Toxic epidermal necrolysis after injection of sclerosing agent and medical adhesive into oesophageal variceal ligation in a patient with a malignant liver tumour: A case report

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Abstract. Chronic liver disease can cause an increase in portal sinus pressure, which may lead to rupture and bleeding of esophageal and gastric varices. Oesophageal variceal ligation, with use of sclerosing agent and tissue glue injection is commonly used in clinical practice to address oesophageal bleeding. A 58-year-old male patient with chronic liver disease was treated with oesophageal variceal ligation, sclerosing agent and tissue glue injection due to oesophageal and gastric variceal bleeding. After 2 days, the skin of the patient exhibited erythema to different degrees. After 10 days of dexamethasone treatment, the whole-body rash worsened, and a severe skin reaction appeared that was suggestive of toxic epidermal necrolysis (TEN). Strict mucosal care was provided, and corticosteroids, γ globulin and adalimumab were concurrently used for treatment. After 20 days, the patient recovered from the skin problems. To the best of our knowledge, TEN after endoscopic surgery has rarely been reported in the relevant literature. Furthermore, when patients being treated with multiple drugs have erythema multiforme, physicians should be alert to the possibility of its development into TEN. The present case report summarizes the treatment methods for patients with TEN, providing a practical clinical basis and direction for the future diagnosis and treatment of the condition.

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Introduction

Toxic epidermal necrolysis (TEN) is one of the few acute and severe allergic diseases in dermatology. The incidence rate is low (1.58-2.26 cases/million individuals), but the mortality rate can reach ~61% (1). Drugs are the most common pathogenic factors for this condition. Certain antibiotics, such as sulfonamide and penicillin, as well as some psychotropic drugs, such as barbiturates and phenytoin, have been occasionally reported to cause TEN (2). However, the pathogenic factors of TEN do not only include drugs, but also other factors. For example, ultraviolet radiation (UVR), which everyone is exposed to in daily life, but which can also trigger TEN in the form of photodistributed TEN (3).

The onset of TEN exhibits certain typical features, with local erythema of the body at the initial stage, accompanied by pain. After 1 to 2 weeks, the disease can rapidly develop from erythema to bullous skin lesions, after which peeling skin tissues can appear. During patient care, external forces (such as rubbing or squeezing) can cause patches of bullous skin to peel off (which is known as the Nikolsky sign), and the peeled wound is similar to a deep second-degree scald. The skin-stripping area is an important index for evaluating TEN. According to the percentage of skin-stripping area compared with the whole-body surface area, the disease is referred to by different names (4). A ratio <10% is referred to as Stevens-Johnson syndrome (SJS), a ratio >30% is referred to as TEN and a ratio >10% but <30% is referred to as overlapping SJS and TEN (5). In addition to skin symptoms, there can also be systemic symptoms, such as fever, fatigue, chills and muscle soreness. Exfoliation can also occur in other parts

of the mucosa, such as the eyes, lips and external genitalia. If the disorder is combined with the exfoliation of other parts of the mucosa, it indicates that the condition has become notably serious. If the disorder is not properly treated, patients are prone to electrolyte disturbances and can even die due to the dysfunction of multiple organs (6). The aim of the present study was to highlight the fact that physicians should be alert to the possibility of the development of erythema multiforme into TEN when patients are treated with multiple drugs. The study summarizes the treatment methods and experiences of patients with TEN both domestically (China) and internationally, providing reference for the diagnosis and treatment of TEN in the future.

Case report

A 58-year-old male patient was hospitalized in Shaoxing People's Hospital (Shaoxing, China) in April 2022 for treatment due to haematemesis and tarry stool for 1 day. Preliminary diagnoses included the following: i) Oesophageal and gastric variceal bleeding; ii) chronic hepatitis B; iii) malignant liver tumour; iv) portal hypertension; v) portal vein embolism; vi) anaemia; vii) ascites; and viii) spleen enlargement. The basis for this diagnosis was a previous history of hepatitis B, cirrhosis and gastrointestinal bleeding, and end-stage chronic liver disease. A physical examination revealed an anemic facial appearance and abdominal wall varicose veins. Palpation revealed splenomegaly with positive results for ascites. The main laboratory tests revealed the following results: Red blood cell count, $2.67x10^{12}$/l (normal, $4.5\text{-}5.5x10^{12}$/l); hemoglobin level, 82 g/l (normal, 120-160 g/l); hepatitis B virus surface antigen, >250.00 IU/ml (normal, <0.05 IU/ml); hepatitis B virus e antibody, 0.89 PEIU/ml (normal, 0-0.2 PEIU/ml); hepatitis B virus core antibody, 12.84 PEIU/ml (normal, <0.9 PEIU/ml); total protein, 58 g/l (normal, 60-80 g/l); and albumin, 29.6 g/l (normal, 35-50 g/l). A routine ultrasound examination revealed liver cirrhosis and a liver mass, portal vein widening with thrombosis, liver and spleen enlargement, gallbladder wall oedema and a large amount of ascites. After admission, the patient was treated with Losec® (40 mg, twice a day, intravenous) for gastric acid inhibition, Stilamin® (3 mg, every 8 h, intravenous) and terlipressin (1 mg, every 6 h intravenous) for increased blood pressure, furosemide (20 mg, once a day at 10 am, intravenous) for diuresis and polyene phosphatidylcholine (456 mg, once a day at 10 am, intravenous) for liver protection and rehydration.

Diagnosis and treatment. In April 2022, on the 6th day after hospitalization, the patient underwent endoscopic surgery with the use of a venous ligation ring, sclerosing agent (10 ml lauromacrogol injection; the main ingredient is 100 mg lauromacrogol, while other ingredients include ethanol and sterile water for injection) and medical adhesive (2 ml COMPONT, Beijing COMPONT Medical Equipment Co., Ltd; the main component is α-N-butyl cyanoac rylate, and other components include small amounts of stabilizers, such as hydroquinone, toluene yellow acid and sulfur dioxide). On the second day after endoscopic surgery, the patient developed a scattered rash with itching; therefore, the patient was advised to stop using Stilamin and instead use octreotide injections. Dexamethasone (10 mg, once a day at 8 am, intravenous) was used for relieve the skin allergy symptoms.

After 3 days of treatment with dexamethasone (10 mg, once a day at 8 am, intravenous), the number of rashes increased. The patient experienced a burning and pain sensation on the lips and conjunctiva, and in addition, oedematous skin erythema, loose epidermis and a bullous appearance was observed. Increased secretion was observed in the corners of the eyes. Dermatologists diagnosed erythema multiforme based on the aforementioned symptoms. The possibility of drug allergies was considered, but the patient denied a history of antipyretic and analgesic drugs, anti-inflammatory drugs, new drugs or sensitizing drugs within 1 month before admission. Subsequently, it was found that dexamethasone had a poor therapeutic effect on the skin symptoms. The rash symptoms were not effectively treated and gradually worsened. The doctor's assessment indicated that the patient needed to use steroids for a longer period, and the dosage of steroids used was high. Therefore, dexamethasone treatment was stopped and changed to treatment with methylprednisolone (60 mg, once a day at 8 am, intravenous). As methylprednisolone has minimal side effects on the digestive system and liver function (7), it was hypothesised that using methylprednisolone would be more effective for treating the patient.

On the thirteenth day after endoscopic surgery, a large number of blisters appeared on the patient's back, and some of the blisters fused. The overall area of skin lesions had increased compared with previously. Furthermore, part of the skin became exfoliated, the wound was eroded (Fig. 1A-C), and Nissl's sign was positive. The laboratory examination results were as follows: IgG, 24.85 g/l (normal, 7-16.6 g/l); and IgA, 0.3 g/l (normal, 0.7-4 g/l). Other immunoglobulin levels were generally normal. In addition, the blisters on the lips of the patient partially ruptured and expanded to the surrounding area, with epidermal erosion and bloody exudation. The pain was more severe compared with before, and some skin lesions were covered with a grey-white pseudomembrane (Fig. 2A). Pain and swelling in both eyes, conjunctival congestion, increased discharge from the corners of the eyes and difficulty opening the eyes were observed (Fig. 2B). Combined with the aforementioned symptoms, the revised diagnosis was TEN. When considering that patients with upper gastrointestinal bleeding should not use an excessive dose of corticosteroids, according to the recommendations of the Guideline for Primary Care of Drug Eruption (2022) (8), γ globulin (20 g, qd8, intravenous) and methylprednisolone (100 mg, qd8, intravenous) were administered. The gastrointestinal bleeding of the patient improved, and the patient could tolerate oral medication. Therefore, a new generation proton pump inhibitor, rabeprazole sodium enteric-coated tablets (20 mg, once a day in the morning, oral), with greater efficacy, was used instead. The patient's disease had now progressed to TEN, so the risk factors of TEN should be reduced as much as possible. Therefore, the use of omeprazole sodium (Losec®) and octreotide injection for treatment was discontinued.

After 4 days, the rash had still not obviously improved, and the erosion and exfoliation of the trunk skin were worse compared with before (with obvious pain). Adalimumab (40 mg, once, subcutaneous) was used for treatment, and Kangfu New Liquid-soaked gauze (Innermongolia Jingxin

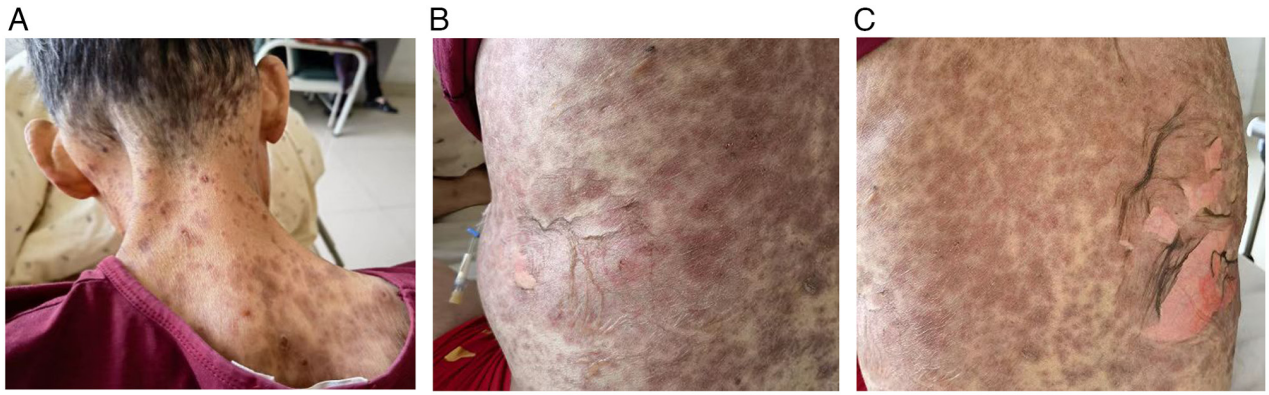

Figure 1. Initial skin symptoms of the patient with toxic epidermal necrolysis. (A) Rash on the back, shoulder and neck. (B) Exfoliation of skin on the back. (C) Exfoliation of surface layer of back skin.

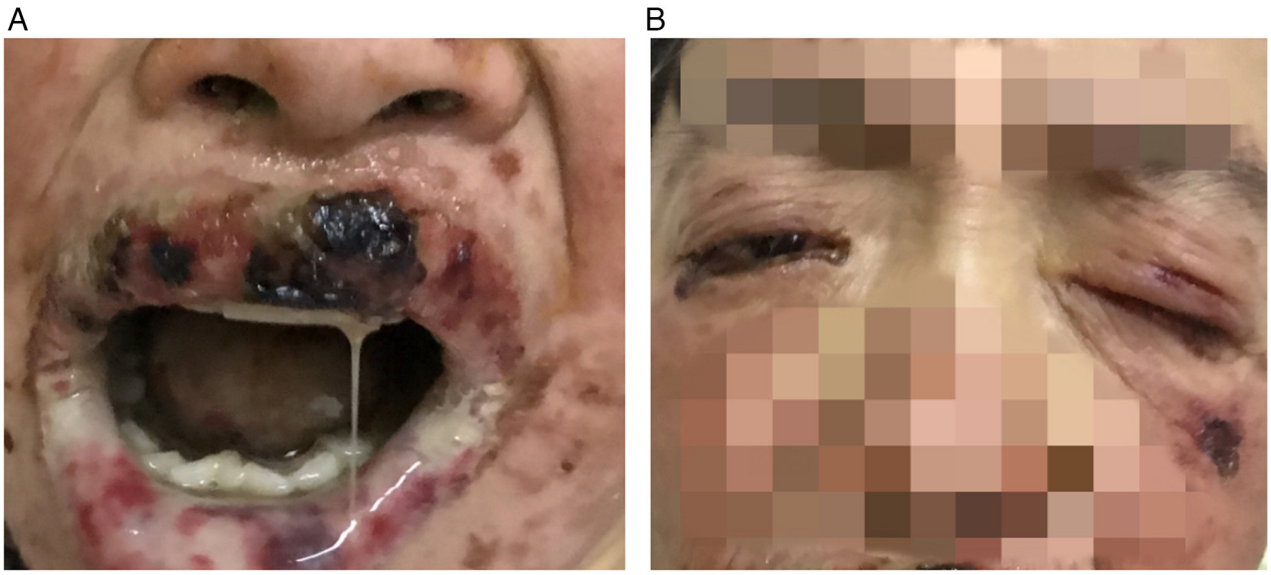

Figure 2. Oral and eye symptoms of the patient with toxic epidermal necrolysis. (A) Blisters on the lips of the patient have partially ruptured and expanded to the surrounding area. (B) Conjunctival congestion, increased secretion from the corners of the eyes and difficulty opening the eyes.

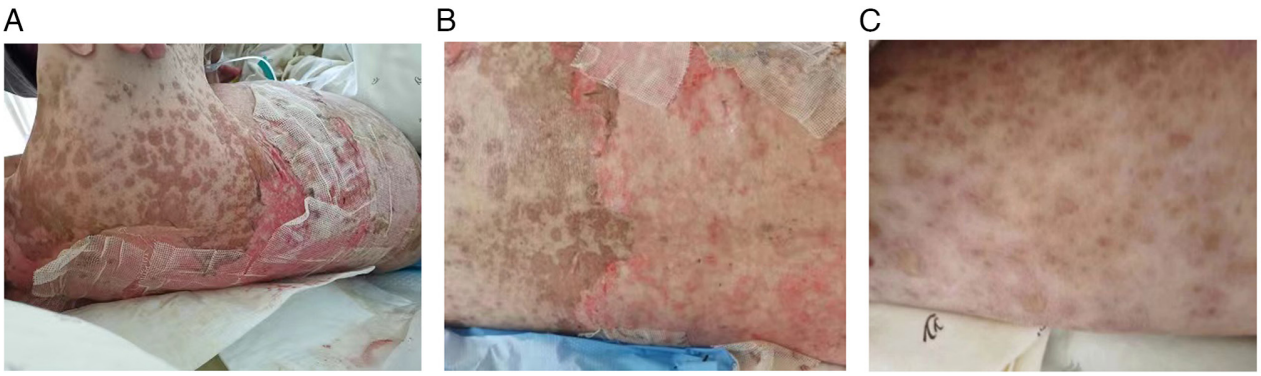

Figure 3. Treatment and recovery of patient with toxic epidermal necrolysis. (A) Kangfu New Liquid gauze wet compress. (B) Wound convergence and partial scab peeling. (C) Rash is mostly cured.

Pharmaceutical Co., Ltd) was applied on the wound (Fig. 3A), and erythromycin ointment to resist mucosal infections. After 2 days, the rash had improved. On the 4th day after treatment with adalimumab, the wound was dry, and part of the scab skin fell off (Fig. 3B). After 10 days, the rash had generally recovered (Fig. 3C). At the time of writing this case report, there have been no signs of recurrence of the patient's rash.

Discussion

TEN is a type of acute and severe allergic autoimmune skin reaction. It can also be caused by a number of other factors, but the majority of them involve drugs. The research on its pathogenesis has not reached a unified consensus (9). Based on current international medical research, HLA genes can be closely related to drug-induced TEN (10). Mutation of the cytochrome P450 gene can lead to a slower metabolism of related drugs (such as diazepam, warfarin and phenytoin), thereby increasing the risk of TEN (11). Certain infectious factors, such as human herpesvirus, Epstein-Barr virus and *Mycoplasma pneumoniae*, are also associated with the onset of TEN. Autoimmune diseases and active malignant tumours are also potential factors for the onset of TEN (12).

The treatment of TEN should be considered from multiple aspects, and multiple methods of combined treatment should be started as soon as possible (12). It is necessary to avoid the presence of pathogenic factors, reduce the clinical symptoms of patients and provide supportive treatment for preventing secondary internal organ failure (13). Discontinuation is required of the drugs that the patient is currently using that may cause TEN. Use of medications with adverse reactions, such as rashes or skin allergies, should be avoided as much as possible. Garcia-Doval *et al* (14) reviewed the clinical data of 113 patients with SJS or TEN and revealed that early cessation of allergenic factors (drugs) can significantly reduce patient mortality. In addition, supportive treatment for TEN should be provided (15), including maintaining the fluid and electrolyte balance of the patient (16), symptomatic management of skin lesions and mucous membranes and prevention and control of infection (17). Appropriate medication is actively used for treatment, including glucocorticoids (18), immunosuppressants (19,20), traditional Chinese medicine (21,22), human immunoglobulins (23-25), cyclosporine (26), cyclophosphamide and thalidomide, among others. The main function of these treatment plans is to maintain the balance of vital signs in the body, improve the body's own immunity, reduce other harmful factors and accelerate the skin healing ability. By using these comprehensive treatments, the patient's disease can be effectively alleviated. Han *et al* (27) reported the use of plasma exchange to treat patients with TEN, but Clark and Huang (28) suggested that using plasma exchange alone to treat TEN still has certain shortcomings. Although plasma exchange can remove some toxins from the blood, it may also consume coagulation factors, increase the risk of bleeding and lead to electrolyte deficiency (such as hypocalcemia). After plasma exchange, the body's immune system is still very poor, which is not conducive to recovery from the disease (28).

The patient in the present case suffered from both acute gastrointestinal bleeding and end-stage chronic liver disease. After hospitalization, a number of types of drugs were used, so the root cause of TEN is relatively complex. The patient developed a rash on the second day after endoscopic surgery (and also the second day after the use of sclerosing agent and medical adhesive), therefore the timing of the occurrence was quite important. According to the relevant literature (29,30) and combined with the characteristics of the present case, the time of the skin allergic reaction after using omeprazole sodium for injection (Losec), somatostatin for injection (Stilamin) or terlipressin is inconsistent with the actual time the skin rash developed in the present case. Therefore, the present study focused on the hypothesis that the predisposing factors of TEN were related to the use of medical adhesives or the sclerosing agent.

The rash of the present patient was initially considered to be erythema multiforme, which is usually associated with infection (31). The typical skin pathology in the initial stage mainly involves erythema with different degrees of target lesions (or iris lesions), which is a skin disease related to acute onset and inflammation that is usually accompanied by mucosal damage and can heal itself; however, it can easily recur, and its mortality rate is low (32,33). As demonstrated by the experience of diagnosis and treatment in the present case, if erythema multiforme appears in patients with complicated medication usage, it is necessary to examine whether this may constitute an important precursor of SJS or TEN.

The current patient developed a rash after 2 days of digestive endoscopy and rapidly developed TEN, which, to the best of our knowledge, is rarely reported. In addition, life support treatments (such as supplement of effective circulating blood volume, desensitization with glucocorticoids, wet compresses with Kangfu New Liquid-soaked gauze, erythromycin ointment to resist mucosal infections, intravenous injections of human γ globulin to enhance the disease resistance of the body and treatment with adalimumab, which is a TNF antagonist) can have beneficial effects. Adalimumab can be used to treat rheumatoid arthritis and ankylosing spondylitis and improve symptoms, such as joint stiffness, pain, redness, swelling and deformation. Considering that adalimumab can exert an antagonistic effect on TNF, it was also suitable for the present patient (34). Compared with the anti-inflammatory effects of glucocorticoids such as dexamethasone and methylprednisolone, adalimumab plays a regulatory role in the biological response induced or regulated by TNF, thereby regulating immune suppression (35). Therefore, on the basis of comprehensive treatment, adalimumab exerts specific advantages, which results in the skin symptoms of patients becoming benign. In addition, if patients are initially treated with adalimumab when their skin exhibits erythema multiforme, it is unclear whether the development of TEN can be controlled. In future clinical practice, the identification of valuable cases for in-depth study is necessary to obtain new insights into the development of TEN.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LH and WC wrote the draft of the manuscript. WC and ZZ obtained the clinical data and conceived the methodology. XG, QL and HC performed the research and analyzed the data. LH and ZZ made substantial contributions to conception and design, acquisition, analysis and interpretation of data, and writing/editing/revising the manuscript. YZ wrote and reviewed the manuscript. YZ and JD contributed to the conception and design of the study and confirmed the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient who participated in the study provided written informed consent for the publication of any associated data.

Competing interests

The authors declare that they have no competing interests.

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