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## CASE STUDY

# LYELL, A LETHAL SYNDROME

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**ABSTRACT**

The Lyell Syndrome is a severe toxicodermy, rare, characterized by fever, cutaneous necrosis, and epidermal desquamation in over 30% of the body, including mucositis. It is a late anaphylactic reaction caused mainly by pharmacies. The authors present a case of a woman, aged 22, VIH positive at A1 stage, medicated during 5 days, the 15 days before admission, with carbamazepine (CMZ) for a trigeminal neuralgia, admitted to the emergency room (ER) with fever (40ºc) and a generalized cutaneous rash including hand palm, oral, genital and eye mucous membranes. Blood cultures and serology were negative. The rash kept evaluating despite the beginning of corticotherapy, with the appearance of skin detachment, Nikolsky sign and uncontrolled pain. At the 5th day of admission, the patient entered in Toxic Shock, with multiorgan dysfunction, and was transferred to a Burn Unit (IBU), where she died with a septic shock caused by Acinetobacter baumanni bactaeriemia.



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## INTRODUCTION

Toxic epidermal necrolysis (TEN), or Lyell Syndrome, is a severe mucocutaneous reaction, which is associated with high mortality. Is mainly caused by medications, such as sulphonamides, anticonvulsants, beta-lactam antibiotics and nonsteroid anti-inflammatory. Although its physiopathology is yet uncertain, it involves a T-Cell activation often triggered by a culprit drug, leading to general keratinocyte apoptosis, and there is an association with the genes encoding human leukocyte antigens (HLA-B*15:02, and HLA-A*31:01). The incidence and mortality in HIV + patients is increased. The authors present a severe case of a Carbamazepine-induced TEN, with the objective to alert practitioners for the possibility of TEN when they´re prescribing pharmacies, especially in HIV patients, that seem more exposed to this kind of reaction and configures worse prognosis.

### Case Presentation

A Woman, 22 years old, HIV + at the A1 stage, admitted to the emergency room (ER) with fever, fatigue, and a painful generalized itching erythema with oral, genital and ocular mucosa affection with 24hrs evolution (Figure 1). Before 14 days of admission, she was admitted to ER with a trigeminal neuralgia, and discharged home with Carbamazepine. Despite the pain improvement, she stopped by herself the medication on the 5th day because of nausea and vomiting which she associated to the anticonvulsant.This rash began with purpuric maculae in the legs (Figure 2) and progressed thru the trunk (Figure 3), arms (Figure 4), palm hands, and head. There was also ocular hyperemia and oral mucosa involvement with painful hemorrhagic crusting of the lips and mucosal erosions, associated with ocular and facial edema (Figure 1). Blistering vesicles were also present in the arms (Figure 4) and at the chest (Figure 3). She presented blood pressure 92/50 mmHg, respiratory rate 20 cpm, cardiac frequency 120 bpm and high fever (auricular temperature - 40,3ºc), with pulse oximetry revealed oxygen saturation 99%. The rest of the physical exam was unremarkable. At 3rd day, she began systemic corticotherapy, stopped fever, but still progressed the generalized erythema to the exfoliation of more than 30% body surface, and uncontrolled pain. At the 5th day, she progressed to a total desquamation (Figure 5) with Nikolsky positive sign (figure 6) and toxic shock, with posterior admission in a burn intensive care unit. She died from a septic shock by Acinetobacter baumanni bacteraemia on the 14th day.

### Investigations

**The laboratory exams:**

- Hemoglobin - 13.2 g/dL; Plaquets- 166000 /uL; Leukocites – 9980/uL
- Proteín C-Reactive - 1.92 mg/dL
- Renal function unremarkable.
- Thorax X-ray: unremarkable
- Blood and urine cultures (admission): negative
- Rickettsias serology: negative
- Herpes varicella zoster: negative

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- Syphilis: negative
- Blood and urine cultures (Burn Unit Admission): *Acinetobacter baumannii*

## Treatment

The causative agent, Carbamazepine, was suspended by the patient.Treatment consisted of fluid infusion, systemic steroids, antibiotics (Ceftriaxone) and pain management. Infection control measures with sterile handling and reverse-isolation procedures, daily dressings and repeated cultures of the skin, as well as blood and urine, were performed. Ocular and conjunctiva disorders were managed with extensive lubrication of the eyes and local antibiotics. Oral ulcers were treated by applying local sucralfate.

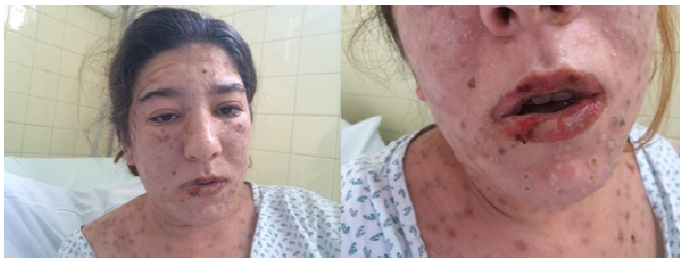

**Figure 1. Facial maculopapular rash affecting oral mucosa with crusting lesions with orbitaledema**

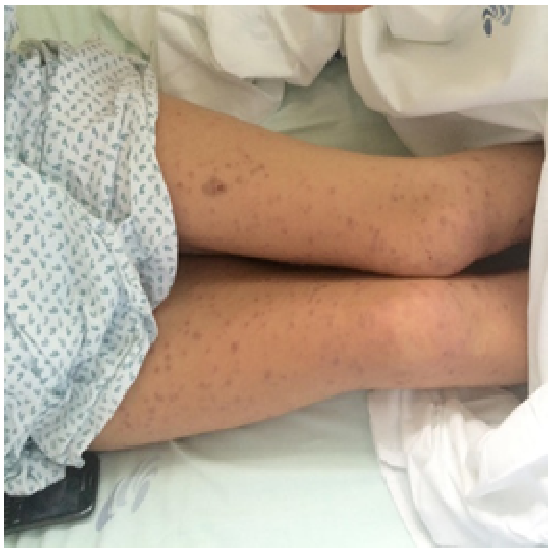

**Figure 2. Maculopapular lesions spreading throughout the legs**

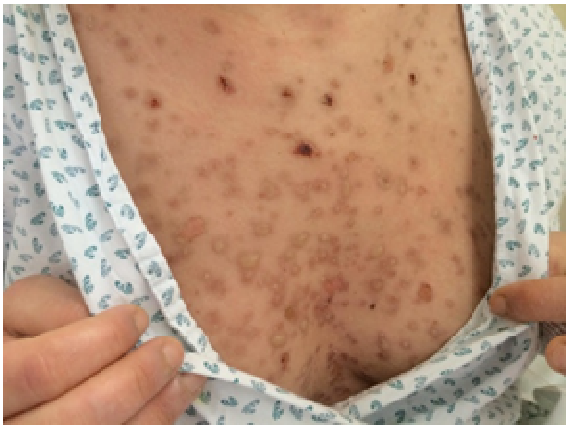

**Figure 3. Progression of the macular-papular rash throw the trunk with crusting lesions**

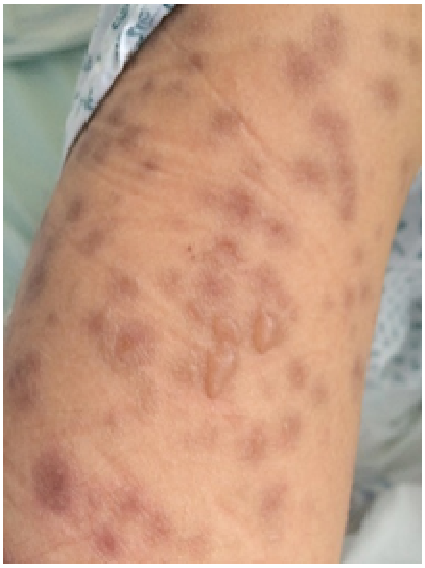

**Figure 4. Maculopapular rash with bullae in the arm, is a frequent cutaneous finding in TEN**

**Figure 5. Total desquamation with areas of epidermis denuded**

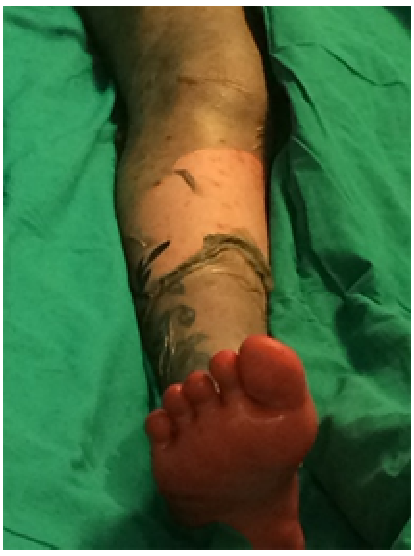

**Figure 6. Positive Nikolsky sign in the leg with epidermis detachment**

**Table 1. SCORTEN severity of illness scale**

| Independent Prognosis factors | | Weight |
|---|---|---|
| Age | ≥ 40 | 1 |
| Malignancy | Yes | 1 |
| Body surface area detached | ≥ 10% | 1* |
| Tachycardia | ≥ 120 /min | 1* |
| Serum Urea | >10 mmol/L | 1* |
| Serum glucose | >14 mmol/L | 1 |
| Serum bicarbonate | < 20 mmol/L | 1* |
| SCORTEN | | 7 |

*present on our patient at day 3

**Table 2. Mortality rate according to SCORTEN score**

| SCORTEN Score | Mortality rate |
|---|---|
| 0-1 | 3% |
| 2 | 12% |
| 3 | 35% |
| 4 | 58% |
| ≥5 | 90% |

## DISCUSSION

Stevens-Johnson Syndrome or TENis a severe mucocutaneous reaction, most commonly triggered by medications. Although their triggers and pathophysiology may be the same, the severity of the body surface may distinguish both, considering STS in cases with less than 10 % of the body, SJS/TEN with 10-30%, and TEN when more than 30% of skin detachment is noted. Normally, the syndrome occurs within 1 to 3 weeks after drug exposure, and there are some medications strongly associated, as Allopurinol, Carbamazepine, Phenobarbital, Sulfonamides, Nevirapine, or Phenytoin and NSAIDS. TEN is more severe and therefore less frequent than SJS, more common in women, and 100 times more frequent among HIV patients, than in general population. (Mittmann *et al*., 2012) This disparity has been associated with a decrease in the number of skin-directed CD4(+) CD25 (+) cells and an increase in the ratio of CD8(+) to CD4(+) cells in TEN lesions in the HIV patients. (Yang *et al*., 2014) Carbamazepine cutaneous adverse reactions are known to be present in approximately 5-10% of the patients, (Pratt *et al*., 2012-2017) and there are genetic factors as certain HLA types, associated with increased risk of TEN, as HLA-B*15:02, who is strongly associated with high risk of TEN, which explains the 10 times higher risk in areas where this mutation is frequent, as in Southeast Asia. Other alleles, such as HLA-A*31.01, HLA-B*1511 were recently described as a risk factor, as well as some polymorphisms, but their role is still uncertain. (Wang *et al*., 2017) According to the FDA (Food and Drug Administration) and the CPNDS (Canadian Pharmacogenomics Network for Drug Safety), genetic testing for positive HLA-B*15:02 mutation should be done in all naive patients before taking carbamazepine, although the recommendation level is A for those who belong to frequent HLA-B*15:02 mutations and C, intended as optional, for those patients originating for patients with rare cases of HLA-B*15:02 mutations – as the reported case.

Its physical presentation generally starts like in this case, with a prodrome of high fever, and a skin rash with coalescing erythematous macules with purpuric centres. Skin is tender to touch and often painful, and lesions progress to vesicles and bullae formation and the skin begins to slough within days. Nikolsky sign often appears within few days after the beginning of the symptoms. Mucosal lesions are typical, not just oral but also ocular and vaginal lesions are common. There is a severity of illness score that predicts the in-hospital mortality called SCORTEN (Table 1) (Fouchard *et al*., 2000; Micheletti and Noe, 2017), and in our case reported, the patient presented a SCORTEN of 0 at day 1, and a SCORTEN of 4 at day 3, which means a 58% of mortality rate (Table 2). Although TEN is more common in HIV patients, HIV is not included in the SCORTEN, so, not considered as a mortality predictor factor. In this case, despite the multidisciplinary medical team, involvingophthalmology, dermatology, plastic and reconstructive surgery, internal medicine and urology, the progression of the disease was explosive. Although the stoppage of the culprit medication before diagnosis, supportive care was taken since admission (Schneider and Cohen, 2017), corticosteroids trial (prednisolone 1 mg/Kg/day) initiated (Gupta *et al*., 2016), the patient died of the most common associated complication, septic shock caused by an Acinetobacter baumanii bactaeremia. According to Knight *et al*. (2014) it seems to be a higher mortality in HIV patients with TEN or SJS, but this study was performed in Africa with HIV patients in more advanced stages of disease, with HIV comorbidities such as tuberculosis, and low CD4 count (median of 137 cells/$mm^3$) which was not the case of our patient. The gram-negativebactaeremia where more frequent within the infections, as we`ve seen in our case, and there seemed to be an association between gram-negative skin infections and bacterial systemic infections, which might be the starting point of our patient´s bactaeremia. This is why the patient must be at an appropriate level of care, in a sterile environment (burn unit recommended). There´s still no specific treatment besides supportive measures in patients with TEN and corticosteroids benefits are stillquestionable (Law and Leung, 2014). Some specific treatments seem to be beneficial as IVIG (human immunoglobulins), but more studies are required. (Ye *et al*., 2016; Creamer *et al*., 2016) There are some promising treatments including Cyclosporine A, plasmapheresis or biological therapies, but data is insufficient (Han *et al*., 2017).

### Conclusion

HIV patients are more susceptible of TEN, and precaution on prescribing drugs associated with this syndrome should be taken. An HLA-B*15:02 testing should be considered in these patients in case of using carbamazepine. SCORTEN is a mortality predictor score, although does not include HIV as a mortality factor. The real impact and the relation between HIV and TEN is yet a challenge.

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