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SHORT COMMUNICATION

Dangerous Leg Cramps: Severe Pustular Exanthema Caused by an Over-the-Counter Drug

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Severe cutaneous drug reactions are a significant cause of morbidity. When dealing with readily available over-the-counter (OTC) drugs, identification of the culprit substance in order to prevent future re-exposure may present a major diagnostic challenge.

CASE REPORT

A 62-year-old woman was referred to our clinic for emergency admission. She had a 4-day history of a generalized pustular skin eruption with sudden onset and massive progress under treatment with oral and intravenous antihistamines as well as prednisolone. Her general condition was markedly reduced. She had fever up to 38.6°C, nausea and vomiting.

Clinical examination revealed a papulo-pustular exanthema. The maximum density of exanthema was visible on the proximal extremities, with numerous pinpoint pustules on an extensive dusky-erythematous, partly haemorrhagic skin (Fig. 1 a, b). The Nikolsky sign was negative, and no enanthema was found. Pronounced cervical, axillary and inguinal lymphadenopathy was palpable.

The patient reported being otherwise healthy and denied taking any regular medication. Some 5 h before the onset of symptoms, she had, however, taken Limptar N™ (quinine sulphate) for the first time in order to treat or prevent painful nocturnal leg cramps. The day before, she had taken ibuprofen for the same reason. After repeated questioning, she reported at least 3 other episodes of a similar, though less pronounced rash. She specifically remembered a previous reaction to a "modern drink", a beverage containing tonic water. At the time, she had self-diagnosed an allergy to food colourings, and hence avoided them.

Histological examination of a skin biopsy confirmed subcorneal neutrophilic pustules, which proved sterile in bacteriological culture. Comprehensive laboratory testing on admission revealed a pronounced leukocytosis (23,500/µl, 94.7% neutrophils, 2.3% lymphocytes, 0.9% eosinophils) and an increased C-reactive protein (8.06 mg/dl), but no other pathologies. The liver enzymes subsequently increased, reaching their maximum on day 8 of the reaction (aspartate transaminase 146 U/l, alanine transaminase 337 U/l, gamma glutamyl transpeptidase 42.9 U/l). Eosinophils increased to 900/µl. A reactivation of herpes simplex virus type 6 was excluded serologically. Glucose-6-phosphate dehydrogenase levels were within the normal range. An abdominal ultrasound did not reveal any pathological results. Under treatment with topical steroids, the exanthema completely resolved within 3 weeks, and laboratory findings normalized.

The allergy diagnostic work-up included skin-prick, intradermal, and patch-testing with quinine (that is Limptar N™ tablets ground in a mortar for prick and patch testing as pure substance, and quinine hydrochloride in a 1:1,000 dilution for intradermal testing), ibuprofen, and various corticosteroids, as well as skin-prick tests with food additives and colourings. Positive results of skin-prick and intradermal tests with quinine were recorded after 6 (Fig. 1c), 24 and 48 h. Patch-tests with quinine exhibited a crescendo pattern and evolved into a pustular reaction within 48 h (Fig. 1d). Control skin tests with quinine were non-irritating in 3 healthy volunteers. All other skin test results were negative, and subsequent oral challenge with ibuprofen and prednisolone was well tolerated.

The patient was provided with an allergy alert and advised to strictly avoid quinine, not only as a drug, but also as an ingredient in food or drinks.

DISCUSSION

We report here a case of a severe pustular exanthema following self-administration of quinine sulphate. While the sudden onset of high-grade fever, extensive erythema, and multiple sterile pustules was consistent with a diagnosis of acute generalized exanthematous pustulosis (AGEP), the accompanying lymphadenopathy and increase in hepatic enzymes and eosinophils are characteristic signs of drug-induced hypersensitivity syndrome (DIHS). There was, however, no evidence of

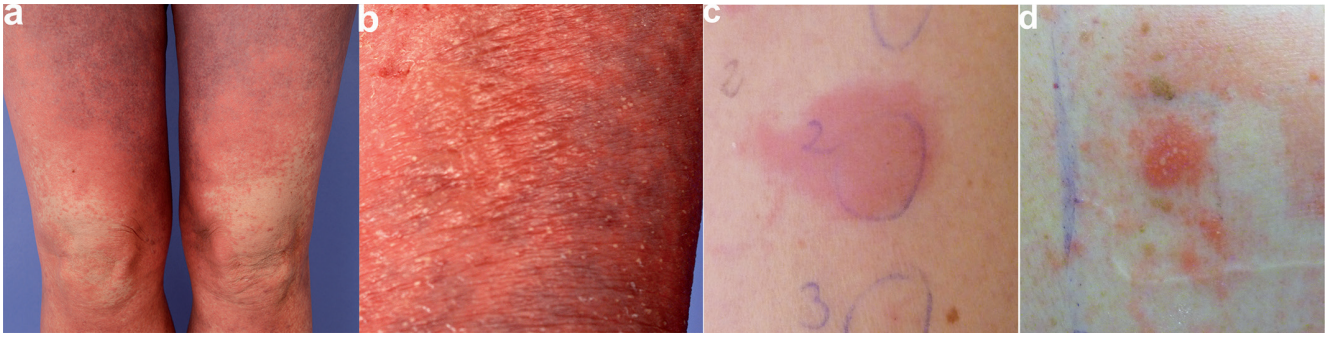

Fig. 1. Papulo-pustular exanthema on the extremities: (a) (close-up in b). (c) Intradermal skin testing on the volar forearm with quinine exhibited infiltrated erythema after 6 h. (d) Pustular quinine patch test reaction on the back after 48 h.

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a reactivation of herpes simplex virus type 6 (1) and the condition took a relatively benign, self-limited course within a couple of weeks. While similar AGEP-DIHS overlaps have been described on several occasions (2, 3), in our opinion, this case is illustrative of the sometimes difficult delineation between these 2 patterns of drug reactions. In the treatment of patients with AGEP and DIHS, adequate supportive care and identification of the culprit drug are crucial. While the immunogenetic pathophysiology of AGEP is, to date, largely unclear, mutations in the *Il36RN* gene as a cause of uncontrolled pro-inflammatory Il-36 signalling have been described recently in a subset of patients (4, 5).

Quinine, an alkaloid derived from the bark of the *Cinchona* tree, has been the drug of choice to treat malaria for more than 300 years. Although numerous antimalarials with a more favourable safety profile have been introduced during the past few decades, it still plays an important role in certain critical circumstances, including malaria in pregnancy, severe malaria, and the treatment of chloroquine-resistant *Plasmodium vivax* infections (6). For many years, the substance has additionally been used to treat involuntary muscle cramps, a bothersome, though basically harmless, condition. Reports of serious adverse events to the US Food and Drug Administration (FDA), however, led to its withdrawal from OTC use in the USA and, subsequently, to an official warning against its prescription for all indications other than malaria (7). Irrespective of the above, quinine remains licensed for the treatment of muscle cramps in many European countries and was available as an OTC drug in Germany until its official withdrawal by the Federal Institute for Drugs and Medical Devices in April 2015 (8). Regardless of its medical properties, bitter-tasting quinine is a popular flavouring agent, and small quantities are blended into numerous beverages, such as bitter lemon, tonic water, and various alcoholic drinks.

Gastrointestinal symptoms, as well as hearing and visual impairment, constitute common dose-dependent side-effects attributed to quinine and are reversible upon discontinuation of treatment (7). Hypersensitivity reactions, such as thrombocytopaenia, haemolytic uraemic syndrome, and disseminated intravascular coagulation, however, may arise at minor doses and take a severe or even lethal course (7, 9). Several cases of quinine-induced fixed drug eruptions, DIHS, allergic urticaria, photoallergy, and possibly toxic epidermal necrolysis have been reported in the medical literature (10–14).

The case reported here adds to the spectrum of serious quinine-induced cutaneous adverse reactions. Moreover, it demonstrates the importance of a targeted allergy diagnostic work-up based on a meticulous patient history to diagnose severe drug hypersensitivity reactions. Repeated and active questioning may prove necessary, as the consumption of OTC products is commonly not mentioned or even kept secret (11, 15). While quinine remains an important antimalarial, we wholeheartedly welcome its recent withdrawal from OTC use in Germany.

The authors declare no conflicts of interest.

REFERENCES

1. Chen YC, Chiang HH, Cho YT, Chang CY, Chen KL, Yang CW, et al. Human herpes virus reactivations and dynamic cytokine profiles in patients with cutaneous adverse drug reactions – a prospective comparative study. Allergy 2015; 70: 568–575.
2. Kostopoulos TC, Krishna SM, Brinster NK, Ortega-Loayza AG. Acute generalized exanthematous pustulosis: atypical presentations and outcomes. J Eur Acad Dermatol Venereol 2015; 29: 209–214.
3. Bouvresse S, Valeyrie-Allanore L, Ortonne N, Konstantinou MP, Kardaun SH, Bagot M, et al. Toxic epidermal necrolysis, DRESS, AGEP: do overlap cases exist? Orphanet J Rare Dis 2012; 7: 72.
4. Navarini AA, Valeyrie-Allanore L, Setta-Kaffetzi N, Barker JN, Capon F, Creamer D, et al. Rare variations in IL36RN in severe adverse drug reactions manifesting as acute generalized exanthematous pustulosis. J Invest Dermatol 2013; 133: 1904–1907.
5. Navarini AA, Simpson MA, Borradori L, Yawalkar N, Schlapbach C. Homozygous missense mutation in IL36RN in generalized pustular dermatosis with intraoral involvement compatible with both AGEP and generalized pustular psoriasis. JAMA Dermatol 2015; 151: 452–453.
6. WHO. In: Guidelines for the treatment of malaria. 3rd edn. Geneva: WHO; 2015.
7. El-Tawil S, Al Musa T, Valli H, Lunn MP, Brassington R, El-Tawil T, et al. Quinine for muscle cramps. Cochrane Database Syst Rev 2015; 4:CD005044.
8. BfArM 2015. Available from: http://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RV_STP/a-f/chinin-stp.html.
9. Brinker AD, Beitz J. Spontaneous reports of thrombocytopenia in association with quinine: clinical attributes and timing related to regulatory action. Am J Hematol 2002; 70: 313–317.
10. Kaku Y, Ito T, Wada M, Nozaki Y, Kido-Nakahara M, Furue M. Tonic water-induced generalized bullous fixed eruption. Acta Derm Venereol 2015; 95: 505–506.
11. Gréco M, Dupré-Goetghebeur D, Leroy JP, Karam A, Jantzem H, Sassolas B, et al. (DRESS syndrome related to Hexaquine (quinine and thiamine)). Ann Dermatol Venereol 2006; 133: 354–358.
12. Callaway JL, Tate WE. Letter: Toxic epidermal necrolysis caused by "gin and tonic". Arch Dermatol 1974; 109: 909.
13. Hickey JR, Dunnill GS, Sansom JE. Photoallergic reaction to systemic quinine sulphate. Contact Dermatitis 2007; 57: 384–386.
14. González R, Merchán R, Crespo JF, Rodríguez J. Allergic urticaria from tonic water. Allergy 2002; 57: 52.
15. Eichenberg C, Auersperg F, Rusch BD, Brähler E. Self-medication: a nationwide representative survey on motives, reasons and sources on consuming over-the-counter medication. Psychother Psychosom Med Psychol 2015; 65: 304–310.