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CASE REPORT

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Stevens-Johnson Syndrome/Toxic epidermal necrolysis complicated with fulminant type 1 diabetes mellitus: a case report and literature review

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Abstract

Background Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but life-threatening skin lesion triggered by hypersensitive drug reaction. They are characterized by extensive epidermal necrosis and skin exfoliation. Fulminant type 1 diabetes mellitus (FT1DM) is featured by a rapid-onset of hyperglycemia with ketoacidosis due to severely destroyed β-cell function. Fulminant type 1 diabetes mellitus as a sequela of SJS/TEN has rarely been reported.

Case presentation We present a 73-year-old female patient who developed SJS/TEN skin allergic reaction after taking carbamazepine and phenytoin for 35 days. Then, hyperglycemia and diabetic ketoacidosis occurred 20 days after discontinuation of antiepileptic drugs. A very low serum C-peptide level (8.79 pmol/l) and a near-normal glycosylated hemoglobin level met the diagnostic criteria for fulminant T1DM. Intravenous immunoglobulin (IVIG) and insulin were promptly administered, and the patient recovered finally.

Conclusions This rare case indicates that monitoring blood glucose is necessary in SJS/TEN drug reaction, and comprehensive therapy with rehydration, insulin, antibiotics, and IVIG may improve the prognosis.

Keywords Severe cutaneous adverse reactions (SCARs), Stevens-Johnson syndrome, Toxic epidermal necrolysis, Antiepileptic drugs, Fulminant type 1 diabetes mellitus

Background

Severe cutaneous adverse reactions (SCARs) are clinically classified into several subtypes, including drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP). SJS and TEN are rare and life-threatening, which are characterized by extensive bullae formation, epidermal necrolysis, and exfoliation. SJS and TEN share the same pathophysiology and are classified into three categories according to severity of cutaneous lesion: lesion area less than 10% of the total body surface area

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(BSA) is defined as SJS; lesion area covering 10–30% of BSA is defined as SJS/TEN; lesion area over 30% of the total BSA is defined as TEN [1]. Most cases of SJS/TEN are triggered by infections and medications, the later including aromatic antiepileptics, sulfonamides, and allopurinol [2, 3].

Fulminant type 1 diabetes mellitus (FT1DM) was first described as a new subtype of type 1 diabetes mellitus (T1DM) by Imagawa in 2000 [4]. It is characterized by rapid-onset hyperglycemia with ketoacidosis due to destroyed β-cell function and near-normal glycosylated hemoglobin levels. The islet-related autoantibodies are negative, and increasing levels of serum pancreatic enzyme are often observed [4]. It mainly occurs in Asian populations, including Japan, Korea, China, and the Philippines. FT1DM accounts for around 20% of T1DM in Japan and 7% of T1DM in South Korea [5, 6]. A variety of pathological factors, including genetics, viral infection, pregnancy, autoimmunity, and drugs, are considered to contribute to the pathogenesis of FT1DM [7], but the specific mechanism of the disease remains largely unknown.

In recent years, clinical case reports have demonstrated that drug reaction with eosinophilia and systemic symptoms (DRESS) can trigger the storm of FT1DM [8]. DRESS typically presents with fevers, facial edema, erupting skin rash, eosinophilia, atypical lymphocytosis, and lymphadenopathy [9]. However, SJS/TEN induced FT1DM has rarely been reported. Herein, a case of FT1DM and SJS/TEN triggered by antiepileptic drugs was reported.

Case presentation

A 73-year-old female was admitted to the hospital with complaints of seizures for two months and pruritus for 25 days. She had been in a good, healthy state until seizures attacked her two months ago. Carbamazepine and phenytoin sodium were administered (carbamazepine 0.1 g three times a day orally and phenytoin sodium 0.1 g twice a day orally), and symptoms were well controlled. She discontinued these two medications 35 days later due to the advent of severe skin lesions. Red and purpuric rashes appeared on the face, upper torso, and proximal upper extremities. Erosion and exudation occurred in mucosa of the eyes and mouth, which provoked a mixed sensation of burning pain and itching. She presented with swollen eyelids, dry mouth, and ulcerated lips. Then the epidermis became loose and detached, and the dermis was exposed to the outside (Fig. 1.a.b.c). She had a fever simultaneously. There was no evidence of weight loss. Medications were administered for symptom relieving, including eye drops with levofloxacin, tobramycin, and dexamethasone. Four days before her admission, a blood glucose of 23.8 mmol/L and highly positive urine ketones were detected.

The medical history included hypertension for 15 years, which was well controlled with irbesartan tablets. There were no reported allergies to other medications or food, and no family history of diabetes was indicated. Her mother had a history of similar seizures. Physical examination showed that the patient was lethargic with generalized red and desquamative skin lesions. The face and eyelids were swollen, with inflamed conjunctiva in both eyes. The eyelids and lips were ulcerated. The ratio of body surface area involved was approximately 23%, using the patient's own hand area (palm plus digits) as a tool to estimate. Lymphnodes behind the ears and under the jaw were enlarged and palpable. Her vital signs were 37.2 °C for body temperature and 141/62 mmHg for blood pressure. The pulse rate was 92 beats per minute and the respiratory rate was 19 times per minute.

Laboratory tests revealed increased white blood cell and neutrophil count, but no eosinophil count. The white blood cell count was 33.62×10^9/L, while the neutrophil cell count was 18.5×10^9/L. The high-sensitive C-reactive protein was 11.0 mg/L. Liver transaminase and myocardial enzymes were increased with abnormal coagulation function. Thyroid function revealed a state of nonthyroid illness syndrome with normal TSH levels (1.38 μIU/ml) but slightly lower FT3 (2.09 pmol/L) and FT4 (8.87 pmol/L) values. The results of the arterial blood gas analysis demonstrated that the patient had metabolic acidosis, with PH 7.16, pCO2 11.1 mmHg, pO2 155.3 mmHg (under a state of oxygen inhalation), actual bicarbonate 3.8 mmol/L, standard bicarbonate 6.9 mmol/L, base excess −25.1 mmol/l, lactic acid 5.87 mmol/L, and SpO2 98.2%. Her HbA1c was 7%, and her fasting serum C-peptide level was extremely low at 8.79 pmol/L. Diabetes associated autoantibodies (GAD-Ab, IC-Ab, IA-Ab, IAA-Ab, ZnT8-Ab) were all negative. Pathogens including respiratory syncytial virus, adenovirus, influenza virus, parainfluenza virus, mycoplasma pneumoniae, chlamydia pneumoniae, echovirus, and coxsackievirus B were negative. Tests for viral hepatitis, syphilis, and the human immunodeficiency virus were negative. Autoimmune antibodies, including anti-SSA, anti-SSB, anti-SM, anti-dsDNA, anti-mitochondrial, rheumatoid factor, were negative. The main laboratory test results are listed in Table 1.

SJS/TEN and fulminant T1DM were clinically diagnosed based on the morphology and extent of skin lesions and blood glucose profile. The patient was transferred to the ICU, where pumped intravenous insulin, fluid infusion, and other symptomatic relieving medications were administered. Exudate from the buccal mucosa was taken for pathogen culture before cefodizime sodium was used for anti-infection. High-dose steroids were not given

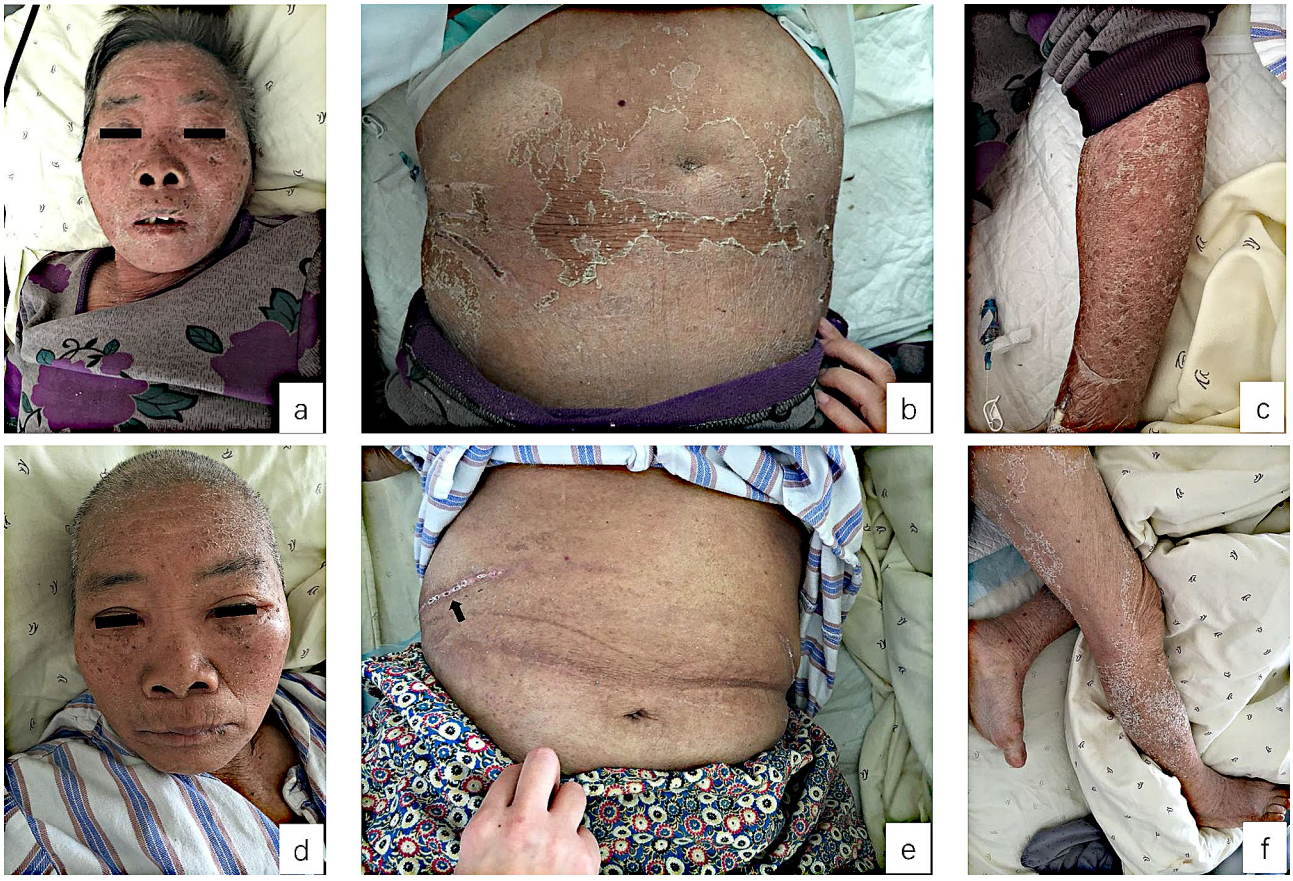

Fig. 1 Skin lesion in a patient with SJS/TEN and FT1DM. Figure a, b, and c showed generalized skin rashes and desquamation on the surface of the face, abdomen, and arms on admission. She had swollen face and eyelids and inflammation of conjunctiva. Ulcerations were detected on the eyelids and lips. Figure d, e, and f showed that rashes receded noticeably during therapy. The black arrow mark in Figure e indicates a positive Nikolsky sign, which manifests blisters and skin erosion upon a gentle rubbing on the lesion and leaves a glistening surface beneath

considering the possible side effects on hyperglycemia and bacterial infections. Intravenous immunoglobulin (IVIG) at 400 mg/kg/day (25 g/d) was given for 3 days to alleviate infection and the immune response storm. Nutritional support, i.e., TPF-D, was given through the enteral feeding tube before the patient was able to tolerate normal diet. Daily oral examinations and cleanings were performed by ICU nurses. The wound care was guided by a dermatologist. The skin was inspected daily for the extent of detachment and infection. Regular cleansing was carried out with gently warmed saline or chlorhexidine. Topical antimicrobial agent mupirocin was applied to sloughy areas. Non-adherent dressings were utilized to protect the denuded dermis. The general condition was stabilized, and glycemia and urine ketone were well controlled. Five days after admission, the skin lesions receded dramatically (Fig. 1.d.e.f.). Subcutaneous injections of insulin Glulisine were given before each meal, along with insulin Detemir before sleep time. The blood glucose fluctuated greatly, as in the case of classic T1DM patients. After 10 days of treatment, the patient recovered and was discharged from the hospital. The timeline is shown in Fig. 2.

Discussion and conclusions

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare types of severe drug hypersensitive reactions with high mortalities (4.8% for SJS and 14.8% for TEN, respectively) [10]. SJS has an incidence of 8–9 cases per million people annually, while TEN has a low incidence of 1–2 cases per million people annually [10]. They frequently manifest with extensive erythema, erosions, blisters, fever, and mucocutaneous symptoms and complicate with varying degrees of hepatic, renal, and respiratory impairment. Malaise, fever, and upper respiratory tract symptoms often precede the skin rash by a few days. Mucosa of the eyes, mouth, and genitalia are mostly involved in SJS/TEN [11]. They have a positive test for the Nikolsky sign, which manifests blisters and skin erosion upon a gentle rubbing on the lesion and leaves a glistening surface beneath [12].

Antiepileptic drugs (carbamazepine, phenytoin, phenobarbital and lamotrigine), antibiotics, antipyretic

Table 1 Laboratory data from the female patient with SJS/TEN and FT1DM

Items	Values		Reference range
	Day 1 Admission	Day 10 Admission	
Fasting serum C-peptide	8.79	ND	(260.00-1730.00) pmol/L
2-hour postprandial serum C-peptide	8.89	ND	Not given
Fasting blood glucose	14.55	3.20	(3.90–6.10) mmol/L
2-hour postprandial blood glucose	24.97	6.10	(3.90–7.80) mmol/L
White blood cell count	33.62	4.27	(3.50–9.50) ×10^9/L
Neutrophil count	18.45	2.01	(1.80–6.30) ×10^9/L
Lymphocyte count	12.81	1.38	(1.10–3.20) ×10^9/L
Monocyte count	2.29	0.85	(0.10–0.60) ×10^9/L
Eosinophil count	0.00	0.00	(0.02–0.52) ×10^9/L
Basophil count	0.07	0.03	(0.00-0.06) ×10^9/L
Platelet count	287.0	194.0	(125.0-350.0) ×10^9/L
Hemoglobin	118.0	101.0	(115.0-150.0) g/L
High-sensitivity CRP	11.0	5.2	(0.0–4.0) mg/L
ALT	420.3	103.5	(7.0–40.0) U/L
AST	87.4	84.1	(13.0–35.0) U/L
ALP	98.4	83.5	(50.0-135.0) U/L
γ-GGT	50.0	33.1	(7.0–45.0) U/L
Albumin	26.8	20.8	(40.0–55.0) g/L
Urea nitrogen	14.99	3.97	(2.86–8.20) mmol/L
Creatinine	72.8	46.0	(45.0–84.0) pmol/L
LDH	401.7	211.6	(120.0–250.0) U/L
HBDH	239.8	144.5	(72.0-182.0) U/L
CK	37.0	25.7	(26.0–140.0) U/L
CK-Mb	27.7	10.8	(0.0–25.0) U/L
cTnI	< 0.1	ND	(0.0–1.0) ng/ml
FT3	2.09	3.28	(2.43–6.01) pmol/L
FT4	8.87	10.91	(9.01–19.05) pmol/L
TSH	1.38	3.81	(0.35–4.94) μIU/ml

ND: not done; CRP: C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; γ-GGT: gamma-glutamyl transpeptidase; LDH: lactic dehydrogenase; HBDH: hydroxybutyrate dehydrogenase; CK: creatine kinase; CK-Mb: creatine kinase-MB; cTnI: cardiac troponin I; FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyroid stimulating hormone;

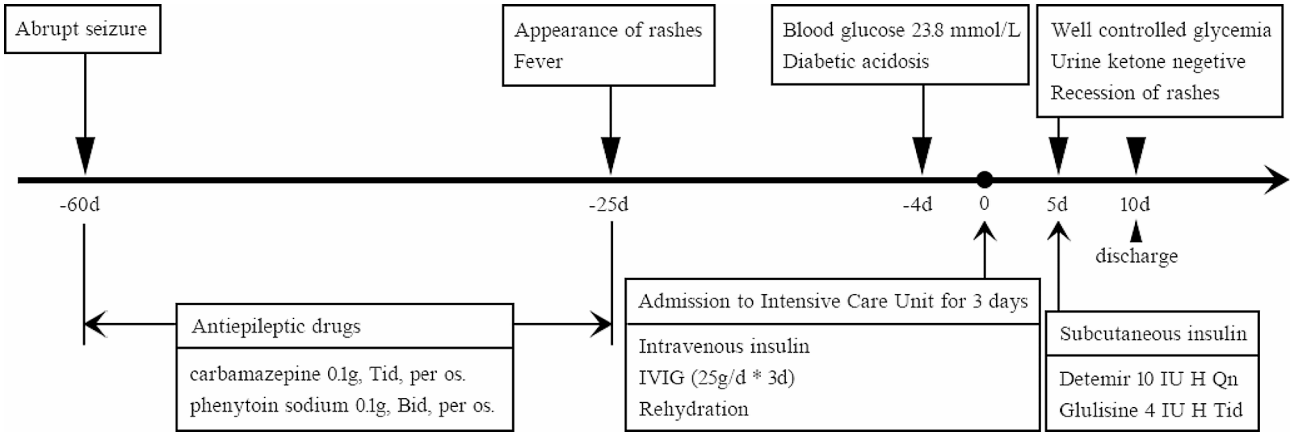

Fig. 2 Timeline of the case progression. IVIG: intravenous immunoglobulin

analgesics, and sulfonamides are the main causes for SJS/TEN [13]. In rare situations, HIV [14], mycoplasma [15], immune checkpoint inhibitors (ICIs) [16], COVID-19 infection and vaccination [17] may precipitate SJS/TEN. The histopathological features of SJS/TEN are extensive necrosis of epidermal keratinocytes, mainly mediated by drug-specific cytotoxic T cells [18].

In this case, abrupt hyperglycemia was another prominent clinical manifestation, meeting the diagnostic criteria for fulminant T1DM [19]. Diagnosis of FT1DM could be made when all three criteria could be fulfilled. (1) Occurrence of diabetic ketosis or ketoacidosis after the onset of hyperglycemic symptoms (approximately within 7 days); (2) Plasma glucose level ≥ 16.0 mmol/L and glycated hemoglobin level < 8.7% at the first visit; (3) Urinary C-peptide excretion < 10 μg/day or fasting and 2-hour postprandial serum C-peptide level < 0.3 ng/mL (< 0.10 nmol/L) and < 0.5 ng/mL (< 0.17 nmol/L), respectively. Our patient presented with remarkable hyperglycemia, ketoacidosis, HbA1c 7%, low fasting serum C-peptide, and negative islet-associated antibodies. All these features point to a diagnosis of FT1DM.

Several studies found that FT1DM was induced by severe cutaneous adverse reactions (SCARs), especially by drug reaction with eosinophilia and systemic symptoms (DRESS). Onuma et al. concluded that the incidence of DRESS-related FT1DM was 0.54%, higher than that of idiopathic FT1DM (0.01%) in Japan papulation [20]. FT1DM usually occurs after the summit of medication reactions and during the glucocorticoids tapering period. A survey of 145 patients with DRESS, conducted by the Asian Research Committee on Severe Cutaneous Adverse Reactions, showed that the incidence of DRESS induced FT1DM was 3.45% [21]. However, SJS/TEN syndrome induced FT1DM has rarely been reported. Herein, we describe an elderly female patient who developed SJS/TEN after taking antiepileptic medicine for 35 days. FT1DM occurred 20 days after the discontinuation of medication.

The pathogenesis of FT1DM associated with SJS/TEN remains unclear. Genetic susceptibility and drug induced overactive immune responses may be involved. Drug-induced SJS/TEN has been demonstrated to be an HLA class I-restricted CD8 + T cell-mediated disease [22]. The systemic immune response may destroy pancreatic β cells and pancreatic exocrine function via activated cytotoxic T cells [23].

Therapeutic regime for SJS/TEN includes discontinuation of allergenic drugs, glucocorticoids, nutrition support, insulin, and intravenous immunoglobulin (IVIG) [24]. Extensive epidermolysis and necrosis lead to thermoregulation disorder, fluid loss, and blood volume shortage. Skin infection induced sepsis is the major cause of death [25]. Thus, rehydration and antibiotics are dominant forces in improving outcomes. Corticosteroids, IVIG, cyclosporine, TNF-α inhibitors, and plasma exchange have some beneficial effects on mitigating skin lesions [26], while the evidence for lowering mortality remains controversial. It should be noted that long-term and high-dose glucocorticoids may increase the risk of sepsis and have a detrimental impact on blood glucose control in FT1DM. Therefore, for those who cannot tolerate glucocorticoids, intravenous immunoglobulin (IVIG) or immunosuppressive agents are an alternative.

In conclusion, SJS/TEN is a rare but severe systemic drug adverse reaction, mostly involving generalized skin and mucosa. It may occasionally precipitate pancreatic β-cell destruction and lead to FT1DM. Therefore, monitoring blood glucose is necessary in those patients, and comprehensive therapy with rehydration, insulin, antibiotics, and IVIG may improve the prognosis of the disease.

Abbreviations

SJS	Stevens-Johnson Syndrome
TEN	Toxic Epidermal Necrolysis
FT1DM	Fulminant Type 1 Diabetes Mellitus
IVIG	Intravenous immunoglobulin
SCARs	Severe cutaneous adverse reactions
DRESS	Drug reaction with eosinophilia and systemic symptoms
AGEP	Acute generalized exanthematous pustulosis

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Author contributions
Patient evaluation: D.L. and X.S.; Patient treatment: X.Z. and D.H.; Visualization and figure: D.H.; Conceptualization: D.L. and X.S.; Data analysis and literature review: X.Z. and J.M.; Original draft preparation: X.Z.; draft revision and editing: J.M. All authors have read and agreed to the published version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All methods were carried out in accordance with relevant guidelines and regulations. The patient provided written informed consent for data collection. The study was approved by the ethics committee of Shaoxing People's Hospital.

Consent for publication
Written informed consent has been obtained from the patient for publication of this case report.

Competing interests
The authors declare no competing interests.

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