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# Stevens Johnson Syndrome/Toxic Epidermal Necrolysis and It's Interface with Coagulation Activation

Research Article

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## Abstract

Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis are rare but life-threatening, immune-mediated adverse drug reaction characterized by fever, bullae formation and dermal necrosis. Eyes are most often involved and may lead to corneal blindness. The role of cytotoxic lymphocytes in initiating the specific immune reaction in SJS/TEN via a human leukocyte antigen allele restricted pathway is well known. Following an IRB approved protocol, blood samples were obtained from subjects suspected of SJS/TEN and normal healthy volunteers. In addition, exudates from mucosal swabs were isolated following addition of 0.25 ml of saline and double centrifugation. The discharges and plasma samples were analyzed using SELDI-TOF Bio. Rad. Richmond, CA. In addition to blood samples, confirmatory biopsies were performed in all SJS/TEN subjects, with 4 subjects having confirmed SJS/TEN and 7 subjects having suspected SJS/TEN. Immunohistochemical staining was performed on these skin biopsy sections using antibodies against granulysin. This study highlights the immune-mediated activation of coagulation. Although the platelet microparticle levels, PAI-1 levels, Protein C levels, and antithrombin levels did not show a significant difference between the study groups, however there was a wider range in all four parameters in the confirmed/unconfirmed SJS/TEN patients. Furthermore, there were statistically significant increases in monocyte chemotactic protein-1 (p = .0078), IL-6 (p= .0078), and TNF-alpha (p=.0078) in the tissue biopsies of confirmed SJS patients when compared to normal human plasma. Analysis of mucosal swab exudates of confirmed SJS patients, using surface enhanced laser desorption-time of flight (SELDI-TOF) technique revealed distinct peaks at 15.1 kDA and 14.2 kDA while a control cohort of an adverse drug reaction group exhibited a peak at 11.2 kDA. Immunofluorescent staining of the skin biopsy slides revealed increased expression of granulysin at the epidermal-dermal layer in biopsy confirmed SJS/TEN patients when compared to the controls.

**Keywords:** Immune-Mediated Reaction; Necrolysis; Coagulation Activation; Multi-Organ Failure; Sepsis; Disseminated intravascular Coagulation.

## Introduction

Stevens-Johnson Syndrome (SJS) is a life-threatening, immune-mediated adverse drug reaction characterized by fever, bullae formation, and dermal necrosis. SJS can progress to a related condition known as Toxic Epidermal Necrolysis (TEN) if total body skin detachment area exceeds 30%.[1] The incidence of SJS/TEN in the United States is estimated to be 1.58 to 2.26 cases/million people; however, compared to this relatively low incidence rate the mortality rate of this devastating hypersensitivity reaction is estimated to be 4.8% in SJS and 14.8% in TEN.[2] In addition to the highly lethal nature of these syndromes, they are incredibly expensive on hospital systems as these patients require a complex level of care across multiple disciplines of medicine. Specifically, it has been shown that these patients have a longer hospital course when compared to patients who do not develop these symptoms

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by 9.82 days, and they have a mean inflation-adjusted cost of care difference of $10,253 for patients with SJS and $47,670 for patients who develop TEN. In other words, these patients have a 4-fold longer duration and a 5-fold higher mean cost of hospitalization compared with that of an average hospital admission. [2] For these reasons, and many more, it is of vital importance to better understand these two conditions for the improvement of patient outcome as well as cost-savings for the hospital systems at large.

Both SJS and TEN were once considered variants of a disease known as erythema multiforme exudativum and was only later associated with ocular complications by Crocker in 1903.[10, 11] These dual dermatological and ocular diseases were first considered to be complications of microorganism infections such has herpes simplex virus and M. pneumoniae.[12] Later in the 20th century, more severe cases in pediatric patients spurred discussion amongst the medical community that ultimately resulted in the distinction between SJS/TEN from microorganism related infections. These cases, distinguished by prolonged high fever, a more generalized distribution and devastating cutaneous involvement were pontificated to be attributable to certain drug therapies such as sulfonamides and certain infections such as mumps, HSV, or atypical pneumonias. Further advancement in histopathological testing revealed stark differences between erythema multiforme, as well as related cutaneous conditions from SJS and TEN. It was more commonly understood that SJS/TEN was not limited by age and more related to an idiosyncratic drug reaction whereas erythema multiforme normally followed microorganism infection.[14] Later on in the 1990s, a classification scheme was made to distinguish these two different cutaneous conditions based on their clinical manifestations. SJS/TEN was noted to consist of a more extensive eruption of atypical lesions and sloughing of the skin [15]. In addition, the role of HSV in erythema multiforme further distinguished these two conditions in the 1990s, indicating a drastic shift in management when a patient presented with a cutaneous manifestation that may border these two similar conditions.[16] Thus, while it is understood today that erythema multiforme has a viral etiology, it is not well understood what the underlying etiology is to the hypersensitivity to certain drugs leading to SJS/TEN.

The clinical features of SJS/TEN are most predominantly characterized by erythematous patches that often progress from the cranial to caudal direction. In addition, widespread blistering is a feature of both SJS and TEN that sometimes resembles a second degree burn or scalding. Erosive mucosal lesions are also present, especially in the mouth but also includes the lips, conjunctivae, and genitals. In addition, there is a sequence of non-specific symptoms that often precede these more defining features and those are fever, discomfort with swallowing, and stinging eyes.[3] Upon progression to SJS/TEN, the Bastuji-Garin et al. criterium [4] is a commonly used set of clinical criteria in which patients are classified into three categories based on the degree of skin detachment; or alternatively, the international classification uses the affected body surface area with SJS affected 10% and TEN affecting greater than 30%. Moreover, a common feature of both SJS and TEN in many patients is the acute as well as long term ocular sequelae that patients suffer from as a result of the disease. The ocular complications of SJS/TEN can include lacrimal puncta, corneal opacification with conjunctivalization and severe dry eyes that can lead to partial vision loss or total blindness.[5] Furthermore, histologic examination shows keratinocyte necrosis accompanied by basement membrane vacuolization that results in subepidermal blistering.[6]

The international outbreak of coronavirus disease 2019 (COVID-19) began in late 2019 and has created widespread panic and disarray throughout the world. This disease is a highly contagious respiratory tract infection, that spans a wide spectrum of clinical presentation from asymptomatic to acute respiratory distress syndrome. SJS/TEN has been recognized as a complication in patients suffering from COVID-19 as a result often from the treatment they receive for their condition. For example, hydroxychloroquine was reported as a supportive drug for shortening the duration of COVID-19 symptoms and reducing the inflammatory response. However, Davoodi et al. reported a hypersensitivity response to this drug that was characterized by widespread cutaneous erythematous eruptions.[18] Hydroxychloroquine has been also associated with SJS/TEN in rheumatoid arthritis patients [19]. This renders a complication in treating patients with this drug, as the serious long-term problems associated with SJS/TEN may not outweigh the subtle clinical improvements of patients with COVID-19. These matters are important to consider when selecting for new treatments for novel conditions. COVID-19 was widely misunderstood, with a variety of different treatment modalities being explored for therapeutic effect. Yet, hypersensitivity reactions such as SJS/TEN may not have been considered as seriously as they should have in the wake of the pandemic, with pressing concerns such as a highly contagious viral illness. These kinds of hypersensitivity reactions must be considered before prescribing novel medications to patients, with special attention to certain drugs that have a higher likelihood, as proven in the literature, to cause SJS/TEN like syndromes.

The mechanism behind SJS/TEN can be broadly classified as a hypersensitivity reaction. While more than 200 drugs have been implicated as causes, the most common are sulfonamides, allopurinol, and aromatic antiepileptic drugs. Previous work has established the role of cytotoxic lymphocytes in initiating the specific immune reaction in SJS/TEN via a human leukocyte antigen allele restricted pathway. Indeed, in early blister fluid samples of SJS/TEN patients, cytotoxic CD8+ T cells and NK-like cytotoxic T cells are the most important cells. Furthermore, many of these CD8+ T cells were found to be SMX/TMP or CBZ specific and granzyme B positive suggesting that the cytotoxicity may be due to granzyme B mediated mechanisms.[7] A theorized mechanism of action could be that the culprit, hypersensitivity inducing drug interacts with HLA complexes altering the antigen binding clef, leading to the binding of peptides with immunogenic neoepitopes, in turn activating the aforementioned CD8+ granzyme B+ T cells and release of cytotoxic components that lead to cellular apoptosis and epidermal-dermal detachment. In addition, activation of cytotoxic T-lymphocytes may result in the release of pro-inflammatory and pro-thrombotic cytokines such as TNF-alpha resulting in additional hemostatic activation in these patients. Furthermore, Sinha et. al. showed that patients who are found to have higher levels of CD8+ T-lymphocytes as well as TNF-alpha were associated with microvascular dysfunction. In addition, these same patients were found to have elevated levels of inflammatory biomarkers such as D-dimer and C-reactive protein that corresponded with their microvascular dysfunction.[8] Therefore, in SJS/TEN, the clinical syndromes may be worsened due to a state of increased pro-thrombotic factors causing hemo-

static instability and impaired vascular function.

Indeed, it has been suggested in the past that a prevalent complication of SJS/TEN is disseminated intravascular coagulation (DIC). DIC, being a disorder of hemostatic dysregulation, can be a vital syndrome to be mindful of when managing patients with SJS/TEN due to its high mortality rate when superimposed onto patients already suffering from this hypersensitiy syndrome [9]. The pathomechanism behind the superimposed DIC on top of SJS/TEN is depicted in figure 5 as suggested by Chen et al.[9] We hypothesize that the immuno-dysregulation can secrete pro-thrombotic cytokines as well as pro-inflammatory cytokines that may induce ongoing inflammation to be accompanied by disrupted homeostasis. The ongoing inflammation then worsens the disrupted homeostasis by altering permeability dynamics as well as clotting factors.

## Materials and Methods

Our team set out to explore evidence of increased pro-thrombotic cytokine parameters via enzyme-linked immunosorbent assay as well as immunohistochemistry. Following an IRB approved protocol, blood samples were obtained from subjects suspected of SJS/TEN and normal healthy volunteers. In addition, exudates from mucosal swabs were isolated following addition of 0.25 ml of saline and double centrifugation. The discharges and plasma samples were analyzed using SELDI-TOF Bio. Rad. Richmond, CA. SELDI-TOF technique involves the application of protein solutions to spots of ProteinChip Arrays and subsequent analysis by a ProteinChip Reader adapted to achieve high-sensitivity quantification and good reproducibility. These patients were recruited from Loyola University Medical Center and were under the care of the Ophthalmology service and Dermatology-Pathology service. In addition to blood samples, confirmatory biopsies were performed in all SJS/TEN subjects, with 4 subjects having confirmed SJS/TEN and 7 subjects having suspected SJS/TEN.Chung et. al. has shown the presence of granulysin in the extracted fluid of bullae from SJS/TEN patients.[21] Immunohistochemical staining was performed on these skin biopsy sections using antibodies against granulysin. All slides were stored and processed in the same manner. Slides were first deparaffinized by washing three times with xylene for 5 minutes each. The slides were then rehydrated using a progressive ethanol gradient. They were washed twice in 100% ethanol (EtOH) for 2 minutes, once in 95% EtOH for 5 minutes, and once in 70% ethanol for 5 minutes. Slides were then rinsed with distilled water for 1 minute and washed for 5 minutes in a phosphate buffer solution (PBS). All slides were blocked using 10% normal donkey serum (NDS) with 0.01% sodium azide for 1 hour. Slides were then treated with granulysin primary antibody and incubated overnight in a humidified dark box at 4°C. Following incubation, the biopsies were washed 3 times with PBS and incubated with secondary donkey anti goat IgG fluorescein isothiocyanate (FITC), and diamino-2 phenylindole (DAPI) antibodies for 30 minutes. After washing with PBS, slide covers were mounted with fluorogel. For each slide stained with primary antibody, an additional control slide was prepared. These control slides were incubated with 10% NDS instead granulysin primary antibody and stained with secondary donkey anti goat IgG, FITC, and DAPI antibodies. These control slides were utilized to determine the level of background auto-fluorescence in all tissue samples. Deconvolution immunofluorescence (IF) was performed on all slides using a DeltaVision microscope equipped with a digital camera. Exposure times and settings were kept constant for all samples. Cytokine levels were measured using the Cytokine High Sensitivity array biochip from Randox Laboratories Limited (Crumlin, UK). Thrombin-antithrombin complexes, fibrinopeptide A (F1.2), plasminogen activator inhibitor-1 (PAI-1) and platelet microparticles were measured using commercially available ELISA kits. Antithrombin was measured using a chromogenic method, and Protein C levels were measured using a clotting method. All of these laboratory biomarkers were chosen for their historically defined role in pro-thrombotic, inflammatory, and disrupted hemostatic states.

## Results

Firstly, the ELISA results revealed increased F1.2 levels and TAT levels in the confirmed and unconfirmed SJS/TEN patients when compared to the controls (Figures 1). Microparticle levels, PAI-1 levels, Protein C levels, and antithrombin levels did not show a significant difference between the study groups, however there was a wider range in all four parameters in the confirmed/unconfirmed SJS/TEN patients (Figure 1). Furthermore, there were statistically significant increases in monocyte chemotactic protein-1 ($p = 0.0078$), IL-6 ($p=0.0078$), and TNF-alpha ($p=0.0078$) in the tissue biopsies of confirmed SJS patients when compared to normal human plasma (Figure 2, table 1). Mucosal swab exudates of confirmed SJS patients, revealed distinct peaks at 15.1 kDA and 14.2 kDA while a control cohort of an adverse drug reaction group exhibited a peak at 11.2 kDA, using SELDI-TOF technique (Figure 3). Immunofluorescent staining revealed increased expression of granulysin at the epidermal-dermal layer in biopsy confirmed SJS/TEN patients when compared to biopsy unconfirmed patients (Figure 4).

## Discussion

SJS/TEN is a devastating hypersensitiy reaction that results in multiorgan dysfunction, and long-term clinical effects. The results of our study suggest a clearer involvement of hemostatic proteins and biomarkers of inflammation. The statistically significant increase in expression of monocyte chemotactic protein-1, IL-6, and TNF-alpha support the current understanding of SJS/TEN and its inflammatory etiology. Furthermore, it has been shown that therapeutic agents targeting TNF-alpha has improved clinical outcomes in patients with CTL-mediated adverse drug reactions.[22] It has been suggested that TNF-alpha is responsible for keratinocyte apoptosis, but the role of monocyte chemotactic protein and IL-6 are less understood. IL-6 has been theorized to result in pulmonary complications of SJS/TEN such as interstitial pneumonia,[23] and also has been used as a marker for disease severity. [24] Indeed, IL-6 is widely recognized as an acute phase reactant that is markedly elevated in a number of inflammatory disorders, however treatment directly targeting this interleukin has yet to be elucidated as a benefit towards patients with SJS/TEN. Moreover, monocyte chemotactic protein-1 has been associated with rheumatologic disorders, atherosclerotic disorders, as well as other visceral diseases. [25-27] However, expansive literature review did not reveal many studies that explored its role in hypersensitivity reactions such as SJS/TEN. Monocyte chemotactic protein-1 is a metabolically active adipokine, and thus our research revealing elevated levels in our patients may suggest met-

**Figure 1. ELISA results of hemodynamically active cytokines/proteins in confirmed/unconfirmed SJS/TEN patient' plasma compared to normal. F1.2 levels and TAT showed increases in the confirmed and unconfirmed SJS/TEN patients when compared to the controls Microparticle levels, PAI-1 levels, Protein C levels, and antithrombin levels reveal a wider range in all four parameters in the confirmed/unconfirmed SJS/TEN patients.**

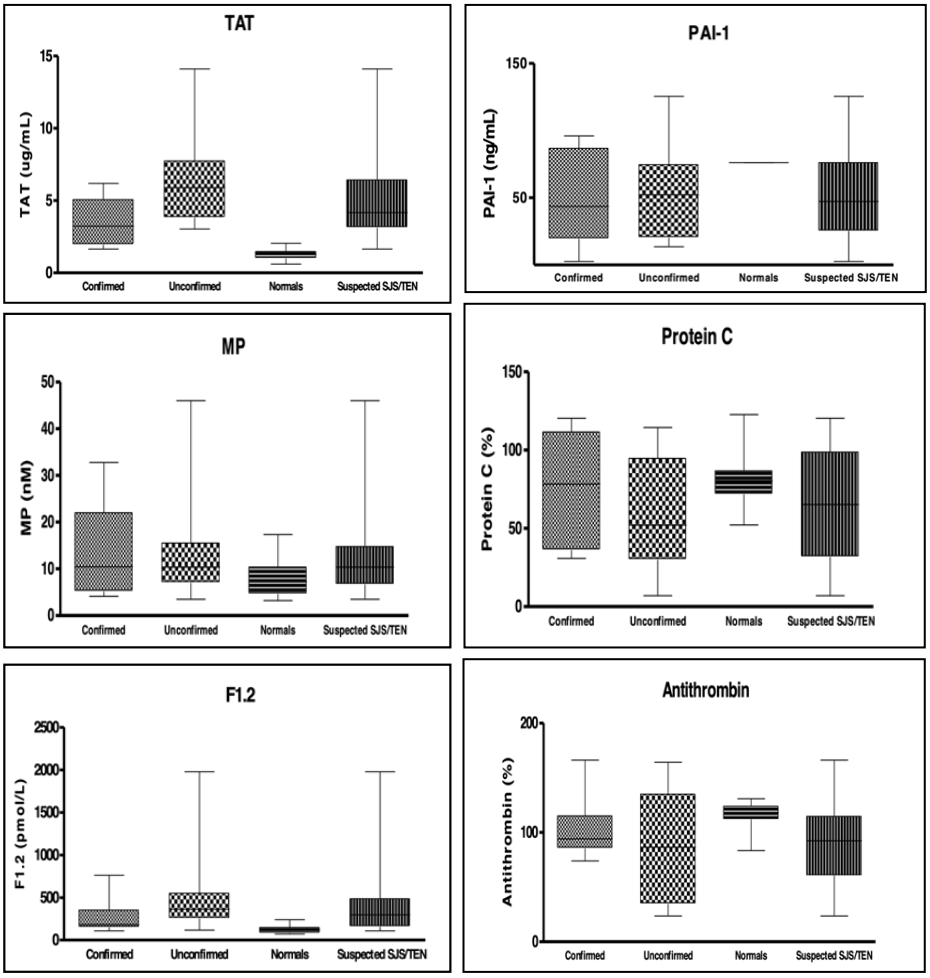


**Figure 2. ELISA results for SJS patients when compared to controls. All three inflammatory cytokines showed statistically significant increases when compared to healthy controls (p = .0078).**

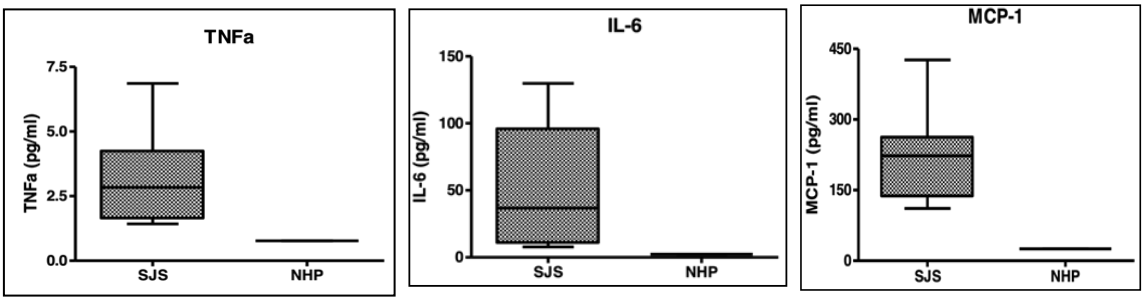


**Figure 3: Mucosal swab exudates of confirmed SJS patients. Distinct peaks at 11.2 kDa and 15.1 kDa can be appreciated.**

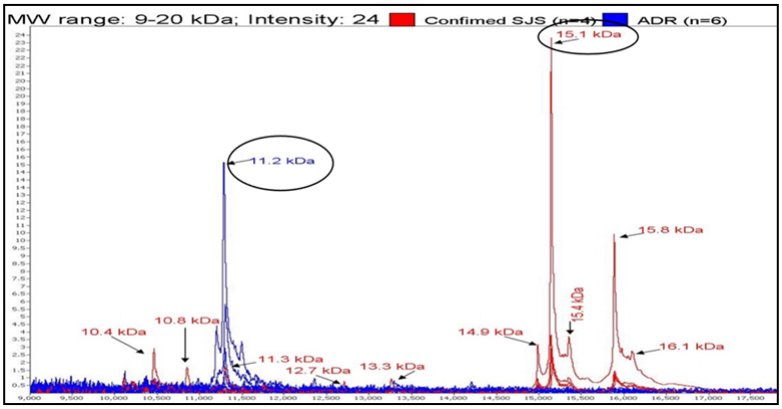

**Figure 4: Representative image from immunofluorescent microscopy. Shown on the right is increased hybridization and immunofluorescent signaling for granulysin when compared to normal controls.**

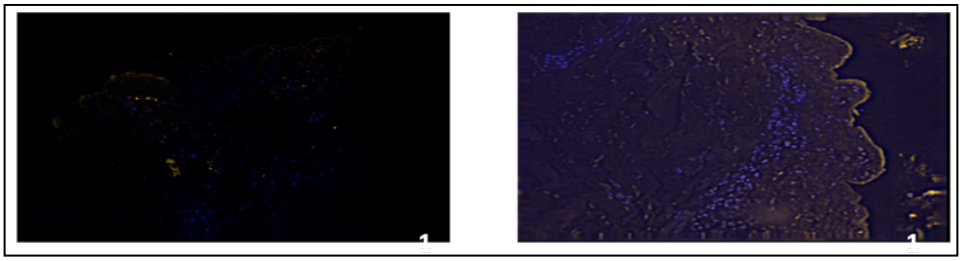

**Figure 5: Proposed mechanism behind the development of disrupted hemostasis in the setting of SJS/TEN. Dysregulation of the immune system leading to impaired cellular function and coagulopathy.**

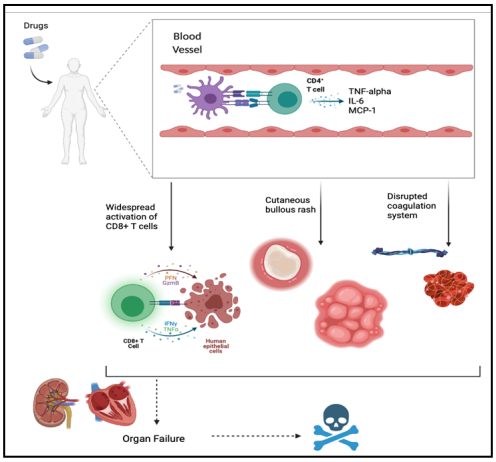


**Table 1: Mean difference in inflammatory proteins/cytokines between SJS and normal human control patients. All results showed a statistically significant elevation of p =.0078.**

| | SJS | NHP |
|---|---|---|
| | Mean | Mean |
| MCP | 222.7 | 25.28 |
| IL-6 | 50.25 | 2.35 |
| TNF-alpha | 3.2 | 0.77 |

abolic derangements that SJS/TEN can cause. While SJS/TEN is primarily a dermatological disorder, further work into exploring the potential metabolic derangement as a result of increased monocyte chemotactic protein-1 can improve our understanding of the total body effect of these diseases.

In addition to elevations in the aforementioned inflammatory biomarkers, ELISA analysis also revealed increased levels of hemostatically active components, namely F1.2 and TAT. These two biomarkers have been used in the past as a proxy to measure hypercoagulability. [28] Our results indicate that SJS/TEN patients suffer from a hypercoagulable state that increase their risk of embolic disease. The thromboembolic risk in SJS/TEN patients has sparsely been explored, and while septicemia is the leading cause of morbidity and mortality during the early stages, this risk places patients at a greater risk for clinical complications. Furthermore, while our research did not show statistically significant increase in Microparticle levels, PAI-1 levels, Protein C levels, and antithrombin levels, their increased variance suggest altered activation when compared to normal human samples. Other reports of expression of endocan, IL13, IL-33 and TGF-β may have complementary roles in immune-mediated activation of coagulation in SJS/TEN.[29, 30] The combination of these results highlight the disarray on the hemostatic system that SJS/TEN can have, and that further research into this area is necessary to better our treatment of these devastating diseases.

## Conclusion

The results of our study show an increase in variance of prothrombotic factors in plasma of patients with confirmed SJS and suspected SJS when compared to controls. In addition, there was found to be increased expression of immunologically active proteins such as granulysin, TNF-alpha and monocyte chemotactic protein-1 as well as an unidentified peak at 15.1 kDA on mucosal swab that could reveal to be an immunologically important protein contributing towards the disease process. While the interface between coagulation and SJS/TEN has sparsely been explored, these preliminary results reveal that there may be contribution from widespread hypercoagulability and endothelial dysfunction involved in the disease process.

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