International Journal of Ophthalmology & Eye Science (IJOES)
ISSN: 2332-290X

A New Eruptive Fever Associated With Stomatitis And Ophthalmia

Editorial

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A Century-old story of Stevens Johnson Syndrome/Toxic Epidermal Necrolysis – Need for a paradigm shift in its management.

Albert Stevens, a surgeon and Frank Johnson, a pediatrician, published a paper entitled "A New Eruptive Fever Associated with Stomatitis and Ophthalmia" in the American Journal of Diseases of Children in 1922 [1]. The paper described two young boys who presented with skin eruptions of oval, dark red to purplish spots separated by normal tissue associated with fever, conjunctivitis, inflamed mucous membrane. One boy had total loss of vision. This was the first description of a condition which was later known as Stevens-Johnson Syndrome (SJS/TEN). It is unfortunate that even after a century of its first identification, the pathophysiology of SJS/TEN is still not completely understood. Despite significant advances, the incidence, prevalence, severe mucocutaneous involvement with long-term ocular sequelae, and challenges in the managementof SJS/TEN continue to remain unabated. Albeit rare but fatal, SJS/TEN are a disease continuum, often drug-induced, manifested by immune-mediated Severe Cutaneous Adverse Reaction (SCAR), frequently involving the eyes that may lead to corneal blindness requiring corneal transplantation and conjunctival lesions requiring amniotic membrane transplantation. Although, this condition is most often drug-induced, with most common culprit drugs such as sulfa drugs and non-steroidal anti-inflammatory drugs and others, in at least 25% of cases, no culprit drugs are identified. Other microorganisms such as Mycoplasma pneumoniae and herpes simplex virus are also known to induce this condition. Given that most often this condition is drug-induced with more than 200 drugs known to be serious culprits, the existing and future drug pipelines should be ideally subjected to strict pharmacovigilance surveillance to minimize its incidence. Although, HLA genes are associated with this condition together with specific culprit drugs, but identification of how the HLA genes interact with the drug in the host system is of paramount importance in disease prevention, and prompt earlier diagnosis such that a strategic multidisciplinary and multipronged approach could be designed in its management. With the advent of Precision Medicine, newer study designs pertaining to randomized clinical trials for rare diseases, need to be established and technological advances such as next generation sequencing and exome sequencing used in order to achieve tangible clinical outcomes.

Goldstein J. et al in this issue of the journal present interesting findings related to immune-mediated activation of coagulation resulting in increased levels of F1.2 and thrombin antithrombin complex (TAT) in the plasma of patients with SJS/TEN. Although, platelet microparticle, PAI-1, Protein C and antithrombin levels did not show a significant difference between the study groups, however, there were statistically significant increases in monocyte chemotactic protein-1 (MCP-1), IL-6 and TNF-α levels in patients with SJS/TEN. In addition, mucosal swabs of patients with SJS/TEN analyzed using surface enhanced laser desorption ionization-time of flight (SELDI-TOF) technique revealed distinct peaks at 15.1 and 14.2 kDA while a cohort of an adverse drug reaction group exhibited a peak at 11.2 kDa. Further characterization of these proteins is required. Increased expression of TNF-α in the plasma of patients with SJS/TEN would trigger the release of various other cytokines [2-4]. Immune-mediated activation of coagulation as evidenced by deposition of soluble fibrin in various organs of the body resulting in multi-organ failure, sepsis and imminent death should be a cause of concern warranting immediate attention and prompt treatment. This raises a question whether anticoagulation should be a part of the treatment in patients with SJS/TEN. Although, it is well known that SJS results in death in 10% of patients and in 30% for those with TEN, mostly due to sepsis, acute respiratory distress syndrome and multiorgan failure, anticoagulation is rarely discussed as a part of an armamentarium to fight this devastating condition. Timing of the administration of anticoagulation is important. Perhaps there is a need of anticoagulation much before the expression of TNF-α in this condition, which in turn activates the triggering of the expression of other cytokines resulting in fulminant immune-mediated activation of coagulation. Anticoagulation perhaps is not considered for fear

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Received: July 07, 2021
Published: July 22, 2021

Citation: Omer M. Iqbal. A New Eruptive Fever Associated with Stomatitis and Ophthalmia . *Int J Ophthalmol Eye Res.* 2021;9(1e):1-2.

of bleeding in this devastating condition where there is mucocutaneous involvement and extensive skin sloughing. The use of anticoagulants should be considered before the manifestation of mucocutaneous lesions and skin denudation. This emphasizes the incorporation of cheminformatic-aided pharmacovigilance and other pharmacovigilance strategies and early diagnostic measures. It is possible that the extensive epidermal detachment in patients with Toxic Epidermal Necrolysis (TEN), may be because of cutaneous microvascular thrombosis resulting in apoptosis and necrosis of the skin. While deposition of soluble fibrin in the vasculature of multiple organs of patients with SJS/TEN could result in multiorgan failure and sepsis, it could as well result in skin, the largest organ in the body. There is a need to study the presence of cutaneous microvascular thrombosis in SJS/TEN. Evidence of coagulation activation, multiorgan failure and sepsis justifies the use of anticoagulation. Although, the choice of anticoagulants could be debatable but not the need. A bewildering wide array of anticoagulants are available. After evaluation of risk-benefit profile, a suitable anticoagulant may be carefully selected. Precision Medicine with incorporation of a right anticoagulant to the right patient at a right time will create a paradigm shift in the management of patients with SJS/TEN.

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