

# The severe complication of Stevens–Johnson syndrome induced by long-term clozapine treatment in a male schizophrenia patient: a case report

Ming-Kung Wu<sup>1</sup>  
Weilun Chung<sup>2</sup>  
Ching-Kuan Wu<sup>2</sup>  
Ping-Tao Tseng<sup>2</sup>

<sup>1</sup>Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan; <sup>2</sup>Department of Psychiatry, Tsyr-Huey Mental Hospital, Kaohsiung Jen-Ai's Home, Kaohsiung, Taiwan

**Introduction:** Stevens–Johnson syndrome (SJS) is a severe adverse drug reaction that can result in disability and mortality. SJS is defined as having a widespread distribution throughout the whole body surface area with <10% extent of skin detachment and skin lesions. Some drugs, such as carbamazepine, have been reported to have a greater correlation to SJS. Although clozapine use has been mentioned as a risk factor for development of SJS, no report has clearly described the features of SJS as a reaction to clozapine use. Herein, we report the case of a patient presenting SJS after long-term clozapine treatment.

**Case report:** Mr A was a 54-year-old male with a diagnosis of chronic schizophrenia. He was hospitalized in a mental institute and received clozapine 200 mg/day for 2 years, without discomfort or drug side effects. He developed acute-onset mouth edema, multiple oral and ocular ulcers, oral and ocular mucosa swelling, and multiple erythematous skin rashes over his entire body and extremities with hypertension and high fever. SJS was diagnosed after referral to a general hospital.

**Results:** The SJS subsided under supportive treatment.

**Conclusion:** Accumulated lymphocytes and macrophages in the epidermis and elevated TNF- $\alpha$  might cause an immune reaction and apoptosis and result in the clinical presentation of SJS. Clozapine is believed to modulate the immunologic reaction, and therefore might induce SJS through immunomodulation. This case highlights the importance of considering the possibility of SJS resulting from the use of drugs for which there are no reports of such a severe complication.

**Keywords:** psychiatry, side effect, pharmacotherapy, adverse reaction, pharmacy

## Introduction

There have been many reports and articles discussing skin eruptions due to different classes of medication.<sup>1–4</sup> These reactions result in different presentations, based on severity, from the simplest urticaria to the most severe reaction, Stevens–Johnson syndrome (SJS).<sup>5</sup> SJS is a rare but severe adverse drug reaction with a cutaneous presentation, and can progress rapidly and even result in disability and mortality.<sup>6,7</sup> SJS is considered to be a spectrum disease, a group that consists of SJS, erythema multiforme, and toxic epidermal necrolysis.<sup>8</sup> In a report by Roujeau, SJS was defined as having a widespread distribution with <10% extent of skin detachment and skin lesions including macules, blisters, flat atypical targets, and mucosal lesions.<sup>8</sup> It also consists of some nonspecific symptoms and signs, such as occasional high fever,

Correspondence: Ping-Tao Tseng  
Department of Psychiatry, Tsyr-Huey  
Mental Hospital, Kaohsiung Jen-Ai's  
Home, No 509, Fengping 1st Road,  
Daliao District, Kaohsiung City 831,  
Taiwan  
Tel +886 7 703 0315 ext 3153  
Fax +886 7 701 2624  
Email ducktseng@gmail.com

arthralgia, and general weakness. When affected, patients enter the most severe phase rapidly and may develop severe complications, such as septic shock.<sup>9</sup> Mortality ranges widely according to different studies.<sup>5,10</sup> The etiology of SJS is unclear and idiosyncratic. Some drugs, such as carbamazepine and phenytoin, have been reported to have a greater correlation to SJS than others.<sup>9</sup>

Clozapine is one of the most widely used atypical antipsychotics in current clinical practice. Despite its excellent effect on refractory psychosis, it has numerous side effect profiles,<sup>11</sup> which include leukocytosis, hypersalivation, sedation, pneumonia, electrolyte imbalance, seizure, agranulocytosis, and its most severe complication, neuroleptic malignant syndrome. Although clozapine has been mentioned as a risk factor for the development of SJS,<sup>12</sup> there is no report clearly describing the features of SJS in patients with clozapine use. Herein, we report the case of a patient presenting SJS after long-term clozapine treatment.

## Case report

Mr A was a 54-year-old male who had been diagnosed as having chronic schizophrenia, paranoid type. The initial presentation of his psychosis consisted of auditory hallucination and delusions of persecution. He was hospitalized in the chronic ward of a mental institute. He had no previous physical illness history. The baseline laboratory data when hospitalized revealed no significant abnormality, and the routine chest X-ray and electrocardiography showed no significant finding. He had received clozapine 200 mg/day for 2 years without discomfort or drug side effects. Two weeks before the event of SJS, he developed acute gastroenteritis with nausea and vomiting, and recovered from it spontaneously. However, he developed an acute onset of mouth edema, oral and ocular multiple ulcers, injected oral and ocular mucosa, and multiple erythematous skin rashes over his entire body and extremities. When the event of SJS came, he only took clozapine 200 mg daily without any other concomitant drugs. His vital signs revealed hypertension, 153/101, with a high fever of 39.1°C. Because of the emergent condition, he was soon referred to a general hospital for intensive care, where SJS was diagnosed. The laboratory data at that time revealed acute inflammation with elevated C-reactive protein (143.2 mg/L) and leukocytosis ( $1.47 \times 10^4/\mu\text{L}$ ). There was not any acute renal or hepatic failure noted. After supportive treatment, his critical condition subsided and he returned to our hospital 1 month later. The follow-up laboratory data 1 month later revealed gradually improved leukocytosis. His psychotic symptoms were well controlled under risperidone 3 mg/day, which was prescribed after this event subsided.

He did not have any obvious drug side effects under risperidone treatment.

## Results

To the best of our knowledge, this is the first report to describe in detail the whole course of SJS in a patient with long-term clozapine use. Our patient fulfilled most of the diagnostic criteria of SJS found in different reports.<sup>7,8</sup> Besides, according to the Naranjo algorithm, the probability of adverse drug reactions by clozapine is highly probable, with a score of 6.<sup>13</sup> He recovered smoothly under supportive treatment, and had no sequelae.

## Conclusion

The etiology of SJS is still unclear. Some researchers have focused on the relationship between HLA-B\*1502 and SJS with carbamazepine use.<sup>14</sup> However, this finding could be replicated only in Han Chinese subjects receiving carbamazepine; in Japanese and Korean subjects receiving carbamazepine, different HLA-B families are found to be related to SJS.<sup>15,16</sup> At the present time, most published reports are focused on the relationship between HLA-B families and antiepileptic drugs only.<sup>17,18</sup> Although some reports suggest that genetic screening techniques should be devised to screen for the risk of SJS before prescribing such drugs for patients with either epilepsy<sup>19,20</sup> or mood disorder,<sup>21</sup> another report has tried to investigate the implication of this pharmacogenetics technique in terms of other drugs, but this seems not implacable to be promoted to other drugs at the present time.<sup>22</sup>

However, the pathologic mechanism of SJS is still poorly established. In pathological reports, accumulated CD8<sup>+</sup> T lymphocytes and macrophages (eg, Langerhans cells) in the epidermis<sup>23,24</sup> and TNF- $\alpha$  elevated by macrophages<sup>25</sup> might cause a cytotoxic cellular immune reaction and apoptosis in the epidermis and result in the clinical presentation of SJS.<sup>9</sup> Clozapine actually is believed to elevate plasma TNF- $\alpha$  levels.<sup>26,27</sup> Besides, in another report, clozapine revealed its ability to modulate the immunologic reaction, including that of IL-1 $\beta$ , IL-8, monocyte chemotactic protein (MCP-1), and NF- $\kappa$ B.<sup>28</sup> Therefore, clozapine might, at least partially, induce SJS through its potential ability of immunomodulation. However, we still need direct study to prove this hypothesis.

This case highlights the importance of monitoring and considering the possibility of SJS as a reaction to drugs for which there are no previous reports of such severe complications.

## Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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