LYELL'S SYNDROME IN MEDICO-LEGAL AND PATHOLOGICAL-ANATOMICAL PRACTICE

L.N. Zimina[1], A.I. Ibraeva[1], G.V. Mikhailova[2], T.K. Osipenkova-Vichtomova[3], V.A. Strokova[2], V.V. Titova[1]

[1] N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Healthcare Department,

[2] Forensic Medical Examination Bureau Healthcare Department,

[3] Russian Centre of Forensic Medical Examination of the Ministry of Health of Russian Federation, Moscow, Russian Federation

ABSTRACT	We report 9 clinicopathologic cases of Lyell's syndrome, known as toxic epidermal necrolysis (TEN). Five deceased patients had dermal exposure to cow parsnip, grey mercury ointment or whitening agents. In 4 cases, TEN developed in the course of drug treatment as a part of polytherapy, and in one of them it was accompanied with the infection. All of TEN patients suffered from acute or chronic diseases, endogenous or exogenous intoxication, immunodeficiency.
Keywords:	Lyell's syndrome, toxic epidermal necrolysis, drugs, cow parsnip, grey mercury ointment.

AIDS – acquired immune deficiency syndrome
ICD – ischemic heart disease
NSAIDs – nonsteroidal anti-inflammatory drugs
SJS – Stevens-Johnson syndrome
TEN – toxic epidermal necrolysis

Lyell's syndrome (toxic epidermal necrolysis – TEN) is an acute, serious and life-threatening allergic reaction characterized by bullous lesions of the skin and mucous membranes, epidermal necrolysis and skin exfoliation, combined with severe intoxication and impaired function of all organs and systems [1].

TEN is 0.3% of all cases of drug allergy. Analgesics, antibiotics, NSAIDs, anticonvulsants, psychotropic drugs, vitamins and nutritional supplements [2, 3] are more often mentioned as allergenic drugs. Due to the lack of specific laboratory tests we cannot reliably confirm the role of drugs in the development of TEN.

Percutaneous poisonings with the grey mercury ointment, used for self-medication for pediculosis, increases the risk of Lyell's syndrome development by 2.4 times if the ointment is exposed for more than a week [4].

There are also cases of Lyell's syndrome associated with a contact with a variety of plants – cow parsnip, poison ivy, primrose, chrysanthemum, buttercup, tobacco, inula, arnica, sumac, etc. [5, 6].

Most manifestations of drug allergy are the result of mixed reactions of several types (anaphylactic, cytotoxic, and immunocomplex). In the domestic and foreign literature acute bullous dermatitis such as erythema multiforme, Stevens-Johnson syndrome (SJS) and TEN are considered as different stages of a single process. SJS and TEN represent a single pathological process and differ only in the area of skin lesions involved: SJS – 10-30%, and TEN – more than 30% [7, 8]. The disease develops acutely and has a high mortality rate from 30 to 90% [7, 9].

Lethal outcomes of Lyell's syndrome are usually studied by pathologists. Recently, it has been more often mentioned in the forensic practice, particularly as a cause of sudden death [10].

Aim of study: to perform a clinical and anatomical analysis of the material and identify a distinctive feature of the pathological process in the deceased of Lyell's syndrome, caused by various etiological factors.

MATERIAL AND METHODS

We performed a clinical and anatomical analysis of autopsy material from 9 deceased of Lyell's syndrome. There were 5 men aged 27, 32, 33, 50 and 53 years and 4 women aged 53, 55, 66 and 79 years. Seven patients died at the N.V. Sklifosovsky Research Institute for Emergency Medicine, one patient died in the City Clinical Hospital no. 6 and one case was admitted to the Russian Centre of Forensic Medical Examination.

Medical records were studied: in-patient cards, records of forensic and pathological acts. We examined the autopsy material using conventional histological techniques, as well as data and history catamnesis derived from the words of patients and their relatives. In 5 cases, bacteriological and bacterioscopic studies were also conducted.

RESULTS AND DISCUSSION

In 8 patients, TEN developed at home, and they were admitted in a serious condition with generalized skin lesions, intoxication and hypotension. In one patient, TEN developed on day 9 of the hospital stay. The duration of

the disease from the time the skin lesions appeared, its location and etiological factors are listed in the Table 1.

Table 1

Information on the deceased from the time of cutaneous manifestations and development of TEN

№	Patient	Gender	Age	Etiology	Reason for contact	Disease duration (days)	Location of the skin lesions
1	K-a	f	53	Contact with cow-parsnip, percutaneously	Accidental contact	3	Left lower limb (foot, lower leg, thigh)
2	K-o	fl	66	Polytherapy. Orally, parenterally	Chronic diseases	3	Head, trunk, upper limbs and lower limbs
3	L-v	m	27	Contact with cow-parsnip percutaneously	Accidental contact	3.5	Upper and lower limbs
4	K-v	m	50	Unknown	Pain syndrome	4	Right lower limb (foot, lower leg, thigh)
5	D-a	f	55	Contact with whitening agents, percutaneously	Whitewashing the ceiling	10	Head, trunk, limbs
6	G-a	f	79	NSAIDs orally, polytherapy	Pain syndrome	14	Neck, right upper limb, chest, abdomen
7	S-n	m	53	Polytherapy, orally	Chronic diseases	17	Upper and lower limbs, chest
8	D-v	m	33	Grey mercury ointment, percutaneously	Pediculosis	22	Total skin lesion
9	I-v	m	32	Grey mercury ointment, percutaneously	Pediculosis	29	Trunk, thighs, perineum

Notes: NSAIDs — nonsteroidal anti-inflammatory drugs; TEN — toxic epidermal necrosis

The peculiarity of our observations was the prevalence of percutaneous options for TEN (5 observations of 9). The area of skin lesions ranged from 35% of the body surface to the total.

Seven patients who died at the Institute, were hospitalized late, transferred from other hospitals in critical condition, or stayed in the toxic or burn resuscitation units for a short time.

There were no mentions on previously experienced allergies in histories pf 5 patients, one patient experienced an allergic reaction to Analgin, and the other — to Bicillin. In 2 patients, physicians failed to collect the allergic background due to the severity of a condition and the short stay in the Institute (25 minutes and one day).

Seven patients had a variety of chronic diseases and received polytherapy (Table 2).

Table 2

Major, underlying and concomitant diseases in patients with TEN

№	Patient	Age	Disease in patients with TEN
1	K-a	53	IHD, hypertension, type II diabetes, chronic alcohol intoxication
2	K-o	66	Bacterial trombotic endocarditis of the mitral valve, septicopyemia, rheumatic mitral valve, aortic atherosclerosis, stenosing coronary arteriosclerosis, chronic pyelonephritis, peptic ulcer
3	L-v	27	Opium addiction, HIV infection, chronic hepatitis *HCV*
4	K-v	50	Aortic atherosclerosis, arteries of lower extremities with chronic occlusion of both femoral arteries and longtime common iliac artery stent. Hypertension
5	D-a	52	Chronic duodenal ulcer. Allergic reaction to Analgin
6	G-a	79	Rheumatoid polyarthritis, widespread atherosclerosis, vascular encephalopathy
7	S-n	53	IHD, chronic obstructive bronchitis
8	D-v	33	No allergic background, healthy
9	I-v	32	No allegric background, healthy

Notes: HIV — human immunodeficiency virus; IHD — ischemic heart disease; TEN — toxic epidermal necrosis

All patients had acute onset and rapid progression of the disease. The first symptoms were usually regarded as the beginning of ARVI (hyperthermia to 38-40 °C, catarrhal phenomena in the upper respiratory tract, sore throat, appearance of skin eruption). In 6 patients, the eruption usually appeared within the first hours or days after the onset of the disease. We failed to detect the drug which induced TEN in patients under polytherapy as well as in case of mixed etiology (drug + sepsis).

For example, in 66-year-old female patient K., TEN could have been caused by the combined effect of an infectious agent and drugs in polytherapy. The patient was hospitalized in the Cardiology Department of the Institute with IHD and unstable angina, and was treated with Niperten, Losap, Amlodipine, Acecardol, Atoris orally and intravenous infusions of polarizing mixture of glucose, magnesium. On the day 6, there was a rise in the body temperature to 38.8°C, on day 8-9 spotted skin eruption appeared, foci of necrolysis and detachment of the epidermis were noted. After consultation with an infectious diseases specialist and dermatologist, Lyell's syndrome was diagnosed, all scheduled drugs were cancelled, Prednisolone and Suprastin were indicated. On the day 11, the patient died with symptoms of persistent asystole. Upon autopsy, there were blisters and large superficial defects with the epidermal detachment on the back, buttocks, thighs area up to 50 cm in diameter (Fig. 1a). On the lower

limbs, the skin detached in the form of stockings and on the hands in the form of gloves (Fig. 1b). The area of exfoliated epidermis was 70% of body surface, and looked like a third-degree burn. Upon internal investigation of the heart, verrucous gray-pinkish coating on the mitral valve cusps of 1.5x2x0.3 cm was revealed. Cusps were thickened, deformated and calcificated, chords were thickened and shortened as well. The bacterioscopic test found polymorphic microflora: staphylococci, streptococci, pneumococci.

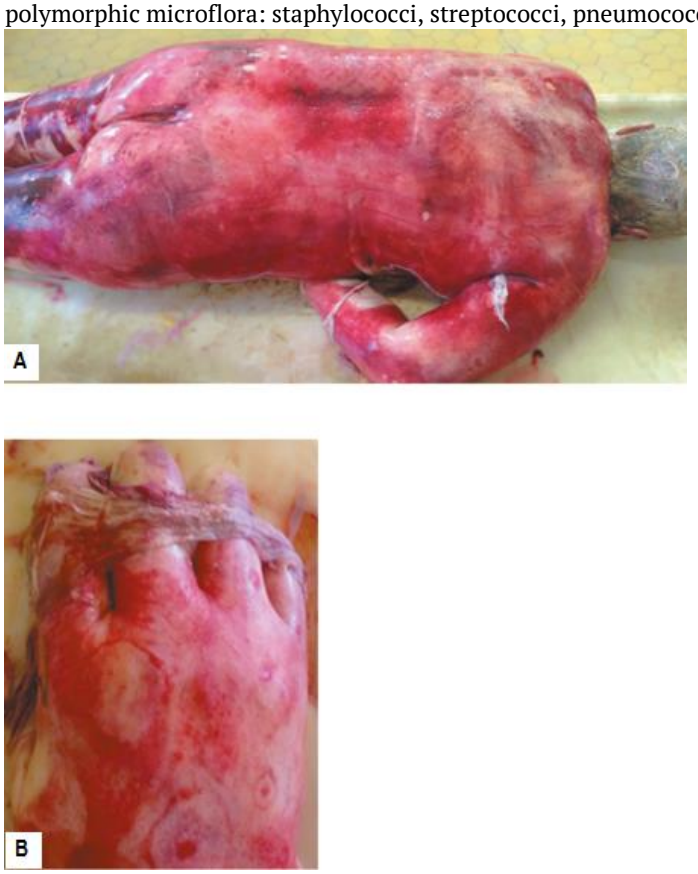

Fig. 1. Toxic epidermal necrolysis: mixed type, sepsis+polytherapy. *A* — erythematous-papular eruptions with blisters, 70%-lesion of the body surface; *B* — *hand gloves* epidermal detachment

In this case, two competing diseases were identified upon autopsy: 1) bacterial trombotic endocarditis on the background of rheumatic mitral valve complicated with septicopyemia, not clinically diagnosed, and 2) TEN with 70% of body surface area involved.

Histologic tests revealed massive colony of Gram+ cocci on the mitral valve cusps in the area of necrosis (Fig. 2a). In this study, signs of endotoxic shock were noted: empty cavities of the heart, liquid blood.

Morphological changes of the skin varied: from the typical TEN signs (blisters and necrolysis) to the presence of bacterial emboli in the lumen of blood vessels of the dermis and underlying tissue (Fig. 2b). Some blisters were intra dermal with splitting of stratified squamous epithelium layers and preservation of its basal parts (Fig. 2c). The most area of the affected skin had complete epithelial detachment with coagulation necrosis of the dermis and lymphohistiocytic infiltrates, detritus, sequestration of its parts with necrotized vessels and elements of cutaneous appendages (Fig. 2d).

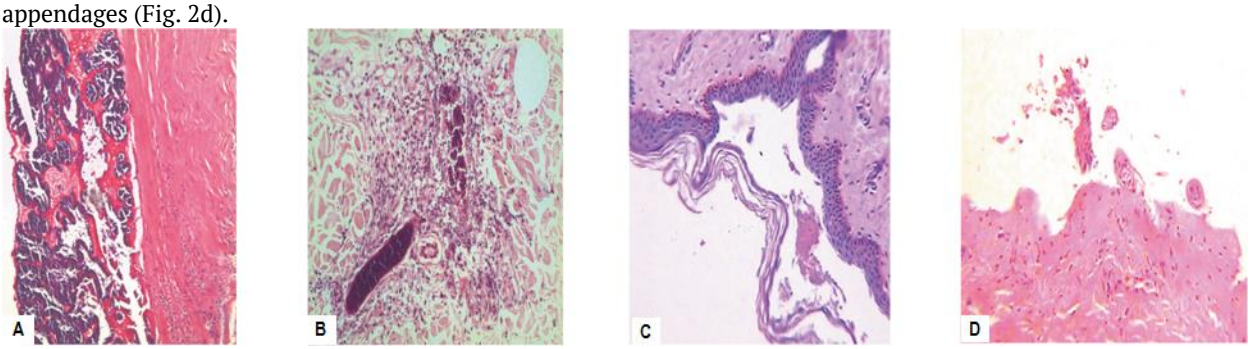

Fig. 2. A 66-year-old female patient K. Mixed type of toxic epidermal necrolysis. Hematoxylin-eosin stain, magnification x100. *A* — colonies of Staphylococcus aureus on the cusp of the mitral valve; *B* — bacterial embolus in the dermis; *C* — splitting of the epidermis with formation of intradermal blister; *D* — erosive surface of the skin in the area of epidermal detachment

Histologic examination revealed multiple bacterial emboli in a lumen of renal, myocardial, dermal, lineal, pia mater vessels and lienal pulp hyperplasia as well.

In all cases of percutaneous TEN, the skin lesions exceeded the initial area which contacted with an agent. A 55-year-old female patient had been doused with a chemical composition for whitewashing the ceiling in the scalp area 12 days prior to admission to the Institute. Reddish spots, erosive areas, blisters with cloudy hemorrhagic content and bleeding erosions of the tongue and oral mucosa appeared on the day 2 on the face, neck, trunk, front and back surfaces of thighs and upper limb. The patient was admitted to the burn intensive care unit in critical condition. Esophagogastroduodenoscopy was performed later on the same day and revealed bulbar duodenal ulcer with signs of recent bleeding, hemoglobin 154.0-73.0-93.0 g/l, hematocrit 41.6%-19.5%-26.8%. The condition progressively worsened. Resuscitation measures gave no effect, and 6.5 days later the patient died.

The external examination upon autopsy: dull and dirty-grey skin of the scalp, with macrolaminar peeling and areas of complete hair loss. The multiple sites with *parchment* skin of a dull, grayish and reddish color, devoid of the epidermal surface were revealed on the forehead, eyelids, upper lip, along naso-labial folds, in mental and sub-mandibular areas. The skin of the neck, chest (circularly), anterior and lateral walls of the abdomen, the lumbar region, throughout the left gluteal and inner quadrants of the right gluteal region had no epidermis, and were of brownish-red color, with membranous dirty-gray overlays. A similar type of changes was observed on both shoulders (circularly), forearms, the upper third of thighs, with clear boundaries of 0.5-6.0 cm in diameter, which alternated with areas of preserved epidermis. The preserved epidermis was dull, wrinkled, peeled off with blisters, had a transparent liquid content, was easily injured and detached upon examination as patches, exposing the pale pink surface. The lesion area was 50% of the body surface (Fig. 3a). Histologic examination of the skin revealed a wide range of injuries, from blistering and detachment of layers of squamous epithelium with fragments of hair on the head to necrosis of the epidermis, sharp congestion of dermal blood vessels with perivascular lymphocytic infiltration (Fig. 3b). The autopsy also revealed a chronic duodenal ulcer, histologic tests revealed fatty liver, perivascular cardiosclerosis, generalized acute cardiomyocyte damages.

In 2 patients who received burns contacting with cow-parsnip, the rash appeared 2 hours after the exposure. The next day, the skin lesion area significantly exceeded the contacted surface. The development of TEN occurred against the background of immunodeficiency.

A 55-year-old female patient with chronic alcohol intoxication, accidentially contacted cow-parsnip during a long heavy drinking. A 27-year-old male patient had an intravenous injection of heroin after a contact with cow-parsnip. The patient had been suffering with opioid addiction, HIV and hepatitis *C* virus for several years.

A distinctive feature of skin lesions in both observations was infected wounds and deep inflammatory infiltration of the dermis and subcutaneous adipose tissue (Fig. 3c). In the patients suffering from drug addiction, the bacteriological examination identified *Staphylococcus Aureus, Streptococcus Pyogenus,* and inflammatory infiltration involved the thigh muscles in the form of a phlegmon. The morphological study of autopsy material of the woman revealed fatty liver disease, cardiomyopathy, multiple sclerosis and lipomatosis of the pancreas, subdural hematoma, cysts in the cortex of the right temporal lobe. The morphological examination of the male patient revealed chronic active hepatitis, degenerative changes of cardiomyocytes, nephrocytes, atrophy of lymphoid follicles of the spleen, thrombosis of intra-alveolar and glomerular capillaries.

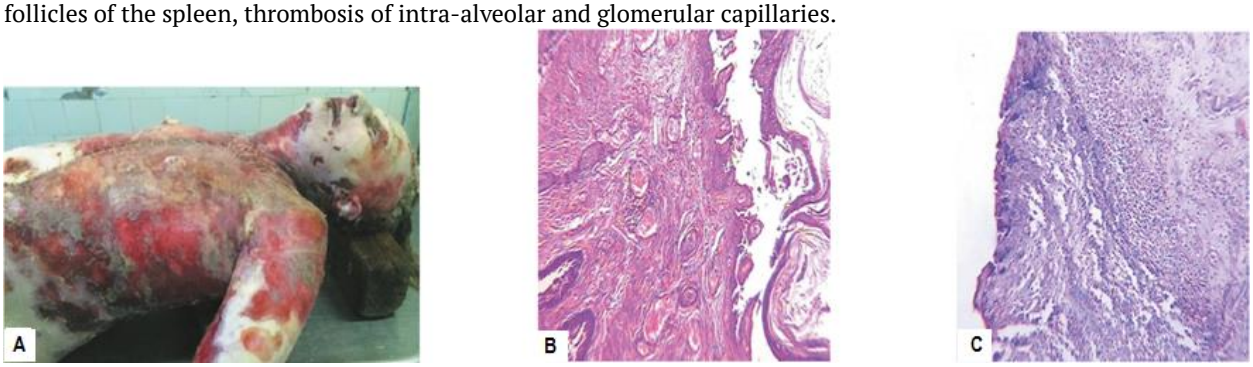

Fig. 3. Toxic epidermal necrolysis after percutaneous exposure to whitewash (a, b) and cow-parsnip. *A* — confluent erosions, 50% of the body surface area. *B* — detachment of the epidermis with fragments of hair on the head. Hematoxylin-eosin stain, magnification x100; *C* — inflammatory infiltration of the dermis, subcutaneous fat and underlying tissues after detachment of the epidermis. Hematoxylin-eosin stain, magnification x100

A 32-year-old patient I. And 33-year-old patient D., who had rubbed gray mercury ointment onto the skin of the pubic area, were transferred from regional hospitals to the Toxicology Department of the Institute in a serious condition with typical symptoms of mercury poisoning: lesions of the gastrointestinal tract such as stomatitis and colitis, nephropathy, encephalopathy. Dermatitis developed in the area of pubis, perineum, inner thighs within first 24 hours after the application of an ointment. Generalized skin rash appeared 2 weeks later and progressed after repeated application until the total ointment skin lesions in patient D., at low mercury concentration (0.20 mg/ml in the blood and 0.16-0 ml/mg in the urine) and its complete disappearance in the course of complex treatment, including antidotes and hemosorption. The mercury concentration in the urine of patient I. after complex treatment decreased from 3 mg/ml down to 0 mg/ml. But acute renal failure developed in the somatogenetic phase of exotoxicosis. Gross liver damage similar to toxic hepatitis was detected in both cases. The morphological study of

the skin revealed intradermal blisters with detachment of superficial dermal layers, occupying large areas of the body.

Expansion of skin lesions outside the areas of ointment application in these observations suggest the role of toxic-allergic component in the pathogenesis of TEN [11].

CONCLUSION

1. Causes of toxic epidermal necrolysis are different, including contact exposure to mercury ointments, whitening agents, cow-parsnip, but also oral medications for the treatment of acute or chronic diseases.

2. Specific morphological changes of the skin in toxic epidermal necrolysis, regardless of etiology, are erythematous-papular rash, blistering with the tendency to merge, detachment of the epidermis; progression of the disease, manifested as coagulation necrosis of the dermis with foci of its sequestration, colonization of polymorphic microflora with an inflammatory response in the dermis and underlying tissue.

3. We can not exclude the role of acute, chronic diseases and immunodeficiency in the development of toxic epidermal necrolysis.

REFERENCES

1. Tuzlukova E.B. Farmakoterapiya allergicheskikh zabolevaniy [Pharmacotherapy of allergic diseases]. In: Khaitov R.M., Il'ina N.I. *Allergologiya i immunologiya* [Allergy and immunology]. Ch. 3. Moscow: GEOTAR-Media Publ., 2014. 71–121. (In Russian).
2. Andreeva I.V., Stetsyuk O.U. Allergicheskaya reaktsiya na antibiotiki [Allergic reaction to antibiotics]. *Klinicheskaya farmakologiya i terapiya*. 2013; 2: 5–10. (In Russian).
3. Latysheva T.V., Myasnikova T.V. Urgentnye situatsii v dermatologii [Urgent situation in dermatology]. *Consilium medicum*. 2005; 3: 193–196. (In Russian).
4. Koryakov V.V., Gol'dfarb Yu.S. Ostrye otravleniya seroy rtutnoy maz'yu [Acute poisoning with grey mercury ointment]. *Anesteziologiya i reanimatologiya*. 1995; 3: 59–60. (In Russian).
5. Kutsyk R.V., Zuzuk B.M., Kurovets P.M. Lekarstvennye rasteniya i perspektivy antiallergicheskoy terapii (obzor literatury) [Medicinal plants and prospects of anti-allergic therapy (review of literature)]. *Provizor*. 1998; 8: 25–37. (In Russian).
6. Chebotarev V.V., Tamrazova O.B., Chebotareva M.V., Odinets A.V. Kontaktnye dermatity i toksikodermii [Contact dermatitis and toxicodermia]. In: V.V. Chebotarev, et al. *Dermatovenerologiya* [Dermatovenereology]. Ch. 10. Moscow: GEOTAR-Media Publ., 2013. 294–317. (In Russian).
7. Bastuji-Carin S., Rzany B., Stern R.S., et al. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch. Dermatol*. 1993; 129 (1): 92–96.
8. Pereira F.A.,Mudgil A.V.,Rosmarin D.M. Toxic epididermal necrolysis. J *Am Acad Dermatol*. 2007; 56 (2): 181–200.
9. Lissia M., Mulas P., Bulla A., Rubino C. Toxic epidermal necroolysis (Lyell' disease). *Burns*. 2010; 36 (2): 152–163.
10. Boyko Yu.I., Eremina A.F., Denisov V.E. Bolezn' Layella (Layla) kak sluchay skoropostizhnoy smerti v sudebno-meditsinskoy praktike [Lyell's disease as a case of sudden death in forensic practice]. *Aktual'nye voprosy sudebnoy meditsiny i ekspertnoy praktiki: sb. nauch. tr.* [Actual problems of forensic medicine and expert practice: collection of scientific works]. Novosibirsk, 2000. 5: 224–228. (In Russian).
11. Gol'dfarb Yu.S., Koryakov V.V., Luzhnikov E.A., Ostapenko Yu.N. Diagnostika, klinika i lechenie ostrykh otravleniy seroy rtutnoy maz'yu [Diagnosis, clinic and treatment of acute poisonings with grey mercury ointment]. *Toksikologicheskiy vestnik*. 1996; 2: 9–12. (In Russian).

Article received on 17 Dec, 2015

For correspondence:
Larisa Nikolayevna Zimina,
D. Med. Sci., Leading Researcher at the Department of Pathological Anatomy,
N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Healthcare Department
E-MAIL: JNMP@MAIL.RU