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Title: Levofloxacin-induced symmetric drug-related intertriginous and flexural exanthema.

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Dear Editor,

A 50-year-old female presented with multiple erythematous patches over the bilateral axillae and groins (Figure 1) lasting 3 days. These skin lesions developed 6 days after taking levofloxacin 500mg every other day for the treatment of a urinary tract infection. The dosage of levofloxacin was adjusted according to her renal function. Her medical history included hypertension, hyperlipidemia, anxiety, and end-stage renal disease requiring peritoneal dialysis. She was additionally taking gemfibrozil, clonazepam, and alprazolam for 2 months.

Physical examination showed well-demarcated erythematous patches symmetrically distributed over the bilateral axillae and inguinal areas, as well as in the cubital and popliteal fossae. There were no blisters, scales, or pustules, and no mucosal involvement nor systemic symptoms were present.

Laboratory investigation revealed eosinophilia (11.0%); otherwise, no deterioration of the coagulation profile, renal and liver function were noted. Serology testing showed negative results for a viral infection, including Parvovirus B19, cytomegalovirus and Epstein-Barr virus. A lymphocyte activation assay was performed by measuring granulysin and granzyme B levels according to a previously published protocol.¹ Levofloxacin was diluted in a RPMI-1640 medium (GIBCO Invitrogen, Life Technologies, Carlsbad, CA) supplemented with 10% autologous serum, Interleukin-7 (1 ng ml⁻¹; Invitrogen) to obtain a concentration reflecting the physiological therapeutic level. A positive result of these tests was defined as a 1.20-fold increase in granulysin and granzyme B expressions compared to the tolerant controls. This cut-off value was calculated by using the values of mean and 2-fold standard deviation from the tolerant controls. The results revealed 1.63-fold and 2.59-fold elevations of granulysin and granzyme B levels compared with negative control of phosphate buffered saline, respectively. A diagnosis of symmetric drug-related

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intertriginous and flexural exanthema (SDRIFE) due to levofloxacin was made based on the above findings. The causality of levofloxacin induced SDRIFE was also “probable” according to the Naranjo Adverse Drug Reaction Probability Scale (a score of 6). Levofloxacin was thus discontinued and prednisolone (10 mg/day) was administrated, after which the cutaneous lesions gradually resolved within two weeks. The patient did not return to the clinic for further follow-up due to the COVID-19 outbreak, so an additional work-up (patch tests and drug provocation) could unfortunately not be performed.

Levofloxacin is a fluoroquinolone antibiotic which exerts its antimicrobial activity via the inhibition of bacterial DNA gyrase and topoisomerase IV. Published mucocutaneous adverse effects of levofloxacin include anaphylaxis², fixed drug eruption³, and toxic epidermal necrolysis⁴. However, to our knowledge, no case of levofloxacin-induced SDRIFE has been reported before.

SDRIFE is a drug-related eruption that typically affects the intertriginous or flexural area. The skin rash often developed hours to (up to 7) days after exposure to a culprit drug. In 2004, Häusermann et al. have proposed the following criteria to establish a diagnosis of SDRIFE: 1) exposure to a systemically administered drug either at the first or repeated dose (excluding contact allergens); 2) sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area; 3) involvement of at least one other intertriginous/flexural localization; 4) symmetry of affected areas; and 5) absence of systemic symptoms and signs.⁵ The most common offending drugs are β -lactam antibiotics, especially amoxicillin.⁵ In addition, many other antibiotics have also been described as causative drugs, such as cephalexin, erythromycin, and clindamycin.^{5,6}

SDRIFE is considered a type IV hypersensitivity reaction. One recent study has demonstrated that the histopathologic findings of SDRIFE are characterized by a

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vacuolar interface dermatitis induced by cytotoxic T lymphocytes and neutrophilic granulocytes.⁷ The pathogenesis of SDRIFE may be associated with a type IVc and IVd hypersensitivity reaction. The diagnosis of SDRIFE is clinical and might be supported by, for example, patch tests, (delayed readings of) prick and intradermal tests, and lymphocyte transformation tests; however, low sensitivity limits their diagnostic values.⁸ Granulysin and granzyme B are cytolytic molecules expressed mainly in neutral killer cells and cytotoxic T cells, and they may play a role in the pathogenesis of type IVc hypersensitivity reaction. Porębski et al. have demonstrated that in-vitro cytotoxicity-based assays, including granulysin and granzyme B, may be useful for the diagnosis of delayed drug hypersensitivity reactions.⁹ Moreover, a previous report also supported the diagnostic value of such assay in the diagnosis of SDRIFE.¹⁰

In conclusion, we reported a first case of levofloxacin-induced SDRIFE in which the causality was confirmed by a lymphocyte activation assay. Further studies are warranted to evaluate its clinical usefulness in the diagnosis of delayed-type hypersensitivity, including SDRIFE.

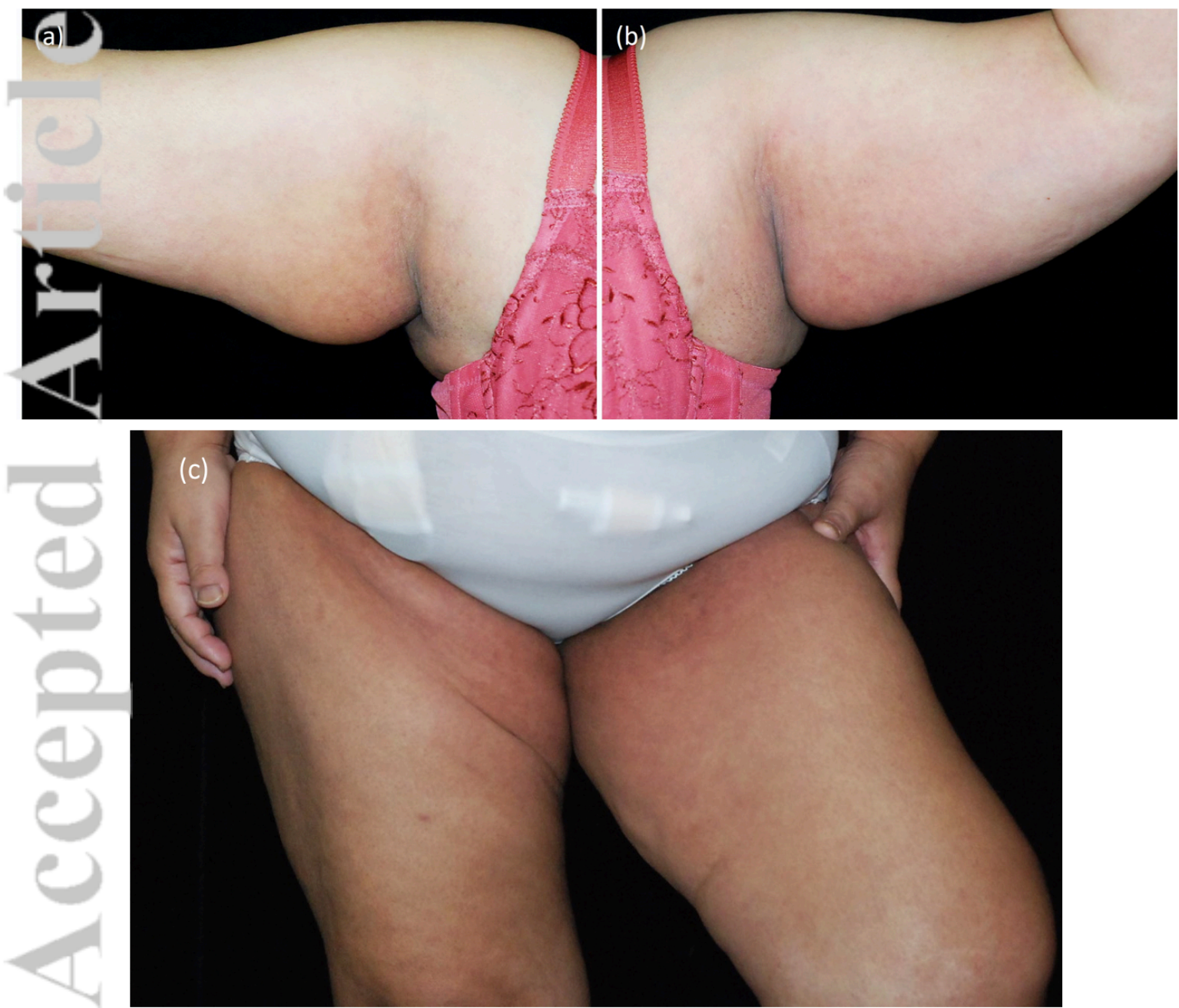
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Figure legends

Figure 1 (A) (B) Erythematous patches symmetrically distributed over the bilateral axillae. (C) Sharply demarcated and V-shaped erythema in the inguinal area.



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