

# Asthma-like symptoms in a patient with rheumatoid arthritis and Adalimumab treatment

*Simptome astmatice la un pacient cu artrită reumatoidă și tratament cu Adalimumab*

Ioana Mărgineanu,  
Radu Crișan,  
Traian Mihăescu

University of Medicine  
and Pharmacy  
"Grigore T. Popa" Iași,  
Clinic of Pulmonary Diseases

Corresponding author:  
Ioana Mărgineanu  
Clinic of Pulmonary Diseases Iași,  
30 dr. I. Cihac str., 700115 Iași  
E-mail: ismargineanu@gmail.com

## Abstract

After the introduction of anti-TNF $\alpha$  medication for treatment of autoimmune conditions, clinicians have investigated not only other possible uses for the drugs, but also less common side-effects and interactions with other pathologies.

Despite some succes registered with Adalimumab as an antiinflammatory agent in severe asthma, there have been case reports of patients developing asthma or asthma-like symptoms following anti-TNF $\alpha$  therapy. The case presents a patient without previous family or personal history of respiratory or atopic conditions that developed bronchospasm immediately after the initiation of Adalimumab and Methotrexate treatment for rheumatoid arthritis. Despite the patient presenting asthma characteristics (expiratory wheezing, dry cough, partial reversibility at post bronchodilator test) and asthma medication alleviating simtomathology, biological markers (eosinophil granulocytes in sputum, serum IgE) for asthma are absent. The relationship between bronchospasm and medication and other possible causes for her respiratory symptoms are discussed.

**Keywords:** asthma, rheumatoid arthritis, drug interactions

## Rezumat

În urma introducerii medicației anti-TNF $\alpha$  în planul terapeutic al patologiilor autoimune, clinicienii au investigat nu numai alte utilizări pentru această clasă medicamentoasă, dar și efectele secundare mai puțin obișnuite, cât și interacțiunile cu alte patologii.

În ciuda unui anumit succes înregistrat de adalimumab ca și agent antiinflamator în tratamentul astmului sever, au existat mai multe cazuri prezentate în care pacienți au dezvoltat astm bronșic sau simptome astm-like în urma terapiei cu anti-TNF $\alpha$ .

Această prezentare de caz descrie o pacientă fără antecedente personale sau heredocolaterale de patologii pulmonare sau atopie, care a dezvoltat bronhospasm imediat după inițierea terapiei biologice cu adalimumab și metotrexat pentru artrită reumatoidă. În ciuda caracteristicilor clinice reprezentative pentru astmul bronșic (wheezing expirator, tuse seacă, reversibilitate parțială la test bronhodilatator) și faptul că medicația specifică pentru astmul bronșic i-a ameliorat simptomatologia, markerii biologici (prezența eozinofilelor în spută, IgE-ul seric) sunt absenți. Sunt discutate relația între bronhospasm și medicație și alte posibile cauze pentru simptomatologia respiratorie.

**Cuvinte-cheie:** astm, poliartrită reumatoidă, interacțiuni medicamentoase

## Case

A 57-year-old woman was admitted in our pulmonary clinic for shortness of breath, dry cough and fatigue.

In 2008 she was diagnosed with rheumatoid arthritis and began treatment with Leflunomide and Salazopyrin. In 2010, because the patient rated the pain as a 7/10, and her disease had progressed, her medication was changed to Adalimumab 40 mg per 2 weeks and Methotrexate 10 mg concomitally. Her pain dropped to 4/10. Two weeks following innitiation of biological treatment she developed wheezing, mucous cough and shortness of breath and was referred to our clinic. At first presentation pulmonary functional tests showed moderate obstructive ventilatory disfunction. After treating the initial asthma exacerbation, we treated her with Budesonide 320/ Formoterol 9mcg in an outpatient setting. 5 year follow-ups showed mild obstructive ventilatory disfunction and a controlled asthma

– no daytime or nighttime symptoms, no limitations of activities and no exacerbations. She has continued Adalimumab and Methotrexate treatment during this period.

She reported no known family or personal history of asthma previous to the diagnosis and no known allergies. She had never smoked and was a retired factory worker.

At the clinical examination the patient appeared anxious. Blood pressure was 120/70mmHg, pulse 96 beats per minute, respiratory rate 20 breaths per minute, oxygen saturation 90% breathing ambient air and 94% while she was breathing oxygen through a nasal canula at a rate of 2 litres per minute. She had tumefied hand and knee joints, with a relative pain of 2 out of 10 and a DAS28 (Disease Activity Score) of 2,91 – low rehumatic disease activity. Chest auscultation revealed difuse, bilateral, wheezing sounds.



**Figure 1.** Chest X-ray illustrating bilateral interstitial drawing



X-Rays showed highlighted interstitial drawing bilaterally (Figure 1).

Pulmonary function tests revealed mild-moderate obstructive ventilatory dysfunction: VC=80.3%, FEV1=66.3%, FEV1/VC=67.7 out of reference values (VC-2.36L, FEV1=1,76L), drop in FEV1 of 33,7% with partial reversibility at inhalatory bronhodilator: 9,52% and with distal obstruction (MEF50=33,9%).

Apart from an inflammatory syndrome (CRP=24 mg/l), blood analysis was normal. There were no eosinophils present in sputum, but there was an intense inflammatory reaction associated with *Streptococcus pneumoniae* 2+. Serum IgE was normal.

We treated the pulmonary infection and the patient's pulmonary function tests improved: FEV1=85,4%, VC=92,5% out of reference values (VC-2.36L, FEV1=1,76L).

Her final pulmonary diagnoses were: mild-moderate asthma exacerbation; streptococcal infection of the respiratory tract; partially controlled asthma.

## Discussion

Chronic inflammation present in asthma and rheumatoid arthritis (RA), albeit similar, is triggered by two different lymphocytes. In asthma, T helper 2 lymphocytes stimulate the antibody-mediated response, activate mast cells and recruit eosinophils. In rheumatoid arthritis, T helper 1 cells activate macrophages in a delayed-type hypersensitivity reaction<sup>(1)</sup>. The fact that both activation cells belong to the CD4+ family has prompted research into the similarities between the immune response of multiple autoimmune conditions.

Research performed on mice has demonstrated that the activation of glucocorticoid-induced TNFR family-related protein (GITR) exacerbates murine asthma and collagen-induced arthritis<sup>(2)</sup>.

Further populational research highlights the relationship between asthma and RA. A 2014 cohort study on 27,602 of patients suffering from RA has estimated a relative risk for asthma of 2.07 greater in the RA cohort than in the non-RA cohort<sup>(3)</sup>. This study suggests that patients with RA have a significantly higher risk of developing asthma than healthy people in all sex and age subgroups. Stratified analysis showed that there was a higher risk in women than in men and higher in younger patients.

As the therapeutical experience with TNF- $\alpha$  agents grew, so did scientific knowledge about clinical outcomes and potential side-effects. These agents were developed after studies performed in the 1990s proved the pivotal role of TNF $\alpha$  in Th1 mediated immune response diseases, such as rheumatoid arthritis. Early trials proved that addition of an anti-TNF agent to MTX significantly improved patient outcomes. A meta-analysis of 12 randomized, controlled clinical trials suggested a clear benefit effect of anti-TNF agents over placebo or MTX, even in the early stages of the disease, with all three available agents (Adalimumab, Infliximab and Etanercept) having similar efficacy. On the other hand, Adalimumab and Infliximab, recombinant human and, respectively, chimeric humanized IgG1 anti-TNF $\alpha$  monoclonal antibodies, seem to be superior in their ability to contain structural damage (radiographic changes). Moreover, combination of TNF $\alpha$  antagonists + MTX appears better than TNF $\alpha$  antagonists

alone, which, in turn, appears better than MTX alone when data on structural damage is considered<sup>(4)</sup>.

There common aspects of asthma and rheumatoid arthritis immune responses and the idea that asthma is generated by both Th1 and Th2 immune responses have prompted trials inquire about the usage of anti- TNF $\alpha$  agents in asthma, with improvement in severe, refractory or poorly responsive disease<sup>(6,7,8)</sup>. Unfortunately, the risk-benefits did not warrant further research.

Studies have focused on the relationship between anti-TNF $\alpha$  agents and side-effects, including allergenic sensitisation, increase risk of infection and asthma.

A study performed on 40 RA patients, 20 with anti-TNF $\alpha$  therapy (Infliximab) and 20 without proved that the anti-TNF $\alpha$  group manifested increased prevalence of sensitisation to airborne allergens<sup>(5)</sup>.

It is notable that all anti-TNF drugs, including Adalimumab, increase the risk of infections, particularly of the respiratory tract, skin, soft tissues and urinary tract and infections of the respiratory tract are a known trigger for asthma exacerbation. It is to be noted though that Adalimumab users have a lower risk for infection than Etanercept users, suggesting that there might be an intra-class difference in infection risk amongst TNF antagonists<sup>(9,10)</sup>.

A systematic search of the literature revealed several reports similar to ours. S Dubey et.colab highlight bronchospasm associated with anti-TNF treatment, presenting exacerbation of asthma and emphysema at 4 weeks of therapy with Adalimumab and, similar to our case, the patient had an obstructive pattern without significant reversibility<sup>(11)</sup>. Another case presented in

Rheumatology highlights a patient that developed a diurnal bronchial wheeze with shortness of breath 2 weeks after initiation of Adalimumab treatment. Lack of treatment options prompted treating the obstructive pattern symptomologically, with Beclomethasone, with significant improvement<sup>(12)</sup>.

Bennet et al. assumed that the pathological mechanism causing Adalimumab was a class effect of anti-TNF $\alpha$  blocking the Th1 pathway and thus leaving allowing the Th1 axis to express itself as asthma. But a case presented in BMJ-Thorax shows a patient that used Etanercept, Infliximab and Adalimumab and only reacted to the latter, refuting the hypothesis and suggesting a drug-specific effect<sup>(13)</sup>. On the other hand, Laurent Guillemainault et al. present five cases with various anti-TNF $\alpha$  agents that unmasked asthma<sup>(14)</sup>.

## Conclusion

Our case reopens the discussion on the intricate relationship of autoimmune diseases and immune-modulatory drugs. The patient could have developed asthma because of her former field of work, even if she did not have a previous history of family atopy, asthma and even if she was not a smoker. She could have developed asthma as a result of the rheumatoid arthritis or because of Adalimumab treatment. Moreover, her exacerbation could have been favored by anti-TNF $\alpha$  treatment. It is clear that with more anti-TNF $\alpha$  usage, we will be able to have less sporadic case reports and a systematic analysis could be performed. We suggest, as a first step, to create a more comprehensive database of all the reported cases of anti-TNF $\alpha$  therapy and respiratory pathology. ■

## References

- Elias JA, Lee CG, Zheng T, Ma B, Homer RJ, Zhu Z. New insights into the pathogenesis of asthma. *J Clin Invest* 2003; 111(3): 291–297.
- Patel M, Xu D, Kewin P, Choo-Kang B, McSharry C, Thomson NC, Liew FY. Glucocorticoid-induced TNFR family-related protein (GITR) activation exacerbates murine asthma and collagen-induced arthritis. *Eur J Immunol* 2005; 35:3581–3590.
- Shen TC, Lin CL, Wei CC, Tu CY, Li YF. The risk of asthma in rheumatoid arthritis: a population based cohort study. *Q J Med* 2014; 107:435–442.
- Lin J, Ziring D, Desai S, Kim S, Wong M, Korin Y, Braun J, Reed E, Gjertson D, Singh RR. TNF $\alpha$  blockade in human diseases: An overview of efficacy and safety. *Clinical Immunology* 2008;126: 13–30.
- Machado P, Santos A, Pereira C, Loureiro C, Silva J, Chieira C, Malcata A. Increased prevalence of allergic sensitisation in rheumatoid arthritis patients treated with anti-TNF $\alpha$ . *Joint Bone Spine* 2009;76:508–513
- Brightling C, Berry M, Amrani Y. Targeting TNF- $\alpha$ : A novel therapeutic approach for asthma. *Journal of Allergy and Clinical Immunology* 2008;121:5-10.
- Cazzola M, Polosa R. Anti-TNF- $\alpha$  and Th1 cytokine-directed therapies for the treatment of asthma [abstract] *Curr Opin Allergy Clin Immunol* 2006;6:43-50.
- Wenzel SE, Barnes PJ, Bleecker ER, Bousquet J, Busse W, Dahlén S-E, Holgate ST, Meyers DA, Rabe KF, Antczak A, Baker J, Horvath I, Mark Z, Bernstein D, Kerwin E, Schlenker-Herceg R, Lo KH, Watt R, Barnathan ES, Chanez P. A Randomized, Double-blind, Placebo-controlled Study of Tumor Necrosis Factor- $\alpha$  Blockade in Severe Persistent Asthma. *Am J Respir Crit Care Med* 2009;179:549-58.
- Henrique da Mota LM, Cruz BA, Brenol CV, Pollak DF, da Rocha Castelar Pinheiro G, Laurindo IMM, Pereira IA, de Carvalho JF, Bertolo MB, de Medeiros Pinheiro M, Freitas MVC, da Silva NA, Louzada Júnior P, Barros PDS, Giorgi RDN, Lima RAC, Andrade LEC. Safe use of biological therapies for the treatment of rheumatoid arthritis and spondyloarthritis. *Rev Bra Reumatol* 2014;124.
- Chiang YC, Kuo LN, Yen YH, Tang CH, Chen HY. Infection risk in patients with rheumatoid arthritis treated with etanercept or adalimumab. *Comput Methods Programs Biomed* 2014;116:319-27.
- Dubey S, Kerrigan N, Mills K, Scott DG. Bronchospasm associated with anti-TNF treatment. *Clinical Rheumatology* 2009;28:989-992.
- Bennett N, Wong M, Zain A, Panayi G, Kirkham B. Adalimumab-induced asthma. *Rheumatology (Oxford)* 2005;44:1199-200.
- Janssen R, Krivokuca I, Kruize AA, Koenderman L, Lammers JWJ. Adalimumab-induced bronchospasm: not a class effect. *Thorax* 2008;63:472-473.
- Guillemainault L, Carré P, Beau-Salinas F, Taillé C, Dieudé P, Crestani B, Diot P, Marchand-Adam S. Asthma Unmasked With Tumor Necrosis Factor- $\alpha$ -Blocking Drugs. *Chest*. 2011;140:1068-1071.