Case Report

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Paracetamol Overdose May Cause Transudative Pleural Effusion in Adults

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Abstract

Paracetamol is the most widely used and prescribed drug word-wide. It is the most common cause of the poisoning and of the fatality due to the toxic administration throughout the world. A 34-year-old female patient applied to our ED with the complaint of swallowing 33 g of paracetamol. After routine toxicity treatment, on the third day of the hospitalization, dyspnea and pain on the right hemithorax and right flank occurred. Chest X-ray showed blunted right sinus. CT revealed bilateral pleural effusion. With thoracentesis, clear, colorless and odor-free fluid of about 500cc was drained. Laboratory examination of the fluid confirmed it as transudate. We believed pleural effusion is related to high-dose paracetamol intake and it occurred due to decrease in pleural permeability and the consequent decrease of the fluid absorption. In conclusion, high-dose intake of paracetamol might cause transudative pleural effusion as a complication.

Keywords: paracetamol, acetaminophen, over dose, pleural effusion

Introduction

Since its first clinical introduction about 50's in the United States, acetaminophen (paracetamol, N-acetyl-p-aminophenol, APAP) is one of the most widely used drugs in the world as a result of its strong antipyretic, analgesic, low peripheral anti-inflammatory and antiplatelet activity[1, 2]. It is a medication of many of over-the-counter and prescription medications used worldwide. It is highly effective and safe in the recommended doses[2]. Although it is a remarkably safe drug, it is also the most common cause of the poisoning and of the fatality due to the toxic administration throughout the world and in Turkey[3]. Liver and kidney damage after its toxic administration are well-known, but the direct damage in other organs was rarely reported[1, 2, 4].

Our objective with this case report is to present an adult patient, who had pleural effusion after high-dose administration of acetaminophen.

Case Report

A 34-year-old female patient applied to our emergency department (ED) with the complaint of swallowing 66 tablets, each containing 500 mg paracetamol (total 33 g). The patient took the drugs in a suicidal attempt 3 hours before her application. The initial vital signs were within normal range (blood pressure: 111/70 mmHg, pulse: 55 beats/minute, respiratory rate: 8/minute, fever: 36.7°C, oxygen saturation at the fingertip: 98%). Physical examination was normal. After the insertion of the nasogastric tube, gastric lavage was performed and few drug particles were aspirated. Activated charcoal (50 gr) was administered through the nasogastric tube. Afterwards, N-acetylcysteine therapy (a total of 200 mg/kg) was initiated in accordance with the 21-hour IV administration protocol. There were no pathological findings in the whole blood count, liver functions and bleeding time tests. The patient was hospitalized in the intensive care unit (ICU) of our ED.

On the third day of the hospitalization, dyspnea and pain on the right hemi-thorax and right flank occurred. There was a decrease in the respiratory sounds at the right lung base. The abdominal examination was normal. The vital signs and the laboratory analysis were within the normal range. Liver function tests values were in normal ranges. Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) values of admission, 24th hour, 48th hour and 96th hour were respectively 21,10; 14, 9; 17,12 and 17,10. The posteroanterior chest X-ray showed blunted right sinus, which was not observed in the first radiological examination (Figure 1a, b). To rule out pulmonary embolism, contrast-enhanced CT angiography was conducted which revealed bilateral pleural effusion that was more prominent on the right side and had a thickness of 4 cm at the thickest part (Figure 2). Additionally, minimal free fluid was observed in the cross-sectional

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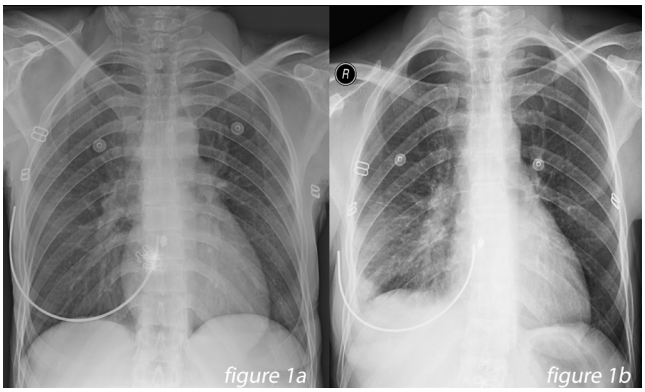

Figure 1a: The posteroanterior initial chest X-ray with normal findings; b, the chest roentgenogram after 3 days of the same patient showing blunted right sinus.

abdominal images. She had no abdominal pain, fever and leukocytosis. There wasn't any pathological finding in the echocardiography performed by cardiologists.

She was hospitalized in the pulmonology department on the third day of observation in ICU of our ED. With thoracentesis, clear, colorless and odor-free fluid of about 500 cc with the characteristics of transudate was drained. Laboratory analysis of the pleural fluid were as follows: pH: 7.48, glucose: 147 mg/dl, albumin: 1,1g/dl, total protein: 2 g/dl, LDH: 83 U/L, white blood cells: 300, neutrophils: 200, hemoglobin: 0,1 g/dl, cholesterol: 20 mg/dl. In the simultaneous blood analysis, LDH was 83 U/L, total protein was 5.4 g/dl and cholesterol was 82 mg/dl. There was no microbial growth in the blood, sputum, urine and pleural fluid cultures. ARB staining did not reveal tuberculosis bacilli. Mycobacterium by PCR analysis was negative. Procalcitonin level was measured as 0.2 ng/ml. No pathological change in the liver function tests and in other laboratory analysis was encountered during this period. The patient left the hospital of her own accord, while her monitoring was on-going in the pulmonology department.

Discussion

The pleural fluid is a parietal supernatant from the capillaries, which penetrates through mesothelial barriers into the pleural cavity[5] . Pleural effusion is defined as an abnormal fluid accumulation as a result of the penetration of excessive fluid in the pleural cavity or of the decrease of the absorption of the fluid or of both[6]. Increase of the interstitial fluid in the lung as a result of the increase in the pulmonary capillary pressure or permeability, decrease of the intrapleural pressure, decrease of the pleural oncotic pressure, increase of the pleural membrane permeability and obstruction of the lymphatic flow, defects of diaphragm, rupture of the ductus thoracicus are the potential causes of the pleural fluid

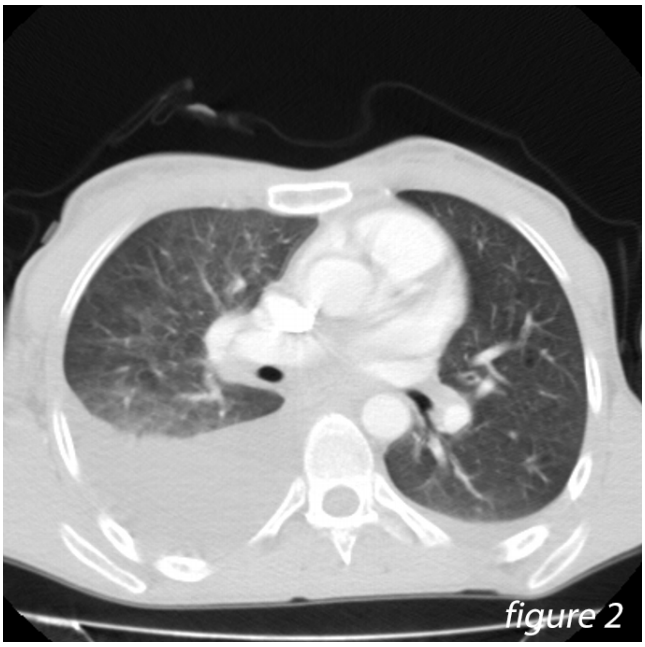

Figure 2: contrasted thorax computerized tomoghraphy image of the patient on the third day demonstrating bilateral pleural effusion that was more prominent on the right side and had a thickness of 4 cm at the thickest part.

accumulation. Although pleural effusion can develop as a complication of various diseases; heart failure, pneumonia, tuberculosis and pulmonary embolism are the most common underlying factors in adults[6].

Pleural effusion due to drug intake is rare. Even though hypersensitivity reactions, oxidative stress on the mesothelial cells, dose-dependent direct toxic exposure, fluid retention and chemical inflammation are blamed as the cause of the drug-induced pleural fluid accumulation, the clinical mechanism is not fully elucidated[7, 8]. There are more than thirty drugs which are known to cause drug-induced pleural damage[8]. Drug-induced pleural effusion may appear just after the first dose of the drug or after its usage for many years[7, 8]. However, there is no such general knowledge about the relationship between APAP and pleural effusion. In a clinical study on IV paracetamol, it was reported that pleural effusion might occur as a rare adverse effect in the pediatric patient population. There was no reports on the risk in adults[9, 10].

Under physiological conditions, the approximate amount of the pleural fluid is between 0.26-1ml/kg for each hemithorax and this amount is determined by the dynamic balance between its production and resorption[5]. The drainage of the fluid from the pleural cavity occurs through a few different mechanisms. The channels and pumps in the mesothelial cells in the pleural surface, lymphatic stomata located in the parietal pleura, passive diffusion caused by the Starling forces and the removal of the large molecules with transcytosis enables the excretion of the pleural fluid. The balanced microvascular filtration rate or pleural fluid

flow rate is equal to the excretion rate from the lymphatic stomata[5, 11]. Pharmacological substances may influence the amount of the pleural fluid[5]. It was shown that paracetamol and the NSAIDs blockaged the Na^+ channels and the Na^+/K^+ pumps in the normally functioning parietal pleura. As a result of this blockage, the permeability of the pleural membrane decreases. Thus, the absorption of the fluid from the pleural membrane is also decreased[12, 13]. In an in vivo study conducted on rats, paracetamol and NSAIDs were shown to delay pleural fluid absorption in rats with postoperative hydrothorax[13]. In our case report, we think that high-dose paracetamol reduces pleural fluid absorption and disrupts the balance in terms of fluid accumulation, similar to the literatüre. This disruption in normal functioning resulted in pleural effusion in our patient.

In the literature, there was only one case report with similar features to our patient, and this report was about a 6-month-old girl[14]. However, as far as we know, we have not encountered a case report about an adult patient. In addition, in a report published by the U.S Food and Drug Administration (FDA) on the use of APAP intravenously, it was stated that APAP may cause pleural effusion in pediatric patients, although the incidence is below 1%[15]. In a clinical review published by the FDA in 2009 showed treatment-emergent adverse events (an event that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state-TEAE) after IV paracetamol injection. In this publication, it was stated that pleural effusion as an adverse event constitutes 7.8% of all TEAEs in adolescents and 2.1% in neonates[16].

In the evaluation of the patients with pleural effusion, the first step is to determine whether the fluid is transudate or exudate[6]. In the clinics, with the help of the Light criteria, exudative fluids can be easily distinguished from the transudates[6]. The pleural effusion of our patient had the characteristics of a transudate both macroscopically and regarding the Light criteria. Moreover, there were no cardiovascular, pulmonary, renal or hepatic findings, which might explain the transudative character of the pleural effusion. We believe that the cause of the pleural effusion in our patient was the variability of the pleural permeability and the consequent decrease of the fluid absorption caused by the high-dose intake of paracetamol.

Conclusion

Pleural effusion is common in adult patients and its causes are difficult to diagnose. We think that this is the main reason why there is no similar case reports in the literature. The clues in the diagnosis process of our patient were; the absence of a chronic disease in the history, the occurrence of the event during the follow-up of the patient immediately after drug intake, the transudative character of the fluid and the exclusion of other conditions that may cause pleural effusion.In conclusion, it should be kept in mind that high-dose intake of paracetamol might cause transudative pleural effusion as a rare complication.

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The written consent form is taken from the patient.

"The case report has written in an anonymous characteristic, thus secret and detailed data about the patient has removed. Editor and reviewers can know and see these detailed data. These data are backed up by editor and by reviewers."

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