Rare vardenafil-associated Stevens-Johnson syndrome: toxic epidermal necrolysis

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DESCRIPTION

A previously healthy 52-year-old single Caucasian man presented with Stevens-Johnson syndrome (SJS) toxic epidermal necrolysis (TEN): extensive mucocutaneous damage characterised by blistering and epithelial shedding on torso, mouth and genitalia following uptake of 20mg vardenafil hydrochloride over the counter (OTC), two times in 5 days, 12 days prior. Three days before hospital presentation, he developed a febrile (38,5°C) influenza-like prodrome with runny nose, malaise and cough. Two days later, he noted the appearance of red-purple macules on the extremities (figure 1A), mouth (lips, palate, tongue, buccal mucosa) (figure 1B) and genitals that turned into blisters; detachment of the skin and mucous membranes and painful erosions (figure 1C). He presented with persistent hiccups (3 days); however, otorhinolaryngology consultation was impossible to solicit. The patient's history was free from medications, and drug or other allergies.

Nikolsky sign was positive, and no lymphadenopathy was notable. Systemic examination was unremarkable. Tests for SARS-CoV-2, venereal disease research laboratory test (VDRL), mycoplasma, herpes virus family (HSV1/2, VZV, CMV, EBV, HHV6) and human immunodeficiency virus (1&2) were all negative. A skin biopsy confirmed SJS. Laboratory examination revealed elevation of non-specific inflammatory markers: C-reactive protein (CRP): 19mg/dL (<0.5), erythrocyte sedimentation rate (ESR): 95 (0–10), ferritin: 2624ng/mL (16–323), Antinuclear Antibody

(ANA): negative, C3 and C4 within normal range. A team approach had been implemented and he received supportive care, monitoring, prophylactic therapy (antibiotics and antivirals), systemic corticosteroids, metoclopramide and careful protection of the skin and mucosa.¹ He was discharged 3 weeks later. Despite the severity of his condition, he only revealed the aetiologically causative drug 7 days inpatient (Naranjo score=7 'probable').² Given the clinical features, the temporal association with the drug and the patient's free medical history, vardenafil-induced SJS/TEN was diagnosed.

Phosphodiesterase-5 inhibitors (PDE5i), such as vardenafil, are used in the treatment of erectile dysfunction.³ Adverse drug reactions (ADRs) are scarce, however, ocular complications, hearing loss and fixed drug eruption have been reported.^{4–6}

Severe cutaneous adverse reactions (SCARs) are uncommon and potentially life-threatening immune-mediated ADRs, with diverse clinical phenotypes, including SJS/TEN. At least 200 drugs have been reported to be associated with the onset of the disease, including nonsteroidal anti-inflammatory drugs, sulfa-derived medications, lactam antibiotics and anticonvulsants.⁷

SCARs like SJS/TEN are type IV delayed-type hypersensitivity reactions, mediated either by direct cytotoxicity of CD8 +T cells or by release of CD4 +derived cytokines via antigen presenting cells, such as macrophages and dendritic cells.⁷ Macrophages are major cellular producers of ferritin and remarkable serum ferritin was observed in the patient, in the setting of ongoing inflammation, together with other acute-phase reactants, such as ESR and CRP.⁸

Sexual and reproductive health is a significant public health issue, and the COVID-19 quarantine had an impact in mental and physical health and to the best of our knowledge, this is the first vardenafil-induced SJS case.⁹ Recently, drug eruption with eosinophilia and systemic symptoms has been reported, and an increase in PDE5i concentrations was detected in wastewater.¹⁰ Therefore, a possibility of an increased consumption

Figure 1 (A) Atypical red-purple macules and dusky erythema on the extremities. (B) Erosive cheilitis, extensive mucosal erosions of the buccal and labial mucosa. (C) Mucositis of the genitalia and confluent involvement of the scrotum and the glans penis.

Patient's perspective

COVID-19 quarantine made me feel uncertain of what the future will hold. Recently engaged, I was stressing to maintain an active sex-life during self-isolation, since we spent so much time together. A friend advised me of an OTC "help". Unfortunately, not only did this choice end to a severe side effect, but it has forever scarred me.

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Learning points

- ▶ Phosphodiesterase-5 inhibitors (PDE5i), such as vardenafil, are used in the treatment of erectile dysfunction, either over the counter or under prescription and are generally well tolerated.
- ▶ Stevens-Johnson syndrome-toxic epidermal necrolysis overlap represents an extremely rare adverse effect of vardenafil.
- ▶ The COVID-19 pandemic had an impact in physical and mental health with a possible PDE5i uptake increase.

requires pharmacovigilance for early management in probable upcoming SCARs.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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