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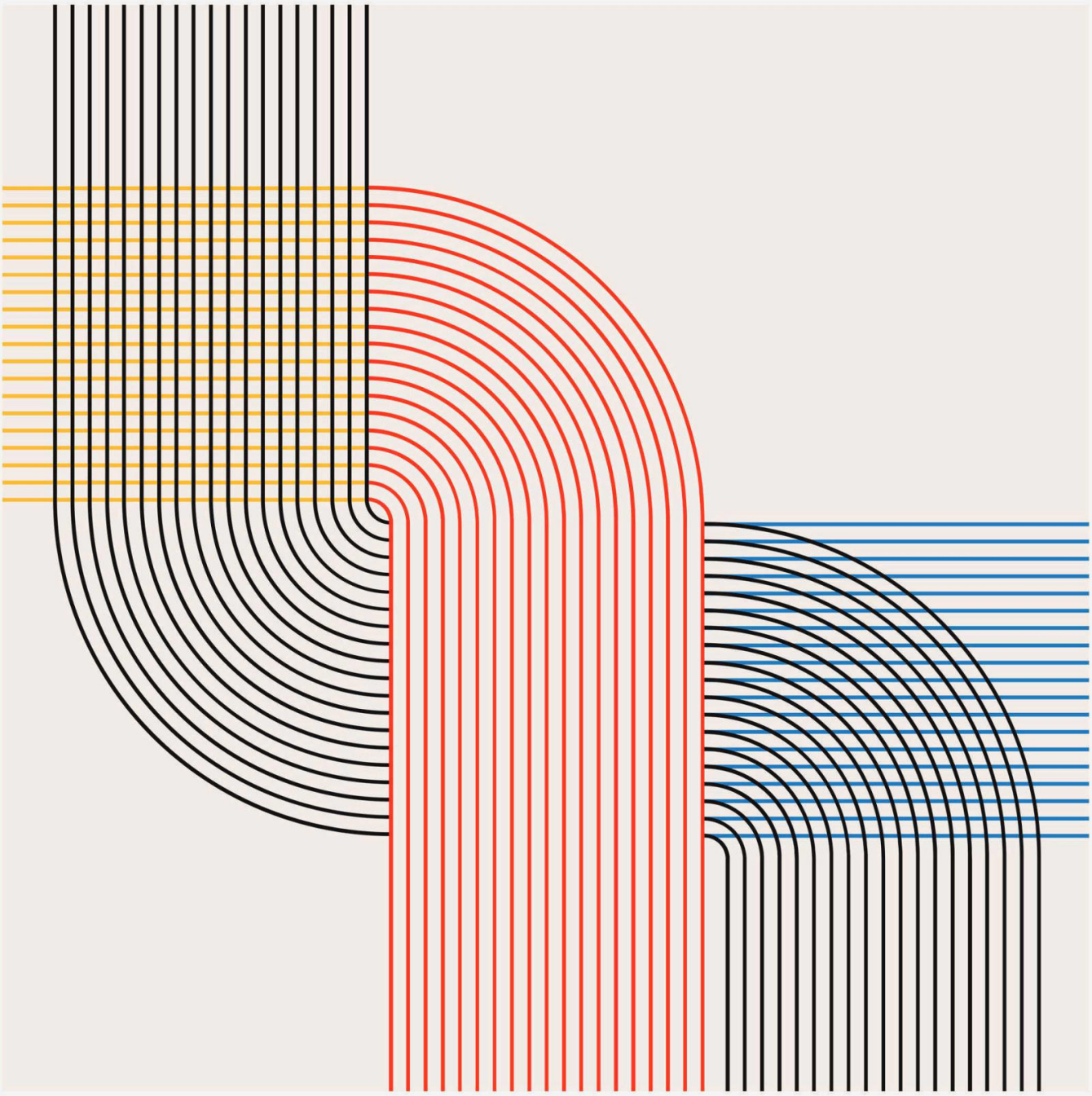

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EDITORIAL

Cytisine: On guard at the Bastiani fortress

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The exhaustion of existence in an absurd futility, waiting for a glorious event to justify it. In his novel, *The Tartar Steppe*, Dino Buzzatti narrates the vital tragedy of the young lieutenant Giovanni Drogo, assigned to defend a forgotten frontier, on the edge of a desertic steppe.[1] In this metaphysical landscape arises the Bastiani fortress, an ancient bastion only sustained due to the remote possibility of a foreign attack. His time slips away as he awaits the arrival of imaginary invaders and a bronze destiny.

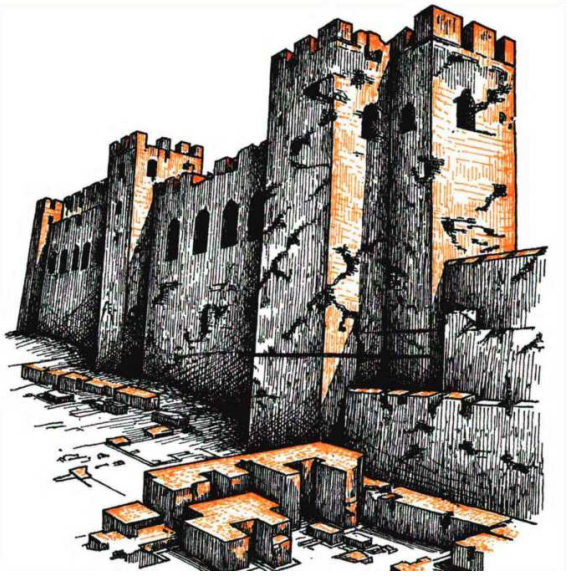
Cytisine was the first drug for smoking cessation in history. Its synthesis began in Bulgaria in 1964 (Tabex®), when it was part of the so-called Eastern Bloc.[2] With the fall of the Soviet Union, its distribution was restricted by the impossibility of conforming to European standards.[3]

We recently published a systematic review, identifying 12 randomized controlled trials (RCT). Eight of these compared cytisine with placebo at the standard dose covering 5922 patients, 2996 of whom took cytisine, delivering a risk ratio (RR) of 2.25 [95% confidence interval (CI) = 1.42-3.56; I^2 = 88%) rated as moderate-quality evidence.[4] Meta-analyses of all non-serious adverse events in the cytisine group versus placebo groups yielded a RR of 1.24 (95% CI = 1.11–1.39; studies = 8; I^2 = 0%; high-quality evidence).

In addition, a recent network meta-analysis (NMA) concluded that cytisine was associated with a higher smoking cessation rate at 6 months or longer, in comparison to placebo with an odds ratio (OR) of 2.21, 95% credible interval [CrI] of 1.66 to 2.97, rated as high certainty of evidence.[5] The authors point to cytisine as the most effective intervention, along with varenicline (OR = 2.33; 95% CrI = 2.02 to 2.68) and e-cigarettes with nico tine (OR = 2.37; 95% CrI = 1.73 to 3.24) for smoking cessation, compared to nicotinic replacement therapy (NRT), bupropion and nortriptyline.

In terms of its cost-effectiveness, an economic analysis by the National Institute for Health and Care Research (NIHR) in the United Kingdom (UK), reported that the economic model estimated more average life years and quality-adjusted years of life, and lower average living costs for treatment with cytisine than with varenicline.[6]

In July 2021, Pfizer issued a voluntary recall of twelve lots of varenicline due to nitrosamines, above the established acceptable level.[7] Chronic exposure to N-nitroso-varenicline may be associated with an increased oncogenic risk. The U.S. Food and Drug Administration (FDA) temporarily did not oppose the marketing of generic varenicline, until the impurity could be removed or reduced.[8] Nevertheless, varenicline is still not available in the European Union



(Credits: Meta AI)

(EU), the UK, South America, and most of North America.

In this context, cytisine constitutes an alternative of even greater relevance. However, public accessibility continues to be very limited worldwide. According to data from the World Health Organization (WHO), cytisine is only available in Azerbaijan, Bulgaria, Ivory Coast, Canada, Czechia, Georgia, Germany, Hungary, Italy, Kazakhstan, Latvia, Lithuania, Portugal, Russia, Serbia, Spain, Sweden, Ukraine, Uzbekistan and Zambia.[9] In February 2024, through an update to the National Institute for Health and Care Excellence (NICE) guidelines, the availability of cytisine in the UK changed, recommending its use.[10]

Over time, the fortress becomes ruins and oblivion, and Drogo becomes an old man without redemption, in a useless wait. Let's hope that for cytisine the end will be different.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1 Buzzati D. The Tartar Steppe. United Kingdom: Canongate Canons; 2018. 288 p. ISBN 13: 9781786891648

2 Giulietti F, Filipponi A, Rosettani G, Giordano P, Iacoacci C, Spannella F, Sarzani R. Pharmacological Approach to Smoking Cessation: An Updated Review for Daily Clinical Practice. High Blood Press Amp Cardiovasc Prev. 2020 Jun 23;27(5):349-62. Available from: https://doi.org/10.1007/s40292-020-00396-9

3 Prochaska JJ, Das S, Benowitz NL. Cytisine is the world's oldest smoking cessation aid. BMJ. 2013 Aug 23;347. Available from: https://doi.org/10.1136/bmj.f5198

4 De Santi O, Orellana M, Di Niro CA, Greco V. Evaluation of the effectiveness of cytisine for the treatment of smoking cessation: A systematic review and meta-analysis. Addiction. 2023 Dec 31. Available from: https://doi.org/10.1111/add.16399

5 Lindson N, Theodoulou A, Livingstone-Banks J, Aveyard P, Fanshawe TR, Ordóñez-Mena JM, Sutton AJ, Freeman SC, Agrawal S, Hartmann-Boyce J. Pharmacological and electronic cigarette interventions for smoking cessation in adults: component network meta-analyses. Cochrane Database Syst Rev. 2022 Mar 30;2022(3). Available from: https://doi.org/10.1002/14651858.cd015226

6 Leaviss J, Sullivan W, Ren S, Everson-Hock E, Stevenson M, Stevens JW, Strong M, Cantrell A. What is the clinical effectiveness and cost-effectiveness of cytisine compared with varenicline for smoking cessation? A systematic review and economic evaluation. Health Technol Assess. 2014 May;18(33). Available from: https://doi.org/10.3310/hta18330

7 Pfizer. New York City: Pfizer; Pfizer Issues A Voluntary Nationwide Recall for Twelve Lots of CHANTIX® (varenicline) Tablets Due to N-Nitroso Varenicline Content. 2023 [updated 2021 Jul 16]. Available from: https://www.pfizer.com/news/announcements/pfizer-issues-voluntary-nationwide-recall-twelve-lots-chantixr-varenicline

8 US Food & Drug Administration (FDA). Silver Spring, MD: FDA; c2023 [updated 23 Aug 2021]. Laboratory analysis of varenicline products. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-nitrosamine-varenicline-chantix

9 World Health Organization (WHO). The global health observatory; Cytisine - place available (Tobacco control: Offer help). 2024 [updated 31 Oct 2023]. Available from: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/gho-tobacco-offerhelp-medication-cytisine-place-available

10 National Institute for Health and Care Excellence (NICE). 2024 exceptional surveillance of tobacco: preventing uptake, promoting quitting and treating dependence; NICE guideline NG209 [updated 21 Feb 2024]. Available from: https://www.nice.org.uk/guidance/ng209/resources/2024-exceptional-surveillance-of-tobacco-preventing-uptake-promoting-quitting-and-treating-dependence-nice-guideline-ng209-13312648045/chapter/Surveillance-decision?tab=evidence

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CASE REPORT

Severe glitter poisoning: Case report

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ABSTRACT. Glitter, also referred to as 'bronze dust' or 'gold dust,' is a highly toxic substance typically produced by grinding bronze and combining it with zinc and stearin. It is commonly used in paints to achieve golden tones and is widely employed in crafts, cosmetics, and school projects. Ingestion or inhalation of glitter can lead to potentially fatal poisoning in children. This article describes the case of a 3-year-old girl exposed to glitter who developed acute respiratory distress and altered sensorium, requiring ventilatory support. In cases of glitter ingestion and/or inhalation, bronchoscopy with bronchoalveolar lavage should be performed immediately, even in the absence of respiratory symptoms

Key words: *Glitter; Gold dust; Copper; Bronchoalveolar lavage; D-penicillamine.*

Exposure to toxic substances accounts for 0.3% of pediatric emergency cases, of which 5-10% are considered potentially fatal. Ninety percent of childhood poisonings occur at home, primarily in children aged 1 to 4 years, which coincides with the highest prevalence of domestic accidents.[1,2]

Glitter, also referred to as 'bronze dust' or 'gold dust,' is a highly toxic substance typically produced by grinding bronze (an alloy of copper and tin) and combining it with zinc and stearin. The latter is a fatty acid that acts more as an additive to improve the texture and handling of the product, but it does not have a significant impact on its toxicity. Glitter is used in paints to achieve golden tones and is widely employed in crafts, cosmetics, and school projects. Accidental ingestion or inhalation is rare but potentially fatal in children.[3] We report the case of a 3-year-old girl who presented with respiratory distress and altered consciousness over a short period following exposure.

CLINICAL CASE

A 3-year-old female patient with no significant medical history was accidentally exposed to glitter through inhalation (aspiring a large amount of dust), dermal contact, oral ingestion, and ocular exposure. The glitter was being used by a family member for the commercial decoration of ornaments. She was brought to the emergency department of our hospital, presenting with respiratory distress, cyanosis, vomiting, and abdominal pain. Her vital signs upon admission were: HR 143 bpm, RR 42 bpm, and SpO2 92% (FiO2 0.21). Fig. 1 shows pulmonary involvement on the thoracic X-ray, 2 hours after admission to the Emergency Department (ED). It demonstrated signs of air trapping with bilateral reinforcement of the lung pattern.

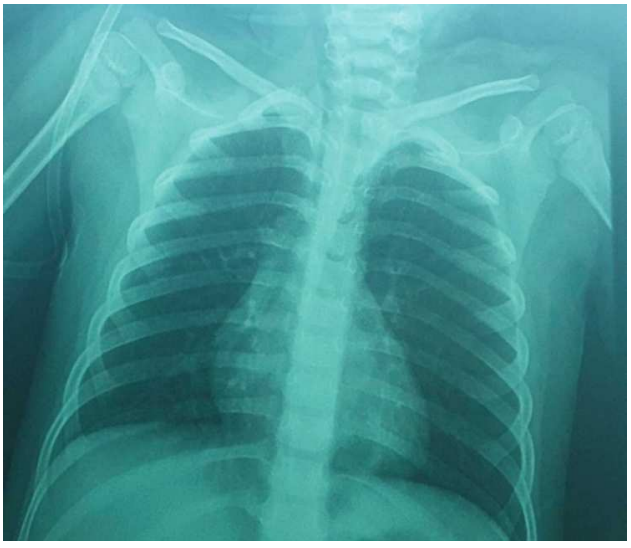

Figure 1. The chest X-ray upon admission showed signs of air trapping and bilateral increased lung markings.

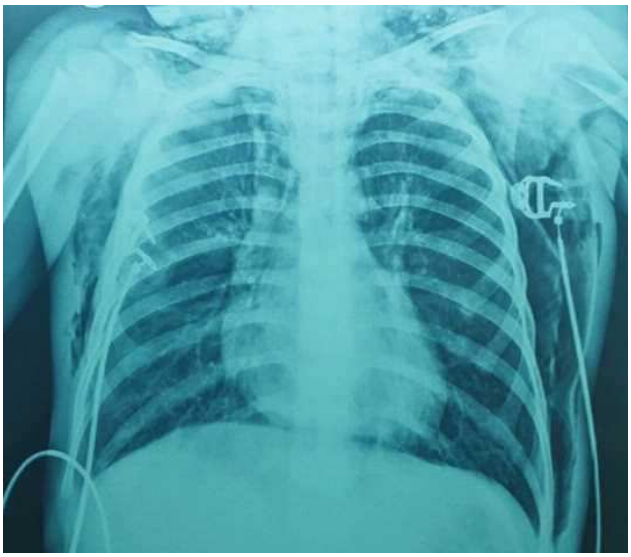

Figure 2. Thoracic X-ray 48 hours after admission to the PICU. Signs of air trapping are observed, along with the presence of bilateral interstitial infiltrates compatible with chemical pneumonitis.

Due to the progression of respiratory symptoms, the patient was admitted to the Pediatric Intensive Care Unit (PICU). Pulmonary involvement was predominantly on the right side (Fig. 2), requiring initial oxygen therapy via a reservoir mask and antibiotic treatment with clarithromycin and ceftriaxone, later switched to clindamycin. 24 hours after her admission to the PICU, the patient required mechanical ventilation for 7 days due to respiratory failure and a decline in her level of consciousness. Laboratory results showed WBC 25,200/mm³, HCT 36%, HGB 12.2 g/dL, PLT 434,000/mm³ and ABG 7.28/48/55/22.6/-4.1.

Over the following 72 hours, a hemolytic anemia was observed, with a HCT 28%, HBG 9.3 g/dL, TB 2.3 mg/dL and IB 2 mg/dL. Subsequently, the antibiotic regimen was changed to piperacillin-tazobactam combined with amikacin, and furosemide was introduced. The patient never required the administration of vasoactive drugs. Among the complications, she developed extensive subcutaneous emphysema in the chest and neck, along with a right-sided grade I pneumothorax.

As a result of symptomatic improvement, the patient was transferred to the Pediatric Inpatient Unit, where clinical and laboratory monitoring continued. The CBC and renal and liver functions were normal. The serum copper level was 152 µg/dL (normal value [NV]: 88-158 µg/dL), urinary copper or *cupruria* was 68 µg over 24 hours (NV: 20-87 µg), and serum zinc was 141 µg/dL (NV: 60-150 µg/dL). Given the results of the metal assays, chelation therapy was not initiated. The patient was discharged 14 days after admission, with normalized laboratory values and plans for follow-up by the Pulmonology Service due to lung sequelae. A chest X-ray and computed tomography (CT) scan were performed 3 months after exposure, revealing findings consistent with bronchiectasis in both lung bases (Fig. 3).

DISCUSSION

Copper is an essential antioxidant micronutrient involved in erythropoiesis and iron metabolism, primarily found in the liver, brain, kidneys, and heart. In addition, it plays a key role in the immune system, protects against cellular damage by free radicals, participates in the mitochondrial electron

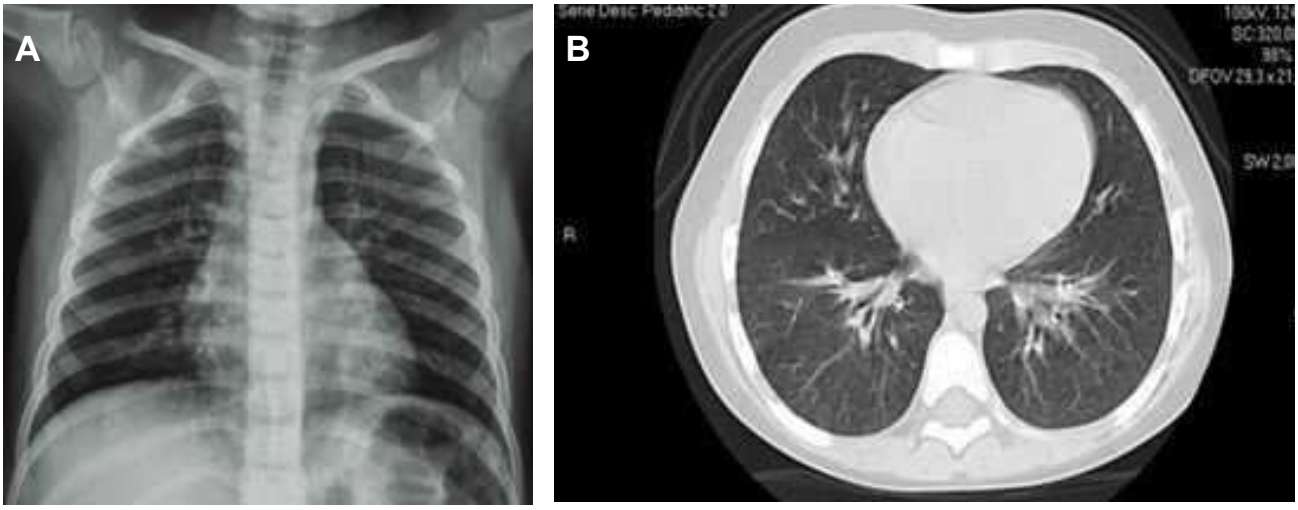

Figure 3. Chest X-ray (A) and CT (B) scan performed 3 months after exposure to glitter. Signs of bronchiectasis can be observed in both lung bases.

transport chain, and is crucial for the synthesis of collagen, elastin, and other biomolecules. However, copper can be highly toxic, and in its Cu^{2+} form, it has the potential to generate free radicals, leading to oxidative stress-induced damage.[3]

Glitter poisoning is infrequent, with only a few reports in the literature. In exposed children, symptoms are primarily determined by copper toxicity. Since fecal and biliary excretion accounts for 80% of ingested copper elimination, systemic toxicity after ingestion is uncommon. Approximately 18% of copper is absorbed and transported via the bloodstream to the liver, where it is stored. Around 2-4% is excreted through urine.[3,4] Gastrointestinal manifestations include nausea, greenish vomiting, abdominal pain, diarrhea, and toxic hepatitis with centrolobular necrosis. Renal involvement can lead to oliguria, hematuria, cylindruria, and may result in acute tubular necrosis. Other clinical manifestations include hemolytic anemia within the first 24 hours, tachycardia, hypotension, methemoglobinemia, rhabdomyolysis, pulmonary edema, seizures, coma, multiorgan failure, and death.[5]

Acute toxicity from the inhalation of copper dust or vapors causes irritation of the upper respiratory tract, accompanied by odynophagia, irritative cough, and sinusitis. In the lower respiratory tract, chemical pneumonitis may occur, depending on the particle size inhaled, which ranges from 3 to 70 microns in the case of glitter. Inhaling these particles may also lead to gastrointestinal irritation, followed by systemic absorption. The presence of vomiting and abdominal pain suggests the passage of copper into the digestive tract, and an elevation in copper levels (*cupremia*) indicates the absorption of copper across the gastrointestinal mucosa and the alveolocapillary barrier into the bloodstream. It can also result in hepatic and/or renal failure.[6]

Gosselin et al. (1984) reported the case of a 2-year-old child who suffered fatal poisoning from gold dust, presenting with fever, gastrointestinal symptoms, renal damage, and severe pneumonitis on autopsy.[7] There is limited literature on the inhalation of gold dust; however, cases of powder or talc aspiration in infants have been reported, with rapid progression to severe pulmonary illness and a mortality rate of 23%.[8-11] These authors report a similar clinical picture in the inhalation of other types of dust, similar to that described with the aspiration of glitter.

Naturally present zinc from food sources does not appear to cause zinc toxicity. However, excessive zinc intake from supplements can lead to adverse health effects, including gastrointestinal distress, nausea, dizziness, headaches, and loss of appetite. Zinc doses exceeding 200 mg can induce vomiting, and gastrointestinal discomfort has been reported with doses as low as 50 mg. A few cases of severe zinc toxicity have been documented following the ingestion of non-food items containing zinc. Chronic and substantial ingestion of zinc-containing coins may result in copper deficiency anemia due to zinc-induced toxicity, particularly in individuals with metal pica. Notably, hematological and neurological manifestations of zinc toxicity resulting from the ingestion of coins or denture cream have improved with the removal of the zinc source and copper supplementation. The inhalation of zinc oxide fumes, common among welders and others working in environments where zinc is heated to high temperatures, can cause a characteristic acute respiratory illness of short duration. This condition is marked by fever and flu-like symptoms and is typically associated with the development of tolerance to continued exposure, with recurrence upon subsequent re-exposure. A second, potentially lethal respiratory condition can arise from exposure to zinc chloride, often from smoke bombs used in crowd control. In such cases, the respiratory distress is severe.[12]

We must distinguish between this patient's exposure to ultra-fine glitter and other larger forms of glitter that become trapped in the upper respiratory tract (trachea and bronchi) without reaching the distal airways. Inhalation of these types of glitter may cause coughing but does not lead to systemic absorption. Due to its toxicity, the sale of glitter should be avoided as a preventive measure.[13] In our clinical case, the primary route of exposure was inhalation, leading to a progressive respiratory condition that required ventilatory support. A latency period of several hours between inhalation and the onset of respiratory symptoms is typically observed. These manifestations, the rapid progression of the clinical course, and the radiological changes observed are similar to those described in the inhalation of other types of dust.

In children with respiratory distress, treatment should include supportive measures such as parenteral hydration, corticosteroids, and bronchodilators. Immediate intubation and bronchoalveolar lavage (BAL) improve the patient's prognosis. Although the number of reported cases where this procedure was carried out is limited, the literature supports its urgent indication in children, even in the absence of respiratory symptoms.[14] This is because BAL can reduce the toxic burden in the lungs and mitigate potential complications.[15] In our patient, it could not be performed due to the unavailability of a specialist, a situation not uncommon in our setting.

The use of chelating agents, such as D-penicillamine, is recommended in cases of acute copper poisoning with evidence of systemic involvement. In asymptomatic patients, chelation therapy should only be initiated after confirming specific laboratory findings. Copper and zinc levels in blood or urine should be monitored, along with a complete laboratory analysis (including a complete blood count, electrolytes, liver and renal function tests), and a chest X-ray in all patients.

Given the hazardous nature of glitter, provincial laws in Argentina have prohibited its sale to minors and its use or handling in educational institutions since 2014. We believe it is essential to implement these regulations nationwide due to the potentially lethal effects on children. Additionally, it is crucial to educate adults on keeping the substance out of children's reach, thereby strengthening preventive measures.[16]

CONCLUSIONS

Exposure to glitter in children can lead to severe poisoning with a potentially fatal outcome. Due to the clinical presentation of our patient, advanced supportive measures were employed, and immediate BAL was recommended. However, this procedure could not be performed due to a lack of specialized personnel at our hospital. Current literature suggests performing this procedure urgently in order to improve the prognosis of poisoned patients.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1 Martínez Sánchez L, Mintegi Raso S. Protocolos diagnósticos y terapéuticos en Urgencias de Pediatría [Internet]. 3rd ed. Madrid: Asociación Española de Pediatría; 2020. Intoxicaciones; p. 321-38. Available from: https://www.aeped.es/sites/default/files/documentos/25_intoxicaciones.pdf

2 Mintegi Raso S, Azkunaga Santibáñez B, Bizkarra Azurmendi I, del Arco León L. Epidemiología de las intoxicaciones en Pediatría. In: Mintegi Raso S, editor. Manual de intoxicaciones en Pediatría. 3rd ed. Madrid: Ergon; 2012. p. 3-8

3 Pascale A, Bello O, Fernández S, Dell'Acqua C. Exposición accidental a polvo de oro. Arch Pediatr Urug. 2003;74(2):119-22. Available from: http://www.scielo.edu.uy/scielo.php?script=sci_arttext&pid=S1688-12492003000200008

4 Donoso A, Cruces P, Camacho J, Carlos Ríos J, Paris E, Jose Mieres J. Acute respiratory distress syndrome resulting from inhalation of powdered copper. Clin Toxicol. 2007;45(6):714-6. Available from: https://doi.org/10.1080/15563650701438912

5 Tsao HS, Allister L, Chiba T, Barkley J, Goldman R. A Case Report of Cake Frosting as a Source of Copper Toxicity in a Pediatric Patient. Clin Pract Cases Emerg Med. 2020;4(3):384-8. Available from: https://doi.org/10.5811/cpcem.2020.7.47267

6 Cabrera-Marutz CD, Velásquez-Alcalá S, Vrhovac-Biljesko J. Enfermedades profesionales en la industria del cobre: extracción, manufactura y reciclaje. Medicina Segur Del Trab. 2014;60(237):756-78. Available from: https://doi.org/10.4321/s0465-546x2014000400010

7 Gosselin R, Smith R, Hodge H. Gold powder. In: Gosselin R, Smith R, Hodge H, editors. Clinical Toxicology of Commercial Products. 5th ed. Baltimore: Williams and Wilkins; 1984

8 Pfenninger J, D'Apuzzo V. Powder aspiration in children. Report of two cases. Arch Dis Child. 1977;52(2):157-9. Available from: https://doi.org/10.1136/adc.52.2.157

9 Motomatsu K, Adachi H, Uno T. Two Infant Deaths after Inhaling Baby Powder. Chest. 1979;75(4):448-50. Available from: https://doi.org/10.1378/chest.75.4.448

10 Pairaudeau PW, Wilson RG, Hall MA, Milne M. Inhalation of baby powder: an unappreciated hazard. BMJ. 1991;302(6786):1200-1. Available from: https://doi.org/10.1136/bmj.302.6786.1200

11 Dekel Y, Rath-Wolfson L, Rudniki C, Koren R. Talc inhalation is a life-threatening condition. Pathol Amp Oncol Res. 2004;10(4):231-3. Available from: https://doi.org/10.1007/bf03033766

12 Ryu MS, Aydemir TB. Present Knowledge in Nutrition. [place unknown]: Elsevier; 2020. Zinc; p. 393-408. Available from: https://doi.org/10.1016/b978-0-323-66162-1.00023-8

13 Comunidad SAP [Internet]. Lesiones por purpurina; [cited 2025 Jan 10]. Available from: http://comunidad.sap.org.ar/index.php/2016/02/19/lesiones-por-purpurina/

14 Alexander CP, Gordon T, Sridhar G, Raghupathy P. Massive powder aspiration in a toddler. Indian Pediatr. 2005;42(3):288-90. PMID: 15817984

15 Dificultad respiratoria aguda por ingestión de purpurina

en polvo en un niño de 15 meses: una urgencia endoscópica. Arch Argent Pediatr. 2022 Feb;120(1). Available from: https://doi.org/10.5546/aap.2022.e29

16 SAIJ [Internet]. Prohibición en establecimientos escolares de uso del producto "Purpurina"; 2014 Nov 17 [cited 2025 Jan 10]. Available from: https://www.saij.gob.ar/7158-local-santiago-estero-prohibicion-establecimientos-escolares-uso-producto-purpurina-lpg0007158-2014-11-11/123456789-0abc-defg-851-7000gvorpyel?&o=3&f=Total%7CTipo%20de%20Documento%7CFecha%5B50%2C1%5D%7COrganismo%7CPublicaci%F3n%7CTema/Cultura%20y%20educaci%F3n/educaci%F3n%7CEstado%20de%20Vigencia%7CAutor%7CJurisdicci%F3n/Local/Santiago%20del%20Estero&t=116

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CASE SERIES

Doxorubicin extravasation: Case series

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ABSTRACT

Background. One of the most severe complications arising from the IV administration of certain cytostatic drugs is the extravasation into adjacent tissue, which causes local irritation, tissue necrosis, and may even result in amputation of the affected limb. According to the literature, the incidence of extravasations in peripheral intravenous administration ranges from 0.1 to 6%.

Clinical cases. Three patients presented suffering from doxorubicin extravasation while undergoing chemotherapy treatment. General measures were applied in all cases, and in one case dimethyl sulfoxide (DMSO) was applied topically as an antidote for 24-48 hrs. All three had favorable responses.

Conclusions. Extravasation is a potentially serious complication of doxorubicin infusion. It is key to adhere to safe chemotherapy administration guidelines in order to prevent issues, as well as to continuously train staff.

Key words: *Extravasation; Chemotherapy; Doxorubicin; Dimethyl sulfoxide; DMSO.*

Doxorubicin (hydroxydaunorubicin or adriamycin) is a chemotherapy medication in the anthracycline family used to treat various cancers, including breast cancer, bladder cancer and hematolymphoid tumors. One of the serious complications that may occur during the IV administration of some cytostatic drugs is the extravasation into adjacent tissue. *Extravasation* refers to the unintended, inadvertent or accidental leakage of IV-administered drugs to perivascular and subcutaneous spaces.[1,2]

Doxorubicin is a vesicant that can cause serious and long-lasting injury to tissue, as well as necrosis. Symptoms can appear immediately after extravasation or after several days or weeks, causing local pain or irritation, mild erythema, pruritus, or edema. Over time, erythema and pain may intensify, resulting in discoloration and skin induration, desquamation and blistering. Significant extravasation may cause necrosis, eschars, and ulcers affecting subcutaneous tissue. Indolent ulcers lack granulation tissue formation and peripheral re-epithelialization.

The actual incidence of extravasation is unknown due to underreporting of cases. The estimated prevalence of extravasation caused by IV-administration of chemotherapy drugs is 0.1-6%, and 0.3-4.7% when administered via central venous catheter.[3] Three cases of doxorubicin extravasation are presented in the following paragraphs, registered in the Oncohematology Service of the Central Aeronautical Hospital of the City of Buenos Aires, Argentina.

CLINICAL CASES

Three cases of doxorubicin extravasation were studied. The following variables were considered: sex, underlying condition, puncture site, type of catheter, drug, instance of the chemotherapy protocol during which the lesion took place, clinical presentation, and treatment.

Clinical case 1

65-year-old female patient, diagnosed with breast cancer. Doxorubicin extravasation occurred on the dorsal side of her left hand, during the third cycle of treatment. Her symptoms were pain, necrotic ulcer, affection to tendinous tissue and functional impairment. Antibiotics, corticosteroids and analgesics were administered as treatment, and subsequent reconstructive surgery was required (Fig. 1).

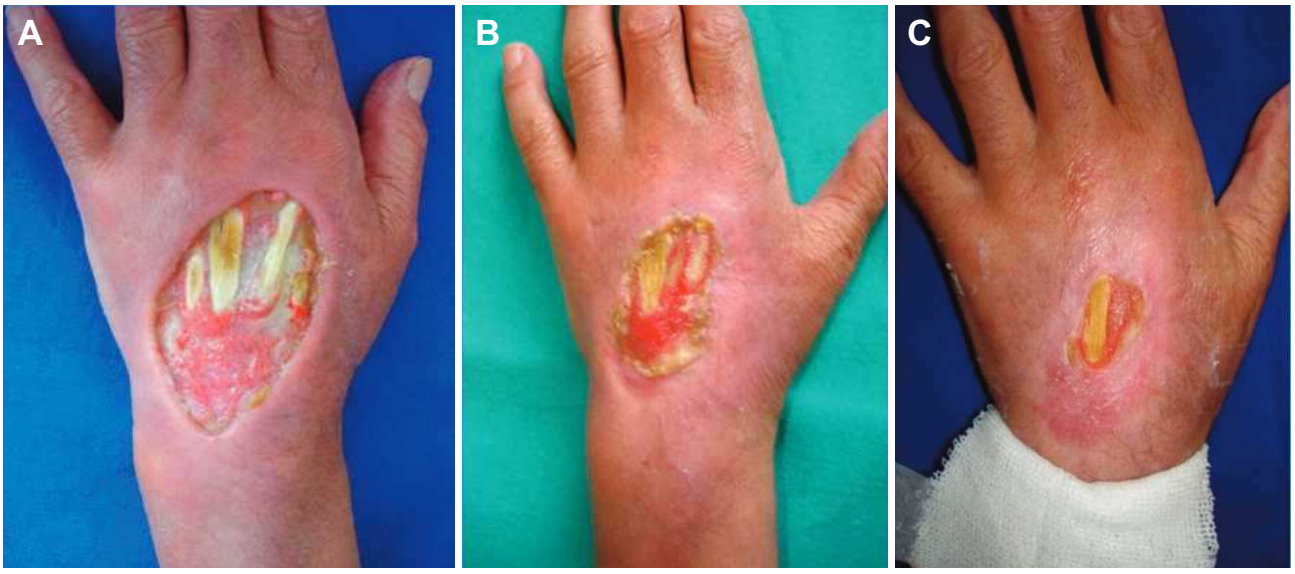

Figure 1 (A, B and C). A necrotic ulcer can be observed in the dorsal part of the left hand, with defined edges and affection to tendinous tissue.

Clinical case 2

53-year-old male patient, suffering from non-Hodgkin lymphoma (NHL). Doxorubicin extravasation occurred on the dorsal side of his left hand, during the fifth cycle of treatment. He presented pain, a necrotic ulcer and affection to tendinous tissue (Fig. 2). Treatment with antibiotics, corticosteroids, and analgesics was administered, and later required reconstructive surgery.

Clinical case 3

72-year-old female patient diagnosed with NHL. Doxorubicin extravasation occurred on the left forearm, during the third cycle of treatment. Upon physical examination, she presented local pain, edema, dispersed papules, erythema and desquamation (Fig. 3), and later developed a necrotic ulcer. Topical treatment was administered, using dimethyl sulfoxide (DMSO) 99%, antibiotics and corticosteroids.

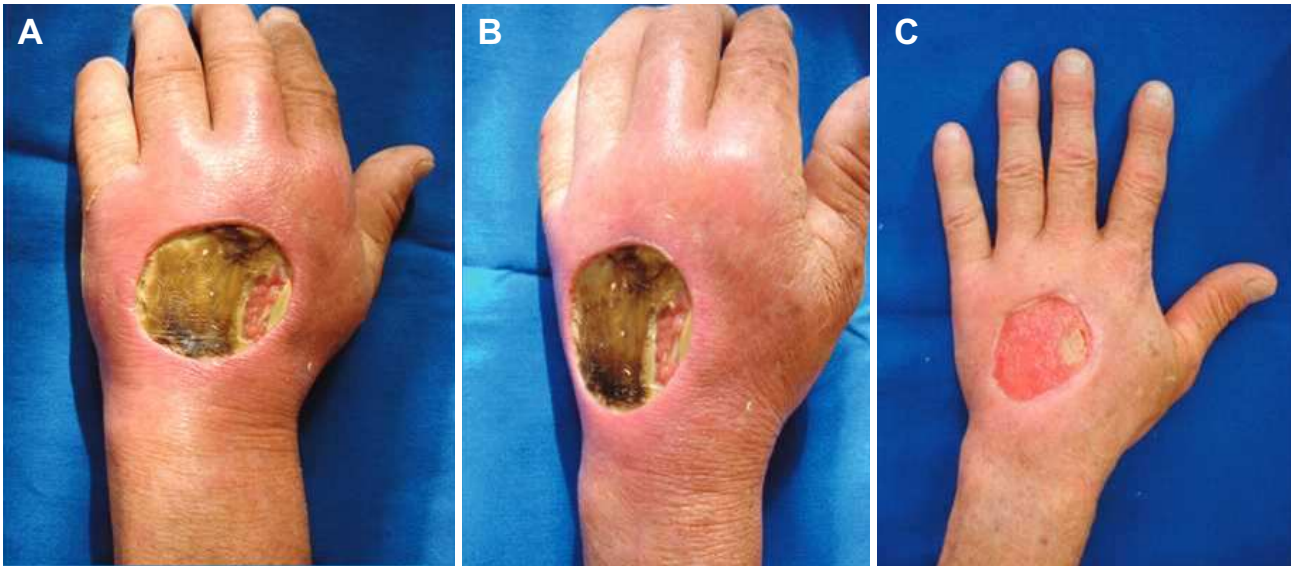

Figure 2 (A, B and C). A necrotic ulcer can be observed in the dorsal part of the left hand, with defined edges, affection to tendinous tissue and fibrinous tissue inside the lesion.

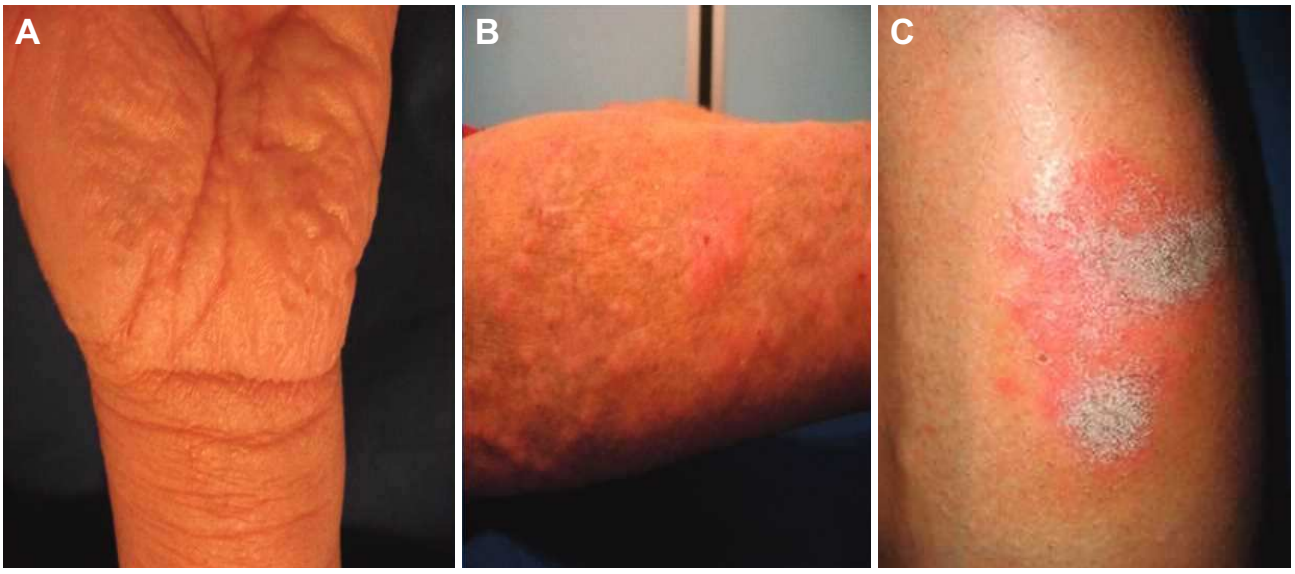

Figure 3 (A, B and C). Edema, erythema and papules can be observed in the left forearm, later developing erythematous plaques and desquamation.

In all three cases a necrotic ulcer lesion was observed, with a shorter recovery time in case 3, after DMSO was administered. The three patients received antibiotic treatment, as well as daily cleansing, surgical interventions and kinesiology rehabilitation due to the loss of sensitivity and movement in the affected limb.

DISCUSSION

Doxorubicin extravasation may cause from local irritation and tissue necrosis to limb amputation, one of the most feared adverse effects. The most relevant aspect when dealing with the administration of cytostatics is the prevention of lesions, training the staff involved and applying careful and standardized drug-administration techniques.[4-6] Any service where this type of agent is infused should have therapeutic algorithms aimed at treating extravasation, as well as kits with materials and medications necessary to treat such cases.[7] When preventive measures are insufficient and extravasation of a vesicant drug occurs, general and specific measures must be implemented.

General measures

Firstly, the infusion of the drug must be stopped immediately, and the equipment and/or system used for the perfusion must be disconnected and removed. The line must be kept in place, with the needle or cannula *in situ* and the limb immobilized. Then, the residual liquid must be removed through the line, aspiring gently. If any subcutaneous blister is observed, its content must be removed using a 1 mL syringe and a fine needle (25G), changing the needle for each blister. The affected limb should be raised to improve venous return and minimize the edema, and a cold compress should be applied. This therapy should be applied for the first hour (as much as the patient endures), and then 3-4 times a day for 15-20 minutes -without interrupting night-time rest-, for 48-72 hrs. Cold therapy induces local vasoconstriction, reducing the distribution of the drug to other areas and, thusly, may reduce the size of the lesion, in addition to reducing pain and inflammation. This approach reduces the absorption of doxorubicin, cisplatin, bleomycin, carmustine, mitomycin, and mitoxantrone, and its synergy with DMSO is confirmed.

Specific measures

While keeping the catheter in place, DMSO 99% can be administered. It is a dissolving antidote that penetrates tissue and eliminates free radicals and enhances the clearance of extravasated drugs, especially anthracyclines and mitomycin. It is applied topically by covering an area twice the size of the affected area, 2 drops per 4cm^2 (≈ 1-2 mL, or 20-40 drops per 7.5 cm by 7.5 cm gauze) for 15-20 minutes, 3-4 times a day, for 7-14 days. This treatment must be started within 10 minutes of the extravasation and left to dry without bandages.[8]

Regarding evidence on the efficacy of DMSO, there are

no randomized clinical trials. Despite initially discouraging results in animal studies,[9] in the 1980s a prospective pilot study of 20 patients showed clinical benefit in the treatment of anthracycline extravasation.[10] Topical application of DMSO was performed immediately after the extravasation, covering twice the affected area. The treatment was repeated twice a day for 14 days. There was no ulceration and no surgical intervention was required. In 1995, a study of the cases of 144 patients treated with DMSO after the extravasation of different chemotherapy drugs was published, including doxorubicin (n = 11).[11] In these cases, DMSO 99% was applied topically, four drops per 10 cm^2 of skin surface, twice over the affected area, and was left to dry without bandages. The treatment was administered within 10 minutes of the extravasation in 84% of patients, and repeated every 8 hrs. for a week. Only 1 patient developed ulceration after epirubicin extravasation. It is important to note that DMSO may cause local erythema, which may lead to an incorrect assessment of the tissue damage.

Other considerations

It is important to apply antibiotic treatment if bacterial superinfection occurs, providing patients with written proscriptions, as it happened in our cases. Documenting the extravasation in the medical history is crucial, as it allows for a proper evaluation of the applicability and efficacy of the institutional protocol for such cases.

Lastly, patients must be informed about post-treatment care before being discharged.[12] It is recommended that patients are periodically examined, every 24-48 hrs. during the first week and on a weekly basis afterwards, until symptoms have disappeared. If necessary, referral to a plastic surgeon is advised.

CONCLUSIONS

Extravasation is a serious complication of doxorubicin chemotherapy. The implementation of therapeutic and diagnostic algorithms, as well as continuously training staff involved in these treatments is crucial for preventing complications and long-term sequels.

Conflicts of interest
The authors declare no conflicts of interest.

REFERENCES

1 Hadaway L. Infiltration and extravasation. AJN Am J Nurs. 2007 Aug;107(8):64-72. Available from https://doi.org/10.1097/01.naj.0000282299.03441.c7. Erratum in: Am J Nurs. 2007 Oct;107(10):15
2 Dougherty L. IV therapy: recognizing the differences between infiltration and extravasation. Br J Nurs. 2008;17(14):896-901. Available from: https://doi.org/10.12968/bjon.2008.17.14.30656
3 Kreidieh FY. Overview, prevention and management of chemotherapy extravasation. World J Clin Oncol. 2016;7(1):87. Available from: https://doi.org/10.5306/wjco.v7.i1.87
4 Mader I, Fürst-Weger P, Mader R, Nogler-Semenitz E, Wassertheurer S. Extravasation of Cytotoxic Agents. Vienna: Springer Vienna; 2010. Available from: https://doi.org/10.1007/978-3-211-88893-3
5 Wengström Y, Margulies A. European Oncology Nursing Society extravasation guidelines. Eur J Oncol Nurs. 2008; 12(4):357-61. Available from: https://doi.org/10.1016/j.ejon.2008.07.003
6 WOSCAN Cancer Nursing and Pharmacy Group. Chemotherapy extravasation guideline, 2009 [cited 2024 Dec 8]. 24 p. Available from: https://hemonc.org/w/images/b/b3/BeatsonWestScotlandExtravasation.pdf
7 Pattison J. Managing cytotoxic extravasation. Nurs Times. 2002;98(44):32-4. PMID: 12451746. Available from: https://pubmed.ncbi.nlm.nih.gov/12451746/
8 SEFH. SOCIEDAD ESPAÑOLA DE FARMACIA HOSPITALARIA. Prevención y tratamiento de extravasaciones de fármacos antineoplásicos. Madrid; 2020. 50 p. Available from: https://gruposdetrabajo.sefh.es/gedefo/images/stories/documentos/2020/monografia_extravasaciones.pdf
9 Dorr RT, Alberts DS. Failure of DMSO and vitamin E to prevent doxorubicin skin ulceration in the mouse. Cancer Treat Rep. 1983;67(5):499-501. PMID: 6850665. Available from: https://pubmed.ncbi.nlm.nih.gov/6850665
10 Olver IN, Aisner J, Hament A, Buchanan L, Bishop JF, Kaplan RS. A prospective study of topical dimethyl sulfoxide for treating anthracycline extravasation. J Clin Oncol. 1988;6(11):1732-5. Available from: https://doi.org/10.1200/jco.1988.6.11.1732
11 Bertelli G, Gozza A, Forno GB, Vidili MG, Silvestro S, Venturini M, Del Mastro L, Garrone O, Rosso R, Dini D. Topical dimethylsulfoxide for the prevention of soft tissue injury after extravasation of vesicant cytotoxic drugs: a prospective clinical study. J Clin Oncol. 1995 Nov;13(11):2851-5. Available from: https://doi.org/10.1200/jco.1995.13.11.2851
12 Pérez Fidalgo JA, García Fabregat L, Cervantes A, Margulies A, Vidall C, Roila F. Management of chemotherapy extravasation: ESMO–EONS Clinical Practice Guidelines. Ann Oncol. 2012;23:vii167—vii173. Available from: https://doi.org/10.1093/annonc/mds294

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IMAGES IN TOXICOLOGY

Chronic silicosis in mining workers

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Abstract. Two clinical cases of silicosis are reported in mining workers from the 'El Nevado' Mining Cooperative in Pacuni (La Paz Department, Bolivia). The symptoms, physical examinations, and complementary tests performed are described in detail. The radiographic findings were characteristic of this pathology.

Key words: *Silica; Silicosis; Pneumoconiosis; Mining; Lung.*

Mining is one of the primary economic activities worldwide. Mineral extraction is conducted in various ways, including underground mining, where workers are exposed to silica (SiO_2). This paper presents a clinical case study of two underground miners from the 'El Nevado' Mining Cooperative in Pacuni (La Paz Department), located in the Bolivian Altiplano at an altitude of 5,003 metres above sea level.

Patient A

A 29-year-old male worker with a 16-year history of silica dust exposure. At the time of consultation, he was working as a drilling miner, having held other positions in the past. He presented with mild dyspnea (Medical Research Council [MRC] Dyspnea Scale grade I), nocturnal cough, and peripheral cyanosis. On auscultation, bilateral rhonchi and wheezing were heard in both lung fields. Vital signs: BP 130/80 mmHg, HR 84 bpm, RR 22 bpm and SpO2 83% (FiO2 0.21). Laboratory results: HCT 60%, HGB 21 g/dL, RBC 6,300,000/mm3, Cr 1.0 mg/dL, and Glu 71 mg/dL. Thoracic X-ray: bone demineralisation, diffuse bilateral nodular lung pattern with nodules up to 3 mm in diameter, more prominent in the upper lobes and hilar region (Fig. 1). Spirometry showed an obstructive pattern with an FEV1/FVC ratio of 65%.

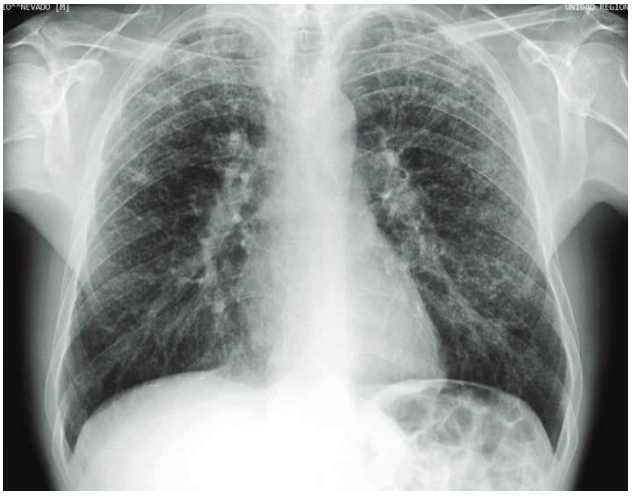

Figure 1. Thoracic X-ray of patient A, 16-year history of exposure to silica dust.

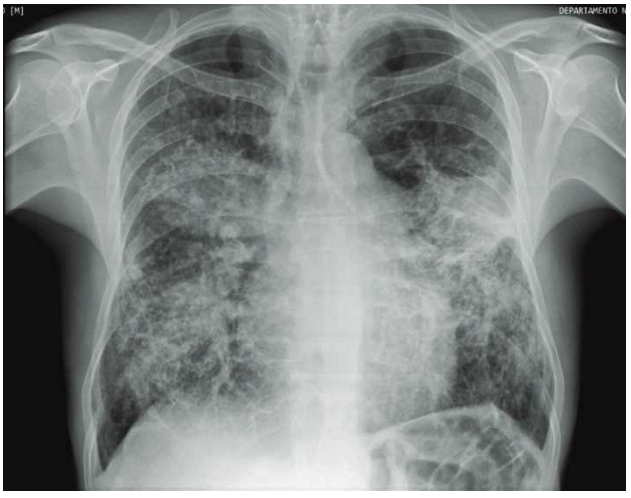

Figure 2. Thoracic X-ray of patient B, 24-year history of exposure to silica dust.

Patient B

A 49-year-old male worker with a 24-year history of silica dust exposure. At the time of consultation, he was working as a cart miner, having held other positions in the past. He presented with moderate dyspnea (MRC grade II), persistent cough predominantly in the morning, and central and peripheral cyanosis. On auscultation, diffuse rhonchi, wheezing, and crackles were heard in both lung fields. Vital signs: BP 150/90 mmHg, HR 80 bpm, RR 24 bpm and SpO2 79% (FiO2 0.21). Laboratory results: HCT 64%, HGB 23 g/dL, RBC 7,500,000/mm3, Cr 1.5 mg/dL and Glu 85 mg/dL. Thoracic X-ray: progressive massive fibrosis with areas of nodular conglomerates associated with fibrocalcifications. A 'tent sign' (juxtaphrenic peak sign) was present in the left lung, and right diaphragmatic blunting. Additionally, there was cardiac silhouette enlargement and pulmonary artery prominence associated with pulmonary hypertension (Fig. 2). Spirometry showed a mixed pattern with FEV1 64%, FVC 70%, and an FEV1/FVC ratio of 61%.

Conflicts of interest

The authors declare no conflicts of interest.

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LETTER TO THE EDITOR

Do not forget the Lichtenstein's Green Racer!

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Abstract. *Philodryas olfersii* is a non-aggressive, diurnal snake widely found in South America. Most snakebites from this species result in mild symptoms. However, in rare instances, the envenomation can present symptoms resembling those of bothropic snake bites, which are more common in the region. This highlights the importance of considering the potential toxicological impact of *Philodryas olfersii* bites to avoid misdiagnosis and inappropriate treatment with bothropic antivenom.

Key words: *Philodryas olfersii; Opisthoglyphous; Snakes; Myotoxins; Fibrinogenolytic proteases.*

To the Editor: *Philodryas olfersii* (Lichtenstein, 1823), also known as 'Lichtenstein's Green Racer,' is a widely distributed species of opisthoglyphous snake found throughout South America. It is characterized by its slender body, elongated head, and smooth, shiny scales. Typically, it exhibits a distinctive coloration, with shades ranging from olive green to brown, and often has subtle banding or darker markings along its back (Fig. 1). Its interaction with humans is generally accidental or a result of intentional handling, facilitated by its diurnal habits, harmless appearance, and non-aggressive behaviour. Bites, which are most commonly observed on the hands, generally

Figure 1. Appearance of *Philodryas olfersii*. It is primarily arboreal, although it can also be found on the ground, especially during the mating season or in search of food (Credits: DuSantos).

cause minimal local symptoms. However, in rare cases, clinical manifestations resembling bothropic envenoming—an ophidic accident more common in the region—can occur.[2] For this reason, it is important not to overlook the toxicological significance of envenomation by *Philodryas olfersii*, in order to avoid diagnostic errors and the inappropriate use of bothropic antivenom.

In October 2023, a 26-year-old woman with no relevant medical history consulted at a regional hospital in Argentina after being bitten by a snake on the lateral aspect of her left wrist. The incident took place at midday in a park, while she was holding the snake to take a photograph. Initially, there was no significant injury at the bite site, except for a complete dental imprint. Three hours later, she developed local edema, erythema, and ecchymosis, which progressed into an extensive hematoma that affected the entire length of the left upper limb, extending to the axillary and pectoral regions (Fig. 2 and 3). The National Poison Center was alerted, and a veterinarian specialized in snakes identified the specimen as *Philodryas olfersii*.

Upon hospital admission, the patient reported pain and functional impairment of the affected limb due to edema. Her vital signs were stable, and laboratory tests ruled out hemolysis, rhabdomyolysis, coagulation disorders, or microhematuria. Doppler ultrasound of the upper limb's arteries and veins showed no abnormal pulse waveforms, and compartment syndrome was excluded. Treatment included anti-edema measures, non-steroidal analgesics, intravenous

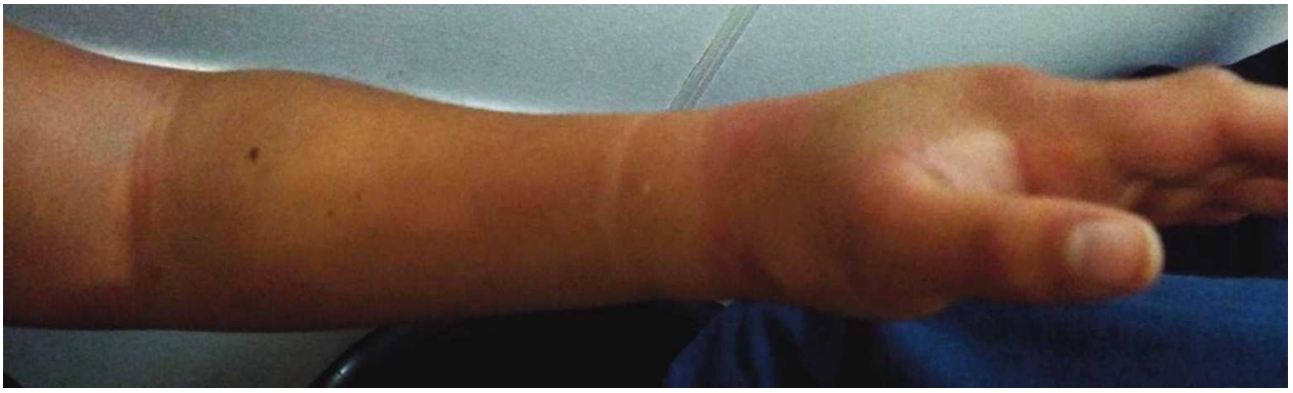

Figure 2. Extensive edema, erythema, and ecchymosis after the bite from *Philodryas olfersii*.

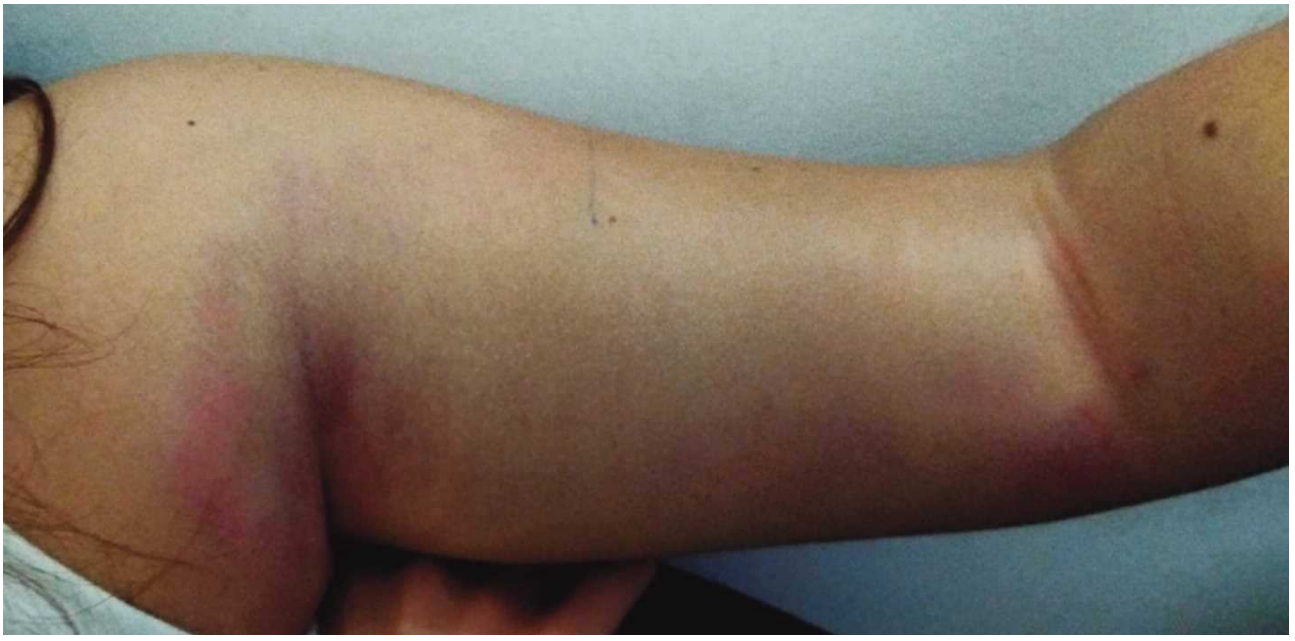

Figure 3. Progression of the hematoma that affected the entire length of the left upper limb, extending to the axillary and pectoral regions.

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corticosteroids, tetanus prophylaxis, and empirical antibiotics. After 24 hours of observation, the patient was discharged with instructions to return for a clinical follow-up in 7 days. By this time, the hematoma had reduced in size, and the edema had significantly subsided.

In the largest series of bites by *Philodryas olfersii*, only 21.3% of cases required symptomatic treatment, and none developed coagulopathy.[3] The venom of this species is known to contain a myotoxin and five fibrinogenolytic proteases, with bioactivity similar to bothropic venom and cross-reactivity with its antivenom.[4] *In vitro*, these toxins cause hemorrhage and vasogenic edema,[5] with myonecrosis described in animal models.[6] It is noteworthy that bites from *Philodryas olfersii* rarely lead to poisoning in humans. This may be explained by inefficient venom delivery due to its opisthoglyphous condition, the absence of striated muscle in the Duvernay's gland, and its limited mandibular retraction ability. However, when the bite is effective, as in the case described, the clinical picture may closely resemble that of bothropic envenoming.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1 Santos E. Wikimedia Commons [Internet]. Philodryas olfersii; 2007 Aug 29 [cited 2024 Dec 29]. Licensed under the Creative Commons Attribution 2.0 Generic license. Available from: https://commons.wikimedia.org/wiki/File:Philodryas_olfersii.jpg

2 Ribeiro LA, Puorto G, Jorge MT. Bites by the colubrid snake Philodryas olfersii: a clinical and epidemiological study of 43 cases. Toxicon. 1999;37(6):943-8. Available from: https://doi.org/10.1016/s0041-0101(98)00191-3

3 Castro FC, Nogueira de Souza S, Maria de Almeida-Santos S, Miyaji KT, Roberto de Medeiros C. Bites by Philodryas olfersii (Lichtenstein, 1823) and Philodryas aestiva (Duméril, Bibron and Duméril, 1854) (serpentes, dipsadidae) in São Paulo, Brazil: A retrospective observational study of 155 cases. Toxicon. 2021;197:55-64. Available from: https://doi.org/10.1016/j.toxicon.2021.04.014

4 Rocha MM, Paixão-Cavalcante D, Tambourgi DV, Furtado MD. Duvernoy's gland secretion of Philodryas olfersii and Philodryas patagoniensis (Colubridae): Neutralization of local and systemic effects by commercial bothropic antivenom (Bothrops genus). Toxicon. 2006;47(1):95-103. Available from: https://doi.org/10.1016/j.toxicon.2005.10.005

5 Assakura MT, Salomão MD, Puorto G, Mandelbaum FR. Hemorrhagic, fibrinogenolytic and edema-forming activities of the venom of the colubrid snake Philodryas olfersii (green snake). Toxicon. 1992;30(4):427-38. Available from: https://doi.org/10.1016/0041-0101(92)90539-h

6 Oliveira JS, Sant'Anna LB, Oliveira Junior MC, Souza PR, Andrade Souza AS, Ribeiro W, Vieira RP, Hyslop S, Cogo JC. Local and hematological alterations induced by Philodryas olfersii snake venom in mice. Toxicon. 2017; 132:9-17. Available from: https://doi.org/10.1016/j.toxicon.2017.03.013

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