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Stevens - Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) In Sarawak: A Four Years' Review

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Abstract:

Background and Objectives:

A retrospective review of cases admitted to Sarawak General Hospital with Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and SJS-TEN Overlap from January 2004 to December 2007 was undertaken aiming to determine the causes and management outcome.

Methods and Results:

Twenty four cases were admitted with 54.2% having SJS, 25% having SJS-TEN Overlap and 20.8% having TEN. Seventy nine percent were drugs induced. Anticonvulsants were the main culprit followed by Allopurinol. A 12.5% mortality rate was recorded. All cases given intravenous immunoglobulin (IVIG) survived.

Conclusion:

It was concluded that SJS, SJS-TEN Overlap and TEN were mainly drug- induced and have high mortality. IVIG treatment seems promising. Judicious use of medications is needed. Early recognition is essential. Optimal care in institution with dermatology service is preferable.

Introduction

Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) are rare bullous muco-cutaneous disease. Although rare with an incidence of 0.05 to 2 persons per 1 million populations per year, it has significant impact on the public health in view of its high morbidity and mortality [1, 2]. Majority of cases were drug- induced [3, 4, 5]. They are also grossly under reported worldwide.

Few studies on SJS and TEN are available in Malaysia due to its rarity [4]. There are no reported studies from East Malaysia. Hence, our study aim to determine the causes and management outcome of cases with SJS, SJS-TEN Overlap and TEN admitted to Sarawak General Hospital for a 4 years period from January 2004 to December 2007.

Materials and Methods

A retrospective review of cases admitted to the Sarawak General Hospital with SJS, SJS-TEN Overlap and TEN was done for a period of 4 years from January 2004 to December 2007. Data were retrieved from clinical notes in the Medical Records Department.

A clinical diagnosis of SJS, SJS-TEN and TEN was done based on the clinical features of the cases. No skin biopsy was performed. They were classified as SJS, SJS-TEN Overlap and TEN based on Bastuji- Garin et al [6]. SJS is characterized by widespread small blisters and skin detachment levels of less than 10% of the body surface area, SJS-TEN Overlap by skin detachment levels of 10% to 29% of the body surface area, and TEN by skin detachment levels of more than 30% of the body surface area.

Clinical notes were studied in detail regarding the demographics, causative drugs implicated, clinical course and management outcome. Data collected were compiled on a Microsoft excel sheet and subjected to descriptive statistical analysis.

Results

Table I shows the demographics of patients admitted to Sarawak General Hospital from January 2004 to December 2007. A total of 24 cases were admitted with 54.2% having SJS, 25% having SJS-TEN Overlap and 20.8% having TEN. There was a male preponderance of

58%. The mean age for cases with TEN was 23.3, SJS-TEN Overlap 44.5 and SJS 40.3 years. They range from 8 to 73 years.

Table I: Demographic data of Patients

	SJS	SJS-TEN Overlap	TEN
Cases	13	6	5
Sex			
Male	10	2	2
Female	3	4	3
Age			
Mean Age (Years)	40.3	44.5	25.4
Range Age (Years)	13-70	8-73	10-42
Race			
Chinese	4	2	1
Malay	3	3	2
Iban	4	0	1
Bidayuh	2	1	1

Seventy nine percent of the cases were due to drugs. Anticonvulsants and Allopurinol were the major culprits, contributing to 7 and 5 cases respectively. Traditional medications were implicated in 2 cases. Other drugs included antibiotics, non steroidal anti-inflammatory drugs, sulpha drugs and anti- helminthes (Table II).

Table II: Drugs Implicated

	SJS (n=11)	SJS-TEN Overlap (n=5)	TEN (n=3)
Anticonvulsant			
Carbamazepine	2	2	1
Phenytoin	2	0	0
Non Steroidal Anti Inflammatory Drugs			
Ibuprofen	0	1	0
Mefenemic Acid	0	0	1
Traditional Medications			
Asam Urat	0	1	0
Chinese Herbs	0	0	1
Anti Gout			
Allopurinol	4	1	0
Others			
Sulfasalazine	1	0	0
Amoxycillin	1	0	0
Albendazole	1	0	0

Four cases were given anticonvulsants for pain disorders while 2 were given for seizure prophylaxis for intracranial haemorrhage. Only one case was on anticonvulsants for epilepsy. All the cases on Allopurinol were given for asymptomatic hyperuricemia.

Table III depicts that the mean incubation time i.e. time from drug initiation to onset of disease ranging from 4.7 days in TEN to 21.6 days in SJS. The hospital stay in cases with TEN were also longer with a mean of 12.4 days compared to only 8.9 days in cases with SJS (Table IV).

Table III: Incubation Period of Drugs

	SJS	SJS-TEN Overlap	TEN
Mean (Days)	21.6	12.4	4.7
Range (Days)	2-40	1-21	2-10

Table IV: Duration of Hospital Stay

	SJS	SJS-TEN Overlap	TEN
Mean (Days)	8.9	9.2	12.4
Range (Days)	2-46	2-23	7-19

ble V represents the treatment administered. All the patients with SJS and two third of cases with SJS-TEN Overlap were given corticosteroids. Eighty percent of cases with TEN were given intravenous Immuno-globulins.

Table V: Treatment Outcome

	SJS (n=13)	SJS-TEN Overlap (n=6)	TEN (n=5)
		Treatment	
Corticosteroids	13	4	1
IVIG	0	0	4
Cyclosporine	0	1	0
Nursing Care only	0	1	0
		Outcome	
Survive	13	4	4
Succumb	0	2	1

There were only 3 deaths noted with a mortality rate of 12.5%. They succumbed to acute respiratory distress syndrome (ARDS) and sepsis. The culprit drug was Jamu Asam Urat containing phenylbutazone (a type of non steroidal anti-inflammatory drugs) in one case whereas no drug was implicated in the other two. They were

given corticosteroids and cyclosporine on admission. All the cases with TEN who were given IVIG survived.

Morbidities seen include skin dyspigmentation (52%), nail dystrophies (10%) and ophthalmic complications (10%). Two patients had visual impairment as a result of severe keratitis.

Discussion

The spectrum of disease from SJS to TEN is mainly drug-induced. We have found that almost 4 out of 5 cases admitted to our centre were drug- induced. Regional and international studies quoted a rate of 50% to 90% of cases [3, 4, 5, 7].

Anticonvulsants are one of the commonest culprit agents implicated [4, 8]. The estimated incidence per 10,000 new users is 1 to 10 depending on the agent used [9]. The drug reactions are more commonly seen in slow drug metabolizer due of genetic polymorphism. In carbamazepine hypersensitivity, the polymorphism is in position 308 and 328 of the promoter region of TNF-α gene [10]. SJS and TEN are considered T cell mediated disorders in which activation of CD8 T lymphocytes lead to destruction and apoptosis of keratinocytes [11]. Drugs can activate T cells by acting as a hapten, as a prohapten or by direct pharmacologic interaction among the drug, Major Histocompatibility Complex (MHC) molecule and a T cell receptor. It is postulated that carbamazepine in its chemically inert form can bind with the MHC and T cell receptor causing activation of T cells contributing to SJS and TEN [12].

We found that 36% of our cases were due to anticonvulsants. Among the anticonvulsant, the majority of cases (71%) were due to carbamazepine. This trend was also seen in India, Taiwan, Singapore and northeastern Malaysia [4, 8, 13]. The increasing utilization of anticonvulsants in pain management and in prophylaxis in neurosurgical patients might explain this. The benefit of prophylactic anticonvulsants in neurologic critical care is controversial and is often not evidence based [14]. Carbamazepine induced SJS and TEN was also found to be more common in Han Chinese with HLA-B1502 phenotype in Taiwan [15]. This might explain the trend in Singapore and some of our cases although no phenotyping was done.

Cases developing adverse drug reactions to carbamazepine should not be given other aromatic anticonvulsants namely phenytoin and phenobarbitone because of the cross reaction among the drugs. Mockenhaupt et al., found that SJS and TEN occurred in 1 to 10 per 1000 new users of aromatic anti-convulsants and 2.5 per 1000 new users of Lamotrigine, a newer class of anticonvulsants [9]. Sodium valproate and other newer anticonvulsants rarely cause adverse cutaneous drug reactions. Therefore, we would suggest that aromatic anticonvulsants be used cautiously. Safer alternatives for pain management should be used. They should also be used with care in those with Han Chinese lineage.

Allopurinol contributed to 26% our cases. Halevy et al., found that in Europe and Israel, Allopurinol is the most common cause of SJS and TEN. They found an increased risk with dosage 200 mg per day or more [16]. All our cases had taken 300mg per day as it is the only form available in Malaysia. Halevy et al. also did not find an

increased risk of Allopurinol induced SJS and TEN with co-medications with diuretics, aminopenicillins, angiotensin converting enzymes inhibitors (ACEI), non steroidal anti-inflammatory drugs (NSAIDs) and aspirin [16]. In Han Chinese, HLA-B5801 allele was strongly associated with severe cutaneous adverse reactions to Allopurinol [17]. Allopurinol was administered in all our cases for asymptomatic hyperuricemia. Other published studies also revealed inappropriate indications for Allopurinol in up to 86% of patients [18, 19]. So, we recommend judicious prescription of Allopurinol. A proper guideline on prescription of Allopurinol should be established in Malaysia to prevent such inappropriate usage. This will hopefully reduce the Allopurinol related life threatening adverse drug reactions.

The highest risk for development of SJS and TEN with drug use occurs within 2 months of initiation [9, 16]. We also noted a similar trend with longest incubation period of only 40 days. Interestingly, we also observed that the shorter mean incubation period was associated with more severe clinical presentation. This observation need to be further clarified by future studies as it has prognostic significance.

Our overall mortality was 12.5% with mortality for SJS-TEN Overlap of 33.3% and TEN of 20%. The reported mortality rate ranges from 5% to 40% [4, 5, 7, 8, 20]. Two of our 3 deaths were children with no apparent drug- related cause. We postulate that they had very severe viral infection and probably had secondary bacterial sepsis. Their immunity was further depressed by the administration of corticosteroids and cyclosporine leading to their death. Hence, immunosuppressive drugs should be used cautiously especially in those with suspected underlying infection. Systemic corticosteroids

has unproven benefit in early cases of SJS and TEN and deleterious in the advanced forms [19, 20].

We noted a 100% survival of the TEN cases that were given IVIG. IVIG is derived from plasma pool of several thousand donors and consists mainly of IgG. It interferes with Fas- Fas Ligand interactions by blocking the Fas binding to its ligand thereby blocking the apoptosis of the keratinocytes [21]. Stella et al., in Turin noted a reduction in mortality from 75% to 26% with the use of IVIG [22]. In a review of 8 studies on the use of IVIG in SJS and TEN, French et al., found that 6 studies points towards a benefit of IVIG on mortality associated with TEN [23]. Thus, the use of IVIG in TEN is very promising. Prospective studies should be done in Malaysia to determine the efficacy of IVIG as a first line treatment in TEN.

Conclusion

We would like to conclude that drugs especially anticonvulsants and Allopurinol were the major causes of SJS and TEN. Thus, a registry for antiepileptic and Allopurinol will help determine the national incidence of SJS and TEN on these medications. This will further enhance our knowledge of these reactions. The mortality rate of SJS and TEN remained high despite major advances in the medical field. IVIG usage in TEN is very promising. A prospective study on the use of IVIG in SJS and TEN will help to determine its benefit in our population. It will also help in establishing a guideline for IVIG use. Finally, we would recommend judicious use of medications to prevent iatrogenic drug eruption with high morbidity and mortality.

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