

Concomitance or consequence? Stevens-Johnson syndrome in COVID-19: A case report

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Abstract. The novel coronavirus infection has been, and still is, a pressing medical problem with a catastrophic effect, not only from a medical point of view, but also from an economic and social one. The cutaneous manifestations of the disease have a diverse morphology and can signal the presence of the infection. The present article reports the case of a 77-year-old male patient admitted at The Sf. Parascheva Clinical Hospital of Infectious Diseases in Iasi (Romania) after testing positive for SARS CoV-2 infection. Initially, the patient presented a pruriginous generalized maculopapular-erythematous eruption with a tendency towards confluence, peri-oro-nasal meliceric crusts and desquamation of the skin on the third anterosuperior and posterior thorax, scalp and forehead, which was accompanied by low back pain, headache and orbital pain. The suspicion of Stevens-Johnson syndrome (SJS) was raised, and treatment was given according to the recommendation of the hospital dermatologist. This association raises multiple questions regarding whether SJS is a cutaneous manifestation of COVID-19 or if there was a concomitance between the viral infection and the immune reaction. The combination of SJS and COVID-19 can have a fatal outcome if not recognized and promptly treated. To our knowledge, this is the first case of SJS in a patient diagnosed with SARS CoV-2 infection in Romania.

Introduction

The pandemic created by SARS CoV-2 infection still represents a pressing medical problem considering the multitude of risk factors for severe disease and the lack of specific symptoms (1-3). Sanitary education of the population and vaccination have served an essential role in prophylaxis by helping individuals understand the risks they are exposed to (4-7).

Literature highlights that cutaneous manifestation of SARS CoV-2 infection presents as lesions with varying morphology that could be classified in four categories: Acro-papular lesions, urticarial eruption, vascular (chilblain-like lesions, commonly known as COVID-19 toes, livedoid and purpuric lesions) and exanthema (morbilliform and papulo-vesicular rash and varicella-like eruption) (8-13).

Stevens-Johnson syndrome (SJS) has the potential to be a lethal skin reaction that has a mortality rate of up to 30%, which is caused by an immune-complex-mediated hypersensitivity reaction. The clinical presentation appears as mucosal and cutaneous tenderness accompanied by erythema, hemorrhagic erosions, and epidermal detachment that can be described as blisters and areas of denuded skin, accompanied by systemic symptoms (14,15). This disease is a dermatological emergency. The recognition in association with prompt and appropriate management can save the patient (16). The present study is a case report of a 77-year-old male with a metabolic, cardiologic and neurological history diagnosed with SARS CoV-2 infection associated with SJS. Few cases have been reported concerning this association, which raises the question of whether, in the case of our patient, SJS appeared independently from COVID-19 or was the primary manifestation of the disease (17-23).

Case report

The present article reports the case of a 77-year-old male patient with a history of stroke, stage-2 arterial hypertension, dyslipidemia, obesity and gout, together with an underlying treatment: Aspirin, 75 mg; bisoprolol, 2.5 mg bidaily; atorvastatin, 10 mg/day; vinoxpectine, 10 mg bidaily; and allopurinol,

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Figure 1. Clinical presentation of the dermatological lesions at hospital admission. The images demonstrate disseminated maculopapular-erythematous eruption with a tendency towards confluence with desquamation of the skin on the third anterosuperior and posterior thorax.

100 mg bidaily. The gout medication was prescribed 14 days before admission to our hospital.

Initially, the patient presented to the Emergency Room of Sf. Spiridon County Hospital for a non-pruriginous generalized maculopapular-erythematous eruption with a tendency towards confluence, accompanied by low back pain, headache and orbital pain. Considering the epidemiological context, a reverse transcription PCR for SARS CoV-2 virus and a CT scan were performed. The result of the molecular test was positive, and the CT examination demonstrated bilateral centrilobular emphysema and bilateral apical pachypleuritis. In the inferior two-thirds of the lungs, bilateral, extensive areas of pulmonary condensation were observed that were predominantly located subpleurally, heterogeneous and imprecise. Based on these results, the patient was directed to Sf. Parascheva Clinical Hospital of Infectious Diseases, which was a designated first-line COVID-19 hospital.

At admission, the patient had a general fair status and was conscious. He was experiencing bradylalia, but stable both hemodynamically and in terms of respiration (blood pressure, 106/67 mmHg; heart rate, 95 beats/min; oxygen saturation, 98% ambient air). This was associated with the aforementioned lesions, as well as peri-oronasal meliceric crusts and desquamation of the skin on the third anterosuperior and posterior thorax, scalp and forehead (Fig. 1).

Considering the clinical and paraclinical evidence (Table I), the suspicion of SJS was raised, and a dermatological consultation was requested, which confirmed the diagnosis. The recommendations were to stop the administration of allopurinol and administer methylprednisolone at 250 mg/day, 20 mg bilastine bidaily, vitamin C intravenously at 500 mg bidaily, gluconic calcium at 10 ml/day (94 mg/ml), vitonal and gentamicin cream (applied bidaily on the lesions located on the peri-oronasal area) and a cream consisting of 5 g urea, 1 g

Table I. Laboratory data.

Parameter	Date of measurement					
	20.11	23.11	24.11	26.11	30.11	3.12
Leukocytes (per mm ³)	27,840	NA	12,820	12,320	9,690	10,210
Neutrophil (%)	70.70	NA	79.2	82.3	87.3	83.40
Lymphocytes (%)	11.20	NA	14.3	11	9.2	13.50
Platelets (per mm ³)	349,000	NA	274,000	233,000	79,000	117,000
C-reactive protein (mg/l)	27.3	NA	31.57	NA	58.66	53.46
ESR (mm/h)	18	NA	20	NA	40	85
INR	1.33	NA	NA	NA		2.42
Fibrinogen (g/l)	1.8	NA	NA	NA	3.29	3.29
IL-6 (pg/ml)		27.19	NA	NA	NA	NA
D-dimer	1235	NA	NA	NA	NA	NA
Urea (mg/dl)	172	NA	86	85	102	118
Creatinine (mg/dl)	1.75	NA	1.2	0.95	0.96	1.11
Glucose (mg/dl)	140	NA	111	NA	103	103
Na (mmol/l)	141	NA	146.1	146.6	146.7	146.7
K (mmol/l)	4.37	NA	3.99	4.05	4.80	4.58
Cl (mmol/l)	97.7	NA	102.6	103.1	105.2	105.4
HCO ₃ (mmol/l)	NA	21.4	NA	13.6	NA	NA
ALT(U/l)	37	NA	62	NA	63	58
AST(U/l)	39	NA	80	NA	88	88
Bilirubin (mg/dl)	1.25	NA	1.31	1.60	1.15	2.64
Ionic calcium (mg/dl)	NA	NA	NA	4.72	NA	4.40
HIV serology	NA	Negative	NA	NA	NA	NA
LDH (U/l)	NA	NA	NA	NA	609	NA
Total protein (g/l)	60.78	NA	NA	NA	75.21	NA
Ferritin (ng/ml)	NA	511	NA	NA	NA	NA

ESR, erythrocyte sedimentation rate; ALT, alanine transaminase; AST, aspartate transaminase; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; INR, international normalized ratio.

hydrocortisone and 100 g Vaseline® (applied bidaily over all affected areas). In addition, antibiotic (meropenem, 4 g/day; linezolid, 1.2 g/day), anticoagulant (enoxaparine sodium, 0.6 mg bidaily), acetaminophen (500 mg) and acetylcysteine (600 mg/daily) were administered.

The algorithm of drug causality for epidermal necrolysis (ALDEN) and the severity-of-illness score for toxic epidermal necrolysis (SCORTEN) were calculated. The ALDEN score for the patient was 5, corresponding to a 'probable' causal link, suggesting that the implicated drug in our case could be allopurinol (Table II). In addition, the SCORTEN was 3 for this patient, indicating a mortality rate of 35.3% (Table III).

After five days of treatment, the dermatological aspects had a favorable evolution, with healing of most of the lesions but persistence of those located on the inferior limbs (Fig. 2). However, the general condition of the patient started to deteriorate. On the 7th day of admission, the patient desaturated to 76% ambient air, requiring an oxygen supplement that corrected saturation to 93% with 15 l of additional oxygen. Therefore, an IL-1 inhibitor was added to his treatment (200 mg on day 1, then 100 mg/day for four days). Considering his status, an

intensive care unit consultation was requested, arterial gases were measured, which suggested that the patient was in metabolic acidosis (low PaCO₂ and HCO₃), and recommendations for intensive care therapy were given.

After 20 days of hospitalization, the patient had a fatal outcome.

Discussion

SJS/toxic epidermal necrolysis (TEN) represents a significant dermatological emergency, being one of the most severe cutaneous adverse reactions and associated with a high risk of mortality. SJS/TEN, due to an immune-complex-mediated hypersensitivity reaction, involves the mucous membranes and skin (24,25). Initial symptoms can be unspecific and include fever, cough, sore throat or eye discomfort, which are followed by the cutaneous manifestations (26).

SJS/TEN is drug-induced in 70-80% of cases. Graft versus-host disease is another well-established but rare cause, independent of drugs (27). A few cases are related to infections (such as with *Mycoplasma pneumoniae*), while others remain unexplained (idiopathic forms) (28).

Table II. ALDEN results for allopurinol.

Score	Value
Delay from initial drug intake to index day	+3
Drug present in the body (on index day)	0
Pre-challenge/Re-challenge	0
De-challenge	0
Type of drug (notoriety)	+3
Other cause	-1
Total ALDEN score	5 ^a

^aThis value corresponds to a 'probable' causal link. ALDEN, algorithm of drug causality for epidermal necrolysis.

Table III. SCORTEN score.

Prognostic factor	Score
Age >40 years	1
Associated cancer	0
Heart rate >120 bpm	0
Serum blood urea >28 mg/dl	1
Detached or compromised body surface >10%	1
Serum bicarbonate <20 mmol/l	0
Serum glucose >250 mg/dl	0
Total SCORTEN	3

Mortality rate according to score: 0-1, 3.2%; 2, 12.1%; 3, 35.3%; 4, 58.3% and ≥ 5 , $\geq 90\%$. SCORTEN, severity-of-illness score for toxic epidermal necrolysis; bpm, beats per minute.

This pathology represents a delayed reaction that usually occurs 4-28 days from the moment of exposure to a drug (29); thus, it is of utmost importance to conduct an in-depth anamnesis and a thorough retrospective pharmacological investigation for an extended period of time preceding the onset of skin manifestations.

The drugs that are associated with SJS/TEN include anticonvulsants, allopurinol, sulfonamides, antibiotics (such as penicillin, cephalosporins, quinolones and minocycline), acetaminophen and nonsteroidal anti-inflammatory drugs (30-33).

The ALDEN score is one of the most valuable tools in the assessment of SJS/TEN, which helps identify the possible drug associated with the severe cutaneous adverse reaction, as well as the drugs that can still be administered to the patient (34). The algorithm gives the suspected causal drug taken by the patient a score that sums between -12 and 10, which corresponds to the probability of having caused the reaction. The total score corresponds to 'causal links' that range from 'very unlikely' to 'very probable' (35). SJS can occur as a rare side effect of allopurinol, which, in this case, could have been favored by the immune stimulation induced by the SARS CoV-2 virus. This idea is supported by the fact that SJS/TEN has been associated with viral replication (human immunodeficiency



Figure 2. Clinical presentation of the dermatological lesions after the treatment.

virus and cytomegalovirus) (36-39), suggesting this could also be possible in SARS CoV-2 infection in our case. Therefore, it may be hypothesized that allopurinol was the causative agent of SJS/TEN, although the fact that SJS/TEN could be a cutaneous manifestation of SARS CoV-2 infection and or represent a consequence in this type of viral infection should not be discounted.

The severity of SJS/TEN can be assessed using SCORTEN, which is a severity-of-illness scale that was defined in 2000 and is a specific predictor of mortality. The score includes the following variables: Age >40, the presence of neoplasia, heart rate >120 bpm, serum blood urea >28 mg/dl, serum glucose >250 mg/dl, serum HCO_3^- <20 mmol/l and >10% detached body surface. Each constant receives one point, and the final score ranges from 0 to 7. (40). In the presented case, the patient had an initial score of 3, which indicated mortality of 35.3%. As the status of the patient started to deteriorate, and the HCO_3^- level decreased to 13.6 mmol/l, the prognosis of mortality grew to 58.3%.

In our case, although correct dermatological treatment led to a favorable evolution of the skin lesions (41,42), the patient's condition was ultimately influenced by the complication of SARS CoV-2 infection, which progressed to respiratory failure associated with major hydro-electrolytic and acid-base imbalance. Together with the negative prognostic factors that the patient presented (hypertension, obesity and dyslipidemia) (43-45), this led to a fatal outcome.

The SCORTEN in our patient led to an estimated mortality rate of 35.3% that later grew to 58.3% as a result of bicarbonate

levels being <20 mmol/l (Table III). Therefore, one might ask whether SJS/TEN influenced the unfavorable evolution of the patient and if SJS/TEN can appear in (or perhaps be a predictor of) severe forms of SARS CoV-2 infection.

In conclusion, although SJS/TEN is a rare pathology, it represents a major dermatological emergency. The combination between SJS/TEN and COVID-19 can have a fatal outcome if not recognized and promptly treated. To the best of our knowledge, this is the first case of SARS CoV-2 and SJS/TEN association in Romania. This association raises multiple questions regarding the possibility of SJS/TEN being a cutaneous manifestation of COVID-19. Whether this association is a simple coincidence or complication of the physiopathological events of the infection with the new coronavirus remains to be determined.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

CM, GAL and FDP designed the study. CS and AV contributed to data extraction and quality assessment. CM, GAL and AV were responsible for the analysis and discussion of data. CM, GAL and FDP drafted the manuscript. AV, CMA and CS revised the manuscript critically and made substantial intellectual contributions. All authors read and approved the final manuscript. CM, GAL, CMA and CS confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Written informed consent was obtained from the patient prior to admission.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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