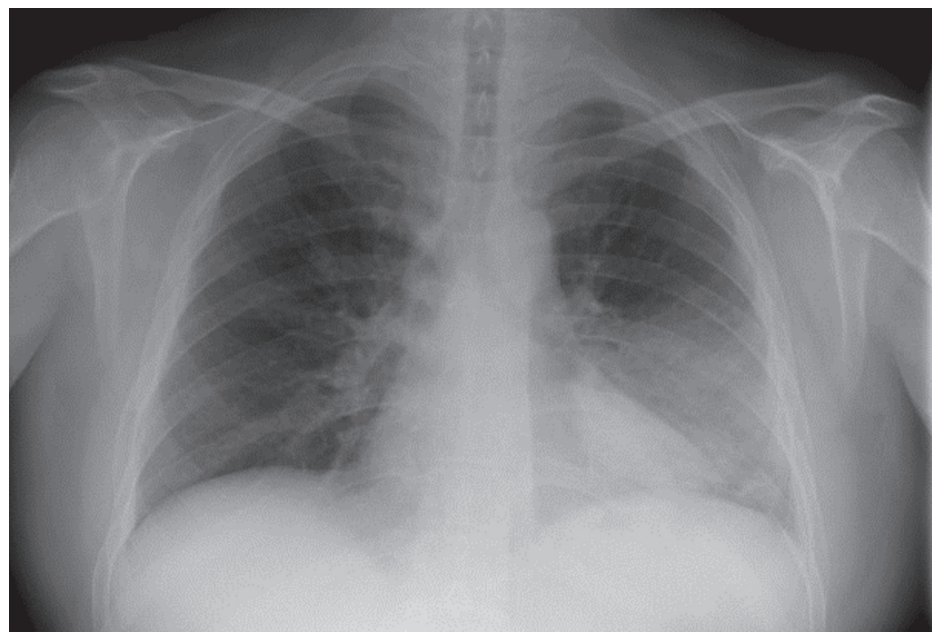


Figure 1. Chest radiography of the patient reveals left lower infiltration

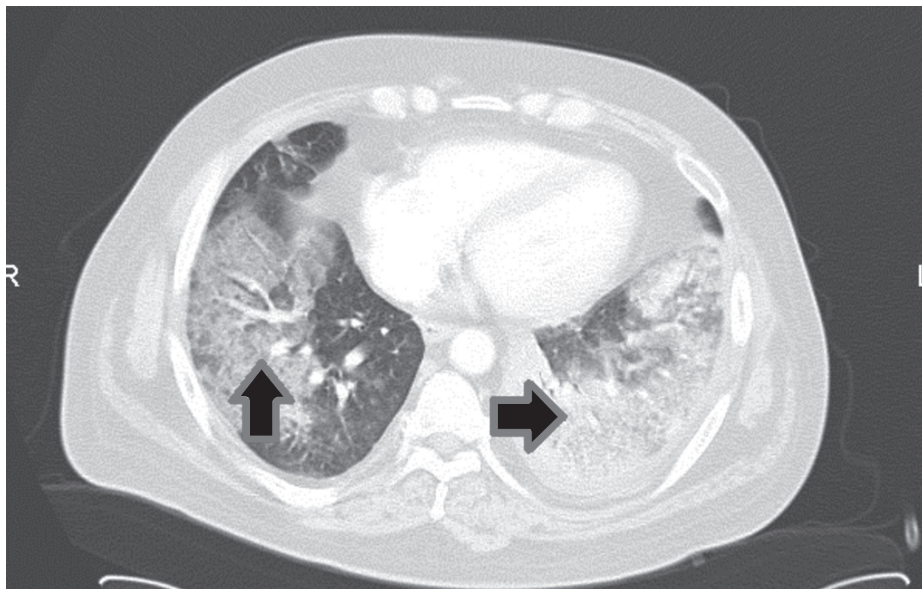


Figure 2. Thorax computed tomography (CT) of the patient; arrows show bilateral pulmonary infiltrates and ground-glass opacifications

gillus species (11). It includes non-invasive and invasive *Aspergillus* infections. Invasive infections include chronic necrotizing pneumonia and invasive pulmonary aspergillosis. A major risk factor for the development of invasive pulmonary aspergillosis is immunosuppression, including that caused by the use of corticosteroids and the presence of neutropenia (12). Underlying disease of the host, such as malignancy, graft-versus-host disease, diabetes mellitus, cytomegalovirus infection, renal or liver dysfunction, and chronic obstructive pulmonary disease increase the risk of *Aspergillus* infection (13). The use of calcineurin inhibitors such as cyclosporine is a well-known risk factor for fungal diseases in general and invasive aspergillosis in particular (14).

Clinical presentation of invasive pulmonary aspergillosis includes pleuritic chest pain, dyspnea, hemoptysis, dry cough, and fever (11). Bronchoalveolar macrophages secrete TNF- α in response to exposure to *Aspergillus* conidia (15). TNF- α has been shown to increase the expression of interleukin (IL)-2 receptors on T-cells, increase antibody production by B-cells, and stimulate phagocytosis and the production of reactive oxygen intermediates by neutrophils (16). Therefore, direct binding and neutralization of TNF- α antagonizes immune functions and gives rise to infectious complications (2). In addition, TNF- α potentiates the expression of toll-like receptor 4 on the cell membrane; this receptor is important for host recognition of such fungal pathogens as *Aspergillus fumigati* (17). Blocking TNF- α results in a reduced influx of neutrophils into the lungs and delayed fungal clearance, increased in

fungal burden, and higher mortality rate (16). For a definitive diagnosis, and to make a differential diagnosis between non-invasive and invasive disease, tissue samples must be obtained (11). In our case, we could not obtain a tissue biopsy due to deterioration of the patient during the bronchoscopy procedure. However, we obtained BAL fluid. The culture of BAL fluid yielded *Aspergillus fumigatus* complex. As currently recommended for routine laboratory practice, the isolated strain was identified at the "species complex" level by conventional evaluation of morphological features (9). Radiographic imaging, which is suggestive for invasive pulmonary aspergillosis, remains nonspecific. Diffuse nodular infiltrates, pleura-based wedge-shaped densities or cavitary lesions, and pleural effusions can be seen (18). Invasive disease may also reveal a "halo" sign, an area of low attenuation surrounding a pulmonary nodule. In addition to this, images on the thorax CT and the sudden deterioration of the patient support that patient had invasive pulmonary aspergillosis. Despite the intensive and immediately started treatment, the patient died from respiratory failure. Since the relatives of the patient did not give permission for post-mortem examination, we could not perform an autopsy.

Our case was evaluated as refractory to DMARDs. Although there are few randomized controlled trials, several case series and reports demonstrated the efficacy of infliximab in refractory AOSD (4, 5). In our case, the patient had previously taken many immunosuppressive drugs. He was also taking cyclosporine and methylprednisolone at the time of inflix-

imab infusion. These two drugs might also have contributed to the immunosuppression. Furthermore, as a low dose of cyclosporine (5 mg/kg/day) appears equally effective and less toxic, we used low dose cyclosporine as well. However, clinical symptoms started one month later after the first dose of infliximab, and 2 weeks later after the second dose (19). Therefore, infliximab seems to be the most responsible agent contributing to the patient's pulmonary aspergillosis.

In 2004 and 2014, the patient presented himself at our clinic with disease flare-ups, and we diagnosed RHS concomitantly. This was compatible with the literature. In a report of 26 RHS cases, in systemic lupus erythematosus and Still's disease, the flare-up of disease alone seemed more likely to induce RHS, rather than infection (20). However, we also excluded the probable infectious causes of RHS in our case.

In conclusion, we present the first case of pulmonary aspergillosis secondary to infliximab therapy in a patient with refractory Still's disease. A health care professional should always be aware of the increased risk of fungal infections after therapy with TNF blockers. Especially, infliximab seems to be more highly associated with this kind of infection at present.

Informed Consent: Written informed consent was obtained from the parents of the patient who participated in this study.

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References

1. Murdaca G, Colombo BM, Puppo F. Anti-TNF- α inhibitors: a new therapeutic approach for inflammatory immune-mediated diseases: an update upon efficacy and adverse events. *Int J Immunopathol Pharmacol* 2009; 22: 557-65. [\[CrossRef\]](#)
2. Tsioudas S, Samonis G, Boumpas DT, Kontoyannis DP. Fungal Infections Complicating Tumor Necrosis Factor- α . *Mayo Clinic Proceedings* 2008; 83: 181-94. [\[CrossRef\]](#)
3. Salmon-Ceron D, Tubach F, Lortholary O, Chosidow O, Bretagne S, Nicolas N, et al. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RA-

- TIO registry. *Ann Rheum Dis* 2011; 70: 616-23. [\[CrossRef\]](#)
4. Al-Homood IA. Biologic treatments for adult-onset Still's disease. *Rheumatology* 2014; 53: 32-8. [\[CrossRef\]](#)
 5. Cavagna L, Caporali R, Epis O, Bobbio-Pallavicini F, Montecucco C. Infliximab in the treatment of adult Still's disease refractory to conventional therapy. *Clin Exp Rheumatol* 2001; 19: 329-32.
 6. Warris A, Bjorneklett A, Gaustad P. Invasive pulmonary aspergillosis associated with infliximab therapy. *N Engl J Med* 2001; 344: 1099-100. [\[CrossRef\]](#)
 7. Lee EJ, Song R, Park JN, Lee YA, Son JS, Hong SJ, et al. Chronic necrotizing pulmonary aspergillosis in a patient treated with a tumor necrosis factor- α inhibitor. *Int J Rheum Dis* 2010; 13: 16-9. [\[CrossRef\]](#)
 8. Larone DH. *Medically Important Fungi*. 5th ed. Washington DC, ASM Press; 2011.
 9. Balajee SA, Houbraken J, Verweij PE, Hong SB, Yaghuchi T, Varga J, et al. *Aspergillus* species identification in the clinical setting. *Stud Mycol* 2007; 59: 39-46. [\[CrossRef\]](#)
 10. Nedel WL, Kontoyiannis DP, Pasqualotto AC. Aspergillosis in patients treated with monoclonal antibodies. *Rev Iberoam Micol* 2009; 26: 175-83. [\[CrossRef\]](#)
 11. Thompson GR 3rd, Patterson FP. Pulmonary aspergillosis. *Semin Respir Crit Care Med*. 2008; 29: 103-10. [\[CrossRef\]](#)
 12. Ho PL, Yuen KY. Aspergillosis in bone marrow transplant recipients. *Crit Rev Oncol Hematol* 2000; 34: 55-69. [\[CrossRef\]](#)
 13. Baddley JW. Clinical risk factors for invasive aspergillosis. *Med Mycol* 2011; 49: 7-12. [\[CrossRef\]](#)
 14. Herbrecht R, Natarajan-Ame S, Letscher-Bru V, Canuet M. Invasive pulmonary aspergillosis. *Semin Respir Crit Care Med* 2004; 25: 191-202. [\[CrossRef\]](#)
 15. Beaman L. Effects of recombinant gamma interferon and tumor necrosis factor on in-vitro interactions of human mononuclear phagocytes with *Coccidioides immitis*. *Infect Immun* 1991; 59: 4227-9.
 16. Schelenz S, Smith DA, Bancroft GJ. Cytokine and chemokine responses following pulmonary challenge with *Aspergillus fumigatus*: obligatory role of TNF- α and GM-CSF in neutrophil recruitment. *Med Mycol* 1999; 37: 183-94. [\[CrossRef\]](#)
 17. Mambula SS, Sau K, Henneke P, Golenbock DT, Levitz SM. Toll-like receptor (TLR) signaling in response to *Aspergillus fumigatus*. *J Biol Chem* 2002; 277: 39320-6. [\[CrossRef\]](#)
 18. Denning DW. Invasive aspergillosis. *Clin Infect Dis* 1998; 26: 781-803. [\[CrossRef\]](#)
 19. Caroli A, Fregonese D, Di Falco G, D'Inca R. *Aspergillus fumigatus* pneumonia during cyclosporine treatment for ulcerative colitis. *Am J Gastroenterol* 2000; 95: 3016-7. [\[CrossRef\]](#)
 20. Dhote R, Simon J, Papo T, Detournay B, Sailler L, Andre MH, et al. Reactive Hemophagocytic syndrome in adult systemic disease: report of twenty-six cases and literature review. *Arthritis Rheum* 2003; 49: 633-9. [\[CrossRef\]](#)