JOURNAL OF FORENSIC SCIENCES

J Forensic Sci, May 2010, Vol. 55, No. 3
doi: 10.1111/j.1556-4029.2010.01338.x
Available online at: interscience.wiley.com

CASE REPORT

PATHOLOGY AND BIOLOGY

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Death Caused by Toxic Epidermal Necrolysis (Lyell Syndrome)

ABSTRACT: Toxic epidermal necrolysis (TEN) is characterized by fever, scalded appearance of the skin, and epidermolysis associated to blister formation and exfoliation, and it is caused by hypersensitivity reaction to a drug. The authors report two cases of death as a result of TEN; both referred to old aged women treated with a polytherapy including allopurinol. Both patients displayed erythematous skin lesions similar to scald burns and epidermolysis at the face, chest, and abdomen and died shortly after hospitalization. Autopsy findings and histological examinations revealed epidermal necrolysis and confirmed the clinical diagnosis. A strict time-correlation between allopurinol administration and symptoms was evidenced. Because of its iatrogenic origin, TEN often arises suspicions of medical liability; however, because of its unpredictable nature, the occurrence of this syndrome cannot be ascribed to the medical staff whose main task is the rapid diagnosis and the correct management.

KEYWORDS: forensic science, toxic epidermal necrolysis, Lyell syndrome, allopurinol, burns, medical liability

In 1956, Alan Lyell described a syndrome clinically characterized by fever and scalded appearance of the skin, followed by widespread epidermolysis, loosening of the epidermis leading to blister formation and exfoliation. Lyell named this syndrome as toxic epidermal necrolysis (TEN), and it is also known by the eponym Lyell Syndrome (1).

TEN is an idiosyncratic, delayed hypersensitivity reaction to a drug with a reported incidence of 1.17–1.89 per million per year (2). The most frequently associated triggers are antibiotics (trimethoprim/sulfamethoxazole, beta-lactams, tetracyclines, quinolones), aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine), nevirapine, abacavir, and nonsteroidal anti-inflammatory drugs (3–11). Also allopurinol has been frequently associated to the occurrence of TEN (12–22).

TEN is characterized by erythematous rash, formation of bullae, separation of large sheets of epidermidis from the dermis, purulent conjunctivitis, and mucositis of the mouth and genital area (23). Mucositis generally precedes skin lesions by a few days (24).

Pereira et al. (25) reported an occurrence of massive necrolysis involving the whole skin surface within 24 h in one out of seven patients, in the vast majority of the cases; however, lesions erupt over a period of 2–15 days. Inflammation of mucosal surfaces especially at the gastrointestinal and respiratory tracts is very common (26); the mucosal involvement can be particularly insidious because of possible life-threatening complications such as respiratory failure or hemorrhages (23,25,27,28). Data about the mortality rate are quite variable: a mortality rate up to the 25–30% was reported by many authors (23,29–32).

Histology can be helpful to confirm the diagnosis: full-thickness epidermal necrosis with the formation of subepidermal bullae and sparse to dense dermal mononuclear infiltration is usually observed (2,32,33).

Case 1

A 76-year-old woman was admitted at hospital after an accidental fall. The diagnosis at the admittance was epiphyseal fracture of the right radius and multiple, bilateral rib fractures. The clinical history revealed the presence of diabetes and hypertension. Clinical observation highlighted 22 respiratory acts per minute, with a pulse rate of 70 beats and blood pressure of 170/85 mmHg. She was given ramipril, clortalidon, octatropine, diazepam, and allopurinol as a therapy. Allopurinol at a dosage of 150 mg/day was prescribed because of hyperuricemia. One week later, the patient started complaining of nausea and abdominal pain. Vomiting, diarrhoea, and anal hemorrhage were also present. A colonoscopy revealed a diffused inflammation of the mucosa. Two days later, her condition worsened: she showed fever (38.2°C), erythematosus lesions to the face and the trunk, rapidly extending to the abdomen and upper extremities. The skin developed flaccid bullae and detached irregularly, sometimes in large sheets. Also the mucosa of mouth and oropharynx was involved, thus making the nourishment difficult. Large sheets of epidermal detachment involved more than 70% of the body surface.

A diagnosis of Lyell Syndrome was clinically made. The therapy was stopped, and the patient received steroids. The skin lesions did not improve after suspension of the therapy. In spite of an urgent transfer to the intensive care unit, the patient died 10 days after appearance of erythema because of multiple organ failure.

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Received 12 Jan. 2009; and in revised form 18 Mar. 2009; accepted 2 May 2009.

Medicolegal autopsy was ordered to confirm the cause of death and evaluated an eventual professional error. A wide facial central area of confluent erythema was evident, while the tongue, mouth, and conjunctiva showed erosive lesions. The neck, the trunk, and the upper limbs were almost completely covered by yellow-reddish areas of dried, leathery skin where the desquamation on the skin lesions had occurred (Fig. 1).

The internal examination displayed sparse erosive lesions of the pharynx and the larynx, while the esophagus and the trachea were spared. Besides mild lung edema and moderate–severe atherosclerosis of the main arteries, no other pathological findings were detected on gross examination.

Microscopy of the skin lesions showed a severe epidermal necrosis with bacterial crust, hyalinosis, and atrophy of the upper dermis (Fig. 2).

The clinical diagnosis of multiple organ failure as a result of TEN was confirmed.

Case 2

A 77-year-old woman was admitted at hospital with diagnosis of acute enteritis with fever and a history of diabetes. As referred, she was treated with allopurinol, paracetamol, and an unspecified antibiotic before hospital admission. Also in this case, hyperuricemia was the reason for prescription of allopurinol at a dosage of 300 mg/day. Progressive muco-cutaneous lesions characterized by loosening of the epidermis occurred in the next few days, and a treatment with steroids, proton pump inhibitors, antibiotics, insulin, and rehydration was started. One day later, she was transferred to the burn injured unit with a diagnosis of "Stevens-Johnson syndrome caused by allopurinol." The clinical situation was complicated by a kidney failure. She refused infusion of immunoglobulin and albumin for religious reasons. The epidermal detachment approximately involved 30% of the body surface. After a dermatologic consultation, cutaneous lesions were treated with topical application of antibiotics and submitted to microbiological analysis that revealed the presence of *Staphylococcus aureus* and *Proteus mirabilis*. The patient died 9 days after admission, with diagnosis of Lyell Syndrome.

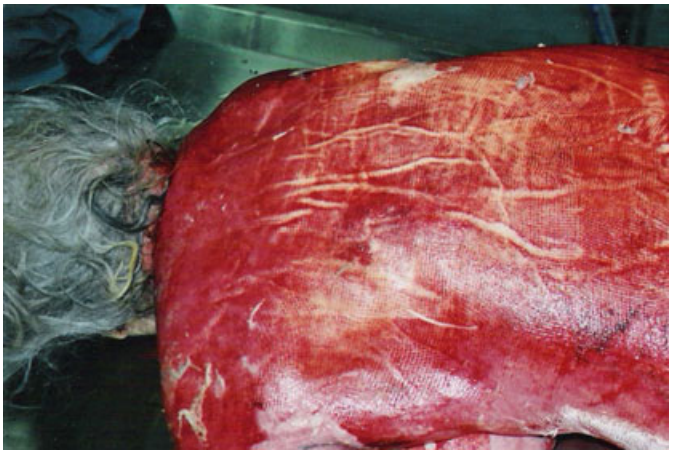

FIG. 1—*Case 1, skin lesions resembling scalds on chest and shoulders.*

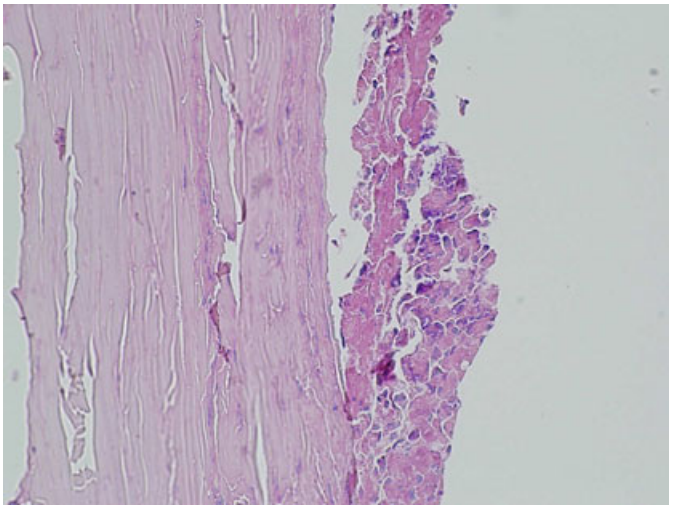

FIG. 2—*Case 1, epidermal necrosis with bacterial crust, hyalinosis, and atrophy of the upper dermis (Hematoxylin and eosin, 40×).*

Even in this case, medico-legal autopsy was conducted to define the cause of death and the correctness of cares. The whole body surface showed spread red areas of erythema alternate with gray-red areas of loosening of the epidermis similar to II or III degree burn lesions, extended to the neck, body trunk, and thighs, the head and the face involving mucosae, and to the shoulders and chest. The heels were interested by pressure ulcers.

The internal examination showed similar lesions similar to black crusts into the mucosa of oropharynx and esophagus. Diffused increased lung density and advanced nephrosclerosis were observed.

The histological examinations revealed epidermal necrolysis, with necrotic crust**,** hyalinosis of the derma, and dilatation of the capillaries.

Discussion

TEN is known to the medicolegal community, especially by the eponym Lyell Syndrome (7,34,35). The classical importance of this illness is the differential diagnosis between TEN and burns. This very interesting fact has, however, a limited practical relevance as, in the majority of the cases, circumstantial information easily leads to the correct diagnosis.

Much more insidious is the differentiation between TEN and other forms of severe skin lesions such as staphylococcal and streptococcal infection.

Staphylococcal infections are more typical in children but also occur in immunosuppressed adults (36). Superficial skin blisters are generally located at areas of friction, and the exfoliation is not as dangerous as in cases of TEN. The absence of mucosal lesions is an important parameter for differential diagnosis (25).

Streptococcal skin infections are clinically characterized by vesicles rapidly evolving into superficial erosions covered by serous crust (37). For the differential diagnosis, microbiological investigations are helpful, but the possibility of superinfections has to be taken into account.

Because of its iatrogenic origin and its frequent lethal course, TEN is more and more the subject of legal inquests in cases of suspect medical professional responsibility. The onset of TEN is not attributable to the medical staff, because of its unpredictable character. The physicians have, however, to rapidly diagnose TEN and to immediately start the correct management, which firstly consists in arresting the offending therapy (25).

The medicolegal expertise should consider the indication of the therapy and the adequacy of the dosages as well as the time of diagnosis and the correctness of the treatment. As lethal cases

unfortunately occur also with adequate care, the hypothesis of medical liability is usually rejected.

Besides age and gender, the most important common element in the two presented cases was the administration of allopurinol in the days before the appearance of TEN.

The literature reports many studies about the drugs responsible for this syndrome. Among these, allopurinol has frequently been cited as potential trigger (12–22).

Besides allopurinol, in our cases, other drugs had been prescribed: even if it cannot be excluded that these drugs played a role in determining the pathology, the clinical course and the data from the literature suggest a correlation with allopurinol.

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