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CASE REPORT

A CASE OF FEVER AND POLYMORPHOUS RASH IN A PATIENT WITH RECENT SARS-COV-2 INFECTION

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Abstract

Introduction. Multisystem inflammatory syndrome in adults (MIS-A) is a rare but potentially life-threatening sequel of SARS-CoV-2 infection, requiring early recognition and treatment. Nevertheless, it is often hard to distinguish MIS-A from other COVID-19-related hyperinflammatory complications.
Case presentation. A 74-year-old male presented to the emergency department with persistent fever, diarrhea, altered consciousness, polymorphous rash with oral lesions and erythema of the palms and soles, with progressive exfoliation. The patient had been hospitalized for COVID-19 four weeks before and was suffering from chronic lymphocytic leukemia, diabetes and hypertension. During his recent hospital stay he received multiple courses of antibiotics and was discharged home with instructions to add sitagliptin and re-initiate therapy with ibrutinib. Upon re-admission, polymerase chain reaction test for SARS-CoV-2 was still positive and inflammatory markers were markedly elevated. Although MIS-A could not be excluded, a presumptive diagnosis of Stevens-Johnson Syndrome (SJS) was made, and the patient was treated empirically with intravenous immunoglobulin and high-dose methylprednisolone. SJS is usually considered an adverse drug reaction that affects the skin and mucous

Résumé

La difficulté à gérer un cas avec fièvre et éruption multiforme après une infection récente par le SRAS-CoV-2

Introduction. Le syndrome inflammatoire multisystémique de l'adulte (MIS-A) est une séquelle rare mais potentiellement mortelle de l'infection par le SARS-CoV-2 nécessitant une détection et un traitement précoces. Néanmoins, il est souvent difficile de distinguer le MIS-A des autres infections liées au COVID-19. complications hyperinflammatoires.
Rapport du cas. Un homme de 74 ans s'est présenté au service des urgences avec une fièvre persistante, une diarrhée, une altération de la conscience, une éruption cutanée polymorphe avec des lésions buccales et un érythème des paumes et des plantes avec exfoliation progressive. Le patient avait été hospitalisé pour COVID-19 il y a quatre semaines et souffrait de leucémie lymphoïde chronique, de diabète et d'hypertension. Au cours de son récent séjour à l'hôpital, il a reçu plusieurs cures d'antibiotiques et a été renvoyé chez lui avec pour instruction d'ajouter de la sitagliptine et de reprendre le traitement par ibrutinib. Lors de la réadmission, le test de réaction en chaîne par polymérase pour le SRAS-CoV-2 était toujours positif et les

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membranes. In this patient, MIS-A was also initially included in the differential diagnosis due to previous COVID-19, despite the patient's advanced age and lack of cardiac involvement or conjunctivitis. The patient only partially fulfilled current diagnostic criteria for MIS-A.

Conclusions. SJS results from a dysregulated immune response and can have a similar presentation to MIS-A. A better characterization of both conditions is required particularly in older adults with comorbidities, to facilitate timely diagnosis and management and to reduce mortality.

Keywords: SARS-CoV-2 infection, multisystem inflammatory syndrome in adults, Stevens-Johnson Syndrome.

List of abbreviations

CLL – chronic lymphocytic leukemia
CT – computed tomography
ESR – erythrocyte sedimentation rate
IVIG – intravenous immunoglobulin
MIS-A – multisystem inflammatory syndrome of adults
SJS – Stevens-Johnson syndrome

Résumé

Introduction. Le syndrome inflammatoire multisystémique de l'adulte (MIS-A) est une complication rare et potentiellement mortelle de la maladie à coronavirus 2019 (COVID-19). Le syndrome de Stevens-Johnson (SJS) est une autre entité clinique rare et fatale, généralement associée à l'administration de médicaments un à quatre semaines avant sa manifestation. Le SJS peut initialement imiter une infection des voies respiratoires supérieures et évoluer ensuite vers sa forme sévère avec atteinte cutanée et des muqueuses. Le diagnostic différentiel entre ces syndromes potentiellement mortels est extrêmement difficile, surtout lorsqu'il concerne des patients ayant reçu de multiples médicaments.

Présentation du cas. Un homme de 74 ans s'est présenté aux urgences pour cinq jours de fièvre (>38°C), nécessitant une oxygénothérapie par canule nasale (6 L/min), une diarrhée, un état cognitif légèrement altéré et un exanthème polymorphe apparu trois jours auparavant. Les lésions cutanées s'étendaient au tronc supérieur et aux extrémités et étaient accompagnées d'un érythème marqué et d'un gonflement des paumes et des plantes, suivis d'une exfoliation progressive. Le patient a également présenté des lésions muqueuses buccales, avec des lèvres rouges et craquelées et des difficultés à déglutir. Le signe de Nikolsky était négatif. Les tests de laboratoire étaient notables pour des marqueurs inflammatoires élevés, notamment la ferritine (>2 000 mcg/L, valeurs normales 24-336 mcg/L), la protéine C-réactive (>230 mg/L, valeurs normales <6 mg/L), la vitesse de sédimentation érythrocytaire (VS) (31 mm/h) et l'interleukine-6 (IL-6) (282, valeurs normales <7). Une numération plaquettaire réduite (37 000/µL) confirmée à l'examen d'un frottis sanguin et une altération de la fonction rénale ont également été observées (créatinine 1,6 mg/dL, urée sanguine 74 mg/dL).

Discussion. Le patient présentait des antécédents d'hypertension, de diabète sucré et de leucémie lymphoïde chronique (LLC) avec une réponse adéquate au traitement par ibrutinib. Le patient était entièrement vacciné et avait reçu une dose de rappel contre le SARS-CoV-2 avec un vaccin à ARNm. Néanmoins, un mois auparavant, il avait été hospitalisé pendant 12 jours pour une infection modérée à sévère au SARS-CoV-2. Il a reçu un supplément d'oxygène, ainsi que de la dexaméthasone, du remdésivir, une antibiothérapie empirique par ceftriaxone, lévofloxacine et méropénem et enfin une thromboprophylaxie par énoxaparine. Durant cette hospitalisation initiale, une hypogammaglobulinémie sévère secondaire à la LLC et une réactivation de l'hépatite B avec séroconversion des antigènes de surface et e ont également été identifiées. Cependant, les marqueurs inflammatoires étaient nettement élevés. Bien que le MIS-A n'ait pas pu être exclu, un diagnostic présomptif de syndrome de Stevens-Johnson (SJS) a été posé et le patient a été traité de manière empirique avec des immunoglobulines intraveineuses et de la méthylprednisolone à haute dose. Le SJS est généralement considéré comme une réaction indésirable aux médicaments qui affecte la peau et les muqueuses. Pour cet individu, le MIS-A a également été initialement inclus dans le différentiel en raison de l'infection antérieure au COVID-19 malgré l'âge avancé du patient et l'absence d'atteinte cardiaque ou de conjonctivite. Le patient ne remplissait que partiellement les critères de diagnostic actuels du MIS-A.

Conclusions. Le SJS résulte d'une réponse immunitaire dérégulée et peut avoir une présentation similaire au MIS-A. Une meilleure caractérisation des deux affections est nécessaire, en particulier chez les personnes âgées présentant des comorbidités, afin de faciliter le diagnostic et la prise en charge en temps opportun et de réduire la mortalité.

Mots-clés: SARS-CoV-2 infection, syndrome inflammatoire multisystémique de l'adulte, syndrome Stevens-Johnson.

Introduction

Multisystem inflammatory syndrome in adults (MIS-A) is a rare and potentially life-threatening complication of coronavirus diseases 2019 (COVID-19)[1]. Nevertheless, the lack of definite criteria for its recognition makes the positive diagnosis difficult. Stevens-Johnson syndrome (SJS) is another rare and fatal clinical entity, mostly associated with drug administration one to four weeks prior to its manifestation. SJS can initially imitate an upper respiratory infection and then develop into its severe form with skin and mucous membrane involvement[2]. The differential diagnosis between these life-threatening syndromes is extremely difficult, especially when it concerns patients who have received multiple pharmaceutical agents.

Case presentation

A 74-year-old male presented to the emergency department for five days of fever (>38°C), need for supplemental oxygen therapy via nasal cannula (6 L/min), diarrhea, slightly impaired cognitive status, and a three-days onset polymorphous rash. The skin lesions extended to his upper trunk and extremities and were accompanied by marked erythema and swelling of the palms and soles, followed by progressive exfoliation (Figures 1A-C). The patient also experienced oral mucosal changes, with red and cracked lips and difficulty swallowing. The Nikolsky's sign was negative. Laboratory tests were noteworthy for increased inflammatory markers including ferritin (>2,000 mcg/L, normal range 24-336 mcg/L), C-reactive protein (>230mg/L, normal range<6 mg/L), erythrocyte sedimentation rate (ESR) (31 mm/hr) and interleukin-6 (IL-6) (282, normal range <7). A reduced platelet count (37,000/µL) confirmed on examination of a blood smear and impaired kidney function were also observed (creatinine 1.6 mg/dL, BUN 74 mg/dL).

His medical history was remarkable for hypertension, diabetes mellitus, and chronic lymphocytic leukemia (CLL) with adequate response to the treatment with ibrutinib. The patient was fully vaccinated and boosted against SARS-CoV-2 with an mRNA vaccine. Nevertheless, one month before, he was hospitalized for 12 days because of moderate-to-severe SARS-CoV-2 infection. He received supplemental oxygen, as well as dexamethasone, remdesivir, empiric antibiotic therapy with ceftriaxone, levofloxacin and meropenem and finally thromboprophylaxis with enoxaparin. During this initial hospital stay, severe hypogammaglobulinemia secondary to CLL and reactivation of hepatitis B with seroconversion of the surface and e antigens were also identified. However,

antiviral therapy for hepatitis B was not initiated at that time. At discharge he was prescribed cefuroxime for five days and his anti-hypertensive regimen was revised from manidipine and perindopril to a fixed combination of valsartan/amlodipine. Moreover, sitagliptin was added to background antidiabetic treatment with metformin and the patient was advised to continue therapy with ibrutinib for CLL.

Upon re-admission, the patient's nasopharyngeal swab persistently checked positive on reverse transcription polymerase chain reaction for SARS-CoV-2. Computed tomography (CT) of the thorax and abdomen revealed lung infiltrates consistent with past COVID-19 infection, although the radiographic findings had improved since his previous hospitalization. The patient had no signs of cardiac dysfunction, echocardiogram indicated a normal ejection fraction with signs of left ventricular dysfunction and laboratory tests, including troponin and B-type natriuretic peptide, were normal. Despite the lack of cardiac involvement, the patient met the other primary clinical criterion (rash without conjunctivitis), as well as three out of four secondary clinical criteria (diarrhea, thrombocytopenia, altered mental status) set forth by the U.S. Centers for Disease Control and Prevention for the diagnosis of multisystem inflammatory syndrome in adults (MIS-A) (Table 1)[3]. He also had laboratory evidence of recent SARS-CoV-2 infection, as well as markedly increased inflammatory markers (ferritin, CRP, ESR, IL-6).

Diagnostic work-up

The differential diagnosis primarily spanned between the following conditions:

- The temporal association of the patient's symptoms with the documented SARS-CoV-2 infection raised the suspicion of MIS-A. Apart from evidence of hyperinflammation and Kawasaki-like exfoliating lesions of the palms and soles, as well as the lips and oral mucosa, the patient did not have evidence of cardiac involvement. Besides that, most cases of MIS-A reported to date are amongst young and middle-aged adults[4].
- Mucocutaneous changes were typical for Stevens-Johnson Syndrome (SJS), which can be regarded as a less severe form of toxic epidermal necrolysis with less than 10-30% of body surface involvement. The patient had received multiple courses of offending antibiotics and was also started on a dipeptidyl-peptidase 4 inhibitor[5,6]. Of note, serologic testing for *Mycoplasma pneumonia* that has been associated with SJS was negative[7].

Other less probable diagnoses that had to be excluded are listed below:

- A polymorphous rash could also be precipitated especially in a patient with CLL by several herpes viruses such as varicella-zoster virus, cytomegalovirus, Epstein-Barr or herpes simplex viruses, but serologic and molecular testing for those pathogens was negative[8]. Coxsackie viruses could also cause vesicular sores with blisters on palms, feet and sometimes on the lips. The respective serologic tests revealed borderline positive IgM antibody titers, but confirmatory testing two weeks later was not consistent with an acute Coxsackie infection[9].
- The case could as well represent biphasic COVID-19 disease in an immunocompromised host, but oxygen requirements were minimal at re-admission and repeat CT scan of the thorax suggested that pulmonary manifestations had alleviated.
- Polyarteritis nodosa or other vasculitis secondary to hepatitis B reactivation (HBV-DNA>1x10^9 normal range<6) or following SARS-COV-2

Table 1.U.S. Centers for Disease Control and Prevention case definition for healthcare providers of multisystem inflammatory syndrome in adults. Available from https://www.cdc.gov/mis/mis-a/hcp.html (accessed on May 1st, 2022)[4].

A patient aged ≥21 years hospitalized for ≥24 hours, or with an illness resulting in death, who meets the following clinical and laboratory criteria. The patient should not have a more likely alternative diagnosis for the illness.	
Clinical Criteria	Subjective fever or documented fever (≥38.0oC) for ≥24 hours prior to hospitalization or within the first THREE days of hospitalization and at least THREE of the following clinical criteria occurring prior to hospitalization or within the first THREE days of hospitalization. At least ONE must be a primary clinical criterion.
Primary clinical criteria	1. Severe cardiac illness 2. Rash AND non-purulent conjunctivitis
Secondary clinical criteria	1. New-onset neurologic signs and symptoms. Includes encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs, or peripheral neuropathy (including Guillain-Barré syndrome) 2. Shock or hypotension not attributable to medical therapy 3. Abdominal pain, vomiting, or diarrhea 4. Thrombocytopenia (platelet count <150,000/μL)

infection (negative ANA, MPO ANCA, PR3 ANCA, Anti-ENA screen, Anti-Sm, Anti-CCP, RA-test, cryoglobulinemia)[10].

- Hospital-acquired bacterial infection leading to potential sepsis, although blood and urine cultures subsequently turned out negative[11].
- Hemophagocytic syndrome associated with CLL[12].

Management and clinical course

Due to the high mortality rate of both MIS-A and SJS and taking into account the patient's immunocompromised status (i.e. CLL with severe hypogammaglobulinemia), we decided to initiate upfront treatment with combined intravenous immunoglobulin (IVIG) plus a glucocorticoid. IVIG was administered at a dose of approximately 1.5 g/kg as a single infusion over 8 –12 hours, while glucocorticoid therapy consisted of methylprednisolone at a daily dose of 2 mg/kg with gradual tapering as soon as fever had resolved and skin lesions had stabilized[13]. Due to the patient's critical condition, and the fact that there was no accurate diagnosis, we chose this treatment option which applies to both clinical syndromes with small differences in dosage range. Because the aforementioned disorders can mimic septic complications and toxic shock syndrome, we also started empiric treatment with a broad-spectrum antibiotic regimen covering potential nosocomial infections which included meropenem, amikacin and teicoplanin. Nevertheless, shortly thereafter we de-escalated antibiotic therapy based on rapid clinical improvement and negative culture results to avoid further aggravation of the underlying SJS. Based on his hepatitis B serological profile, the patient also received concomitant prophylactic treatment with entecavir, given the need for high doses of glucocorticoids and severe immunosuppression.

After five days of treatment, the patient's clinical condition showed gradual improvement with resolution of fever and no further need for oxygen supplementation. Exfoliation was contained within the affected skin areas and most laboratory tests returned to normal. However, platelet count remained below 50,000/μL and gradually restored after the 14th day of treatment. The cause of thrombocytopenia was probably multifactorial. The hyperinflammatory state, the fact that our patient suffered from CLL which is often associated with autoimmune thrombocytopenia and the administration of many different drug therapies that can affect platelet levels, are all factors that can contribute to persistent thrombocytopenia.

At day 45 after discharge the patient was able to withdraw glucocorticoids and skin lesions were minimal and limited in the palms and soles.

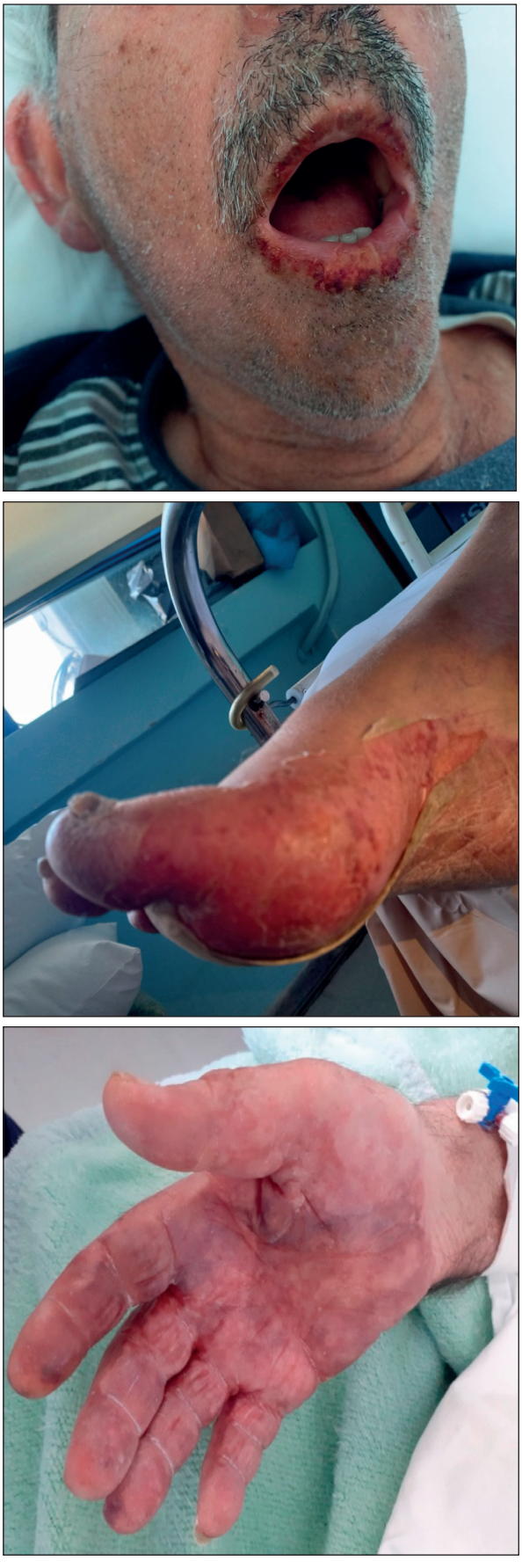

Figure 1. Exfoliating skin lesions with erythema of the palms and soles as well as red and cracked lips (1,2,3).

Implications for practice

MIS-A and SJS have overlapping phenotypes and both conditions are associated with hyperinflammation, blistering skin lesions and conjunctivitis. MIS-A usually affects the palms and soles, as well as the lips, whereas oral cavity involvement is more often seen in SJS. Medications are the leading trigger of SJS, whereas evidence of a preceding COVID-19 infection within two to five weeks is required for the diagnosis of MIS-A. Finally, cardiac manifestations are solely evident in MIS-A.

Adults, particularly those with pre-existing proinflammatory comorbidities such as the patient described herein, are more likely to develop MIS-A, which is characterized by abnormal interferon release that drives macrophage hyperactivation. Hyperinflammation in the context of COVID-19 shares similarities with cytokine release syndromes[4]. On the other hand, a drug-mediated T-cell cytotoxic reaction in keratinocytes is likely implicated in the pathogenesis of SJS. Of note, the underlying mechanisms behind both conditions are yet incompletely understood.

The healthcare of patients with MIS-A is mainly supportive and requires a multidisciplinary team including infectious disease, rheumatology and cardiology specialists. The efficacy of early combination therapy with IVIG plus glucocorticoids is debatable and evidence derives largely from case series in children in whom MIS is relatively more common. Although no apparent difference in mortality rates was noted, combination therapy might reduce the need for hemodynamic support and left ventricle dysfunction[13,14]. Similarly, for SJS observational studies have failed to demonstrate a survival benefit with IVIG and the role of glucocorticoids remains uncertain. Therefore, optimal supportive care including topical management, fluid and electrolytes replacement, nutritional support, pain control and treatment of infections is recommended. Growing data support the potential benefit of using cyclosporine or tumor necrosis factor inhibitors during the first 24 to 48 hours, although the level of evidence is low. Randomized controlled trials are utterly needed to evaluate candidate therapies for these uncommon disorders[15].

Conclusions

In conclusion, it might be difficult for practicing clinicians to differentiate between hyperinflammatory conditions that involve the skin especially in older adults with comorbidities. Presentation of MIS-A and SJS might be indistinguishable, but therapeutic interventions with immunomodulatory agents are aligned.

Author's Contribution:

T.M., A.L, N.K., I.A., S.M., and A.S., were responsible for the clinical diagnosis and treatment decisions in this case, while T.M. and A.L. were responsible for case presentation and writing the manuscript.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article"

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patient included in the study"

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None

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