Original Article

The Role of Frozen Section in the Rapid Diagnosis of Severe Cutaneous Adverse Drug Reactions

Abstract

Context: Early diagnosis is the mainstay in the management of severe cutaneous adverse reactions (SCARs) to drugs. **Aims:** To study the role of frozen section in the rapid diagnosis of SCARs and the impact on outcome of the affected patients. **Settings and Design:** A single-blind, hospital-based study was conducted from December 2014-July 2016. **Methods and Material:** We biopsied 32 adults with SCARs diagnosed by clinical features and standard criteria. The histopathological features seen on frozen sections were compared to that of paraffin blocks. The impact of rapid diagnosis on the clinical outcome was studied in toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP). **Statistical Analysis:** Z test was used to compare two proportions. Kappa statistic, sensitivity, specificity, positive predictive value, and negative predictive value of the frozen section diagnosis were calculated in TEN/SJS and DRESS using MedCalc software. **Results:** Frozen and paraffin sections were done in TEN/SJS spectrum (13), DRESS (17), and AGEP (2). The sensitivity, specificity and kappa values for frozen section diagnosis in SJS/TEN and DRESS were 91.7%, 95%, 0.867 and 94.4%, 100%, 0.937 respectively. The concordance between frozen and paraffin section diagnosis was 100% in TEN, SJS, DRESS and AGEP. All the 6 patients with TEN and 2 with AGEP survived. Taking the worst-case scenario, the mortality in SJS was 28.6%. The mortality among patients with DRESS was 11.8%. **Conclusions:** Frozen section helps in the rapid diagnosis and early treatment of SCARs and differentiates it from diseases that mimic it.

Keywords: *SCARs, frozen section, outcome, rapid diagnosis*

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Introduction

Cutaneous drug reactions are usually diagnosed clinically. Early diagnosis is the mainstay in the management of severe cutaneous adverse reactions (SCARs) to drugs which includes toxic epidermal necrolysis/ Stevens-Johnson Syndrome (TEN/ SJS),[1] drug rash with eosinophilia and systemic symptoms (DRESS)[2] and acute generalized exanthematous pustulosis (AGEP).[3] However, in the early stages, it may be difficult to differentiate between SCARs as the initial presentation of all these conditions may be a maculopapular exanthem.[3,4] Besides, it may be difficult to differentiate DRESS from infectious exanthems, SJS/TEN from SLE (systemic lupus erythematosus), immunobullous diseases, and staphylococcal scalded skin syndrome (SSSS) and AGEP from pustular psoriasis in the early phase of the disease. Currently, no specific diagnostic test is available for the early diagnosis of SCARs. Frozen section, a rapid diagnostic technique, is used mainly in the diagnosis of skin tumors and in Mohs surgery. There are also few reports of its use in the rapid diagnosis of TEN vs SSSS and congenital bullous ichthyosiform erythroderma.[5] A study by Hosaka *et al*.[6] used the frozen section technique to diagnose and predict disease progression in SJS-TEN and erythema multiforme (EM) major. With this background, we did a study to determine the role of frozen section in the rapid diagnosis of SCARs and its impact on the clinical outcome of the patients thus diagnosed.

Material and Methods

A hospital-based prospective, single-blind study was conducted in the Department of Dermatology, Venereology, and Leprosy, at a tertiary

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care hospital in South India from December 2014 to July 2016 (20 months).

Patients

Adults ≥18 years of age with SCARs were included. The diagnosis of the severe cutaneous drug eruption was made based on history, clinical examination and standard criteria where available (SJS/TEN was based on criteria by Bastuji-Garin S *et al*.[7] and DRESS on RegiSCAR criteria).[8] Patients who refused biopsies or had definitive features of an alternative diagnosis other than that of a suspected drug reaction were excluded from the study. The patients included in the study were followed up until discharge to determine the outcome.

Skin biopsies

The pathologist was blinded to the diagnosis for the frozen section. Skin biopsies for frozen section were done from a representative lesion in 32 patients with SCARs using a 4 mm punch biopsy. Frozen and paraffin sections were done from the same sample. Three sections of the sample were processed for frozen sections and the remaining block was processed for paraffin sections. The paraffin sections of 30/32 of the samples were reviewed by the same pathologist, in 2 cases another pathologist reported them.

Histological criteria

Each frozen and paraffin section were analyzed by the pathologist [Table 1] for confluent epidermal necrosis, apoptotic keratinocytes, parakeratosis, epidermal atrophy, spongiosis, lymphocytic exocytosis, basal vacuolar changes, spongiotic vesicles, subepidermal bulla, dermal edema, and dermal infiltrate including the type of infiltrate.[9] The frozen section and paraffin sections findings were compared.

To obtain agreement (kappa) of 0.8, assuming that the chance agreement of 0.5 with alpha and beta errors at 5% and 20%, respectively we needed to study a minimum of 31 patients. Z test was used to compare two proportions. As for reliability measure, kappa statistic, and as validated measures sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the frozen section were calculated using MedCalc software using clinical diagnosis ascertained by standard diagnostic criteria as the gold standard.[7,8,10]

A comparison between means was done using student t-test. Data were entered in Epidata and analyzed using SPSS software. This study was approved by the Institutional Review Board (IRB) and the Ethics committee (IRB number 9083, dated 06/10/2014).

Results

The patient flow chart is shown in Figure 1. There were 38 patients with clinical suspicion of SCARs of whom 4 did not have biopsies. Among the remaining 34 patients, 2 with clinical features of TEN were excluded since the frozen section showed features of pemphigus vulgaris and bullous pemphigoid. One patient who presented with a maculopapular rash and systemic features suggestive of DRESS showed features of TEN on frozen section. The typical clinical features of TEN evolved over the next few days and therefore she was diagnosed to have TEN.

Frozen and paraffin section biopsy of lesional skin was done in 32 patients (17 males and 15 females), their ages ranged from 19 to 66 years (mean 44.8, SD 11.69). The

Table 1: Histological features looked for in each of the conditions[9]

	Histological features
TEN/SJS*	Epidermal necrosis
	Necrotic keratinocytes
	Subepidermal bullae
	Mild dermal inflammatory infiltrate including eosinophils
DRESS†	Apoptotic keratinocytes
	Spongiosis
	Diffuse parakeratotic layer
	Lichenoid interface dermatitis
	Neutrophil exocytosis
	Dermal infiltrates including prominent eosinophils
AGEP‡	Subcorneal or intraepidermal pustules
	Papillary dermal edema
	Lymphohistiocytic perivascular infiltrate with some eosinophils and neutrophils

TEN/SJS*=Toxic epidermal necrolysis/Stevens-Johnson syndrome, DRESS†=Drug rash with eosinophilia and systemic symptoms, AGEP‡=Acute generalized exanthematous pustulosis

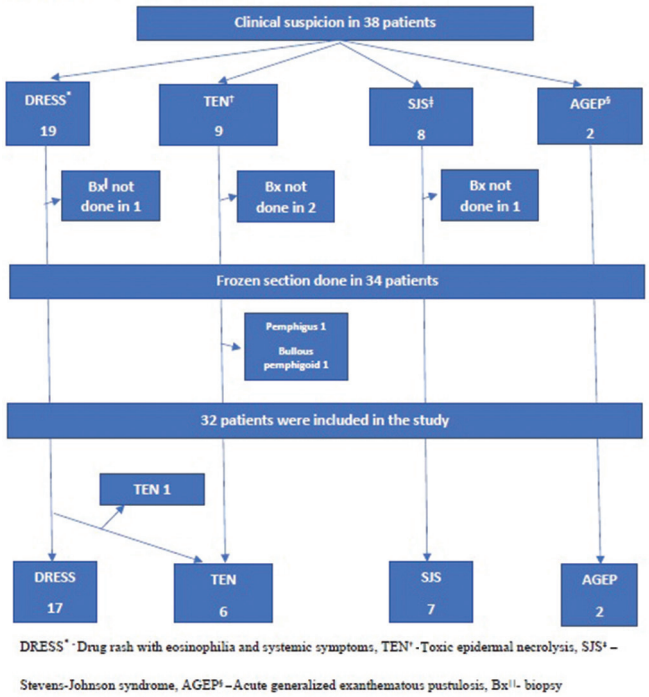

Figure 1: Flowchart of study patients

various SCARs included TEN - 6 (18.8%), SJS - 7 (21.9%), DRESS -17 (53.1%), and AGEP - 2 (6.25%). Twenty-nine patients (90.6%) required hospitalization and included 6 TEN, 7 SJS, 14 DRESS, and 2 AGEP. Three patients with DRESS were followed up in OPD.

Results of histopathological features [Tables 2 and 3]

The histological features assessed in the frozen and paraffin sections of each of the SCARs are shown in Table 2. The comparative frequencies of the salient histological features seen in them are shown in Table 3.

In our study, in both frozen sections [Figure 2a] and paraffin blocks [Figure 2b] of TEN, confluent epidermal necrosis was present in 83.3%, subepidermal vesiculation and mild dermal inflammation in 100% of the patients. One patient did not show confluent epidermal necrosis, but in view of marked apoptosis, overlap with SJS/TEN was suggested. Basal cell vacuolation (16.7% in frozen vs 83.3% in paraffin, $P = 0.02$) and lymphocyte exocytosis ($P = 0.02$) were more evident on paraffin section. As mentioned earlier, the frozen section biopsy of the patient with suspected DRESS showed confluent epidermal necrosis consistent with TEN, the clinical presentation of which evolved over the next few days. Thus, all the patients diagnosed in the TEN spectrum[7] showed the typical histopathological features. However, in one patient the histopathological features preceded the defining cutaneous lesions.

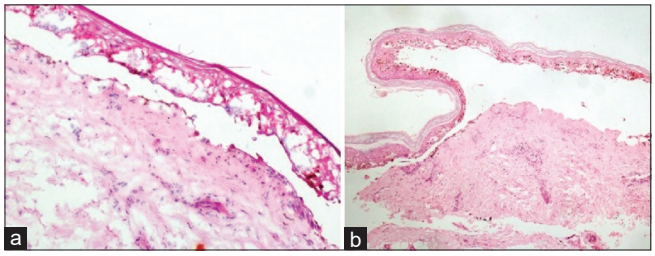

Figure 2: Toxic epidermal necrolysis showing confluent epidermal necrosis. Hematoxylin and eosin (H&E) 100x, (a) frozen section , (b) paraffin section

In SJS, in frozen sections [Figure 3a] and paraffin blocks [Figure 3b], apoptotic keratinocytes and dermal inflammation were seen in 100%. Basal cell vacuolation and lymphocytic exocytosis were better observed in paraffin sections than in frozen sections. Six patients showed the typical histopathological features. In the remaining case, the histopathological features seen were suggestive of a "drug reaction" but lacked the defining features of lesions seen in SJS.

Table 2: Histological features of severe cutaneous adverse drug reactions - frozen and paraffin section findings

Severe cutaneous adverse drug reactions	Histologic features	Frozen (%)	Paraffin (%)	*P*
TEN* (*n*=6)	Confluent necrosis	83.3	83.3	NA†
	Occasional necrotic keratinocytes	33.3	83.3	0.07
	Basal cell vacuolation	16.7	83.3	0.02
	Subepidermal vesiculation	100	100	NA†
	Lymphocytic exocytosis	16.7	83.3	0.02
	Dermal inflammation	100	100	NA†
SJS‡ (*n*=7)	Confluent necrosis	14.3	28.6	0.53
	Epidermal atrophy	42.9	57.1	0.61
	Epidermal apoptosis	100	100	NA†
	Basal cell vacuolation	42.9	71.4	0.3
	Subepidermal vesiculation	14.3	14.3	NA†
	Lymphocytic exocytosis	57.1	71.4	0.58
	Dermal inflammation	100	100	NA†
DRESS§ (*n*=17)	Parakeratosis	17.6	58.8	0.01
	Epidermal apoptosis	5.9	17.6	0.29
	Spongiosis	88.2	88.2	NA†
	Focal basal cell vacuolation	35.3	52.9	0.31
	Lymphocytic exocytosis	58.8	82.4	0.12
	Eosinophilic infiltrate	52.9	100	0.001
	Dermal perivascular infiltrates of lymphocytes and histiocytes	88.2	100	0.14
AGEP‖ (*n*=2)	Apoptotic keratinocytes	0	50	0.24
	Spongiosis	100	100	NA†
	Neutrophilic spongiotic pustules	50	50	NA†
	Dermal lymphocytic infiltrate	0	50	0.24

TEN* = Toxic epidermal necrolysis, NA† = not applicable, SJS‡ = Stevens Johnson syndrome, DRESS§ = Drug rash with eosinophilia and systemic symptoms, AGEP‖ = Acute generalized exanthematous pustulosis

Table 3: Comparative frequency of the salient histological features in severe cutaneous adverse reactions (SCARs)

SCARs		Epidermal changes						Dermal changes
		Confluent necrosis *n* (%)	Epidermal apoptosis *n* (%)	Parakeratosis *n* (%)	Spongiosis *n* (%)	Basal cell vacuolation *n* (%)	Neutrophilic spongiotic pustules *n* (%)	Eosinophilic infiltrate *n* (%)
TEN*	Frozen (*n*=6)	5 (83.3)	0	0	1 (16.7)	1 (16.7)	0	0
	Paraffin (*n*=6)	5 (83.3)	1 (16.7)	1 (16.7)	5 (83.3)	5 (83.3)	0	4 (66.7)
SJS‡	Frozen (*n*=7)	1 (14.3)	7 (100)	1 (14.3)	4 (57.1)	3 (42.9)	0	2 (28.6)
	Paraffin (*n*=7)	2 (28.6)	7 (100)	2 (28.6)	7 (100)	5 (71.4)	0	5 (71.4)
DRESS§	Frozen (*n*=17)	0	1 (5.9)	3 (17.6)	15 (88.2)	6 (35.3)	0	9 (52.9)
	Paraffin (*n*=17)	0	3 (17.6)	10 (58.8)	15 (88.2)	9 (52.9)	0	17 (100)
AGEP‖	Frozen (*n*=2)	0	0	0	2 (100)	0	1 (50)	1 (50)
	Paraffin (*n*=2)	0	1 (50)	1 (50)	2 (100)	1 (50)	1 (50)	1 (50)

TEN* = Toxic epidermal necrolysis, SJS‡ = Stevens Johnson syndrome, DRESS§ = Drug rash with eosinophilia and systemic symptoms, AGEP‖ = Acute generalized exanthematous pustulosis

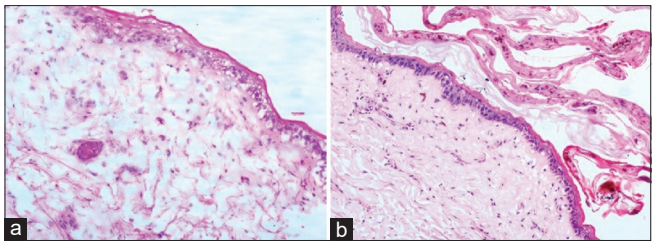

Figure 3: Stevens-Johnson syndrome showing epidermal atrophy, necrotic blister roof and sparse dermal inflammation. Hematoxylin and eosin (H&E) 100×, (a) frozen section, (b) paraffin section

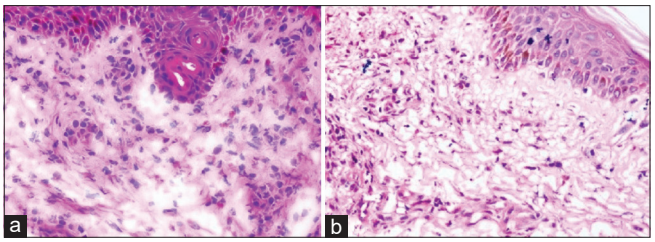

Figure 4: Drug rash with eosinophilia and systemic symptoms (DRESS) showing eosinophilic infiltrate. Hematoxylin and eosin (H&E) 200×, (a) frozen section, (b) paraffin section

In our study [Table 2], spongiosis and dermal perivascular lymphohistiocytic infiltrate were common in both frozen [Figure 4a] and paraffin sections [Figure 4b] in DRESS. Parakeratosis (P = 0.01), eosinophilic infiltrate (P = 0.001), lymphocyte exocytosis, and basal cell vacuolation were better visualized on paraffin sections than on frozen section. Epidermal apoptosis was better observed in the paraffin section [Table 2]. The histopathological diagnosis included "drug reaction" in 12/17 patients (70.6%) and erythema multiforme in 5/17 (29.4%) which is a well-reported histological entity seen in DRESS.[11] The histological features of DRESS are interface dermatitis, eczematous, EM-like, and AGEP-like pustulosis.[12] Taken together, the pathologist was able to identify the histopathological features on the frozen section as consistent with that of a drug reaction/erythema multiforme.

In AGEP [Figure 5a and b], the most common histopathological finding was spongiosis which was seen in both the patients (100%) while apoptotic keratinocytes, neutrophilic spongiotic pustules, and dermal lymphocytic infiltrate consistent with AGEP was seen in 1/2 of the patients (50%).

The concordance between the frozen and paraffin section diagnosis in TEN, SJS, DRESS and AGEP was 100%.

Sensitivity and specificity of frozen section diagnosis

The sensitivity and specificity of frozen section diagnosis were determined by taking clinical diagnosis as ascertained by published criteria as the gold standard.[7,8,10] The sensitivity in TEN-SJS was 91.7% and in DRESS was 94.4%. The specificity in TEN-SJS and DRESS were 95% and 100% respectively. The positive predictive value and negative predictive value were high with kappa nearing 1. The positive predictive value was 91.7% for TEN-SJS and 100% for DRESS. The negative predictive values were 95% and 93.3% for TEN-SJS and DRESS, respectively. The kappa value was 0.867 for TEN-SJS and 0.937 for DRESS [Table 4].

Clinical outcome

All 6 patients with TEN and 2 with AGEP survived. Two of the 7 patients with SJS requested discharge against medical advice. One of them had stage 4 HIV with probable underlying malignancy, seizure disorder, and aspiration pneumonia, while the other had a severe head injury with bilateral temporal contusion and was on tracheostomy. Taking the worst-case scenario, the mortality was 28.6%.

The mortality among patients with DRESS was 11.8% (2/17). One patient died of refractory septic shock, severe metabolic acidosis, and probable drug-induced hepatitis while the other had intracranial

Table 4: Sensitivity and specificity of frozen section diagnosis (*n*=32)

	A‡	B§	C‖	D¶	Sensitivity (%)	Specificity (%)	PPV** (%)	NPV†† (%)	kappa	*P*
TEN/SJS*	11	1	1	19	91.7	95	91.7	95	0.867	<0.001
DRESS†	17	0	1	14	94.4	100	100	93.3	0.937	<0.001

TEN/SJS* = Toxic epidermal necrolysis/Stevens Johnson syndrome, DRESS† = Drug rash with eosinophilia and systemic symptoms. A‡ - frozen section diagnosis positive, clinical diagnosis positive; B§ - frozen section diagnosis positive, clinical diagnosis negative; C‖ - frozen section diagnosis negative, clinical diagnosis positive; D¶ - frozen section diagnosis negative, clinical diagnosis negative. PPV** - positive predictive value. NPV†† - negative predictive value. Sensitivity and specificity were not calculated for AGEP (acute generalized exanthematous pustulosis) since the numbers were very small

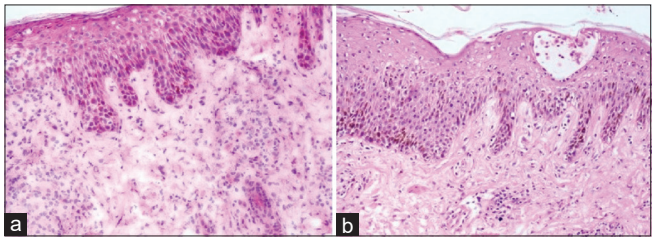

Figure 5: Acute generalized exanthematous pustulosis showing intraepidermal neutrophilic vesicles, spongiosis and moderate perivascular inflammation. Hematoxylin and eosin (H&E), (a) frozen section 200x, (b) paraffin section 100x

hemorrhage, probable acute bacterial meningitis, and ventilator-associated pneumonia.

Discussion

Severe cutaneous adverse reactions to drugs are relatively rare disorders that are associated with significant morbidity and mortality. The overall combined incidence of SJS, SJS/TEN overlap, and TEN is estimated to be 2 to 7 per million cases per year.[13]This study looked at the utility of frozen section in the rapid diagnosis of SCARs and its impact on the overall outcome. The high sensitivity, specificity, positive predictive, negative predictive and kappa values suggest that the test can be used to diagnose SCARs. Frozen section diagnosis is particularly helpful to differentiate TEN from SSSS and immunobullous diseases and DRESS from viral and other infectious causes of exanthem, which may be difficult based on the history and clinical examination in the early phase of the disease. In our study, two patients with features of TEN, were correctly diagnosed as pemphigus and bullous pemphigoid based on the histological features seen on frozen section. This again strengthens its utility in the rapid diagnosis of dermatological conditions. Frozen section also facilitated the early diagnosis of TEN in a patient who initially presented with a maculopapular exanthem and features suggestive of DRESS. Early diagnosis results in timely intervention with appropriate systemic therapy and a better outcome.[14]

Differentiating SJS from TEN is currently based on the criteria of Bastuji-Garin *et al*.[7] A differentiating feature of TEN from SJS on frozen sections in our study [Table 3] was the presence of confluent epidermal necrosis seen in 83.3% of TEN vs 14% in SJS. This will help the clinician to prognosticate better as patients with TEN have a poor outcome. The mortality rate of SJS varies between 1% and 5%, while TEN ranges from 25% to 30%.[15] The outcome of patients with TEN in our study was excellent with no mortality. The two patients with SJS in whom the worst-case scenario was presumed had significant life-threatening underlying morbidity.

Patients with DRESS often present with features indistinguishable from viral exanthem and it is vital to distinguish between the two as the treatment is vastly different, the former requiring systemic steroids. In our study, the histopathological features seen included spongiosis, apoptotic keratinocytes, dermal lymphohistiocytic inflammation along with an eosinophilic infiltrate, and lymphocytic exocytosis, all being well described in DRESS. On the other hand, viral exanthems usually show superficial vacuolar interface dermatitis, lichenoid dermatitis, and mild spongiotic dermatitis.[16] The mortality from DRESS among our patients (11.8%) was almost similar to the reported mortality of 10%.[17]

Based on the findings of our study we recommend frozen sections to facilitate the rapid diagnosis of SCARs, especially when the diagnosis is uncertain. It is also beneficial in differentiating DRESS from an infectious exanthem and TEN from SSSS and immunobullous diseases. However, the higher cost and access to frozen section biopsy in resource-poor settings are limiting factors. Freezing artefacts, poor-quality section, and staining in frozen section biopsies can hamper the diagnosis.[18]

Although this is a preliminary study done on a relatively small number of patients from a single center, it has established the role of frozen section in the rapid diagnosis of SCARs, a group of diseases that currently relies mainly on the clinical features and few ancillary laboratory parameters.

Conclusion

This study has established that frozen section helps in the rapid diagnosis of life-threatening drug reactions by providing a definitive diagnosis required for the initiation of early appropriate treatment and better outcome.

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Conflicts of interest

There are no conflicts of interest.

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