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Paracetamol induced Steven-Johnson syndrome-toxic epidermal necrolysis overlap: The unusual suspect

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Abstract
Paracetamol (acetaminophen, PCM) is widely used as an over-the-counter analgesic and antipyretic drug. It's a remarkably safe drug devoid of serious side effects in therapeutic doses. Intake of large doses of PCM may result in severe hepatic necrosis. While hepatoxicity is its well-known side effect, paracetamol is very rarely implicated to be a culprit of Steven- Johnson syndrome.

Keywords: paracetamol, acetaminophen, SJS, SJS-TEN overlap

Introduction
Steven- Johnson syndrome (SJS) is an uncommon, severe, mucocutaneous blistering disorder with an acute and unpredictable onset causing considerable morbidity. Its more severe form is called Toxic Epidermal Necrolysis (TEN). The difference between the two is the extent of the body surface area (BSA) involved by epidermal detachment. Less than 10% BSA is involved in SJS, 10–30% involvement is known as SJS-TEN overlap and more than 30% epidermal detachment is classified as TEN. The BSA is calculated by simple 'rule of nine' as in case of burns. Previously, SJS was considered as Erythema Multiforme (EM) major, but now is considered distinct from EM on the basis of severity, presence of constitutional signs, atypical target lesions with tendency to confluence, positive Nikolsky's sign, more than one mucosal site involvement, and residual sequelae. Lots of drugs can cause this condition. Paracetamol being one of the rarest one is reported in this case.

Case report
A 19 years old female (Fig.1) reported to the casualty of Govt. Medical College and Guru Nanak Dev Hospital, Amritsar, with complaints of widespread maculopapular rash, stinging in the eyes, oral mucosal ulcerations and high grade fever from last 10-12 days. There was no history of tuberculosis, bronchial asthma, cardiovascular or any other chronic illness or poisoning. She gave history of headache around 20 days back for which she took tablet "Crocin" present in her home. She had consumed 10 tablets of crocin in 3 days. A week after which she started experiencing myalgias, arthralagias and other flu like symptoms. The symptoms got worsened to the present state with appearance of skin ulcerations. She was conscious, apprehensive, co-operative and well oriented to time, space and person. She had mild pallor, no jaundice, no clubbing, no lymphadenopathy and no oedema. The pulse was 90/ minute, regular and very feeble. The blood pressure was 100/70 mmHg. Her respiratory rate was 32/minute, regular with abdomino-thoracic character. The saturation pressure of oxygen was 92% on room air. Her random blood sugar level was 125 mg/dl. She was febrile with temperature of 101.6 degrees. On examination, widespread ulcerative lesions were noted over the skin, eyes, genital areas and oral cavity. Around 30% BSA was involved with predominance over face, neck arms and oral cavity. Urethritis and vulval ulcers were present. Lab investigations showed TLC as 14600/ mm^3 with differential being 78% neutrophils and 20% lymphocytes. Renal function and liver function tests were unremarkable. The cardiovascular, abdominal, respiratory and nervous system examination was grossly normal.
She was given symptomatic and supportive treatment to which she responded very well. She was discharged after 2 weeks of treatment in satisfactory condition.

Discussion
Steven-Johnson syndrome; described classically as "A new eruptive fever with stomatitis and ophthalmia" was termed by Steven and Johnson in 1922 [1, 2]. It can occur due to an adverse hypersensitivity reaction to drugs that can be potentially fatal [1].
SJS may present as a nonspecific febrile illness leading to malaise, headache, cough, rhinorrhea with polymorphic lesions of the skin and mucous membrane characterized by acute blisters and erosions. In the oral cavity, SJS causes widespread ulcerative lesions. Prodromal symptoms are seen in about 30% of cases and may possibly initiate within 1–3 weeks of starting a new drug. Prodrome may last for 1–2 weeks, presenting with flu-like symptoms, sore throat, headache, arthralgias, myalgias, fever, and other rashes. Ocular changes such as dry eyes that resemble those of

mucous membrane pemphigoid may be noted in few cases. Urethritis and vulval ulcers may occur [2].

The incidence of SJS has been estimated to be around 1–6/1,000,000 persons per year with a mortality rate of 1–5% which rises up to 30% in TEN. Multiple drugs have been identified to cause SJS and TEN, antibiotics (sulfonamides) being the most common. Other usual suspects being anticonvulsants (phenytoin, phenobarbital, and carbamazepine), nonsteroidal anti-inflammatory drugs (oxicam derivatives) and oxide inhibitors (allopurinol) [2, 3].

Paracetamol, a considerably safe drug in therapeutic doses, has been reported to be associated with SJS, SJS-TEN overlap and even TEN throughout the world [3, 4, 5]. Although this association is extremely rare and infrequent, the consequences could be fatal because it's not the "usual suspect" implicated for the condition. This often leads to delay in diagnosis and hence, delayed appropriate management which consists of immediate withdrawal of the offending drug. In fact, PCM can continue to feature on the fore- front of treatment chart for management of fever (so often associated with SJS) in cases of ignorance about the entity and could make the matters worse from bad.

Management of patients with Stevens-Johnson syndrome is supportive and symptomatic with close resemblance to management of burns. The domains to look after are: Withdrawal of the suspected offending agent; control and prevention of underlying diseases and secondary infections; airway and hemodynamic stability; fluid replacement and electrolyte correction; wound care and pain alleviation. Oral lesions are taken care with mouthwashes and topical anesthetics. Epidermal necrolysis is treated as burns. Areas of denuded skin must be covered with compresses of saline or Burow solution.

Agents and techniques like Cyclosporine [6], Corticosteroids [7], plasmapheresis [8], cyclophosphamide [9], thalidomide [10] and immunoglobulins [11, 12] have been described in literature for the management of severe cases with varying results.

Conclusion

Acetaminophen is a relatively safe drug devoid of serious side effects, catastrophic severe hypersensitivity reactions can occur with its usage, which can be potentially life threatening. This case highlights the fact that no drug is completely safe and the treating physician should always be careful even while handling "potentially safe" drugs. Although litigation suits are not a routine in India, things are changing thick and fast. As on one hand; proper guidance and explanation of illness, treatment, procedures and potential complications to all patients is beneficial for their own interests; it saves the doctors from unnecessary troubles as well.

Fig 1

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