

# Toxic epidermal necrolysis and Steven-Johnson syndrome in oncologic patients

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**Abstract. – Background and Objectives:** We reviewed our case-load of patients with Toxic Epidermal Necrolysis (TEN) and analysed this oncologic disease in order to define the prevalence of this comorbidity and find eventual clinical and prognostic differences, specific of this subgroup of patients.

**Materials and Methods:** We reviewed charts from January 1995 to December 2005. Only those patients with a TEN diagnosis proved with an histologic examination were included. Causative drugs, symptoms, management and outcome were recorded and analysed.

**Results:** We found 32 patients with TEN and 9 of them (28%) had also cancer. The comparison among oncologic vs. the rest of patients showed no significant differences in age, delay of referral, % surface area epidermal detachment, blood chemistry, immunoglobulins therapy and bacterial isolation of species throughout the recovery ( $p > 0.05$ ).

**Conclusions:** Oncologic diseases were the most frequent comorbidities in our series. There were no differences in the length of stay, duration of disease or mortality between patients with and without cancer. However, due to the small number of patients, future larger prospective studies are necessary to confirm these findings.

## Key Words:

Toxic epidermal necrolysis, Lyell syndrome, Steven Johnson syndrome, Drug reactions.

## Introduction

Toxic epidermal necrolysis (TEN), also called Lyell syndrome, is a complex and rare disease (incidence estimated in 0.4-1.2 cases/million of

citizens/year) that affects both skin and mucosal surfaces. Although progress has been made in the comprehension of cellular and molecular mechanisms underlying pathophysiology, mortality remains severely high involving 30-49% of affected patients<sup>1-3</sup>.

We retrospectively reviewed, at the turn of the 11<sup>th</sup> year of activity, our case-load in the management of this disease at the S. Eugenio Burn Centre of Rome, Italy. We noticed that the most frequent comorbid condition was cancer. For this reason we analysed data in order to assess the prevalence of this comorbidity in our series and find eventual clinical or prognostic differences of oncologic TEN patients with those non oncologic.

## Materials and Methods

We retrospectively reviewed medical charts and computer database of admitted patients at the Burn Centre of S. Eugenio Hospital in Rome, Italy, from January 1995 to December 2005. We included in this study all patients that, after an initial clinical suspicion (wide epidermal-mucosal detached areas following a drug exposure, positive Nikolsky sign), received an histologic diagnosis of TEN (full thickness epidermal necrosis with dermo-epidermal detachment). We excluded all burned patients, those with postinfective exfoliative skin conditions, bullous disease of other origins, clinical and not histologic diagnosis of TEN or patients with uncertain histology.

We recorded patients' demographics, delay of referral, comorbid conditions, precipitating event (event that led to drugs administration), clinical and haematological parameters (fever,

Total Body Surface Area (TBSA) of detached skin at first visit, white blood cells, haemoglobin, platelets, blood urea nitrogen, creatinine, sodium, potassium, transaminases), bacterial isolation throughout the hospitalization (wounds, blood and other sites), immunoglobulin treatment, length of hospitalization and outcome (death). Drug/s involved were determined from patient's or parents' history considering all those administered during the previous 8 weeks before symptoms appearance (risk period for TEN insurgence). Cutaneous or systemic infections were diagnosed on the basis of clinical parameters (pus discharge, fever) and laboratory analyses (leukocytosis, cultures). We used a high supportive fluid overload (with a urine output of 1ml/kg/hour)<sup>4</sup>. Non steroidal antiinflammatory drugs (NSAID's) were used as analgesics only when not administered before TEN and were not suspected of having caused TEN.

### Statistical Analysis

All data analysis were performed using the Statistical Package for the Social Sciences Windows version 13.0 (SPSS, Chicago, Illinois, USA). Descriptive statistics used for continuous variables, after confirmation of normal distribution (histograms, Q-Q plots, Skewness and Kurtosis, Kolmogorov/Smirnov and Shapiro Wilk testings), were mean and standard deviation. Student's t test was used to compare continuous variables among groups after confirmation of normally distribution of data. Descriptive statistics used for discrete variables consisted in frequencies report. Chi-Square test was used to compare discrete variables among groups. Fisher's exact test was used with discrete data and

“small frequencies” observed in cells. All *p* values were considered significant if inferior to 0.05.

## Results

We treated 35 patients with an initial clinical diagnosis of TEN (based only on symptoms and signs). Thirty-two of them received also an histologic confirmation and were included in this study. Initial care was usually administered at peripheral hospitals or from general practitioners and all patients were referred to our centre for the progressive worsening of the cutaneous or systemic situation.

There were 21 women (65.6% of patients) and 11 men (34.4%). Mean age at diagnosis was 44.8 years (standard deviation 20.23, range 4-94). The most frequent drugs administered at the time of TEN appearance were antibiotics (13 patients, 40.6%, including also antiparasitic and antihelminthic drugs) followed by anticonvulsants (10 patients, 31.3%) and nonsteroidal antinflammatory drugs (5 patients, 15.6%).

Neoplastic diseases were the most frequent comorbid conditions (9 patients, 28.1%), followed by infections (5 patients, 15.6%) and surgery performed in the week preceding TEN onset (4 patients, 12.6%) (Table I). The most frequent types of cancer were brain tumors (5 patients), followed by non-Hodgkin lymphoma (2 patients), mesothelioma, Kaposi's sarcoma. Their clinical characteristics are reported in Table II while complete descriptive statistics of oncologic patients vs. all the others are summarized in Table III. No differences in the hospital use of antibiot-

**Table I.** Comorbidities present at TEN appearance.

Comorbidity	Number of patients affected by the comorbidity	Percentage (%) of patients affected by the comorbidity
Infection	5	15.6
Surgery	4	12.5
Stroke	3	9.4
Flu or muscular pain	3	9.4
Renal failure	2	6.3
Sun burn	2	6.3
Viral hepatitis	2	6.3
SLE	2	6.3
Epilepsy	1	3.1
Tumor	9	28.1

**Table II.** Demographics and clinical characteristics of oncologic patients. “Drug 1” is referred to the newly introduced drug, “drug 2” to those already assumed.

Patient no.	Year	Sex	Age	Burn centre delay of referral (days)	Event that led to drug administration	Probably involved drug	Drugs administered in the 8 weeks preceding	TBSA	Duration of fever (days)	Wound culture	Blood culture	Other	Length of hospitalization (days)	Dead (D) or Alive (A)
1.	1996	F	49	4	Postoperative Gram- brain abscess meningioma	Cefamandole	Carbamazepine Phenobarbital	15	11	-	Acinetobacter Baumannii Staph. Aureus	Acinetobacter Baumannii E. Coli (liquor)	9	D
2.	1997	F	69	15	Brain astrocytoma	Phenobarbital	-	65	4	-	-	-	7	A
3.	1998	F	66	5	Pneumonia Pleural mesothelioma	Ceftriaxone	Epidoxonibicin Interferon Bromazepam	90	0	Staph. Aureus Staph. Coag.- Strep. Viridans	Staph. Aureus	-	17	A
4.	1998	F	27	5	Post-transplant chronic renal failure Kaposi's sarcoma	Meropenem	-	21	5	Enterococcus Faecalis	Staph. Coag.-	-	7	A
5.	1998	F	44	5	Glioblastoma	-	-	80	10	Kl. Pneumoniae	Pseud. Aeruginosa Enterobacter Aerogenes Enterococcus Faecalis	Pseud. Aeruginosa (mouth)	30	A
6.	1999	M	55	5	HIV + Non-Hodgkin lymphoma	Fluconazole, Acyclovir, Trimethoprim/ Sulfa- methoxazole, Allopurinol	-	100	19	Staph. Aureus, Acinetobacter Baumannii, Staph. Coag	Staph. Aureus, Acinetobacter Baumannii, Staph. Coag	Staph. Aureus, Acinetobacter Baumannii, Pseud. Aeruginosa (central venous catheter)	19	A
7.	1999	F	54	7	Cutaneous mycosis Non-Hodgkin lymphoma	Fluconazole	-	100	2	Staph. Aureus Pseud. Aeruginosa	Staph. Aureus Pseud. Aeruginosa Acinetobacter Baumannii Staph. Coag.- Pseud. Fluorescens	Staph. Coag.- (pleural essudate)	9	D
8.	2000	M	58	8	Brain astrocytoma	Phenobarbital	Ciprofloxacin Vancomycin	44	17	Staph. Aureus	Staph. Aureus	-	32	A
9.	2003	M	62	8	Brain astrocytoma	Setraline	-	22	8	Staph. Coag.-	-	-	19	A

**Table III.** Statistical analysis of differences between oncologic patients and the others. Continuous variables are expressed as mean  $\pm$  SD. Nominal variables are expressed with frequencies. 1: Student's t test. 2: Fisher's test. 3: Chi-Square test.

	Oncologic (n = 9)	Others (n = 23)	p
Age	53.7 $\pm$ 12.9	41.3 $\pm$ 22.2	NS 1
Sex (M)	3/9 (33.3%)	9/23 (39%)	NS 2
Delay of referral	6.9 $\pm$ 4.3	11 $\pm$ 12.5	NS 1
Number of drugs already on board when TEN started	1.5 $\pm$ 1	1.22 $\pm$ 0.75	NS 1
TBSA (%)	60 $\pm$ 33	63.6 $\pm$ 34.2	NS 1
Presence of fever at hospitalization	8/9 (88.9%)	14/23 (60.9%)	NS 3
Duration of fever	9.5 $\pm$ 6	5.9 $\pm$ 9	NS 1
IgV's therapy	6/9 (66.6%)	13/23 (56.5%)	NS 3
Wound culture positive	7/9 (77.7%)	17/23 (74%)	NS 3
Sepsis	7/9 (77.7%)	11/23 (47.8%)	NS 3
Length of hospitalization	16.5 $\pm$ 9	16.8 $\pm$ 9.4	NS 1
Duration of disease	24 $\pm$ 9	27.7 $\pm$ 13.3	NS 1
Death	2/9 (22%)	9/23 (39%)	NS 2

ic or NSAIDs were observed among the 2 groups. Overall mortality was 34% (11/32 patients).

### Subgroups Statistical Analysis

We compared the oncologic group (n = 9) with all other patients (n = 23) in order to find clinical and outcome differences. The analysis of groups regarded sex, age, delay for referral to our centre since symptoms appearance, TBSA, blood chemistry parameters, intravenous immunoglobulins or other pharmacological therapies, the microbiological isolation of bacteria from patients' wounds or blood throughout the hospitalization and complications during hospitalization. All these characteristics did not show significant differences (Table III). Steven-Johnson Syndrome (SJS, defined as less than 10% of TBSA) was not present in the oncologic group; the undetermined SJS-TEN overlap form (from 10 to 30% of TBSA) only in 3 patients (3/9; 33.3%) (5). In the other group (non oncologic) there was one case of SJS (1/23; 4.34%) and 4 cases of SJS-TEN overlap (4/23; 17.4%).

There were 2 deaths in the oncologic group (2/9; 22.2%) and 9 in the other (9/23; 39%). No statistical differences were observed in the death rate among groups (Table III).

## Discussion

Toxic epidermal necrolysis (also called Lyell syndrome) is a rare and severe adverse drug-induced skin/mucosal disease. To the best of our

knowledge, although many studies described cancer patients with TEN, all of them were case reports or small series and none conducted a systematic focused review. In our centre a high proportion of TEN patients were oncologic and we decided to retrospectively analyse our charts in order to describe their incidence and find specific clinical and prognostic differences with the rest of patients.

We admitted 32 patients affected by TEN and SJS over an 11-years period. All of them were previously treated in other hospitals, and delay of referral has been as high as 30 days. The analysis of comorbidities present at admission revealed that oncologic patients were 9 out of 32 patients (28%). Cancer was the most frequent comorbidity present at admission. Brain cancers accounted for 50% of tumors while hematologic malignancies for 22% (2 lymphomas). All patients in general received several drugs possibly involved in TEN pathogenesis (antibiotics, gout-preventing drugs, non steroidal anti-inflammatory drugs) (Table II). The analysis confirmed 2 of the pathogenetic mechanisms of TEN in oncologic patients: 5 patients developed TEN after antibiotics and anti-fungals given for infections (both cure or prophylaxis) and 3 brain cancer patients after anticonvulsants to prevent epileptic crisis. We ascribe the high prevalence of cancers in TEN patients to the peculiarity of their status, often requiring multi-drug regimens for disease control and for its complications. However, it cannot be excluded that their specific condition can alter the immune system and produce reac-

tions to drugs different than the normal population, including TEN.

The analysis of the oncologic subgroup and the comparison with the remaining patients found no significant differences of clinical parameters. Antibiotics, anticonvulsants and non-steroidal anti-inflammatory drugs, all of them massively used by oncologic patients and common causes of TEN pathogenesis<sup>5-10</sup>, were commonly encountered in our review. Additionally, our observations showed that no statistical differences were present in drugs responsible of TEN pathogenesis among groups. We recorded in our centre an overall high mortality rate (11/32; 34% of all patients) similar to that reported by literature data<sup>1-3,11-14</sup>. Mortality in oncologic patients was 22% (2/9), different from the others (9/23; 39%). The time to transfer for patients to our burn centre for definitive care was high (up to 30 days) and it is fairly well established that patients with these types of diseases have a better prognosis when treated as soon as possible at specialized centers (prolonged treatment at non-specialized centers could confound the analysis of malignancy on outcome). However, such delay involved all patients and not only the oncologic subgroup and, additionally, in most cases it was derived from the difficulty in recognizing TEN and not from severe complications in disease course that could increase the risk for an adverse outcome.

This article is referred first of all to acute caregivers (i.e. burn surgeons). Since results showed no differences between subgroups of TEN patients, we believe that they should be managed similarly and with comparable aggressiveness and not to let the cancer diagnosis affect treatment decisions. Furthermore, it also refers to ordinary caregivers (oncologists). Every oncologist, in fact, should remember the high risk of TEN present in their patient when administering ordinary drugs (antibiotics, NSAIDs, antiepileptics). TEN usually derives in oncologic patients from 3 pathogenetic mechanisms: i) specific reactions to chemotherapy<sup>6-9</sup>, ii) anticonvulsants (given for epilepsy prevention in brain cancer patients or those irradiated)<sup>8-9</sup> and iii) antibiotics (given for concomitant infections due to immunosuppression)<sup>10</sup>. These different mechanisms suggest that the oncologist must be aware, in his clinical practice, of this particular syndrome and should be able to make a correct diagnosis for a prompt referral to appropriate centers.

Our study has even some weaknesses. First of all, being a retrospective analysis, we were

forced to report differences in treatment (as for nutrition or immunoglobulins therapies) or we lacked important clinical data (i.e. tumor staging). Second, we also included in our analysis patients with SJS and SJS/TEN overlapped forms. We did this because the pathophysiologic mechanisms of SJS are the same of TEN and SJS patients were useful to calculate the incidence of cancer in patients hospitalized for severe cutaneous drug reactions. However, it is clear that the pathophysiologic effects of SJS on the organism are different from those of TEN and this could alter the analysis of patients' outcome. Third, due to emergency secondary recovery in our burn centre from other institutions, cancer staging/grading was not present in our medical charts. The lack of survival difference could have easily been due to patients with low-grade/low stage tumors. Finally, the small sample size limits any broad conclusions or recommendations. TEN is a rare disease and standardized prospective multicentric studies would work better in these cases than retrospective small. A multicentric large retrospective study found that pre-morbid malignancy was significantly associated with mortality at the univariate level, however still approached but did not reach significance in the multivariate logistic regression analysis<sup>15</sup>. Maybe we can speculate that in that work the multivariate analysis uncovered influences of other clinical variables on the relationship between cancer and survival that could not be shown from the univariate analysis. In other words, this could suggest that the effect of cancer on mortality is more complex than it simply appears at the univariate analysis and other variables indirectly influence it. For this reason our study, with a smaller sample size, did not find significant differences on mortality between the subgroups of patients and we believe that future prospective and specific studies are necessary to address these findings.

In conclusion, although much has been discovered about the etiology and pathogenesis of toxic epidermal necrolysis and new treatments have become available during the last years, mortality is still high among these patients. The analysis of our results suggest that cancer would give no worse prognosis to TEN patients, leaving most of the mortality to the disease and its short-term consequences (shock, infections). However this study is underpowered to prove differences between groups and future larger prospective works are required to address this issue.

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