Volume 22 Number 3
March 2016

Case report

Mercury toxicity presenting as acrodynia and a papulovesicular eruption in a 5-year-old girl

Olivia Lai[1], Kory K Parsi[2], Davina Wu[2], Thomas H Konia[2], Alexandra Yonts[2], Natasha Sinha[2], Amy McNelis[2], Victoria R Sharon[2]

Dermatology Online Journal 22 (3): 7

[1]Keck School of Medicine of the University of Southern California

[2]University of California, Davis

Correspondence:

Victoria R. Sharon, MD, DTMH
3301 C Street, Suite 1400
Sacramento, CA 95816, USA
Email: VSharon@ucdavis.edu
UC Davis Department of Dermatology

Abstract

Acrodynia is a reaction that occurs in children who have been exposed to mercury. Mercury toxicity has systemic manifestations as well as cutaneous manifestations, which can appear similar to those found in a number of other diseases. We present a case of acrodynia caused by mercury exposure in a previously healthy 5-year-old girl who developed hypertension, palmoplantar pruritus, and a papulovesicular eruption.

Case synopsis

A 5-year-old previously healthy girl was admitted to the hospital for two months of increasing migratory joint pain, new-onset recalcitrant hypertension, irritability, photophobia, decreased appetite, and one week of intensely pruritic palmoplantar papules and vesicles. During hospitalization, her blood pressure increased to a maximum of 159/113 mm/Hg and remained on average 145/105 mm/Hg, necessitating triple anti-hypertensive therapy with amlodipine, labetalol, and hydralazine.

Physical exam revealed palmoplantar erythema with hundreds of monomorphic erythematous pinpoint papules and vesicles concentrated around the dorsal and interdigital surfaces. The papulovesicular eruption improved over the course of one week following triamcinolone ointment. However, her palms and soles remained pink and extremely pruritic for weeks. One week after presentation, she developed hundreds of pinpoint erythematous papules and vesicles on her back, mimicking the prior eruption on her hands and feet (Figure 1). A punch biopsy from an affected finger demonstrated spongiosis, parakeratosis, and collections of intraepidermal neutrophils (Figure 2). The periodic acid-Schiff-diastase stain was negative for fungus.

Laboratory evaluation revealed normal complete blood count, basic metabolic panel, liver function tests, urinalysis, erythrocyte sedimentation rate, C-reactive protein, aldosterone, renin, complement, ammonia, and lactic acid. There was no serological evidence of acute infection with Epstein–Barr virus, parvovirus, and coxsackie virus. Thyroid stimulating hormone was elevated at 7 mIU/mL (normal 0.6-4.40). However, the patient had normal free thyroxine and triiodothyronine levels. Anti-thyroid peroxidase antibodies were not detected. Antinuclear antibody was elevated at 1:80 with a nucleolar staining pattern.

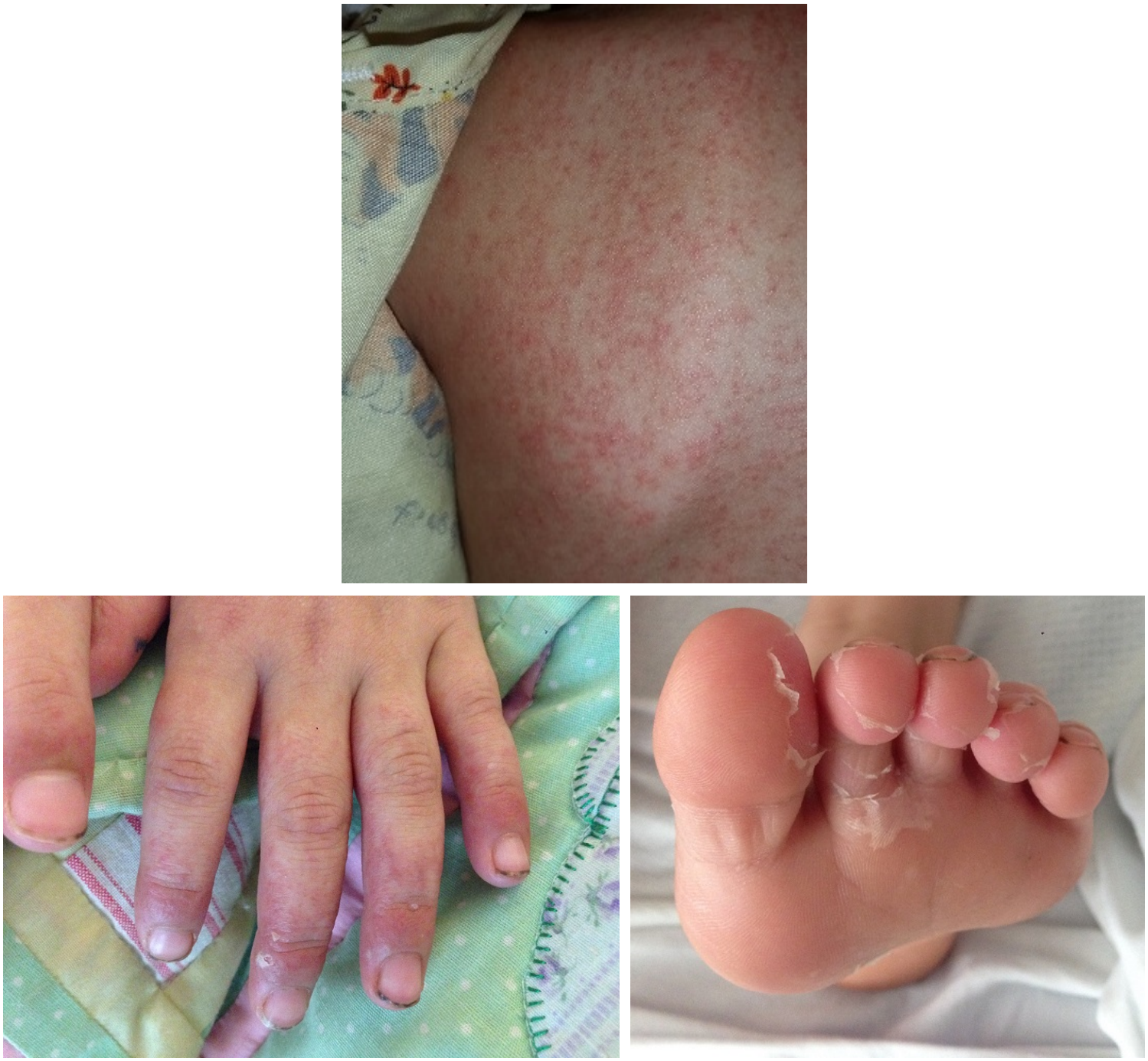

Figure 1. Monomorphic erythematous papules and vesicles on the back (a) and hand (b). Exfoliation is beginning to occur on the distal fingers (b) and toes (c).

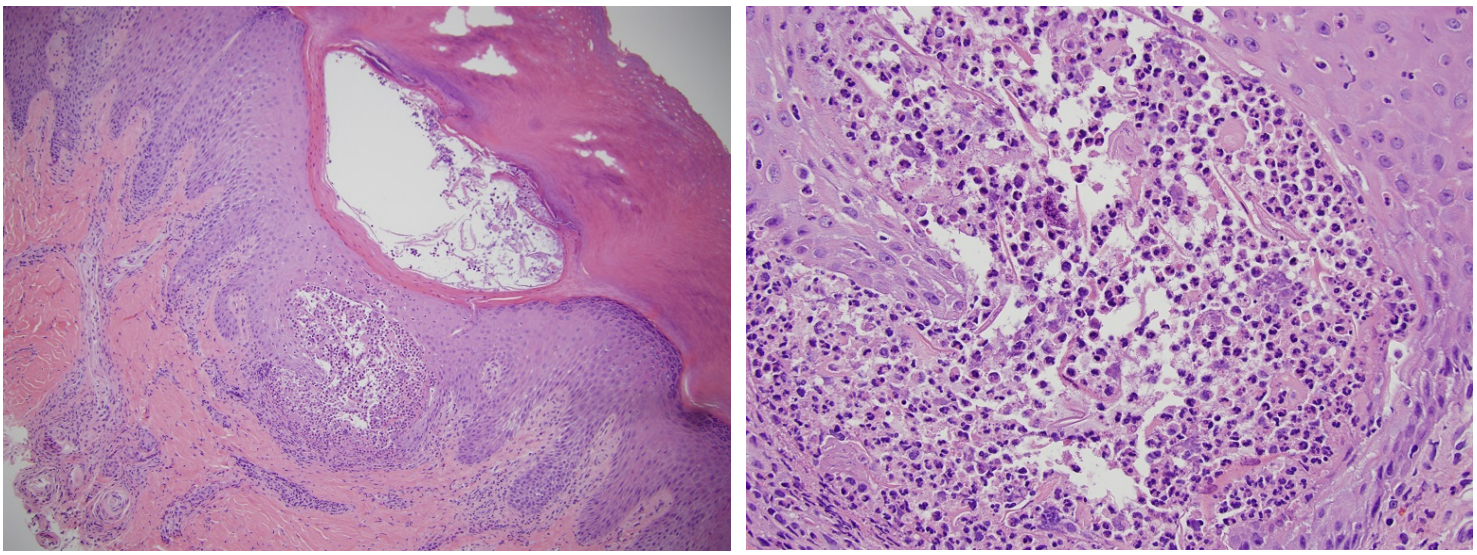

Figure 2. Punch biopsy of a lesion on the finger demonstrates spongiotic dermatitis with an intraepidermal collection of neutrophils at 100x (a) and 400x (b) magnification (hematoxylin & eosin stain).

Chest X-ray, magnetic resonance imaging of the abdomen and brain, renal ultrasound, and echocardiogram were normal. Electrocardiogram showed sinus tachycardia with borderline prolonged QT interval. As her labs did not reveal a diagnosis for her symptoms, mercury toxicity was suspected in the setting of enigmatic hypertension in association with an acral eruption. Urinary catecholamines (dopamine, norepinephrine, and epinephrine) and plasma dopamine were elevated.

A urine heavy metal panel was subsequently performed, which showed elevated levels of urinary cadmium, arsenic, lead, and mercury (Table 1). The elevated levels of urinary cadmium, arsenic, and lead were most likely related to the fact that the patient lives in a historic mining town founded during the California Gold Rush. Environmental contamination with and human exposure to heavy metals often occurs owing to human activities such as mining and smelting. It is quite likely that the patient was exposed to cadmium, arsenic, and lead through the contaminated environment in her hometown [1]. Serum lead levels were undetectable.

Table 1. Heavy metal panel at days 6 and 16 of hospitalization.

Heavy Metal Panel	Hospital Day 6	Hospital Day 16
Cadmium, Urine:Cr (ref 0.0-3.0 ug/g Cr)	**<3.7 (H)**	<2.4
Arsenic, Ur:Cr (ref 0.0-29.9 ug/g Cr)	**85.2 (H)**	**39.3 (H)**
Lead, Ur:Cr (ref 0.0-4.9 ug/g Cr)	**<18.5 (H)**	**<12.4 (H)**
Mercury, Ur, per volume (ref 0-10.0 ug/L)	**23.1 (H)**	**21.0 (H)**
Mercury, Ur- per 24 hr	**27 (H)**	-------
Mercury, Ur:Cr (ref <35.0 ug/g Cr)	**85.6 (H)**	**51.2 (H)**

A diagnosis of acrodynia secondary to mercury intoxication was made. Further history-taking revealed that while in her bedroom the patient had dropped and broken a vial of mercury she found in a shed three months prior to presentation. A toxicology consultant recommended against chelation because of suspected chronic mercury exposure and it was decided to treat the patient with supportive care in the hospital while the department of public health investigated her home environment.

A repeat urine heavy metal panel 10 days after diagnosis demonstrated a steady decline in all of the patient's urinary heavy metal levels. At the time of last contact (2.5 months after diagnosis), her blood pressure was well-controlled at home, ranging from 94-102/72-74. She is currently on atenolol 12.5mg twice daily and amlodipine 2.5mg once daily; these were tapered and discontinued over several weeks. Cyproheptadine, which she took for 2 months, assisted in a modest amount of weight gain. Lastly, her energy levels have returned to normal.

Discussion

Introduction

Mercury, a toxic heavy metal, is the second most common cause of heavy metal poisoning [2]. People have been exposed to mercury for centuries and mercury exposure results in a variety of health consequences [3]. Clinical signs and symptoms of acute mercury poisoning are typically seen when blood and urine concentrations of mercury are greater than 100 mcg/L [4].

Young children typically attain higher bodily concentrations of mercury for any given exposure and children are more vulnerable than adults to the toxic effects of mercury [5]. Mercury vapor is heavier than air and settles near the ground, where young children play and crawl. Children also have higher minute volume respiration per unit of weight and therefore inhale more mercury vapor

than adults do for any given concentration of mercury. Additionally, children's developing nervous systems are more vulnerable to the neurotoxic effects of mercury and their blood-brain barriers are less effective than those of adults at preventing mercury from entering the brain [5–7].

Routes of Exposure and Forms of Mercury

Children are exposed to mercury through 4 routes: inhalation, ingestion, transdermal absorption, and transplacental absorption [7]. The consequences of mercury toxicity exposure vary depending on the form of mercury involved as well as on the timing and dosage of the exposure.

Organic mercury compounds, which include ethylmercury, methylmercury, and thimerosal, cause birth defects in children exposed in utero. Methylmercury, which has a half-life of around 50 days, can be commonly found in seafood, plastics, paper, processed wood, insecticides, and thimerosal vaccines [2,8]. Consumption of seafood contaminated with methylmercury is the main way in which children are exposed to organic mercury [3,7]. Inorganic mercury, which has a half-life of about 40 days, is commonly found in pesticides, antiseptics, germicides, skin-lightening cosmetics, and folk medicines [3,7].

Elemental mercury, which has a half-life of around 60 days, is often found in dental amalgams, thermometers, mercury switches, latex paint, thermostats, and barometers [2,3,7]. Industrial production processes, mercury mining, and artisanal gold mining may also expose people to elemental mercury [7]. Exposure to broken mercury thermometers is one of the most common causes of mercury toxicity in children [2]. Additionally, when elemental mercury is spilled onto carpeting and upholstery, it releases vapors into the air over time and can lead to chronic mercury exposure. This situation, similar to the current case presentation, is a common scenario for pediatric mercury poisoning [3].

Cutaneous Manifestations of Mercury Toxicity

Mercury is toxic to the central nervous system, kidneys, gastrointestinal tract, skin, cardiovascular system, lungs, and immune system [7,9]. Although this discussion will focus on the cutaneous manifestations of mercury poisoning, healthcare professionals should be aware that symptoms such as severe pneumonitis, gum inflammation with excessive salivation, psychiatric symptoms, and intention tremor may be seen [4].

Mercury exposure can lead to a wide variety of cutaneous signs. Some researchers consider acute contact dermatitis to be the most common cutaneous manifestation of mercury exposure. Topical and/or systemic exposure to mercury can lead to painful pruritic or eczematous eruptions [3]. Two clinical patterns of systemic allergic reactions to mercury, acute generalized exanthematous pustulosis and symmetric flexural exanthema, have been described. Most of these patients had been sensitized to mercury compounds in the past and were subsequently accidentally exposed to mercury via broken thermometers [10].

Patients with acute generalized exanthematous pustulosis experience the sudden appearance of small, non-follicular sterile pustules on a widespread background of erythema. They often demonstrate peripheral blood leukocytosis and fever. Patients with symmetric flexural exanthema, on the other hand, typically do not have systemic symptoms [10]. Symmetric flexural exanthema was first referred to as "baboon syndrome" by Andersen et al in 1984 because the buttocks of affected patients appear similar to the red buttocks of baboons. Both contact allergen-induced baboon syndrome and a non-contact allergenic variant that is also referred to as symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) have been described [11].

Symmetric flexural exanthema owing to mercury appears within a few days of mercury exposure. It manifests as a symmetric, diffuse erythematous maculopapular eruption of the flexural areas with a V-shaped pattern on the medial thighs. Buttock erythema is present and pustules may form as the condition progresses [10,11]. The flexural distribution pattern of baboon syndrome may relate to the fact that mercury is excreted by the sweat glands. The accumulation of sweat may lead to a localized type IV hypersensitivity response in flexural areas [10,12].

Acrodynia, or "pink disease," is a condition that may be caused by an allergic reaction to parenteral mercury .[3,7,13]. Acrodynia is typically restricted to young children and infants [3,7]. Historically, many children were exposed to mercury in the form of calomel (mercurous chloride). Calomel was present in teething powders and antihelminthic treatments, but pediatricians realized in the late 1940s that acrodynia was associated with mercury poisoning [14]. Recognition of calomel's toxicity led to bans on the inclusion of mercury in teething powders in the United states and in many other countries; the prevalence of acrodynia has since significantly decreased [2,14–16]. However, products containing calomel can still be found in Southeast Asia and some other parts of the world [17]. Occasional cases of mercury poisoning from calomel and other sources still do occur. Cases of acrodynia have been reported in children with urinary mercury concentrations below 10 mcg/L [7].

Some children are more susceptible than others to developing acrodynia [14,18]. For example, only approximately 1 in 500 children who were exposed to mercury via teething powders developed acrodynia. The underlying cause for this increased susceptibility to mercury was attributed to an idiosyncratic sensitivity to mercury. The underlying pathogenesis of this increased susceptibility to mercury has not yet been elucidated. It is possible that genetic factors may play a role. Interestingly enough, research has shown that mercury sensitivity may be a heritable risk factor for autism spectrum disorders, as the prevalence rate of autism spectrum disorders among the grandchildren of pink disease survivors is significantly higher than in the general population [18].

Initial symptoms of acrodynia include irritability, poor appetite, apathy, and excessive sweating and pain in the extremities. The hands, feet, and nose may swell and turn pink in color [3,7]. A palmoplantar vesicular eruption with subsequent desquamation can also occur [13]. Additionally, a morbilliform, rubeoliform, or scarlatiniform exanthem may be seen. Other potential signs and symptoms include pruritus, increased salivation and gum irritation, nail and tooth loss, photophobia, weakness, insomnia, fever, hypertension, secondary infection of the skin, and gangrene of the fingers and toes [3,7,19]. Hypertension occurs as a result of mercury inactivation of catecholamine-0-methyl transferase. Catecholamine-0-methyl transferase is an enzyme that degrades catecholamines such as epinephrine, norepinephrine, and dopamine. Mercury inactivation of catecholamine-0-methyl transferase, therefore, leads to increased blood pressure via increased levels of catecholamines [20]. Skin biopsy typically shows a dermal inflammatory infiltrate with hyperplastic sweat glands, but the histology may be nonspecific [3,7]. It is estimated that 10% of children suffering from acrodynia die from infections [21]. The prognosis, however, is often favorable [2].

Other cutaneous manifestations of mercury poisoning have also been reported. For instance, mercury injections into the skin can result in mercury granulomas [2]. Additionally, Dantzig reported a possible new cutaneous sign of mercury poisoning in 11 patients who ate seafood-rich diets. These patients presented with an asymptomatic or mildly pruritic papular or papulovesicular eruption that correlated with elevated blood mercury levels. All of these patients improved when provided chelation therapy or a seafood-free diet [9]. Lastly, stomatitis and hyperpigmentation can also occur [3].

Treatment

The first step in the treatment of mercury poisoning is eliminating the source of exposure [7]. Chelators such as succimer (dimercaptosuccinic acid) may be utilized. Chelation therapy should be considered in patients with toxic levels of mercury in their blood or urine and symptomatic patients with confirmed mercury poisoning [2,4]. Chelation is not indicated in cases of chronic, low-level methylmercury toxicity [7]. Succimer is the most common chelator used to treat mercury poisoning in children [22]. Other chelation treatments include unithiol (2,3 dimercaptopropane-1-sulfonate, which is not approved for use in the United States), penicillamine, and British Anti-Lewisite. The response to treatment can be assessed by monitoring the levels of mercury in the blood and in the urine before and after treatment [4]. The two treatments of choice for mercury poisoning are now succimer and unithiol for reasons discussed in Table 2 of this case report, but penicillamine and British Anti-Lewisite were used in the past. The dosing, side effect profile, and usage indications for all of these chelation agents can vary, and all of these properties are also summarized in Table 2 (Table 2) [4,23–27].

Table 2. Properties of various chelating agents used to treat mercury poisoning.

Chelating Agent	Route of Administration	Adult Dosing Regimen	Pediatric Dosing Regimen	Potential Side Effects	Labs + Monitoring	Comments
Succimer (dimercaptosuccinic acid (DMSA))	DMSA is given via oral administration or IV injection [27]	Days 1-5: 10 mg/kg TID Days 6-19: 10 mg/kg BID If necessary, treatment may be repeated, with a 2- week interval between treatments [27]	Pediatric dose is calculated based on the body surface area (BSA). Days 1-5: 350 mg/m² TID Days 6-19: 350 mg/m² BID If necessary, treatment may be repeated, with a 2- week interval between treatments [27]	Neutropenia, GI disorders, skin rashes, and/or flu-like symptoms [27]	Check CBC, renal function, and hepatic function prior to/during treatment [27]	One of the two antidotes of choice for mercury poisoning. DMSA likely works better than DMPS for detoxification of organic mercury compounds. [26]
Unithiol (2,3 dimercaptopropane-1-sulfonate (DMPS))	DMPS is given via intramuscular (IM) or intravenous (IV) administration [4]	Day 1: 250 mg IM or IV every four hours Day 2: 250 mg IM or IV every six hours Days 3-5: 250 mg IM or IV every six to eight hours [4]	DMPS dosage in children not clearly established [25]	Dermatologic symptoms (rash/pruritus), GI symptoms, hepatic effects, neurologic effects, leukopenia, and/or fever [25]	Based on potential side effects of DMPS as described in the potential side effects column, the authors of this case report would recommend to check CBC, renal function, and hepatic function prior to/during treatment [25]	One of the two antidotes of choice for mercury poisoning. DMPS likely is more effective for detoxification of inorganic mercury compounds [26] Not approved for use in the United States [4]

Penicillamine	Penicillamine is given via oral administration [27]	Weeks 1-2: Adults 250 mg PO QID [27]	Days 1-4: 20-30 mg/kg/daily (maximum 250 mg/dose) [27]	Hypersensitivity and/or nephrotoxicity [27]	Check urinalysis, CBC with differential, platelet count, skin, lymph nodes, and body temperature twice weekly during the first month of therapy, then every 2 weeks for 5 months, then monthly; LFTs every 6 months; and monitor for any signs/symptoms of hypersensitivity [23]	Succimer has replaced penicillamine as it is more efficacious and has fewer side effects D-penicillamine is only used for elemental and inorganic mercury toxicity and is not useful for organic mercury toxicity [27]
British Anti-Lewisite (BAL)	BAL is given via IM administration [24]	Day 1: Deep IM: 5 mg/kg initially Day 2-11: 2.5 mg/kg every 12-24 hours [24]	Same as in adults [24]	Nausea, vomiting, hypertension, tachycardia, pain at the injection site, headache, diaphoresis, and convulsions [27]	Check for renal function, urine pH, and/or infusion-related reactions [24]	BAL usage is now contraindicated in mercury poisoning because it increases the brain deposition of inorganic and organic mercury [26]

Conclusion

We present a case of acrodynia and a papulovesicular eruption in a previously healthy 5-year-old girl with new-onset severe hypertension. The diagnosis of acrodynia was not initially suspected owing to the rarity of the diagnosis and the non-specific appearance of the presenting rash and skin histology. Our initial differential diagnosis was broad and included scabies, viral infection, autoimmune-related eruption, dyshidrotic eczema, pustular psoriasis, and miliaria rubra. Given the appropriate clinical context, it is important to include mercury toxicity in the differential diagnosis of acute papulovesicular eruptions. A high index of suspicion is needed to recognize mercury toxicity. Unexplained hypertension coupled with red itchy hands and feet with or without an acute papulovesicular eruption should prompt consideration of mercury exposure. Awareness of the ways in which mercury poisoning can present, including its cutaneous manifestations, will assist healthcare providers in diagnosing this condition and help to prevent resultant long-term morbidity and mortality.

References

1. Tchounwou PB, Yedjou CG, Patlolla AK, Sutton DJ. Heavy metal toxicity and the environment. EXS. 2012 Jan;101:133–64 [PMID:22945569].
2. Jao-Tan C, Pope E. Cutaneous poisoning syndromes in children: a review. Curr Opin Pediatr. 2006 Aug;18(4):410–6 [PMID:16914996].
3. Boyd AS, Seger D, Vannucci S, Langley M, Abraham JL, King LE. Mercury exposure and cutaneous disease. Journal of the American Academy of Dermatology. 2000. p. 81–90 [PMID:10863229].
4. Elinder C-G. Epidemiology and toxicity of mercury. In: Post T, editor. UpToDate. Waltham, MA: UpToDate; 2015.
5. Ozuah PO. Mercury poisoning. Curr Probl Pediatr. 2000 Mar;30(3):91–9 [PMID:10742922].
6. Baughman TA. Elemental mercury spills. Environ Health Perspect. 2006 Feb;114(2):147–52 [PMID:16451846].
7. Bose-O'Reilly S, McCarty KM, Steckling N, Lettmeier B. Mercury exposure and children's health. Current Problems in Pediatric and Adolescent Health Care. 2010. p. 186–215 [PMID:20816346].
8. Clarkson TW. Mercury: major issues in environmental health. Environ Health Perspect. 1993 Apr;100:31–8 [PMID:8354179].
9. Dantzig PI. A new cutaneous sign of mercury poisoning? J Am Acad Dermatol. 2003;49(6):1109–11 [PMID:14639393].
10. Lerch M, Bircher AJ. Systemically induced allergic exanthem from mercury. Contact Dermatitis. 2004. p. 349–53 [PMID:15274725].
11. Cohen PR. Zoledronic acid-associated symmetrical drug-related intertriginous and flexural exanthema (SDRIFE): report of baboon syndrome in a woman with recurrent metastatic breast cancer after receiving zoledronic acid. Dermatol Online J. 2015 Jan;21(8) [PMID:26437156].
12. Sears ME, Kerr KJ, Bray RI. Arsenic, cadmium, lead, and mercury in sweat: a systematic review. J Environ Public Health. 2012 Jan;2012:184745 [PMID:22505948].
13. Wood AJ, Wood I. Pink Disease. Br Med J. 1935 Sep 21;2(3898):527–31 [PMID:20779356].
14. Clarkson TW. Mercury--an element of mystery. N Engl J Med. 1990 Oct 18;323(16):1137–9 [PMID:2215583].
15. Davis L. Unregulated potions still cause mercury poisoning. West J Med. 2000 Jul;173(1):19 [PMID:10903282].
16. Black J. The puzzle of pink disease. J R Soc Med. 1999 Sep;92(9):478–81 [PMID:10645305].
17. Weinstein M, Bernstein S. Pink ladies: mercury poisoning in twin girls. CMAJ. 2003 Jan 21;168(2):201 [PMID:12538551].
18. Shandley K, Austin DW. Ancestry of pink disease (infantile acrodynia) identified as a risk factor for autism spectrum disorders. J Toxicol Environ Health A. 2011 Jan;74(18):1185–94 [PMID:21797771].
19. Rajniti P, Singh UK, Layland FC SS. Poisoning in Children. New Delhi, India: Jaypee Brothers Publishers; 2013. 276 p.
20. Torres AD, Rai AN, Hardiek ML. Mercury intoxication and arterial hypertension: report of two patients and review of the literature. Pediatrics. 2000 Mar;105(3):E34 [PMID:10699136].

21. Groot AC, Nater JP WJ. Unwanted Effects of Cosmetics and Drugs Used in Dermatology. In: 3rd ed. Amsterdam, The Netherlands: Elsevier Science; 1993. p. 782.
22. Mercer JJ, Bercovitch L, Muglia JJ. Acrodynia and hypertension in a young girl secondary to elemental mercury toxicity acquired in the home. Pediatr Dermatol. Jan;29(2):199–201 [PMID:22409470].
23. Lexicomp. Penicillamine: Drug information. In: Post T, editor. UpToDate. Waltham, MA: UpToDate; 2015.
24. Lexicomp. Dimercaprol: Drug information. In: Post T, editor. UpToDate. Waltham, MA: UpToDate; 2015.
25. Varnai V, Blanusa M, Piasek M, Kostial K. New Therapeutic and Experimental Aspects of Chelators as Antidotes of Metal Toxicity. In: Rahman A, Reitz AB CM, editor. Frontiers in Medicinal Chemistry, Volume (4). Sharjah (United Arab Emirates): Bentham Science Publishers Ltd.; 2009. p. 130–82.
26. Cao Y, Skaug MA, Andersen O, Aaseth J. Chelation therapy in intoxications with mercury, lead and copper. J Trace Elem Med Biol. 2015 Jul;31:188–92 [PMID:24894443].
27. Rafati-Rahimzadeh M, Rafati-Rahimzadeh M, Kazemi S, Moghadamnia AA. Current approaches of the management of mercury poisoning: need of the hour. Daru. 2014 Jan;22:46 [PMID:24888360].