Liver injury during long-term Aspirin Treatment After Desensitization (ATAD) in a patient with nonsteroidal anti-inflammatory drugs-exacerbated respiratory disease (N-ERD) – A case report

Uszkodzenie wątroby w przebiegu długotrwałego leczenia aspiryną po desensytyzacji u pacjentki z chorobą dróg oddechowych zaostrzaną przez niesteroidowe leki przeciwzapalne - opis przypadku

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Summary

We report a case of a 65-year-old woman with respiratory problems increased by N-ERD, who after 9 years of daily intake of 650 mg of aspirin after desensitization experienced a significant liver enzymes elevation, consistent with drug-induced liver injury. Clinical symptoms of liver injury and elevated serum transaminases levels resolved after aspirin intake discontinuation.

Keywords: *nonsteroidal anti-inflammatory exacerbated respiratory disease, N-ERD, aspirin asthma, ASA desensitization, aspirin treatment after desensitization, drug-induced complications, liver damage*

Streszczenie

W pracy przedstawiono opis przypadku 65-letniej kobiety z chorobą dróg oddechowych zaostrzaną przez NLPZ (N-ERD, astma aspirynowa), u której po dziewięciu latach codziennego przyjmowania aspiryny w dawce 650 mg wystąpił istotny wzrostu stężenia enzymów wątrobowych wskazujący na polekowe uszkodzenie wątroby. Kliniczne i enzymatyczne cechy uszkodzenia wątroby ustąpiły po zaprzestaniu przyjmowania aspiryny.

Słowa kluczowe: *choroba dróg oddechowych zaostrzana przez niesteroidowe leki przeciwzapalne, N-ERD, astma aspirynowa, desensytyzacja ASA, leczenie aspiryną po desensytyzacji, LAPoD, NLPZ, powikłania polekowe, uszkodzenie wątroby*

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INTRODUCTION

NSAID-exacerbated respiratory disease (N-ERD) is a chronic, eosinophilic inflammatory disorder of the respiratory tract occurring in patients with asthma and/or rhinosinusitis with nasal polyps, which symptoms are exacerbated by NSAIDs, including aspirin [1]. It has been well documented that continuous aspirin treatment after desensitization (ATAD) results in reduced symptoms of chronic rhinosinusitis and asthma and may decrease recurrence rate of the nasal polyps [2-4]. ATAD with a daily dose of aspirin ranging from 300 to 1200 mg is generally well tolerated, however approximately 13% - 30% of patients is not able to continue the therapy mostly because of gastrointestinal side effects. Hepatotoxicity of associated ATAD has not been reported so far [5].

CASE REPORT

65-year-old woman (I. B.) suffering from bronchial asthma, chronic rhinosinusitis with nasal polyps (CRSwNP) and NSAIDs hypersensitivity was referred to the Department of Immunology and Allergy in July 2018 for control, nine years after aspirin desensitization. Since 1992 the patient suffered from symptoms of rhinosinusitis, and 8 years later, one hour after taking a tablet of aspirin the first episode of dyspnea with wheezing occurred. Since that time episodes of respiratory symptoms following NSAIDs intake appeared several times. Asthma run protracted course and she visited the emergency room and was hospitalized several times. In 2002 polyps in the left nasal passage were found, in 2003 first polypectomy and in January 2004 bilateral ethmoidectomy was performed. From 2006 patient

suffered from skin itching and symptoms of recurrent urticaria accompanied by dyspnea, which not always were associated with NSAIDs intake, but also with eating food containing salicylates.

In September 2009 patient underwent aspirin desensitization at the Department of Allergy and Immunology, and during this procedure, after 150 mg of ASA administration, she developed nose blockage, dyspnea with FEV1 decrease and skin symptoms (hands and feet itching, and urticarial weals). During desensitization procedure the tolerance of ASA 325 mg was achieved and patient was discharged, with the recommendation to take 325 mg aspirin twice a day. In addition she was treated with inhaled fluticasone (1000 ug/day), salmeterol daily, oral montelukast (10 mg/day), intranasal fluticasone (27.5 ug twice a day) and fexofenadine (180 mg o.d). Since desensitization the patient remained under pulmonologist's care in the place of residence, while continuing treatment with aspirin and inhaled and intranasal glucocorticoids.

In August 2018, when she visited Immunology and Allergy department she had been continuing treatment with 650 mg aspirin per day for nine years, and only during proceeding month the aspirin dose was decreased to 300 mg before the planned cataract surgery. Retrospective analysis of patient's history, documented improvement in asthma and chronic rhinosinusitis symptoms following the treatment. Asthma was well controlled with inhaled GCS, and there were no asthma exacerbations requiring hospitalization or medical emergency team interventions. Improvement of chronic rhinosinusitis lasted only for 3 years after desensitization, and since than a progressive decrease in the control of nasal symptoms was observed, despite continuous treatment with intranasal glucocorticoids. Severe exacerbations of CRS symptoms occurred at least once a year and were treated with bouts of oral prednisone. Despite suggestions from laryngologist, for over 9 years after desensitization patient refused nasal polyps surgery.

In July 2018, during hospital stay related to uncontrolled asthma, increased levels of serum liver transaminases were found alanine aminotransferase (ALT) 109 U/l and aspartate aminotransferase (AST) 98 U/l. Serological testing for HCV and HBV infections was negative and the ultrasound of liver did not reveal any abnormalities. In October 2018 patient was admitted to hospital because of severe weakness and abdominal pain. Elevated serum levels of transaminases were detected (AST - 1265 U/l and ALT - 1474 U/l). CT scan of abdominal cavity with contrast revealed liver steatosis and fiber rebuilding. Liver damage of probably drug-induced etiology was diagnosed and on October 17, 2018 oral aspirin administration was discontinued. Over the next 2 weeks AST serum level decreased to 432 U/L, and ALT serum level to 670 U/l. Clinical symptoms gradually ceased, and serum transaminase levels steadily decreased over the next two month to AST 224 U/l and ALT 196 U/l in February 2019 (Fig. 1). Since aspirin discontinuation abdominal symptoms have not recurred.

DISCUSSION

Treatment with daily aspirin after desensitization has been routinely used in patients with N-ERD to relieve upper and lower respiratory symptoms and to prevent recurrent nasal polyposis after surgery [3]. However chronic ATAD has been associated with adverse reactions, and their frequency in particular studies varies from 0 to 34% [4]. The most commonly reported side effects included mild gastrointestinal symptoms (dyspepsia, abdominal pain, or gastric irritation), which were also the most common reasons for aspirin therapy cessation. Gastrointestinal bleeding has been rarely reported, and was not associated with serious complications [5]. Other side effects that were reported less frequently during ATAD included skin symptoms (rash, urticaria), epistaxis, ecchymosis, asthma deterioration and nasal symptoms. In one study including 14 patients an overall reduction in urinary creatinine was observed over 3 months of treatment with aspirin, but without impairment of renal function [6].

Here we reported the first case of liver injury associated with chronic treatment with 650 mg of aspirin. Elevation of liver enzymes was detected after almost nine years of continuous treatment and initially was asymptomatic. When abdominal symptom appeared serum levels of AST and ALT were at their peaks, but decreased gradually after aspirin intake was stopped. Although other causes of liver injury cannot be excluded, temporal association between aspirin withdrawal and serum liver enzymes decreases suggests causal relationship, pointing at drug induced liver injury. Furthermore, viral etiology of liver injury has been excluded by laboratory testing.

Interestingly, during 9 years of treatment with aspirin gastrointestinal symptoms were not reported by the patient,

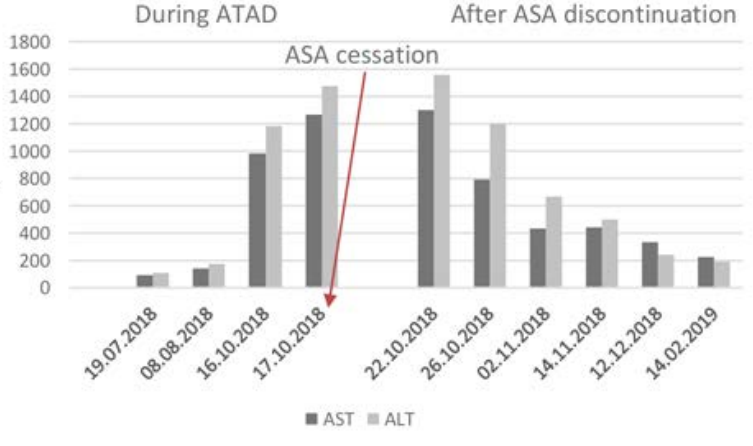

Fig. 1. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values found in the patient during ASA therapy (ATAD) and after its discontinuation

and good gastric tolerance was confirmed by normal endoscopic findings after three and seven years of treatment. In the recent long-term observational study of 285 N-ERD patients who received ATAD on average for 15 years no liver cytotoxicity or other serious adverse reactions have been reported [7].

Drug-induced liver injury (DILI) is the leading cause of acute liver injury and can results in a spectrum of signs and symptoms ranging from asymptomatic elevation of liver enzymes to acute liver failure. It is estimated that it occurs with a frequency of about 10 per 100 thousand patients. In the United States the most common causative agent is acetaminophen (paracetamol), and amoxicillin with clavulanic acid worldwide [8]. Liver damage caused by aspirin in adults is not common, but when ASA is taken in high doses should be considered in differential diagnosis.

Diagnosis of liver damage caused by drugs may be difficult to establish, especially when the patient is using many medications, and co-morbidities, addiction to alcohol, drugs or other liver disease occur. However, there is usually a time relationship between taking the drug and the onset of symptoms and resolving them after discontinuing the medicine.

Our patient with N-ERD syndrome who developed toxic liver damage after 9 years of continuous aspirin intake, raises the question about the safety of long-term treatment with high doses of acetylsalicylic acid after desensitization and draws attention to the possibility of toxic reactions after several years of good tolerance of aspirin.

References

1. Kowalski ML, Agache I, Bavbek S, et al. Diagnosis and management of NSAID-Exacerbated Respiratory Disease (N-ERD)-a EAACI position paper. Allergy 2019; 74: 28-39.
2. Stevenson DD, Pleskow WW, Simon RA, et al. Aspirin-sensitive rhinosinusitis asthma: a double-blind crossover study of treatment with aspirin. J Allergy Clin Immunol 1984; 73: 500-7.
3. Waldram JD, Simon RA. Performing Aspirin Desensitization in Aspirin-Exacerbated Respiratory Disease. Immunol Allergy Clin North Am 2016; 36: 693-703.
4. Kowalski ML, Wardzyńska A, Makowska JS. Clinical Trials of Aspirin Treatment After Desensitization in Aspirin-Exacerbated Respiratory Disease. Immunol Allergy Clin North Am 2016; 36: 705-17.
5. White AA, Stevenson DD. Aspirin desensitization in aspirin-exacerbated respiratory disease. Immunol Allergy Clin North Am 2013; 33: 211-22.
6. Makowska JS, Olszewska-Ziąber A, Bieńkiewicz B, et al. Clinical benefits of aspirin desensitization in patients with nonsteroidal anti-inflammatory drug exacerbated respiratory disease are not related to urinary eicosanoid release and are accompanied with decreased urine creatinine. Allergy Asthma Proc 2016; 37: 216-24.
7. Walters KM, Waldram JD, Woessner KM, et al. Long-term Clinical Outcomes of Aspirin Desensitization With Continuous Daily Aspirin Therapy in Aspirin-exacerbated Respiratory Disease. Am J Rhinol Allergy 2018; 32: 280-6.
8. Rafeeq A, Najam R, Hussain SJ. Aspirin Associated Liver Toxicity – The Optimal Dose of Aspirin in Liver Insufficiency. International Journal of Scientific Research in Knowledge 2016; 4: 028-032.