Rheumatology International (2024) 44:363–367
https://doi.org/10.1007/s00296-023-05483-3

Rheumatology
INTERNATIONAL

CASE BASED REVIEW

Pneumocystosis in a patient with rheumatoid arthritis on adalimumab therapy: a case-based review

Dimitris C. Kounatidis[1] · Vasileios Papadimitropoulos[1] · Konstantinos Avramidis[1] · Evgenia Plenga[1] · Ioanna Tsiara[1] · Elena Avgoustou[1] · Natalia Vallianou[1] · Dimitrios Vassilopoulos[1]

Received: 3 August 2023 / Accepted: 25 September 2023 / Published online: 18 October 2023
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2023

Abstract

Pneumocystis jirovecii pneumonia (PJP) is a potentially fatal type of pneumonitis, which may have devastating consequences. Typically, it occurs in immunocompromised patients, with the natural history varying depending on the presence or not of HIV infection. Staining and polymerase chain reaction (PCR) testing in induced sputum or bronchoalveolar lavage (BAL) is the cornerstone of the diagnosis, while trimethoprim-sulfamethoxazole is the treatment of choice. The etiological association of biologic agents with the occurrence of PJP is not entirely clear. Adalimumab is a fully human monoclonal anti-TNF-alpha antibody, which has been introduced relatively recently in the treatment of autoimmune inflammatory diseases, such as rheumatoid arthritis. In contrast to other biologic agents, such as Alemtuzumab or Infliximab, there are a small number of reports that support the drug's ability to trigger the occurrence of PJP. Hereby, we present a 53-year-old female patient with a medical history of rheumatoid arthritis on Adalimumab therapy, who developed PJP and we will discuss the main characteristics of PJP and the possible contribution of biologics to the occurrence of the infection.

Keywords Rheumatoid arthritis · *P. jirovecii* · Adalimumab · Tremor · Cotrimoxazole

Introduction

Pneumocystosis is a potentially life-threatening respiratory tract infection, caused by *Pneumocystis jirovecii*, occurring almost exclusively in immunocompromised patients and especially those with HIV infection with a low CD_4 count. Biologics are a novel class of drugs, commonly used in the treatment of hematological malignancies and autoimmune inflammatory diseases, such as chronic lymphocytic leukemia, rheumatoid arthritis and Crohn's disease. With the exception of lymphocyte-depleting agents, such as the anti-CD20 monoclonal antibody Rituximab and the anti-CD52 combined T and B cell-depleting antibody Alemtuzumab, the causal relationship of biologic agents with the occurrence of PJP remains unclear. Lymphopenia and prolonged neutropenia are known risk factors for pneumocystosis. The development of lymphopenia is common during treatment with these agents, predisposing to PJP. Thus, current guidelines encourage physicians to prescribe cotrimoxazole prophylaxis in patients receiving Alemtuzumab, in order to reduce the risk of pneumocystosis [1].

The blockade of TNF in patients with rheumatoid arthritis with the use of TNF inhibitors appears to be beneficial in

✉ Dimitris C. Kounatidis
dimitriskounatidis82@outlook.com

Vasileios Papadimitropoulos
bpapad@hotmail.com

Konstantinos Avramidis
avramidiskonst@gmail.com

Evgenia Plenga
e.plegka@gmail.com

Ioanna Tsiara
ts34e@yahoo.gr

Elena Avgoustou
elenaavgoustou@gmail.com

Natalia Vallianou
natalia.vallianou@hotmail.com

Dimitrios Vassilopoulos
dvassilop@med.uoa.gr

[1] Department of Internal Medicine, Hippokration General Hospital, Athens, Greece

disease control, but has been associated with an increased risk of opportunistic infections, such as pneumocystosis. Anti-TNF-a Infliximab, is a chimeric monoclonal antibody that binds to TNF-a, resulting in inhibition of its binding to lamina propria-localized mucosal cell receptors. However, inhibition of the action of TNF-a is not without hazard, as TNF-a plays a crucial role in promoting the maturation of cytokines that ensure the host's defense against pathogenic microorganisms. The main risk factors for the development of PJP in patients receiving Infliximab are advanced age, concomitant chronic lung disease, and the administration of high doses of glucocorticoids [2, 3].

On the other hand, Etanercept is a competitive inhibitor of the binding of tumor necrosis factor to its receptors on the cell surface, thus suppressing cellular responses mediated by TNF, thus, rendering it biologically inactive. As in the case of Infliximab, the main risk factors for the development of PJP among patients receiving Etanercept appear to be advanced age and chronic lung disease, while the contribution of high weekly doses of methotrexate is also important. According to Tanaka et al., the onset of pneumocystosis in patients receiving Etanercept is often characterized by an acute onset of respiratory failure, even with normal levels of lymphocytes or serum IgG [4].

In contrast to the above, a very small number of reports exist, regarding the possible correlation of anti-TNF Adalimumab with PJP. Therefore, we performed a literature search in Pubmed database, using the terms “Adalimumab and Pneumocystis” in August, 2023 and found 21 research items. Among these, six were excluded as they dealt with co-infection with *Mycobacterium tuberculosis*, with rheumatoid meningitis per se, while one reference was written in Japanese, one JPJ case was attributed to the use of leflunomide, one included non PJP and one last occurred in a child. Totally, out of the 21 references, 14 were included in our literature search. In addition, in Pubmed database, we used the words “cotrimoxazole and tremor” and we found 16 references, amongst which the most recent was reported in 2018 and we decided to use only this reference. Herein, we present a case of an adult female patient on adalimumab, who developed PJP.

Case presentation

A 53-year-old female patient presented to the emergency department of our hospital due to fever accompanied by dry cough and mild shortness of breathing for the last 3 days. Her past medical history was remarkable for rheumatoid arthritis, for which she was treated with methotrexate, while in the last month Adalimumab was added to the regimen. In addition, she was treated with escitalopram for depression for the past 10 years. On clinical presentation, the patient was hemodynamically stable, but had fever and

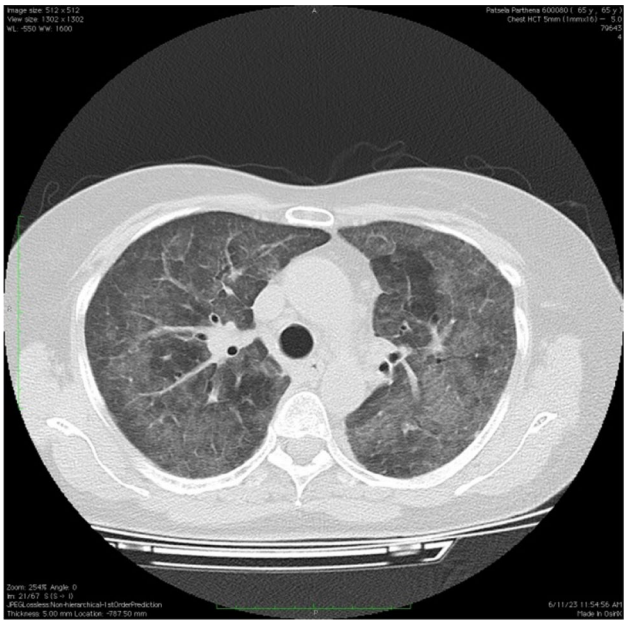

Fig. 1 Ground-glass pattern in HRCT

mild respiratory distress with $SaO_2 = 91\%$. Routine laboratory tests revealed a mild increase in inflammatory markers and anemia, while serum LDH was elevated. Chest X-ray did not show any specific findings, so the patient underwent a high resolution computed tomography (HRCT) of the chest, which showed a ground-glass pattern (Fig. 1).

Based on the patient's medical history, the clinical manifestations and the ground-glass pattern in HRCT, PJP was suspected. Beta-D-glucan assay was positive, the values of which were particularly elevated. Based on the above, we considered the possibility of PJP infection very likely and thus decided to discontinue methotrexate and Adalimumab, while the patient received antimicrobial therapy with cotrimoxazole in combination with prednisolone. The patient gradually experienced remission of fever and dyspnea, as well as an improvement in the laboratory profile. However, she denied performing a bronchoscopy to send bronchoalveolar lavage for PJP. 5 days later, cotrimoxazole was discontinued, as the patient developed severe resting tremor in the upper extremities, as well as electrolyte disturbances, such as hyponatremia and hyperkalemia. The patient received an alternative therapy with primaquine and clindamycin, with total treatment duration of 21 days and was discharged from the hospital in a good clinical condition (Table 1).

Discussion

Pneumocystis jirovecii, formerly known as *Pneumocystis carinii*, is a yeast-like fungus of the genus Pneumocystis, causally associated with the occurrence of pneumonia.

Table 1 Clinical and laboratory findings on admission and revaluation, respectively

	Clinical findings		Laboratory findings	
On admission	Temperature	38.2 °C	WBC	4.710/µL
	Heart rate	95/min	Hb	12 g/dL
	BP	110/70 mm Hg	PLTs	297.000/mm^3
	S_aO_2 on air	91%	Urea	44 mg/dL
			Creatinine	1.4 mg/dL
			Sodium	129 mmol/L
			Potassium	4.5 mmol/L
			SGOT	32 U/L
			SGPT	10 U/L
			LDH	400 U/L
			CRP (Normal range < 5 mg/L)	23.86 mg/L
			Beta-D-glucan (Positive > 80 pg/ mL)	91 pg/mL
On revaluation	Temperature	36.5 °C	WBC	6.690/µL
	Heart rate	80/min	Hb	11.4 g/dL
	BP	130/80 mm Hg	PLTs	321.000/mm^3
	S_aO_2 on air	99%	Urea	21 mg/dL
			Creatinine	0.7 mg/dL
			Sodium	137 mmol/L
			Potassium	3.8 mmol/L
			SGOT	13 U/L
			SGPT	13 U/L
			LDH	210 U/L
			CRP (Normal range < 5 mg/L)	< 0.40 mg/L

Transmission is mainly achieved by the airborne route by person-to-person spread. The main reservoirs of carriers are asymptomatic immunocompetent individuals, where usually PJP replicates within the respiratory alveoli. The main risk factors for PJP are HIV infection, malignancy, transplantation and the administration of specific drugs. Patients with granulomatosis with polyangiitis, treated with prednisolone and cyclophosphamide, are at increased risk, as well as patients receiving Alemtuzumab [5–8]. Main drugs associated with increased risk of PCP infection are listed in Table 2.

The use of biologic agents in the treatment of autoimmune diseases and hematological malignancies is now widespread, with the main disadvantage of their administration being the increased risk of opportunistic infections. Despite the fact that the administration of specific biologic agents, such as Alemtuzumab and Infliximab, is causally related to the occurrence of PJP, for other agents the available data are limited. Proposed risk factors for the development of pneumocystosis in patients treated with biologics are advanced age, history of chronic lung disease, lymphopenia, hypoalbuminemia, and concomitant administration of high-dose of glucocorticoids or weekly methotrexate.

Table 2 Main drugs associated with increased risk for PJP

1	Glucocorticoids
2	Methotrexate
3	Biologic agents (Alemtuzumab, Infliximab, Etanercept)
4	Fludarabine
5	Temozolomide (especially in combination with radiation therapy)
6	Ibrutinib
7	Idelalisib

Adalimumab is a relatively recent recombinant human IgG1 antibody, with increasing use in rheumatoid arthritis, due to its ability to exert anti-inflammatory activity through binding to TNF. The association of the drug with the occurrence of PJP remains unclear, as only few case reports have been reported. Watanabe et al. investigated the clinical characteristics and risk factors of PJP among 17 patients with RA treated with Adalimumab and showed that PJP may occur early in the course of Adalimumab therapy in patients with

RA. The median time to onset of Adalimumab-induced PJP was 12 weeks, and the median age at diagnosis being 68 years old [8].

The major clinical manifestations of PJP are fever, dyspnea and cough, although the clinical expression of the disease differs between HIV and non-HIV patients. In patients without a history of HIV infection, respiratory tract injury usually manifests as acute respiratory failure with fever and nonproductive cough. On the contrary, in HIV patients, the clinical expression of the infection is usually more progressive over days to weeks, while fatigue, chest pain or even weight loss may coexist. The patient typically exhibits hypoxemia on exercise, whereas in severe disease, the patient may also experience extrapulmonary manifestations. Laboratory findings are nonspecific, although a significant percentage of patients have lymphopenia and elevated serum LDH. In addition, an increase in serum beta-D-glucan can be seen, as a result of its presence in the cell wall of *P.jirovecii*.

High-resolution computed tomography may reveal a variety of pathological patterns, with bilateral diffuse interstitial infiltrates, particularly in non-HIV patients, being the most common finding. Alternatively, nodular ground-glass opacities may be seen, as well as nodules, cysts and lobular infiltrates. Pneumothorax is a severe complication of PJP, whereas cavitation and pleural effusions are typically absent. Staining and polymerase chain reaction (PCR) in induced sputum or bronchoalveolar lavage (BAL) specimens is the first step in making the diagnosis. Positive test rates are usually higher in HIV patients, due to a higher burden of the infection. If the above specimens cannot be collected safely, treatment may be given based in the presence of risk factors in combination with compatible clinical and radiological findings and elevated serum beta-D-glucan [9–14].

Cotrimoxazole is the gold standard of treatment with the major drawback its ability to cause systemic toxicity. Cotrimoxazole is an antibiotic agent active against a wide variety of aerobic Gram-positive and Gram-negative bacteria, while at the same time remains the treatment of choice in non-bacterial infections, such as toxoplasmosis and PJP. It consists of trimethoprim and sulfamethoxazole in a ratio of 1:5, with bactericidal action, attributed to the trimethoprim component. Electrolyte disturbances are not uncommon during therapy, in contrast with tremor which is an unusual side effect. Possible mechanisms involved in the occurrence of hyponatremia include the induction of a SIADH-like syndrome, as well as the diuretic effect induced by trimethoprim, which exhibits an amiloride-like effect. This effect of trimethoprim seems to be also responsible for the occurrence of hyperkalemia, through inhibition of epithelial sodium channels in the distal nephron.

On the other hand, cotrimoxazole-induced neurotoxicity appears to be dose-dependent, usually occurring within 2–8 days of drug initiation and resolves in a period of 3–10 days after cotrimoxazole discontinuation. The mechanism by which cotrimoxazole promotes neurotoxicity is unknown, although it may be attributed to the inhibition of phenylalanine metabolism, as well as to the reduction of concentrations of tetra-hydrobiopterin, which in turn contributes to the increased production of serotonin and catecholamines [15].

In patients unable to receive cotrimoxazole, as in our case, alternative treatment options include the combination of primaquine with clindamycin and pentamidine. In mild to moderate PJP, atovaquone is considered as a second-line therapy. Supplementary administration of glucocorticoids is recommended in all patients with HIV and moderate or severe PJP and in selected patients without HIV. The main indications for adjunctive administration of glucocorticoids in non-HIV patients are the presence of room air oxygen saturation (SaO_2) < 92% or a partial pressure of oxygen (P_aO_2) < 70 mm Hg or an alveolar-arterial (A-a) oxygen gradient ≥ 35 mmHg. The total duration of therapy of PJP is 21 days.

Patients receiving immunomodulatory therapy are at increased risk for opportunistic infections, such as PJP. Even though Adalimumab is not an established risk factor for pneumocystosis, recently a few number of cases have shown a possible correlation of its use with the occurrence of pneumonia due to *P.jirovecii*. The more frequent use of Adalimumab in the treatment of autoimmune diseases may trigger new cases of *P.jirovecii* infection in the near future. In this context, Adalimumab may be added to the list of established risk factors for PJP, especially among patients with a history of recent initiation of the drug, in the absence of other known predisposing factors. Nevertheless, risk stratification is essential, based mainly on the number of immunoregulatory agents and the degree of immunosuppression. Therefore, a potential utility of cotrimoxazole prophylaxis in selected cases of severe immunosuppression may be beneficial.

A limitation of the study is that it is only a case report. However, the presentation of our case may have an additive value to the existing limited data. The rising number of reports may shed light on this debatable issue, resulting in changes in the management of patients receiving Adalimumab.

Conclusion

Despite the fact that adalimumab has not been officially appointed as a risk factor for PJP to the extent that chemoprophylaxis with cotrimoxazole should be added to the patient's regimen, more long-term studies are needed to further elucidate that issue. In conclusion, clinicians should bear in mind the possibility of PJP among patients receiving

adalimumab, as the correct and timing diagnosis may be really life-saving.

Author contributions Conceptualization: DK, VP and DV. Methodology and Literature Research: KA, EP, IT and EA. Writing—first draft: DK and NV. Writing—review and editing: DK, NV and DV. All authors have read and have agreed with the context of this manuscript. All authors meet the criteria of ICMJE for authorship.

Funding No funding was received by any of the authors.

Declarations

Conflict of interest The authors declare that there is no conflict of interest regarding this manuscript.

Patient's consent The patients gave her informed consent for the submission of this case report/case-based review to the Journal.

References

1. Baddley JW, Cantini F, Goletti D, Gómez-Reino JJ, Mylonakis E, San-Juan R, Fernández-Ruiz M, Torre-Cisneros J (2018) ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [I]: anti-tumor necrosis factor-α agents). Clin Microbiol Infect Suppl 2:S10–S20. https://doi.org/10.1016/j.cmi.2017.12.025
2. Ito Y, Hozumi K, Okada Y, Kurimoto S (2017) Adalimumab with Methotrexate in treatment-naïve japanese patients with rheumatoid arthritis at risk of progressive structural joint damage: a post-marketing observational study. Rheumatol Ther 4(1):151–166. https://doi.org/10.1007/s40744-017-0059-1
3. Montserrat Ortiz N, Gormaz Torres P, JustesMateos M, Bello Rodriguez G, Vicario Izquierdo E, León Vallés M (2014) Pneumocystis jiroveci pneumonia in a Crohns disease patient treated with adalimumab. Med Intensiva 38(6):397–399. https://doi.org/10.1016/j.medin.2012.04.005
4. Tanaka M, Sakai R, Koike R, Harigai M (2015) Pneumocystis jirovecii pneumonia in japanese patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors: a pooled analysis of 3 agents. J Rheumatol 42(9):1726–1728. https://doi.org/10.3899/jrheum.141510
5. Desales AL, Mendez-Navarro J, Méndez-Tovar LJ, Ortiz-Olvera NX, Cullen G, Ocampo J, Lemus W, Tun AE, Mayoral-Zavala A, Dehesa-Violante M (2012) Pneumocystosis in a patient with Crohn's disease treated with combination therapy with adalimumab. J Crohns Colitis 6(4):483–487. https://doi.org/10.1016/j.crohns.2011.10.012
6. Jobanputra P (2016) Polyarteritis nodosa. Diagnostic challenges in a patient with cutaneous vasculitis, psoriasis, psoriatic arthritis and pancytopenia: fatal progression after treatment with G-CSF. Oxf Med Case Rep 4:86–90. https://doi.org/10.1093/omcr/omw025
7. Lawrance IC, Radford-Smith GL, Bampton PA, Andrews JM, Tan PK, Croft A, Gearry RB, Florin TH (2010) Serious infections in patients with inflammatory bowel disease receiving anti-tumor-necrosis-factor-alpha therapy: an Australian and New Zealand experience. J Gastroenterol Hepatol 25(11):1732–1738. https://doi.org/10.1111/j.1440-1746.2010.06407.x
8. Watanabe K, Sakai R, Koike R, Sakai F, Sugiyama H, Tanaka M, Komano Y, Akiyama Y, Mimura T, Kaneko M, Tokuda H, Iso T, Motegi M, Ikeda K, Nakajima H, Taki H, Kubota T, Kodama H, Sugii S, Kuroiwa T, Nawata Y, Shiozawa K, Ogata A, Sawada S, Matsukawa Y, Okazaki T, Mukai M, Iwahashi M, Saito K, Tanaka Y, Nanki T, Miyasaka N, Harigai M (2013) Clinical characteristics and risk factors for Pneumocystis jirovecii pneumonia in patients with rheumatoid arthritis receiving adalimumab: a retrospective review and case-control study of 17 patients. Mod Rheumatol 23(6):1085–1093. https://doi.org/10.1007/s10165-012-0796-5
9. Al Sona M, Al Battah H, Salama A, Alweis R (2019) Fatal pneumocystis jirovecii pneumonia in a patient on adalimumab: a case report. Am J Ther 28(4):e497–e498. https://doi.org/10.1097/MJT.0000000000001102
10. Koike T, Harigai M, Ishiguro N, Inokuma S, Takei S, Takeuchi T, Yamanaka H, Tanaka Y (2012) Safety and effectiveness of adalimumab in Japanese rheumatoid arthritis patients: postmarketing surveillance report of the first 3,000 patients. Mod Rheumatol 22(4):498–508. https://doi.org/10.1007/s10165-011-0541-5
11. Kalyoncu U, Karadag O, Akdogan A, Kisacik B, Erman M, Erguven S, Ertenli AI (2007) Pneumocystis carinii pneumonia in a rheumatoid arthritis patient treated with adalimumab. Scand J Infect Dis 39(5):475–478. https://doi.org/10.1080/00365540601071867
12. Takeuchi T, Kameda H (2010) The Japanese experience with biologic therapies for rheumatoid arthritis. Nat Rev Rheumatol 6(11):644–652. https://doi.org/10.1038/nrrheum.2010.154
13. Candel FJ, Peñuelas M, Tabares C, Garcia-Vidal C, Matesanz M, Salavert M, Rivas P, Pemán J (2020) Fungal infections following treatment with monoclonal antibodies and other immunomodulatory therapies. Rev Iberoam Micol 37(1):5–16. https://doi.org/10.1016/j.riam.2019.09.001
14. Kameda H, Tokuda H, Sakai F, Johkoh T, Mori S, Yoshida Y, Takayanagi N, Taki H, Hasegawa Y, Hatta K, Yamanaka H, Dohi M, Hashimoto S, Yamada H, Kawai S, Takeuchi T, Tateda K, Goto H (2011) Clinical and radiological features of acute-onset diffuse interstitial lung diseases in patients with rheumatoid arthritis receiving treatment with biological agents: importance of Pneumocystis pneumonia in Japan revealed by a multicenter study. Intern Med 50(4):305–313. https://doi.org/10.2169/internalmedicine.50.4508
15. Brown G (2018) Cotrimoxazole-induced tremor. Can J Hosp Pharm 71(3):217–218

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.