CASE REPORT
OLGU SUNUMU

Obsessive skincare and liver toxicity: a case report on titanium dioxide exposure

Obsesif cilt bakımı ve karaciğer toksisitesi: titanyum dioksit maruziyeti üzerine bir olgu sunumu

Fatih Öner Kaya[1], Mohammad Jamal Abunawas[2], Pınar Mert[1]

[1]Maltepe University Hospital, Department of Internal Medicine, Istanbul, Turkey
[2]Maltepe University, Faculty of Medicine, Istanbul, Turkey

Submitted Date: 5 July 2024, **Accepted Date:** 30 September 2024

Correspondence: Mohammad Jamal Abunawas
Faculty of Medicine, Maltepe University, Istanbul, Turkey
e-mail: mohammadabunawas9@gmail.com

ORCID ID: FOK: 0000-0001-5472-7465
MJA:0009-0005-7178-5196
PM: 0000-0003-4035-3604

SUMMARY

This Case Report highlights the role of titanium dioxide (TiO2) as a perpetrator of liver toxicity when used topically. Although the European Commission has banned titanium dioxide (E171) from being used as a food additive, it is still widely used in dermatological products. Here, we describe a patient who initially presented to our clinic after experiencing a seizure. An inquiry into her history revealed that she had been suffering from generalized body aches and skin rashes for the past month. Incidentally, liver enzymes were found to be significantly elevated, and abdominal ultrasonography revealed hepatomegaly and hepatic steatosis, which was confirmed by a liver biopsy. Further investigation brought to light the patient's obsessive skincare habits, requiring broader tests to detect any toxic exposure. Thereupon, high amounts of titanium were found in her blood results. TiO2 particles are associated with hazardous properties and pose a threat to human health and the environment; thus, its enormous usage in various products requires further studies that investigate the various ways of exposure to minimize those toxic effects.

Keywords: Hepatotoxicity, titanium dioxide, dermatological products side effects

ÖZET

Bu Vaka Raporu, topikal olarak kullanıldığında karaciğer toksisitesinin bir sebebi olarak titanyum dioksitin (TiO2) rolünü vurgulamaktadır. Avrupa Komisyonu, titanyum dioksidin (E171) gıda katkısı olarak kullanılmasını yasaklamasına rağmen, hala geniş çapta dermatolojik ürünlerde kullanılmaktadır. Burada, bir hastanın kliniğimize nöbet geçirdikten sonra başvurduğu ve hikayesinin incelenmesi sonucu son bir aydır yaygın vücut ağrıları ve deri döküntüleri yaşadığı ortaya çıktı. Tesadüfen karaciğer enzimlerinin önemli ölçüde yüksek bulunan bu hastada karın ultrasonografisinde hepatomegali ve karaciğer yağlanması tespit edildi, bu da karaciğer biyopsisi ile doğrulandı. Detaylı araştırma hastanın obsesif cilt bakım alışkanlıklarının ortaya çıkmasına neden oldu, bu da herhangi bir toksik maruziyeti tespit etmek için geniş tarama testleri gerektirdi. Bu testlerin sonucunda anormal olarak kan testlerinde yüksek miktarda titanyum bulundu. TiO2 partikülleri tehlikeli özelliklerle ilişkilendirilmiştir ve insan sağlığı hatta çevre için bile bir tehdit oluşturur; dolayısıyla, çeşitli ürünlerdeki yaygın kullanımı olduğundan bu toksik etkileri en aza indirmek için maruz kalma yollarını araştıran daha fazla çalışmayı gerektirir.

Anahtar Kelimeler: Karaciğer toksisitesi, titanyum dioksit, dermatolojik ürünlerin yan etkileri

Maltepe tıp derg. Cilt:16 Sayı:1/2024
https://doi.org/10.35514/mtd.2024.116

INTRODUCTION

Although the European Commission has banned titanium dioxide (E171) from being used as a food additive in the EU (1), TiO2 is still widely used in a variety of products, such as anti-fouling paints, household products, plastic goods, medications, cosmetics, sunscreens, pharmaceutical additives, and many new applications are under development (2).

In dermatological products, TiO2 may be used either as a white pigment in its microcrystalline form only or as an inorganic ultraviolet (UV) filter, primarily in sunscreens but also in some day creams, foundations, and lip balms, to protect against the known carcinogenic effects of UV radiation (3). TiO2 has long been used in sunscreens since 1952; however, it was only approved by the Food and Drug Administration (FDA) in 1999 as a legal component of sunscreens (4,5).

Idiosyncratic, or unpredictable hepatotoxicity, also known as drug-induced liver injury (DILI), is one of the most challenging liver disorders. It is commonly seen after the intake of oral drugs or herbal supplements (6). Despite that, patients with DILI may develop signs and symptoms of a hypersensitivity reaction, such as fever and rash, acute hepatotoxicity may manifest with malaise, low-grade fever, anorexia, nausea, vomiting, right upper quadrant pain, jaundice, acholic stools, dark urine, and hepatomegaly (7). DILI accounts for approximately 10 percent of all cases of acute hepatitis (8).

CASE REPORT

A 44-year-old female, without prior diagnosis or regular medications, presented to the internal medicine outpatient clinic after a generalized clonic seizure that lasted approximately 40 seconds.

Reviewing the patient's history, she stated that in the last month, she had recurring abdominal bloating, an inability to eat, and generalized body aches. Moreover, the patient noted losing 6 kg in one month. On physical examination, she complained of cramps all over her body, perception was impaired, and skin rashes were inspected. Her body temperature was within normal ranges, and no abnormality was found in cardiac and pulmonary auscultation.

In regard to the seizure in the patient's history, a computed tomography (CT) scan was conducted, revealing a 34×21 mm in size arachnoid cyst at the level of the left sylvian fissure. Further diffusion magnetic resonance imaging (MRI) was obtained, which confirmed the previous finding.

Laboratory testing had shown unpredicted values; the most significant were aspartate aminotransferase (AST) 226 U/L, alanine aminotransferase (ALT) 57 U/L, gamma-glutamyl transpeptidase (γ-GTP) 862 U/L, and direct bilirubin (DB) was 0,47 mg/dL. Furthermore, abdominal ultrasonography was performed, which revealed an increase in liver size, implying hepatomegaly, and increased liver parenchymal echogenicity consistent with grade 2 hepatic steatosis. Therefore, the patient was admitted into the inpatient facility for a close follow-up of her condition. Routine blood work was periodically tested, and her history was thoroughly investigated. The laboratory findings during the follow-up period are summarized in Table 1.

Table 1. Summary of biochemical analysis of patient by date

Date	21.08. 2023	23.08. 2023	28.08. 2023	18.09. 2023	Reference range
AST	226 U/L	66 U/L	88 U/L	73 U/L	5 - 34
ALT	57 U/L	38 U/L	79 U/L	76 U/L	0 - 55
γ-GTP	862 U/L	541 U/L	396 U/L	127 U/L	9 - 36
PT (INR)	1.10	-	1.06	-	0.8 - 1.2
Ammonia	-	107.0 µmol/L	85.0 µmol/L	43.0 µmol/L	15.00 - 55.00

AST: aspartate aminotransferase; ALT: alanine aminotransferase; γ-GTP: gamma-glutamyl transpeptidase; PT: prothrombin time; INR: international normalized ratio.

The patient had not recently taken hepatotoxic medications such as herbal medicines, anti-fungal drugs, anti-tuberculosis drugs, or anti-inflammatory drugs and did not have a history of drug allergies. Moreover, alpha-fetoprotein (AFP) was tested, which was within normal ranges, and antibody tests were performed to rule out viral and autoimmune hepatitis. The results were as follows: anti-HAV IgG (−), anti-HAV IgM (−), HBs Ag (−), anti-HCV (−), CMV IgM (−), ANA (−), anti-smooth muscle Ab (−), ENA Panel (−) and EBV IgM profile was also negative.

Due to her laboratory and radiological findings, the patient was referred for a liver biopsy, and broad blood analysis was instructed. Tru-cut liver biopsy revealed significant macrosteatosis at liver zones 2 and 3, moderate lobular inflammation, centrilobular perisinusoidal fibrosis, and portal fibrosis, all of which denote grade 3, stage 2 hepatic steatosis. Moreover, heavy metal screening uncovered high amounts of titanium, 16.60 µg/L (Table 2); consequently, the patient was questioned about any possible exposure to products that contain the chemical compound, which disclosed that she had been obsessively using several skin creams and cosmetic products containing the inorganic (mineral) filter titanium dioxide.

Table 2. Heavy Metals Extended Profile.

Examined metals	Results	Reference range
Tin (Sn)	0.101 ng/ml	<5.0
Silver (Ag)	0.3 µg/L	<1.0
Titanium (Ti)	16.60 µg/L	0.00 - 1.00
Gold (Au)	6100 µg/L	<8000 Toxicity limit: 10000
Arsenic (As)	0.66 µg/L	0.00 - 12.00
Mercury (Hg)	0.78 µg/L	0.00 - 10.00
Lead (Pb)	0.1 µg/dL	0.0 - 24.9
Nickel (Ni)	1.01 µg/L	<3.3
Cadmium (Cd)	0.50 µg/L	<5.0
Aluminum (Al)	1.12 µg/L	1.0 - 14.0

DISCUSSION

T We have reported a unique case of toxic hepatitis caused by prolonged dermal exposure to TiO2, a compound frequently found in many dermatological products. The laboratory findings summarized in Table 1 provide a clear picture of the patient's hepatic dysfunction. Significantly elevated AST and GGT levels and moderate ALT elevations point toward hepatocellular injury. Additionally, the patient's Tru-cut liver biopsy confirmed hepatic steatosis and fibrosis, indicative of advanced liver injury. These findings are crucial in understanding the extent of hepatic damage in the context of potential toxic exposure, which was also supported by the detection of abnormally high levels of titanium in the patient's blood.

Previous studies proposed that although metabolic derangements often cause seizures and that liver disease is often associated with metabolic derangements and neurological deficits, such as encephalopathy, there is generally no independent association between liver disease and seizures (9). Nevertheless, the neurological condition that the patient was later diagnosed with was exhaustively evaluated to exclude all possible causative pathologies of the liver injury. In the process, we only found one prior report that indicated an isolated elevation in alkaline phosphatase levels in a healthy child that was believed to be associated with a large arachnoid cyst (10). However, the patient in our case had a small cyst, overall elevated liver enzymes, and, more importantly, histological findings of liver toxicity (11). Patients with DILI are usually asymptomatic and diagnosed incidentally with laboratory testing. Hepatocellular hepatotoxicity generally manifests with marked elevation in aminotransferase levels (ALT, AST, or both), which may be followed by hyperbilirubinemia in severe cases (12).

We reviewed the literature for relevant materials regarding

TiO2 dermal exposure. Most studies suggested TiO2 nanoparticles do not penetrate normal animal or human skin (13,14-19). However, in the majority of these studies, the exposures were short-term (up to 48 h); only a few long-term or repeated exposure studies have been published. Nevertheless, some studies indicated that TiO2 could initiate events that can eventually lead to liver fibrosis, liver steatosis, and/or liver edema with oral exposure (20). With concerns, we found a long-term study that demonstrated a small increase in titanium levels in the liver tissue of hairless mice exposed to topical applications of sunscreen containing nano-TiO_2 once a week for 36 weeks (21). In our case, while TiO_2 particles are often used in both microcrystalline and nanoparticle forms, it was not possible to determine the exact form due to the patient's use of multiple skincare products. Nonetheless, previous studies indicate that although TiO_2 nanoparticles generally do not penetrate intact human skin, long-term exposure or compromised skin barriers can increase the risk of systemic absorption and subsequent toxicity, as seen in this patient (21).

Indeed, TiO2 plays a significant role in producing reactive oxygen species (ROS) and other oxidative products, as well as in the depletion of cellular antioxidants (22-28). Once ROS and reactive nitrogen species are formed, hepatocytic proteins, lipids, and DNA are among the cellular structures primarily affected, resulting in structural and functional abnormalities in the liver (29). Several studies have shown that nano-TiO2 induces genotoxic effects, including DNA damage and micronuclei formation indicative of chromosomal aberrations in different cell lines (30,31-34).

CONCLUSIONS

The patient showed typical findings of toxic hepatitis, and high amounts of TiO2 were found in her blood, which could only be explained by the excessive dermal exposure to TiO2. TiO2 particles are associated with hazardous properties and pose risks to human health and the environment; thus, its enormous usage in various products requires further studies that investigate the various ways of exposure to minimize those toxic effects.

Author Contributions: Working Concept/Design: FOK, MJA; Data Collection: MJA; Data Analysis/Interpretation: MJA, PM; Text Draft: MJA; Critical Review of Content: FOK, MJA, PM; Final Approval and Responsibility: FOK; Supervision: FOK.
Conflict of Interest: The authors state that there is no conflict of interest regarding this manuscript.
Financial Disclosure: The authors declared that this study has received no financial support.

Maltepe tıp derg. Cilt:16 Sayı:1/2024
https://doi.org/10.35514/mtd.2024.116

REFERENCES

1.United States Department of Agriculture, Foreign Agricultural Service; Report Category: SP2 - Prevent or Resolve Barriers to Trade that Hinder U.S. Food and Agricultural Exports. Report Name: Titanium Dioxide Banned as a Food Additive in the EU. T Belder. 2022; E42022-0011

2.Skocaj M, Filipic M, Petkovic J, Novak S. Titanium dioxide in our everyday life; is it safe? Radiol Oncol. 2011 Dec;45(4):227-247.

3.EU No 1223/2009. Commission Regulation (EU) on cosmetic products No 1223/2009 Official Journal of the European Union (30 November 2009).

4.FDA. Sunscreen drug products for over-the-counter human use, Final Monograph, Federal Register 64 27666, US Rockville, MD; 2000.

5.Newman MD, Stotland M, Ellis JI. The safety of nanosized particles in titanium dioxide and zinc oxide-based sunscreens. J Am Acad Dermatol. 2009 61:685-692.

6.European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; Clinical Practice Guideline Panel: Chair:; Panel members; EASL Governing Board representative:. EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol. 2019;70(6):1222-1261.

7.Davern TJ. Drug-induced liver disease. Clin Liver Dis. 2012;16:231.

8.Zimmerman HJ. Drug-induced liver disease. Clin Liver Dis. 2000;4:73.

9.Alkhachroum AM, Rubinos C, Kummer BR, et al. Risk of seizures and status epilepticus in older patients with liver disease. Epilepsia. 2018;59(7):1392-1397.

10.Sanneerappa PB, Gul R, Nadeem M, Ramesh N. Arachnoid Cyst: An Unusual Cause for Increased Alkaline Phosphatase. Ir Med J. 2016;109(9):475.

11.Kleiner DE, Chalasani NP, Lee WM, Fontana RJ, Bonkovsky HL, Watkins PB, Hayashi PH, Davern TJ, Navarro V, Reddy R, Talwalkar JA, Stolz A, Gu J, Barnhart H, Hoofnagle JH; Drug-Induced Liver Injury Network (DILIN). Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. Hepatology. 2014 Feb;59(2):661-670.

12.Liver Injury Caused by Drugs - Hepatic and Biliary Disorders - Merck Manuals Professional Edition; 2023. https://www.merckmanuals.com/professional/hepatic-and-biliary-disorders/drugs-and-the-liver/liver-injury-caused-by-drugs

13.Tyner KM, Wokovich AM, Godar DE, Doub WH, Sadrieh N. The state of nano-sized titanium dioxide (TiO2) may affect sunscreen performance. Int J Cosmetic Sci. 2010;33:234-244.

14.Lademann J, Weigmann H, Rickmeyer C, Barthelmes H, Schaefer H, Mueller G, et al. Penetration of titanium dioxide microparticles in a sunscreen formulation into the horny layer and the follicular orifice. Skin Pharmacol Appl Skin Physiol. 1999;12:247-256.

15.Pflucker F, Wendel V, Hohenberg H, Gartner E, Will T, Pfeiffer S, et al. The human stratum corneum layer: an effective barrier against dermal uptake of different forms of topically applied micronised titanium dioxide. Skin Pharmacol Appl Skin Physiol. 2001; 14: 92-97.

16.Schulz J, Hohenberg H, Pflucker F, Gartner E, Will T, Pfeiffer S, et al. Distribution of sunscreens on skin. Adv Drug Deliv Rev. 2002;54:157-163.

17.Schilling K, Bradford B, Castelli D, Dufour E, Nash JF, Pape W, et al. Human safety review of “nano” titanium dioxide and zinc oxide. Photochem Photobiol Sci. 2010;9: 495-509.

18.Senzui M, Tamura T, Miura K, Ikarashi Y, Watanabe Y, Fujii M. Study on penetration of titanium dioxide (TiO2) nanoparticles into intact and damaged skin in vitro. J Toxicol Sci. 2010;35:107-113.

19.Tan MH, Commens CA, Burnett L, Snitch PJ. A pilot study on the percutaneous absorption of microfine titanium dioxide from sunscreens. Australas J Dermatol. 1996;37:185-187.

20.Walter Brand, Ruud J. B. Peters, Hedwig M. Braakhuis, Lidka Maślankiewicz & Agnes G. Oomen. Possible effects of titanium dioxide particles on human liver, intestinal tissue, spleen and kidney after oral exposure, Nanotoxicology. 2020;14:7,985-1007,

21.Osmond-McLeod MJ, Oytam Y, Rowe A et al. Long-term exposure to commercially available sunscreens containing nanoparticles of TiO2 and ZnO revealed no biological impact in a hairless mouse model. Part Fibre Toxicol. 2016;13:44.

22.Dunford R, Salinaro A, Cai LZ, Serpone N, Horikoshi S, Hidaka H, et al. Chemical oxidation and DNA damage catalysed by inorganic sunscreen ingredients. Febs Lett. 1997;418:87-90.

23.Gurr JR, Wang ASS, Chen CH, Jan KY. Ultrafine titanium dioxide particles in the absence of photoactivation can induce oxidative damage to human bronchial epithelial cells. Toxicology. 2005;213:66-73.

24.Long TC, Tajuba J, Sama P, Saleh N, Swartz C, Parker J, et al. Nanosize titanium dioxide stimulates reactive oxygen species in brain microglia and damages neurons in vitro. Environ Health Persp. 2007;115:1631-1637.

25.Lu N, Zhu Z, Zhao X, Tao R, Yang X, Gao Z. Nano titanium dioxide photocatalytic protein tyrosine nitration: a potential hazard of TiO2 on skin. Biochem Biophys Res Commun. 2008;370:675-680.

26.Park EJ, Yi J, Chung YH, Ryu DY, Choi J, Park K. Oxidative stress and apoptosis induced by titanium dioxide nanoparticles in cultured BEAS-2B cells. Toxicol Lett. 2008;180:222-229.

27.Sayes CM, Wahi R, Kurian PA, Liu Y, West JL, Ausman KD, et al. Correlating nanoscale titania structure with toxicity: a cytotoxicity and inflammatory response study with human dermal fibroblasts and human lung epithelial cells. Toxicol Sci. 2006;92:174-185.

28.Wang JX, Chen CY, Liu Y, Jiao F, Li W, Lao F, et al. Potential neurological lesion after nasal instillation of TiO2 nanoparticles in the anatase and rutile crystal phases. Toxicol Lett. 2008;183:72-80.

29.Cichoż-Lach H, Michalak A. Oxidative stress as a crucial factor in liver diseases. World J Gastroenterol. 2014;20(25):8082-8091.
30.Petković J, Žegura B, Stevanović M, Drnovšek N, Uskoković D, Novak S et al. DNA damage and alterations in expression of DNA damage responsive genes induced by TiO2 nanoparticles in human hepatoma HepG2 cells. Nanotoxicology. 2011;5:341-353.
31.Kang JL, Moon C, Lee HS, Lee HW, Park EM, Kim HS, et al. Comparison of the biological activity between ultrafine and fine titanium dioxide particles in RAW 264.7 cells associated with oxidative stress. J Toxicol Environ Health, Part A. 2008;71:478-485.
32.Rahman Q, Lohani M, Dopp E, Pemsel H, Jonas L, Weiss DG, et al. Evidence that ultrafine titanium dioxide induces micronuclei and apoptosis in Syrian hamster embryo fibroblasts. Environ Health Persp. 2002;110:797-800.
33.Wang JJ, Sanderson BJS, Wang H. Cyto- and genotoxicity of ultrafine TiO2 particles in cultured human lymphoblastoid cells. Mutat Res-Gen Tox En. 2007;628:99-106.
34.Xu A, Chai YF, Nohmi T, Hei TK. Genotoxic responses to titanium dioxide nanoparticles and fullerene in gpt delta transgenic MEF cells. Part Fibre Toxicol. 2009;6:3.

Maltepe tıp derg. Cilt:16 Sayı:1/2024
https://doi.org/10.35514/mtd.2024.116