

Stevens–Johnson Syndrome in Association with Hydroxychloroquine Treatment for Covid-19: A Case Series

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Abstract

Stevens Johnson Syndrome (SJS) is a rare immune-mediated hypersensitivity disorder that present with mucocutaneous blistering reactions with epidermal detachment and extensive necrosis. Stevens-Johnson syndrome is mainly a reaction to medication, such as sulfonamide, aminopenicillin, quinolone, and cephalosporin. The aminoquinolines, chloroquine and hydroxychloroquine, are widely used in the treatment of many diseases such as malaria and rheumatoid arthritis. Recently it was suggested as a treatment for COVID-19. We report a series of 11 patients, who developed SJS after intake of hydroxychloroquine. More attention should be given for hydroxychloroquine especially with its increased use during COVID-19 pandemic.

Key words: Stevens-Johnson; Hydroxychloroquine, COVID-19

Introduction

The Stevens Johnson Syndrome (SJS) as a febrile illness with SJS is a rare immune complex-mediated hypersensitivity disorder that is generally described as vesicubullous erythema multiforme of the skin, mouth, eyes, and genitals. [1] Medications appear to be the most common cause of SJS and have been implicated in as many as 60% of cases studied. [2]

The aminoquinolines chloroquine and hydroxychloroquine are widely used in the treatment of many diseases such as malaria, rheumatic arthritis, systemic lupus erythematosus and photodermatoses. They have been suggested as effective prophylaxis and treatment for COVID-19 on the grounds of both anti-inflammatory and antiviral effects. [3,4] Hydroxychloroquine has been widely used to treat COVID-19 infection without any available data from randomized clinical trials to inform clinical guidance on the use, dosing, or duration of treatment.

There are several isolated cases reports of SJS and Toxic Epidermal Necrolysis (TEN) associated with hydroxychloroquine. [5-9] Herein, we report a series of 11 patients, who developed SJS after intake of hydroxychloroquine.

Patients and Methods

We studied a series of 11 patients who were presented to the dermatology department of farwaniya hospital, Kuwait with SJS after intake of hydroxychloroquine tablets from January 2020 to February 2021. The diagnosis of SJS was made mainly on the basis of the clinical findings, which included extensive erythema multiforme, purpuric lesions with bullae and detachment of skin involving at least two mucous membranes. Further, in each patient suspected with SJS, various laboratory tests such as complete blood count, liver function tests, metabolic panel, chest X-ray and other serological test were carried out. Skin biopsies with histopathological examination were also done. Patients were discharged when they had haemodynamically stable condition, with no lesions over oral cavity, genital, conjunctival mucosa and normal laboratory investigations.

Results

Eleven patients of SJS were seen in a period of 13 months. They were 7 females and 4 males. Their ages ranged from 21 to 56 years with a mean of 37.54 ± 2.32 years. Clinical data of the patients were summarized in Table 1. All patients developed SJS after intake of hydroxychloroquine. Three patients out of the 11 patients administered hydroxychloroquine as a prophylaxis for infection during COVID-19 pandemic. In the other 8 patients, hydroxychloroquine was administrated as a part of treatment of COVID-19 infection after appearance of symptoms and positive PCR results.

Clinical Presentation

After 8-10 days of hydroxychloroquine consumption, patients developed pruritic skin rash extending from the trunk towards the extremities, associated with progressive dysphagia, dysuria, and photophobia. Bullous skin lesions, with erosions and crusting, started forming over the face, scalp, and neck then progressed to involve the trunk and upper and lower limbs. Erythema multiforme-like lesions were mainly over the trunk and upper limbs. In addition, the erythematous rash coalesced with many small vesicles, some forming bullae with positive Nikolsky's sign. Oral affection in the form of erosions and crusting of both lips and vesicles were present in all patients. The groin, mainly the genital area, was severely affected in 9 patients [Figures 1 and 2].

At the time of admission, the patients had shown abnormal vital parameters including tachycardia (2 patients) and raised blood pressure (2 patients). Some patients showed abnormal laboratory tests like raised serum creatinine level (one patients), leukocytosis (2 patients) and leukocytopenia (one patients).

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Table 1: Clinical data of 11 patients with Stevens-Johnson syndrome after hydroxychloroquine intake.

No.	Age (years)	Sex	Past history of drug reactions	Family history of drug reaction	Indication for hydroxychloroquine	Dose
1	42	F	no	no	prophylaxis for Covid-19	400mg once then 200mg daily
2	48	F	no	no	prophylaxis for Covid-19	400mg once then 200mg daily
3	56	M	no	yes	prophylaxis for Covid-19	400mg once then 200mg daily
4	33	M	no	no	Treatment for Covid-19	400mg twice daily
5	31	F	no	no	Treatment for Covid-19	400mg twice daily
6	26	F	no	no	Treatment for Covid-19	400mg twice daily
7	43	F	no	no	Treatment for Covid-19	400mg twice daily
8	36	M	no	no	Treatment for Covid-19	400mg twice daily
9	21	F	yes	no	Treatment for Covid-19	400mg twice daily
10	47	M	no	no	Treatment for Covid-19	400mg twice daily
11	29	F	no	no	Treatment for Covid-19	400mg twice daily



Figure 1: Patient with Stevens Johnson Syndrome (SJS) showing oral affection in the form of erosions and crusting of both lips.



Figure 2: Erythematous rash, vesicles, and bullae affecting the patient's back.

Oropharyngeal swab tested positive for SARS-CoV-2 by PCR assay in 8 patients.

Skin biopsies of the lesions were performed for the patients and histopathologic examination showed basket weave hyperkeratosis, acanthosis, intraepidermal vesicle formation, necrotic keratinocytes in epidermis, basal vacuolar degeneration of basal layer, and dense superficial perivascular lymphohistiocytic in the superficial dermis, a picture consistent with SJS.

As the presumptive cause was hydroxychloroquine intake, so it

was stopped and a regimen of methylprednisolone 1 mg/kg-2 mg/kg IV daily was started. The skin lesions were treated twice daily with a mixture of urea and triamcinolone in a lotion base. Clinical improvement occurred after a mean of 14.8 ± 1.32 days and the dose of methylprednisolone was tapered. However, in two patients, SJS progressed to toxic epidermal necrolysis and of which one led to death.

Discussion

Stevens Johnson Syndrome (SJS) is an immunologic reaction to several stimuli, mostly medications, which presents as a spectrum of primarily widespread mucocutaneous lesions, but also with other organ involvement [1]. SJS can be preceded by a prodrome including fever, malaise, sore throat, nausea, vomiting, arthralgias, and myalgias. This prodrome is followed by conjunctivitis, in addition to bullae on the skin and mucosal membranes of the mouth, nares, pharynx, esophagus, urethra, genital and anal regions. [2] Many medications have been blamed of causing SJS such as sulfonamide, aminopenicillin, quinolone, and cephalosporin. [10] SJS also has been linked to herpes simplex virus, mycoplasma bacterial species, and measles vaccine. [11]

Hydroxychloroquine is a well-known treatment for certain inflammatory autoimmune diseases such as rheumatoid arthritis and lupus erythematosus, and has a noteworthy influence on Toll-Like Receptor 9 (TLR-9) activity. [12]

Chloroquine analogs have been shown to inhibit the acidification of endosomes and to exhibit *in vitro* a non-specific antiviral activity at high micromolar concentration against a broad range of emerging viruses (HIV, dengue, hepatitis C, chikungunya, influenza, Ebola, SARS and MERS viruses). [11] Hydroxychloroquine has been shown to have *in vitro* activity against SARS-CoV and SARS-CoV-2 (COVID-19). [12,13]

Hydroxychloroquine treatment for COVID-19 has been described as it lowers coronavirus levels in the blood and shortens recovery time. [14] In their study, Gautret et al. reported a 100% viral clearance in nasopharyngeal swabs in 6 patients after 5 and 6 days of the combination of hydroxychloroquine and azithromycin. In the United States, the Food and Drug Administration issued an Emergency Use Authorization on March 30, 2020, that allowed the use of these drugs in patients with COVID-19 who were not enrolled in clinical trials. Hydroxychloroquine was suggested as treatment for

hospitalized patients with COVID-19 and respiratory difficulty, as indicated by low resting oxygen saturation, during the period in which patients in this report were admitted. ^[13]

Sharma et al. ^[15] revised the adverse dermatologic effects of hydroxychloroquine. The review involved 94 articles encompassing 689 dermatologic adverse effects. A total of 21 unique dermatologic reactions were described, most commonly drug eruption or rash (358 cases), cutaneous hyperpigmentation (116), pruritus (62), acute generalized exanthematous pustulosis (27), Stevens Johnson Syndrome (SJS) or toxic epidermal necrolysis (26), hair loss (12), and stomatitis (11). The range of reported mean cumulative dosages was wide, with some adverse reactions found after as little as 3 g or as much as 2500 g.

Conclusion

SJS is a potentially fatal multiorgan disease with a strong etiologic link to some medications. Severe skin eruptions to hydroxychloroquine were uncommon; however, we reported a case series of 11 patients with SJS due to hydroxychloroquine drug hypersensitivity reactions. The probable dermatologic adverse effects of hydroxychloroquine should be highlighted specially with its increased use during COVID-19 epidemic.

References

1. Wong KC, Kennedy PJ, Lee S. Clinical manifestations and outcomes in 17 cases of Stevens- Johnson syndrome and toxic epidermal necrolysis. *Australas J Dermatol.* 1999; 40: 131-134.
2. Wolkenstein P, Revuz J. Drug-induced severe skin reactions. Incidence, management and prevention. *Drug Saf.* 1995; 13: 56-68.
3. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: What to expect for COVID-19? *Int J Antimicrob Agents.* 2020;55: 105938.
4. Fantini J, Di Scala, Chahinian H, Yahy N. Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection. *Int J Antimicrob Agents.* 2020;55: 105960.
5. Leckie MJ, Rees RG. Stevens-Johnson syndrome in association with hydroxychloroquine treatment for rheumatoid arthritis. *Rheumatology (Oxford).* 2002;41: 473-474.
6. Murphy M, Carmichael AJ. Fatal toxic epidermal necrolysis associated with hydroxychloroquine. *Clin Exp Dermatol.* 2001;26: 457-458.
7. Lateef A, Tan KB, Lau TC. Acute generalized exanthematous pustulosis and toxic epidermal necrolysis induced by hydroxychloroquine. *Clin Rheumatol.* 2009;28: 1449-1452.
8. Koumaki D, Koumaki V, Bertsias G, Boumpouheropoulos S, Katoulis A, Stefanidou M, et al. Hydroxychloroquine-induced erythema multiforme. *Clin Case Rep.* 2020;8: 578-579.
9. Davoodi L, Jafarpour H, Kazeminejad A, Soleymani E, Akbari Z, Razavi A. Hydroxychloroquine-induced Stevens-Johnson syndrome in COVID-19: A rare case report. *Oxf Med Case Reports.* 2020;2020: omaa042.
10. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med.* 1995;333: 1600-1607.
11. Hazir T, Saleem M, Abbas KA. Stevens-Johnson syndrome following measles vaccination. *J Pak Med Assoc.* 1997;47: 264-265.
12. Ewald SE, Lee BL, Lau L, Wickliffe KE, Shi GP, Chapman HA, et al. The ectodomain of toll-like receptor 9 is cleaved to generate a functional receptor. *Nature.* 2008; 456: 658-662.
13. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. *In vitro* antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory Syndrome Coronavirus 2 (SARS-COV-2). *Clin Infect Dis.* 2020;71: 732-739.
14. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents.* 2020;56: 105949.
15. Sharma AN, Mesinkovska NA, Paravar T. Characterizing the adverse dermatologic effects of hydroxychloroquine: A systematic review. *J Am Acad Dermatol.* 2020;83: 563-578.