A NON-FATAL CASE OF LYELL SYNDROME

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ABSTRACT

Lyell syndrome îr òoxic epidermal necrolysis is a rare, severe a potentially life-threatening disorder, characterized by extensive epidermal loss, suggestive of severe scalding. The mortality associated with toxic epidermal necrolysis is in the neighborhood of 30%. Lyell syndrome most commonly is drug induced. However, other etiologies, including infection, malignancy, and vaccinations, may exist. The drugs incriminated in most cases of toxic epidermal necrolysis were the same in both groups (NSAIDs, antibacterials and anticonvulsants).

A non-fatal *case of Lyell's syndrome* is described, that have been managed in the Toxicology clinic and Burn Centre, MHATEM "N. I. Pirogov". 20-yr-old woman, suffering from fever, accompanied by laryngo-pharyngeal pain had been treated with Upsarin and Fervex. Her state worsened during the next days with the appearance of facial rash, which progressively extended to the extremities and trunk, with severe mucosal damage and bullous legions, a fever of 40° C, Intensive care was given together with parenteral feeding. Evolution was satisfactory with epidermization occurring in about 10 days. The patient remained in hospital for one month.

Conclusion Severe adverse drug reactions as toxic epidermal necrolysis are rare. Treatment of Lyell's syndrome includes prompt recognition and withdrawal of suspected drug and hospitalization.

INTRODUCTION

Lyell syndrome îr òoxic epidermal necrolysis is a rare, severe a potentially life-threatening disorder (1, 4). The incidence is between 0.4 and 1.2 cases per million each year. The mortality is in the neighborhood of 30% (11). Microscopically, TEN causes cell death throughout the epidermis. Keratinocytes, which are the cells found lower in the epidermis, specialize in holding the skin cells together, undergo necrosis (uncontrolled cell death). Lyell syndrome most commonly is drug induced. However, other etiologies, including infection, malignancy, and vaccinations, may exist. In 90 % of cases it is triggered by an immuno-allergic reaction to medication (7). The drugs incriminated in most cases of toxic epidermal necrolysis were the same in both groups - NSAIDs, antibacterials and anticonvulsants (6, 8). TEN affects many parts of the body, but it most severely affects the mucous membranes, such as the mouth, eyes, and vagina. The severe findings of TEN are often preceded by 1 to 2 weeks of fever. These symptoms may mimic those of a common upper respiratory tract infection. When the rash appears it may be over large and varied parts of the body, and it is usually warm and appears red. In hours, the skin becomes painful and the epidermis can be easily peeled away from the underlying dermis (1, 3, 4, 5).

A case of Lyell's syndrome or toxic epidermal necrolysis is described, that have been managed in the Toxicology clinic and Burn Centre, MHATEM "N. I. Pirogov".

Case report

20-yr-old woman, suffering from fever, accompanied by laryngo-pharyngeal pain had been treated with Upsarin and Fervex. Her state worsened during the next 2 days with the appearance of facial rash, which progressively extended to the extremities and trunk, with severe mucosal damage and bullous legions, a fever of 40°C, so she was hospitalized in the Toxicology clinic. The patient also has ophthalmologic lesions.

Skin examination: Cutaneous manifestations present as a generalized papular exanthem, purpuric macules, spreading to the entire body and becoming confluent, bullae, erosions. The epidermis easily separates from its underlying surface leaving a characteristic moist, denuded dermis - positive Nikolsky sign.

The oral, ophthalmic, mucosae were affected. Involvement of the oral mucosa results in edema and erythema, blistering. Ruptured blisters form extensive hemorrhagic erosions with grayish white pseudomembranes. Hemorrhagic crusting of the lips was finding.

Ocular involvement - mild inflammation, conjunctival erosion.

Vital signs were temperature – 40°C., pulse 69 beats/ minute; respiratory rate 16 breaths/minute; blood pressure 110 / 60 mm Hg; Lungs had clear breath sounds. Heart sounds were clear with no murmur, rub, or gallop. Abdomen was soft, no guarding or rebound. No hepatosplenomegaly was noted. Extremities had bullous legions. No abnormality were detected on chest X – ray and electrocardiogram studies.

Laboratory data: ***Hematology studies*** (CBC and differential - Íb 135; 130; 103

Hct 0.39; 0,37; Leuc 7,3; 8,6; 4,2 ; St 26 Seg 79; Eî 1;

Bà 4; Ly 16; *platelets* – 200 x 109/l. ***Chemistry:*** BUN, creatinine, electrolytes, total bilirubin, blood glucose tests were unremarkable; total protein – 49g/l, albumin - 31g/l; Liver enzyme tests: ÀLÒ - 58U/l; ***Coagulation studies*** – *unremarkable.* ***Microbiology:***

Skin swabs contained Staphylococcus aureus, Proteus mirabilis, control skin swabs – steril; Rhino-pharyngeal - Staphylococcus aureus, K. Pneumoniae, Candida albicans(+); blood culture – steril; uroculture – steril. On tabl. 1 and 2 are presented the results from the assessment of the humoral and cell mediated immunity of the patient.

Tabl.1 Humoral immunity

Ig	Result (g/l)	*Reference* (g/l)
IgA	0,54	0,70 -3.50
IgG	7.42	7,00 – 16,00
IgM	1,07	Ì. 0,40 – 2,30 F. 0,46 - 2,36

Tabl. 2 Cellular immunity

Population	Phenotype	Result % ly	Result Abs. N	*Reference* % ly	*Reference* Abs. N
T ly	CD3+	53%	1,5	59,4-84,6	1,2
CD3+/CD4+	CD3+/4+	26%	0,8	29,0-59,0	0,7
CD3+/CD8+	CD3+/8+	26%	0,8	19,0-48,0	0,4
Ratio	CD4+/CD8+	1,0		1,9	
NK cell	CD16/56+	34%	1,0	5,6-30,9	0,2
B ly	CD19+	8%	0,2	6,4-22,6	0,2

The management protocol consists of:

· monitoring of various parameters used in burn patients: pulse rate, arterial pressure, body temperature, percentage of oxygen-haemoglobin saturation, urine output, etc.

· laboratory tests to cheek fluid requirements

· periodic surface cultures of the regions affected and blood cultures if there is fever above 38.5.

· management of the patient on an air-fluidized bed in order to avoid decubitus ulcers and to obtain an adequate temperature and humidity state

Treatment of the condition has three primary goals:

· haemodynamic stability

· pain management

· infection control policy

Intensive care was given together with parenteral feeding, local care. Treatment consisted of fluid infusion, H1 and H2 blockers, corticostetroids, antibiotic (Klacid), local treatment, plasma, intravenous immunoglobulin, symptomatic therapy.

Evolution was satisfactory with epidermization occurring in about 10 days. The patient remained in hospital for one month. A plastic surgeon is consulted to débride areas of skin necrosis.

DISCUSSION

Toxic epidermal necrolysis is mainly a severe mucocutaneous exfoliative reaction that requires systemic treatment along with several topical measures.

Lyell's syndrome was for many years attributed to particularly slow acetylating genotypes, leading to the accumulation of toxic metabolites or to immunoallergic mechanisms involving reactive metabolites behaving as highly immunogenic haptenes. Multiple pathophysiologic mechanisms have been proposed, although an immune-complex mediated phenomenon is likely responsible.

One accepted theory suggests that accumulation of drug metabolites in the epidermis of genetically predisposed individuals induces an immunologic process analogous to that which occurs in graft-versus-host disease. $CD8^+$ T lymphocytes and macrophages activate an inflammatory cascade, leading to widespread apoptosis of epidermal cells. At present, several studies (2, 8, 10, 12) point to the role of T lymphocytes directly reacting with the molecule and triggering the synthesis of cytokines, leading to the apoptosis of the keratinocytes and to epidermal necrolysis.

Explanations for the generalized nature of toxic epidermal necrolysis include the belief that overexpression of tumor necrosis factor-alfa (TNF-alfa) in the epidermis occurs. Therefore, TNF- alfa is likely to play an important role in epidermal destruction directly through apoptosis,

indirectly through stimulating cytotoxic T lymphocytes, or both. Moreover, it is known that particular profiles favor the occurrence of Lyell's syndrome, without the precise mechanism being known. These include HIV infection, disseminated erythematous lupus, radiotherapy, bone marrow allograft (11). However, no such factor was found in our patient.

In our case, the severity of infection, the presence of micro organisms as Staphylococcus aureus, Proteus mirabilis, K. Pneumoniae, as well as Candida albicans, suppose adverse immunological state.

The results show decrease level of IgA antibodies, which have important role in protection of mucose membrane. The low level of IgG antibodies, in which class were a part of protein antibacterial antibodies, correlate with low level of CD4 T lymphocyte and explain the severity state of patient.

CONCLUSION

Lyell's syndrome is a severe disease with a high mortality rate in which systemic treatment, along with meticulous cutaneous management, is essential.

Treatment of these severe skin adverse drug reactions includes prompt recognition and withdrawal of suspected drugs and hospitalization.

Cutaneous isolation measures, control of infection, and the management of cutaneous coverage improve the symptoms and facilitate evolution of the injuries towards epithelialization. Mucosal hygienic measures are of fundamental importance to increase the patient's comfort and to prevent the appearance of complications.

After recovery, patients should be advised to avoid not only the suspect drug(s), but also chemically related compounds.

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