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Pulmonary complications in toxic epidermal necrolysis: a prospective clinical study

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Abstract *Objective:* To evaluate the incidence, clinical features, and prognosis of pulmonary complications associated with toxic epidermal necrolysis

Design: Prospective study.

Setting: Dermatology intensive care unit in Mondor Hospital, France.

Patients: 41 consecutive patients.

Interventions: On admission, then daily, respiratory evaluation was based on clinical examination, chest X-ray, and arterial blood gas analysis. When clinical symptoms, X-ray abnormalities, or hypoxemia [partial pressure of oxygen (PO₂)

< 80 mm Hg] were present, fiberoptic bronchoscopy was performed.

Results: 10 patients presented early manifestations: dyspnea (*n* = 10), bronchial hypersecretion (*n* = 7), marked hypoxemia (*n* = 10) (PO₂ = 59 ± 8 mm Hg). Chest X-ray was normal (*n* = 8) or showed interstitial infiltrates (*n* = 2). In these 10 patients, fiberoptic bronchoscopy demonstrated sloughing of bronchial epithelium in proximal airways. Delayed pulmonary complications occurred in 6 of these 10 patients from day 7 to day 15: pulmonary edema (*n* = 2), atelectasis (*n* = 1), bacterial pneumonitis

(*n* = 4). Mechanical ventilation was required in 9 patients. A fatal outcome occurred in 7 patients. Seven patients did not develop early pulmonary manifestations (PO₂ on admission 87 ± 6 mm Hg) but only delayed pulmonary symptoms related to atelectasis (*n* = 1), pulmonary edema (*n* = 4), and bacterial pneumonitis (*n* = 3); bronchial epithelial detachment was not observed. None of them required mechanical ventilation and all recovered with appropriate therapy.

Conclusions: "Specific" involvement of bronchial epithelium was noted in 27 % of cases and must be suspected when dyspnea, bronchial hypersecretion, normal chest X-ray, and marked hypoxemia are present during the early stages of toxic epidermal necrosis. Bronchial injury seems to indicate a poor prognosis, as mechanical ventilation was required for most of these patients and was associated with a high mortality.

Key words Toxic epidermal necrolysis · Stevens-Johnson syndrome · Pulmonary complications · Fiberoptic bronchoscopy · Bronchial epithelial necrosis



Fig. 1 Toxic epidermal necrolysis: typical aspect of skin detachment resembling scalding

Introduction

In 1956, Lyell reported four cases of a skin eruption resembling scalding and related to either drug toxicity, staphylococcal infection, or undetermined etiology [1]. In fact, this original article included three different diseases corresponding to staphylococcal scalded skin syndrome, generalized fixed eruptions due to drugs, and toxic epidermal necrolysis (TEN) [2, 3]. With further cases and larger series, it became generally accepted that TEN was a drug-induced skin reaction. The main drugs incriminated in TEN are antibacterial sulfonamides, anticonvulsants, some nonsteroidal anti-inflammatory agents, and allopurinol [4–6]. In a few cases, TEN has been demonstrated to be related to *Mycoplasma* infection [7] or graft-versus-host disease (GVH) [8]. TEN is characterized by extensive epidermal detachment with mucous membrane involvement (Fig. 1), whereas the Stevens-Johnson syndrome (SJS) corresponds to a mild form of TEN with predominant mucosal involvement but epidermal detachment affecting less than 10% of the body surface area. TEN is rare since its incidence is estimated to be in the range of 1 to 1.5 cases/million per year. However, it is a life-threatening disease, fatal in 30% of cases, and death is mainly related to sepsis or visceral involvement such as gastrointestinal or pulmonary complications [9, 10]. Pulmonary manifestations have been poorly studied but appear to be heterogeneous, including specific bronchial mucosal necrosis, pulmonary edema, and infectious pneumonitis, as described in a few isolated case reports or rare postmortem studies [11–15]. The aim of the present study was therefore to evaluate the incidence of pulmonary manifestations in TEN, to define their clinical characteristics, and to determine their prognosis in a large prospective series.

Patients and methods

Patients

Forty-one consecutive patients admitted to our Dermatological Intensive Care Unit (Henri Mondor Hospital, Créteil, France) with epidermal detachment affecting more than 10% of the body surface area (BSA) were enrolled in the study from January 1992 to September 1995. Cases of TEN associated with human immunodeficiency virus infection, *Mycoplasma* pneumonitis, or GVH disease were not included. Patients were clinically classified as overlap SJS-TEN when the epidermal detachment ranged from 10 to 30% of BSA and as TEN when the epidermal detachment exceeded 30% of BSA [16]. The diagnosis was confirmed by a skin biopsy showing detachment of full thickness epidermis and/or total epidermal necrosis. Drug causality was assessed according to the official method of the French Pharmacovigilance Centers [17].

On the day of admission, then daily, respiratory monitoring was performed, based on clinical examination, chest X-ray, and arterial blood gas analysis. When clinical symptoms were present, such as polypnea (respiratory rate > 30 breaths/min) or bronchial hypersecretion, and were associated with X-ray abnormalities or hypoxemia [partial pressure of oxygen (PO_2) < 80 mm Hg in room air], a diagnostic procedure using fiberoptic bronchoscopy (FOB) was performed. Four patients were excluded from the study due to previous chronic obstructive pulmonary disease ($n = 3$) or chronic heart failure ($n = 1$) associated with a low baseline PO_2 . In these cases, PO_2 values on admission were 68 ± 4 mm Hg but remained unchanged after recovery. FOB was not performed despite a PO_2 < 80 mm Hg on admission. The study group therefore consisted of 37 patients.

FOB and associated procedures

Bronchoscopy was performed using an Olympus BF P30 fiberoptic bronchoscope (Olympus, France) in the usual manner. After endobronchial examination, bacterial analysis was performed according to the Plugged Telescoping Catheter (PTC) procedure, using a PTC unit (Combicath 5828.20; Plastimed Lab, Saint-Leu la Forêt, France) [18]. A positive culture was defined as the recovery of > 10^3 colony-forming units/ml of a potential pathogen. When bronchial mucosa detachment was present, repeated FOBs were performed in order to aspirate epithelial fragments.

For each patient, at least three bronchial biopsy specimens were taken at different levels in the right bronchial tract. Samples were fixed by immersion in Bouin's solution and then paraffin embedded or fixed by 2.5% glutaraldehyde in 0.045 M cacodylate buffer, pH 7.4 for semithin section processing.

Ancillary studies

Blood cell count, blood cultures, and serological studies for *Mycoplasma* were performed routinely for each patient. Skin bacterial samples were cultured on petri dishes every 48 h. Pulmonary function was monitored by repeated blood arterial gas analyses during the course of TEN.

Patient classification according to pulmonary manifestations

Patients were classified into three groups according to pulmonary manifestations: group 1 comprised patients with no pulmonary manifestations on admission or during the course of the disease; group 2 had patients with pulmonary manifestations during the

Table 1 Clinical characteristics of the study patients (\neq Deceased patients, *BSA* body surface area, *TEN* toxic epidermal necrolysis, *SJS* Stevens-Johnson syndrome, *TMP-SMX* trimethoprim-sulfamethoxazole, *ND* not determined) (Pulmonary edema, Bacterial pneumonitis in full in column 8)

Patients	Age (years)	Sex	Offending drug	Skin feature	% BSA	Early pulmonary complications	Delayed pulmonary complications	PO ₂ in room air
Group 1								
1	25	F	Salazosulfapyridine	SJS/TEN	10	Absent	Absent	105
2	14	F	Carbamazepine	SJS/TEN	15	–	–	90
3	16	M	Adiazine	TEN	35	–	–	91
4	30	F	Carbamazepine	TEN	35	–	–	99
5	20	F	Depamide	TEN	40	–	–	108
6	85	M	TMP-SMX	SJS/TEN	15	–	–	88
7	25	M	Mintezol	SJS/TEN	20	–	–	88
8	14	M	TMP-SMX	TEN	60	–	–	98
9	61	F	TMP-SMX	TEN	35	–	–	90
10	14	F	Chlormezanone	SJS/TEN	15	–	–	106
11 \neq	85	F	TMP-SMZ	TEN	30	–	–	90
12	45	F	ND	SJS/TEN	15	–	–	105
13	41	F	Piroxicam	SJS/TEN	10	–	–	90
14	39	F	TMP-SMZ	SJS/TEN	20	–	–	92
15 \neq	43	M	Allopurinol	TEN	75	–	–	113
16 \neq	56	M	ND	TEN	35	–	–	90
17	36	F	ND	SJS/TEN	20	–	–	90
18	57	F	Chlormezanone	TEN	30	–	–	95
19	54	M	Ceftriaxone	SJS/TEN	20	–	–	85
20	54	F	Fenofibrate	TEN	40	–	–	89
Group 2								
21 \neq	72	F	ND	SJS/TEN	20		Death	50
22 \neq	76	F	Amoxicillin	SJS-TEN	15		Death	64
23 \neq	36	F	ND	SJS/TEN	25	Bronchial	Death	56
24 \neq	45	M	Piroxicam	TEN	100	epithelial	Death	72
25 \neq	55	M	Phenobarbital	SJS/TEN	20	necrosis	Pulmonary edema	55
26 \neq	50	M	Salazopyrine	TEN	40	(<i>n</i> = 10)	Bacterial pneumonitis	54
27	26	F	Ibuprofen	TEN	60		Atelectasis	64
28	16	F	Fluvoxamine	TEN	60		Bacterial pneumonitis	65
29 \neq	32	F	Chlormezanone	TEN	30		Bacterial pn/ARDS	47
30	43	M	Phenobarbital	TEN	70		Pulmonary edema bacterial pneumonitis	60
Group 3								
31	43	F	Phenobarbital	TEN	35	Absent	Pulmonary edema	90
32	33	F	Paroxetine	TEN	35	–	Pulmonary edema	98
33	48	M	Carbamazepine	SJS/TEN	25	–	Bacterial pneumonitis	85
34	37	M	Allopurinol	TEN	40	–	Atelectasis	86
35	59	F	Allopurinol	TEN	50	–	Pulmonary edema/bac- terial pneumonitis	85
36	36	F	Depamide	SJS/TEN	25	–	Bacterial pneumonitis	80
37	53	M	Carbamazepine	TEN	40	–	Pulmonary edema	85

first 48 h after admission; group 3 included patients with delayed pulmonary manifestations appearing more than 48 h after admission to our department.

Statistical analysis

Intergroup comparisons were made using Student's *t*-test and, when appropriate, the Mann-Whitney nonparametric test. The Fisher exact test was used to compare the proportion of deceased patients in each group.

Results

Study population

Altogether, 73 % of patients were admitted from other French hospitals, as our dermatology unit is considered as a national reference center. The delay between the first mucocutaneous symptoms and admission to our center was in the range of 1 to 4 days. Table 1 summarizes the clinical features and lists the offending drugs in the 37 patients studied. There were 14 males and

23 females, with a mean age of 42 ± 19 years (range 14–85 years). Sixteen patients were classified as overlap SJS-TEN and the remaining 21 patients were classified as TEN. Overlap SJS-TEN and TEN were related to an adverse drug reaction in 32 patients and in 5 patients the cause was not determined. BSA involvement was 10 to 100 % (mean 34 ± 20 %). Mucous membrane lesions in the oral cavity were associated with skin lesions in all patients.

Patients without pulmonary manifestations (group 1)

Of the 37 patients, 20 were classified as group 1 [54 %; 95 % confidence interval (CI) 37–70 %]. The mean age in this group was 41 ± 22 years. The mean BSA involvement was 29 ± 17 % (range 10–75 %). All patients had associated oropharyngeal mucosal lesions. Chest X-ray was normal and arterial PO_2 was 95 ± 8 mmHg on admission and remained in the normal range during the course of TEN. Three patients in this group died of septic shock during the course of TEN.

Early pulmonary manifestations (group 2)

Clinical features

Of the 37 patients, 10 were classified as group 2 (27 %; 95 % CI 14–44 %) (Table 1). The mean age in this group was 45 ± 19 years. The delay between first symptoms and admission was in the range of 1 to 3 days. The mean BSA involvement was 44 ± 28 % (range 15–100 %). All patients presented with respiratory symptoms on admission. Dyspnea associated with increased respiratory rate was a constant clinical feature. Bronchial hypersecretion was observed in 7 of the 10 patients. Hypersecretion was abundant and appeared as a yellow, fluid, transparent sputum without any purulence, as demonstrated by sputum cytological examination. None of the patients in this group had evidence of bronchial casts in their sputum. Chest X-ray was normal in 8 patients but showed interstitial infiltrates in 2 patients. Blood gas analysis in room air during the first 48 h revealed a marked hypoxemia with a mean PO_2 of 59 ± 8 mmHg (range 47–72 mmHg) associated with respiratory alkalosis. PO_2 values on admission in group 2 were significantly lower than in groups 1 or 3 ($p < 0.0001$).

FOB results

Bronchoscopy examination revealed a pattern of diffuse loss of bronchial epithelium involving the proximal airways. Patients were investigated during the first 48 h after admission, corresponding to day 3 to 4 from the on-

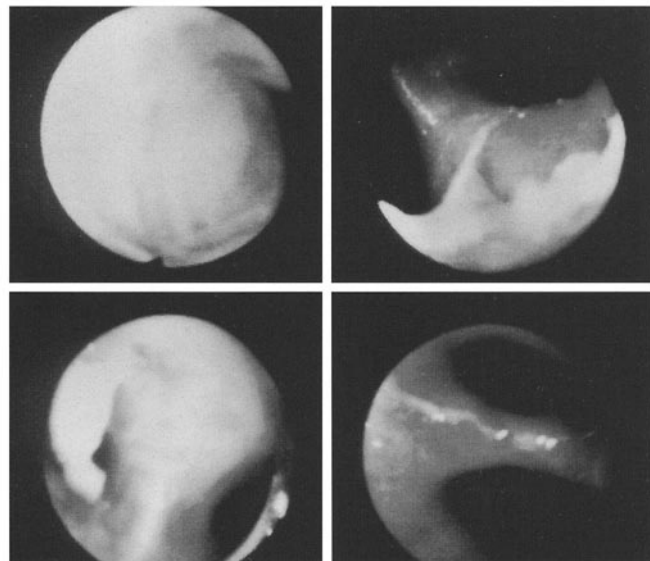


Fig. 2 Endoscopic view of bronchial mucosa: **a** thickness of bronchial mucosa giving a white ground-glass appearance at the early stage of detachment, **b** mucosal ulceration due to bronchial mucosal detachment, **c** mucosal membrane clogging lobar bronchus, **d** diffuse abrasive pattern after complete sloughing of bronchial epithelium

set of skin manifestations. Mucosal detachment involved up to 50 % of bronchial mucosa by the first examination and was close to 100 % of bronchial surface area at later stages. Bronchial involvement was characterized, in the early stages, by areas of white ground-glass appearance, evolving toward areas of red denuded mucosa associated with the presence of bronchial casts. At later stages, the confluence of bronchial ulcerations contributed to form a diffuse abrasive pattern (Fig. 2). Protected bronchial sampling remained sterile in every case.

Histologic findings

Bronchial biopsies confirmed epithelial necrosis as suggested macroscopically by large ulcerations or complete abrasion of bronchial epithelium. The lamina propria was only lined with denuded basement membrane and the inflammatory features were the presence of numerous infiltrating mononuclear cells, including lymphocytes, monocytes, and plasma cells, and by dilatation of small vessels (Fig. 3). There was no evidence of histologic criteria consistent with an infectious process such as predominant polymorphonuclear cell infiltration or multinucleated giant cells suggesting viral infection. Repeated FOB and biopsies were performed during the course of TEN in 3 surviving patients in group 2, allowing assessment of the time of re-epithelialization. Normal bronchial mucosa began to recover at the same time as skin re-

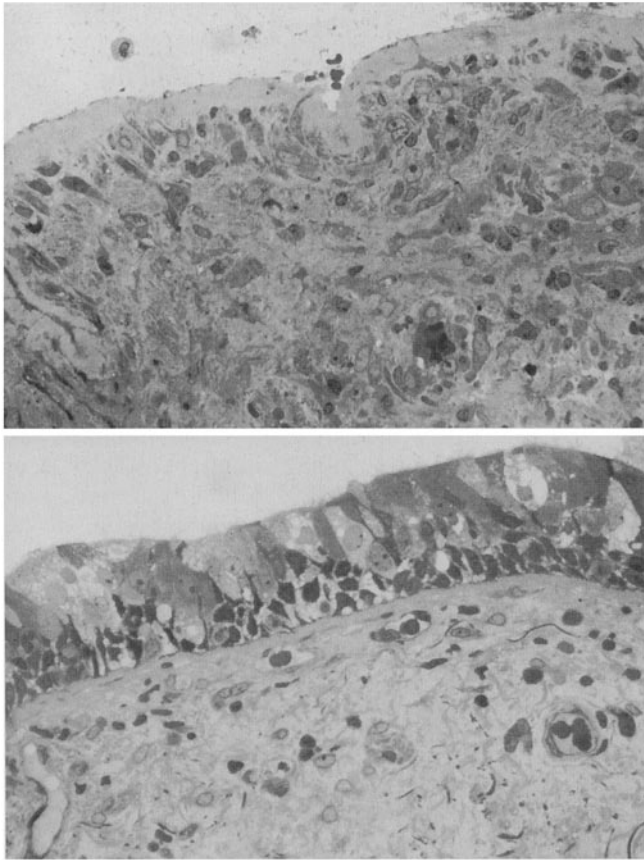


Fig. 3 Toluidine blue stained semithin section of a representative bronchial biopsy: **a** TEN-specific bronchial epithelial involvement is characterized by complete epithelial detachment. The lamina propria is infiltrated by inflammatory mononuclear cells including lymphocytes, plasma cells, and monocytes. The capillary lumina are dilated. **b** Bronchial epithelial repair at day 21 in the same patient. The epithelium shows signs of squamous metaplasia

pair about day 15, and repair was complete in the 3 patients at day 21. Two of these patients developed bronchial epithelial metaplasia corresponding to glandular ($n = 1$) or squamous ($n = 1$) bronchial metaplasia (Fig. 3).

Outcome

Mechanical ventilation in this group, was required for 9 patients and nasal oxygen therapy was required in 1 patient. Four patients died from acute respiratory failure during the first few hours despite early ventilatory support. The 6 remaining patients developed further delayed complications, including atelectasis ($n = 1$), pulmonary edema ($n = 2$), and bacterial pneumonitis ($n = 4$). One developed both pulmonary edema and infectious pneumonitis. Bacterial pathogens isolated by the PTC procedure consisted of methicillin-resistant

Staphylococcus ($n = 1$), *Acinetobacter baumannii* ($n = 2$), and *Pseudomonas aeruginosa* ($n = 2$). Two pathogens were identified (*Staphylococcus* + *Acinetobacter*) in 1 patient. In all cases, pathogens had been previously isolated from skin samples. Three of these 6 patients died from septic shock or the adult respiratory distress syndrome (ARDS) related to bacterial pneumonitis, despite appropriate antibiotic therapy. The remaining 3 patients recovered. The mortality in group 2 appeared to be statistically higher than that reported for patients without bronchial injury (groups 1 + 3) ($p < 0.002$).

Delayed pulmonary manifestations (group 3)

Clinical data

Seven of the 37 patients were classified as group 3 (19%; 95% CI: 8–35%) (Table 1). The mean age was 44 ± 10 years. The delay between first symptoms and admission was in the range of 2 to 5 days. The mean BSA involvement was $35 \pm 9\%$ (range 25–50%). The patients had no pulmonary manifestations on admission (mean PO_2 87 ± 6 mmHg) but developed nonspecific pulmonary manifestations, including atelectasis ($n = 1$), pulmonary edema related to fluid overload ($n = 4$), and bacterial pneumonia ($n = 3$), from day 5 to day 10. One patient developed both pulmonary edema and bacterial pneumonitis. Bacterial pathogens isolated by the PTC procedure consisted of methicillin-resistant *Staphylococcus* ($n = 1$), *Acinetobacter baumannii* ($n = 1$), and *Streptococcus pneumoniae* ($n = 1$).

FOB data

Bronchoscopy examination was performed from day 5 to day 10. The macroscopic appearance of the mucosa was normal in all 7 patients.

Histologic findings

Three bronchial biopsies in each patient confirmed the absence of bronchial epithelial necrosis. In 2 patients, a mild polymorphonuclear cell infiltration was observed in the bronchial lamina propria and was related to associated bacterial pneumonitis, as demonstrated by the PTC procedure.

Outcome

None of the patients in group 3 required ventilatory support. All recovered from the delayed pulmonary complications with appropriate therapy.

Discussion

Pulmonary complications have been occasionally reported in the course of TEN in a few isolated cases [11–14]. However, to our knowledge, this study is the first prospective evaluation of respiratory tract involvement in a large series of patients with TEN. In our study, early pulmonary complications occurred in about 25 % of cases (95 % CI 14–44 %) and corresponded to bronchial mucosal sloughing, as demonstrated by FOB. Respiratory symptoms related to bronchial epithelium detachment developed within the 4 days after the onset of mucocutaneous symptoms.

Bronchial involvement in TEN does not appear to be correlated with the extent of epidermal detachment or with related offending drugs. In this series, and in most of the cases reported in the literature, dyspnea and bronchial hypersecretion are usually the first clinical symptoms. Interestingly, hypersecretion was present in 7 out of 10 patients and was characterized by a fluid, yellow, nonpurulent sputum, suggesting plasma exudation across the altered bronchial epithelial barrier. It is noteworthy that the chest X-ray was normal on admission in most cases but further X-rays soon revealed interstitial infiltrates highly suggestive of pulmonary edema. However, alveolar epithelial involvement was not established in this study as none of the patients who died of acute respiratory failure were autopsied.

In one case of TEN with multiple organ failure described in the literature, necrosis of the alveolar walls was reported but autopsy was performed after a long period of assisted ventilation and septic complications, raising the question of the specificity of these pathologic findings [13]. Other pulmonary manifestations related to bronchial mucosal involvement have been described elsewhere, including mild hemoptysis [12] or expectoration of bronchial mucosal casts, which seems highly suggestive of bronchial mucosal involvement [14]. In all cases, acute respiratory failure developed rapidly after the onset of skin detachment. In 6 cases in this series, respiratory distress was associated with severe hypoxemia (≤ 60 mmHg) at the time of admission and required immediate ventilatory support. In the remaining 4 cases, arterial PO_2 was moderately altered (ranging from 64 to 72 mmHg) on admission but dropped dramatically during the following 24 h, justifying mechanical ventilatory assistance in 3 out of 4 patients.

Our results are in agreement with those previously reported since ventilatory support was required in all cases described in the literature [11–13]. Mechanical ventilation was used according to the recent consensus conference guidelines [19]. In patients with ARDS, volume-controlled ventilation using 7 to 10 ml/kg tidal volume was performed in order to keep the pressure plateau below 35 cm H_2O . Positioning of these patients (supine/prone) was not routinely performed since the ben-

efit of this strategy has not been proved. Moreover, skin lesions made it difficult to turn these patients. In contrast, the 27 patients with no early respiratory symptoms or hypoxemia did not require ventilatory support in the course of the disease. However, in absence of respiratory symptoms, FOB was not performed and therefore we cannot exclude the possibility of bronchial involvement in group 1. Interestingly, FOB was performed in 7 patients who developed only delayed complications between day 5 and day 10 after the onset of TEN, an interval which would reasonably exclude the possibility of early re-epithelialization. No bronchial mucosal detachment was observed in these 7 patients. Such results therefore suggest that bronchial involvement is associated with early respiratory symptoms and marked hypoxemia developing simultaneously with or very soon after the onset of skin manifestations. Furthermore, bronchial mucosal involvement seems to be related to a poor prognosis, constituting a high risk factor for acute respiratory failure.

FOB appeared to be a simple procedure to identify bronchial mucosal detachment in TEN. Moreover, this study demonstrated a good correlation between the bronchoscopic appearance of the mucosa and histological lesions of the bronchial epithelium. In 10 patients with early pulmonary manifestations and the appearance of mucosal erosions at bronchoscopy, histological examination revealed large areas of epithelial necrosis identified at different levels of the bronchial tree, whereas in 7 patients with only delayed pulmonary complications, there was no evidence of bronchial detachment at bronchoscopy and bronchial biopsy specimens were normal. Histological findings were characterized by extensive necrosis of bronchial epithelium without any alteration of basement membrane or lamina propria. Cell alterations consistent with viral infection such as cell ballooning, viral inclusion, giant cells, or syncytia formation were absent. Moreover, bacterial analysis of bronchial protected samples remained negative, leading us to consider that an infectious process was unlikely. Interestingly, airway sloughing and skin detachment appeared to be synchronous and both regenerated over the same time interval, suggesting “specific” TEN bronchial epithelial involvement.

The basic mechanisms responsible for skin and/or bronchial mucosa necrosis in TEN remain unknown. Cell-mediated cytotoxicity has been suggested by infiltration of inflammatory cells in areas of epidermal necrosis [20, 21]. Among these cells, monocytes/macrophages and T-cell lymphocytes infiltrating dermis and epidermis could play a crucial role via local $TNF\alpha$ and cytotoxic secretion [22–24]. It is noteworthy that the predominant inflammatory cells infiltrating bronchial mucosa in patients developing “specific” TEN bronchial mucosal involvement mainly consisted of mononuclear cells. Recent studies have emphasized the role of the

toxicity of metabolites of offending drugs [25, 26]. Such variations of metabolism could be related to genetic susceptibility [26, 27]. Toxic and immunological mechanisms are not mutually exclusive, since cell-mediated cytotoxicity might develop against toxic metabolites [28].

Delayed pulmonary complications were observed in all surviving patients displaying bronchial epithelial detachment and in 25 % of patients with no early pulmonary manifestations. They mainly consisted of pulmonary edema and infectious pneumonitis. The mechanisms of pulmonary edema were not clearly established in our series. Although alteration of the bronchopulmonary epithelial barrier can be suspected in patients with bronchial mucosal detachment, fluid overload seems to occur more frequently in pulmonary edema since treatment of TEN requires a large fluid intake, including water, electrolytes, and macromolecular solutions [5]. Moreover, fluid balance control is not easily obtained, since central venous pressure monitoring is avoided due to the risk of systemic infection [29].

Bacterial pneumonitis is another frequent complication of TEN. Interestingly, we found a good correlation between bacteria isolated from the skin and those iso-

lated from lung samples by PTC. Such findings could be useful to treat bacterial pneumonitis empirically before complete identification of the pathogens responsible for pneumonitis. In conclusion, the present study indicates that bronchial epithelial necrosis occurs in about 25 % of cases of TEN and corresponds to a specific TEN-related disorder. This bronchial involvement appears to be an index of poor prognosis, as demonstrated by the short-term progression toward acute respiratory failure and the frequent development of delayed complications. Therefore FOB appears to be useful in patients with suspected pulmonary complications: (i) to identify bronchial involvement, (ii) to evaluate the prognosis, and (iii) to eliminate associated pneumonitis using appropriate bacterial sampling. Moreover, bronchial aspiration during FOB prevents atelectasis produced by sloughing of bronchial epithelium. To our knowledge, there is no demonstrated specific treatment for TEN and obviously for bronchial involvement. Further prospective studies would be required to determine the value of early ventilatory support to reduce early mortality related to the progression of pulmonary complications.

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