Management of Ocular Manifestations in Toxic Epidermolisis: An Emergency? A Case Series

Prise en charge des manifestations oculaires des toxidermies medicamenteuses : Une Urgence ?

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ABSTRACT
***AIM*:** To evaluate ocular manifestations and treatment of patients with ocular involvement in toxic epidermolysis disease spectrum.
METHODS. We retrospectively reviewed the files of patient's diagnosed toxic epidermal necrolysis or Lyells disease / Stevens Johnson Syndrome attending the Ophthalmology Unit in the University Hospital center in Yaoundé (CHUY) from 2005 to 2011. The outcome measure were etiological factors causing Stevens Johnson syndrome / Toxic epidermal necrolysis (TEN), the pattern of ocular lesions and the management.
***RESULTS*:** Sixteen patients were managed. All patients had bilateral involvement but with asymmetrical presentations with a higher female representation (sex ratio F/M of 2:2) . Three of these were known HIV infected and were taking antiretroviral drugs. The mean times lag from onset of symptoms to the ophthalmologist consultation was 14.91 days (range 5 -35 days). Lids involvement was noted in 87, 50 % of cases followed by infections in 68, 75% of cases. All patients were managed medically with topical antibiotics and local anesthetic with preservatives. The most frequently identified possible cause was the antimalarial drugs in 50% of cases.
***CONCLUSION*:** Toxic epidermolysis should be considered as an ocular emergency to be presented to ophthalmologist as soon as the diagnosis is made. Preservatives free antibiotics should be used to reduce the local toxicity of the ocular surface.
***KEY WORDS*:** Stevens Johnson syndrome, Toxic epidermal necrolysis TEN, eye, ocular emergency

RÉSUMÉ
***OBJECTIF* :** Évaluer les manifestations oculaires et leur prise en charge chez un groupe de patients diagnostiqués comme toxidermies médicamenteuses, nécrolyses épidermiques toxiques ou Lyell et /ou Syndrome Stevens-Johnson.
MÉTHODE. Revue rétrospective des dossiers de patients diagnostiqués comme épidermolyses toxiques / syndrome Stevens Johnson et ayant été reçu dans le service d'Ophtalmologie du Centre Hospitalier et Universitaire de Yaoundé entre 2005 et 2011. Les paramètres étudiés étaient les facteurs étiologiques des toxidermies, Stevens Johnson Syndrome / Toxic epidermal necrolysis, la présentation clinique oculaire et la prise en charge.
RÉSULTATS 16 patients ont été pris en charge avec un sexe ratio de 2:2 en faveur des femmes. Tout les cas étaient bilatéraux mais asymétriques à la présentation. Trois patients étaient connus immunodéprimés sous antirétroviraux. Le temps moyen écoulé entre le début des symptômes et l'arrivée chez l'ophtalmologue était de 14.91 jours (range 5-35 jours). Les manifestations palpébrales étaient présentes dans 87,50%, suivies des infections dans 68,75 % des cases. Tous les patients ont reçu un traitement médical conservateur avec des antibiotiques topiques et des anesthésiques locaux contenant des conservateurs. Les antipaludéens étaient les médicaments les plus incriminés (50.25% de cas°.
CONCLUSION Les toxidermies médicamenteuses sont des urgences ophtalmologiques à référer à un ophtalmologiste des que le diagnostic est posé. L'utilisation des antibiotiques sans conservateurs est une priorité pour éviter la toxicité de la surface oculaire.
MOTS CLÉS : Syndrome de Stevens Johnson- Necrolyse épidermiques toxiques, Toxic epidermal necrolysis , urgence oculaire

INTRODUCTION

Toxic epidermolisis are acute inflammatory disorders affecting the skin and mucocutaneous membranes, usually due to adverse drug reactions and although rare they are life- threatening. The pathogenesis of SJS/TEN is not fully understood. A number of theories have been proposed that may have implications for treatment. It is believed to be immune-mediated, as re-challenging an individual with the same drug can result in rapid recurrence of SJS/TEN [1,2]**.** Toxic epidermal necrolysis or Lyell syndrome is the most severe variant in its manifestation with a mortality rate of 34% next to Stevens Johnson syndrome 5% [3,4]**.** Resulting ocular lesions are especially problematic because they have a high risk of sequelae[5] . As many as 40% of survivors of toxic epidermal necrolysis have residual potentially disabling lesions that may cause blindness Some evidence suggests that EM may be an entirely distinct disorder from Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis(TEN) spectrum of a single disease process[6,7]**.** This study evaluate , the time lag between the onset of signs and first consultation and lag time between first consultation and ophthalmic consultation, ocular manifestations and treatment administered to a group of patients with ocular involvement in SJS/TEN ,seen in the Ophthalmology Unit in the University Hospital Center in Yaoundé, Cameroon

METHODOLOGY

In this retrospective study, we recruited consecutive cases of patients diagnosed with toxic epidermolysis, SJS / TEN, with ocular manifestations who were referred to and managed in the Ophthalmology Unit of the University Central Hospital of Yaoundé Cameroon from March 2005 to May 2011. Diagnosis was made clinically and, supported by the history reported the patients or legal guardians. These included the history of medication, age, the maximal body surface area detached and tachycardia > 120 /min. As reviewed by Roujeau we considered in this series SJS and TEN to be variant of the same disease with different levels of severity graded by the volume spread of the disease on the skin [8].

Serum urea nitrogen , blood glucose and bicarbonate levels were not considered for the working diagnosis because they were not done. The discussion of diagnosis was made on the basis of the age, the maximal and body surface area detached and tachycardia > 120 /min. Nevertheless because of lack of diagnostics tools do not discuss the ocular manifestations separately in this series. We experienced Roujeau's remarks reporting that for the differential of SJS and TEN could be difficult and confusing at disease onset[1]**.**

The data assessed were age, sex, presumed causative drug, ocular lesions and management. Concerning the management, we considered time lag , and drug administered.

For assessment of ocular manifestations, complications and sequellae the patients had comprehensive ocular examination with emphasis on the lids and ocular surface, conjunctiva and cornea. We looked for infections lesions and opacities.

The data assessed analyzed using a using the statistical software STATA version 16.0. Descriptive statistics such as means standard deviation were used to summarize quantitative variables. For Ethical approval and administration authorizations permission

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RESULTS

Patients

Sixteen patients among which 11 females and 5 males were studied. with a sex ratio of 2:2 in favour of females. The mean age at disease onset was 25.25 ± 14.27 years (range 6-48 years). Two patients had AIDS and were on anti retroviral drugs no cases of tuberculosis no chronic diseases was registered.

Presumed causative drugs

Antimalarial drugs were implicated in 9 of the 16 cases (56.25%). Table 1 summarises the distribution of the presumed causative drugs.

Table 1: Distribution of presumed causative drugs among the 16 patients

Presumed causative drug	Brand name	Number	Percentage
Antimalarial **sulphonamides, sulfadoxine Arthesunate, Lumefantrin**	Maloxine	**4**	**25**
	Fansidar	**3**	**18,75**
	Coartem	**2**	**12,50**
Antipyretiques	Paracetamol	**1**	**6,25**
Cotrimoxazol		**2**	**12,50**
Sulphamides	Bactrim	**1**	**6,25**
Antiretroviral	Zidolan	**1**	**6,25**
Aminopenicillines	Clamoxyl	**1**	**6,25**
Antifilarial	Mectizan	**1**	**6,25**
Total		**16**	**100**

Lag time of onset of podromal signs to the first consultation

Mean lag time between onset of podromal signs to the first consultation or admission to hospital was 5, 08 days (range 2-14 days) and from the internist care to the ophthalmologist 9, 83 days (range 3-21 days). Thus the cumulative mean from the onset of symptoms to the ophthalmology consultation is 14.91 days range (5 -35days).

Ocular lesions
Lids were involved in 87, 50% of cases with positive, Nikolsky's sign. Ocular infections were reported in 12 (75%) always bilateral 24 eyelids. Superficial keratitis and, epithelial erosion were in 11 cases (68.75%).
Late complications such as trichiasis in 7 (43.75 %) cases, dry eyes in 12 cases (75%). and 2 7 (43.75 %) cases with stenosis of lid lacrimal punctae . Two patients benefited from an amnioctic graft out of the Cameroon. Table 2 summarises the distribution of ocular lesions among our patients.

Tab 2: Distribution of ocular lesions among our 16 patients

Ocular lesions	Number	%
Early stage acute to Subacute		
Ocular infections, purulent exudates	12	75,00
Lids, positive Nikolsky's sign	14	87,50
Fibrovascular membrane, Symblepharon/ Ankyloblepharon	8	50,00
Superficial Keratitis epithelial deffect	11	68,75
Late stage 6 months after crisis		
Trichiasis lid retraction conjunctiva scarring	7	43,75
Dry eyes, xerosis	12	75,00
Pannus, corneal peripheral neovascularisation corneal opacities	7	43,75
Stenosis of lid lacrimal punctae .	4	25,00

Management
After irrigation with normal saline solution, topical antibiotics to be administered 4 times daily was the management of ocular infections, Cephalosporins were mostly prescribed in, preference to disinfectants and mixtures of steroids. Benzalkonium chloride was the preservatives found in the topical ocular medication.
Glass Roding twice daily for 5 to 7 days was the method we used in all cases to release or to prevent adhesions. Removal of necrotic tissue was performed using conjunctival forceps and applying topical anaesthetic and topical antibiotic drops and ointment with no preservative.
In late stages, artificial tears were prescribed as needed as well as corticosteroids
Eventual outcome. Two patients ended up with corneal vascularisation and, conjunctivalisation of the cornea. One patient died while on care.

DISCUSSION
Patients
We received 16 cases in 7 years. The reported incidence of TEN/SJS is 1- 2 cases per million per year [9]. With the increasing use of antiretroviral drugs and the prevalence of tuberculosis [9, 10,11], we expected a higher frequency of TEN/SJS. This implies toxic epidermolysis patients do not present to ophthalmologists on time, therefore the ophthalmic emergency is neglected. The acuteness of the life threatening disease will direct the cases to intensive care unit or medical wards at first, only seeking ophthalmic care when complications or infections occur. Considering the lag time, these results imply that many patients could have died before they could consult the ophthalmologist. Moussala and collegues reported a death within 48 hrs after the podromal signs[12]. A detailed analysis of this condition should include the Emergency Units, Intensive Care Units and Medical Wards. We only analyzed the patients who were referred to the Ophthalmology Unit.
All our cases were referred with a working diagnosis of SJS (31.25%) Lyell (68.75%). By the time of first ophthalmologist consultation, we estimated that they were all TEN after assessment. This could be explained by conversion, the disease could be progressing and changing pattern while admitted as complication as discussed by Roujeau[1] .

Age and Sex
The mean age at disease onset was 25.25 years comparable to previous reports of studies in Cameroon [12]. While in other countries it ranged from 20 to 35 years [5, 7,13] . Nevertheless our study age group is younger compared to that reported by Yip and collaborators [14]. Several epidemiologic studies have shown that females have higher incidences of toxic epidermal necrolysis than males [15]. We observed a similar trend with a female to male sex ratio 2.2 females for each male.

Causative drugs
All the presentations were drug induced, similar to the other reports [2,13,16]**.** Antimalarial drugs were most often implicated as seen in 8 out the 16 patients 56,25 %,. These findings are consistent with reports of other authors who registered the use of long acting Sulfamides. Sulfamides and the combination of sulphadoxines and pyrimethamines for prophylaxis of malaria have been implicated in several cases and are on the increase in incidence because of resistance to other drugs such as chloroquine [12,17,18].
For Yip, antibiotics were the most commonly implicated drug especially cotrimoxazole , followed by anti epileptic drugs (allopurinol and phenytoin) [14] , while Chang reported Carbamazepine and allopurinol as most common causes of TEN [15]. These drugs belong to the common practice in Cameroon but the specific unit were the patient requiring this drugs are referred is lodged in Central Hospital of Yaoundé. It will be advisable to search for cases in epileptic clinics as well as in intensive

care units. The implicated causative drugs were only known from history, no immunoallergic test or treatments were undertaken as recommended by Yip as a way of confirmation [14] **.**
Not all patients were tested for HIV, but two were HIV positive. Boni reported in that regard that, the genome of the HIV positive patients could be modified to the point that uncontrolled interactions in polymedications easily occur [19]**.**

The mean lag time between the diagnosis of toxic epidermolysis by internists and consultation by ophthalmologists was 9,83 days (range 3-21 days), similar to the report of Pitche in Togo with a lag time of 16 days[11]**.** Morales reported that eye symptoms appear before or simultaneously with the skin leions [20). Williams reported a case of blepharoconjunctivitis within 24h of presentation in ICU [21]. This highlights the fact that ocular manifestations are not considered as emergency as they should. So, the management starts really late.

Ocular lesions
In our series, all patients had ocular symptoms as reason for seeking ocular consultation. Sotozono reported similar results in emergency rooms SJS outpatient clinics; 94% of ocular involvement[22]. Skin superinfection with *staphylococcus aureus* was noted by Pitche in Togo. It can be discussed that the same occur to the eye through the lids[11]. Ocular involvement has been observed in acute phase by Power and Guedry who reported to have an incidence ranging from 69% and 82% [23,24].
Acute conjunctivitis usually occurs simultaneously with the skin eruptions indicating the initiation of SJS/TEN with conjunctival involvement in 49% to 81% [25] . Keratitis, corneal erosions, and a sicca like syndrome may develop as late complications causing severe visual impairment and even blindness [1,22] . We saw our patients at different stages of the disease for the first consultation mostly late this can explain our finding more sequellae like.
By Yip, the severity of ocular involvement depended on SJS or TEN but this could not be proven statistically [13]. Geudry in a recent study with a large group concluded that ocular involvement was common in patients with SJS and TEN [23]**.** Chang reported 18.8% of ocular sequelae[15]. Although TEN is a more severe form than SJS? the difference in late or acute phase does not significantly influence or predict the ocular complications or manifestation [13]. Caution should be taken even in mild cases.
In SJS, it has been noted that the severity or systemic involvement determine the likelihood of the ocular complications[25]. Late complications are common in patients with severe initial eye involvement, but may also develop in patients without apparent initial ocular symptoms. We cannot comment on visual prognosis because of the short follow up time.

Management
Glass roding with topical anaesthetic agent and topical antibiotics were our line of management. This was also the practiced by Chang and Moussala [12,16]. Yip warns about the use of local or topical antibiotics and local non steroidal anti inflammatory drugs containing preservatives, pointing at the risk of ocular surface damage just as described by Geudry [24]. Because of the fhe fact that the preservatives found in topical antibiotics are known for their ocular toxicity, it is important to avoid them and use preservative free lubricant eye drops [26].
Ocular toxicity of local antibiotics has been described because of the preservatives, thiomersal and phenylmercuric nitrate but also a direct toxicity of the topical antibiotics on the accessory tear gland [26,27].
The current strategies of treatment with systemic and topical steroids have not been proven to prevent ocular complications [23]. Sotozono and Maya proved that, the treatment with topical steroid from disease onset is important for the improvement of visual prognosis [22,29].

Conventional management still remains unsatisfactory, as long term complications are not prevented. New trend have been advocating intravenous immunoglobulin but it does not limit ocular complications and damages of the tissues [30]. Although rarely practiced in our milieu, transplantation of amniotic membrane known for its anti inflammatory effects and improve wound healing is described as one of the current options [31]**.** Scleral gaz permeable contact lenses have been recommended as useful devices in the management of complications due to SJS and TEN [32].
Outcome The low turn up and irregular rate in our study group did not allow us to comment on the late complications of the disease[24]. Due to failure of the ocular surface and chronic inflammation, the disease can progress at variable periods following the attack period disease episode [6,7] , and the overall mortality rate is 20%to35% [13,33].

CONCLUSION
Early and adequate management of ocular disease in SJE/TEN may prevent late complications, it should be considered as an ocular emergency to be presented to ophthalmologist in other to prevent blindness. Because ocular manifestations are present in the acute phase or in the late phase the sequelae remaining for years long term follow up are recommended. The preservative free antibiotic and lubricants should be given priorities in treatment and made available.

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