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Cytomegalovirus reactivation in non-severe COVID-19: two emblematic cases of oropharyngeal mucositis in immunocompromised patients

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Background

- This new phase of COVID-19 pandemic is characterized by a more sustainable burden, as it is dominated by less virulent variants interacting with a limitedly susceptible population, due to the presence of a broad specific immunization (either natural or due to large-scale vaccination programmes), in immunocompetent individuals
- In this milder phase, increasing interest is dedicated to the understanding of COVID-19 post-acute sequelae and to obtain a clearer view its clinical heterogeneity. In particular, focusing on non-severe COVID-19 may reveal the mechanisms of a subacute clinical progression, and highlight the role of coinfections and reactivations of latent pathogens, particularly high-prevalence viruses, such as herpesviruses
- Undoubtedly, immunocompromised subjects represent the main challenge of the current phase, due to a limited response to vaccines, prolonged viral shedding, and reactivation of microorganisms.
- Cytomegalovirus (CMV) is a well-known exacerbating factor of severe COVID-19, particularly of pneumonia, but wide knowledge gaps remain about CMV role in non-severe COVID-19, especially when dermatological clinical features are concerned. As a consequence, specific therapeutic management is not clearly defined.

Cases description and discussion

- The two reported cases (detailed in the Table) presented some important common features. Both were immunosuppressed due to a rheumatological disease (F, 48 years; mixed connective tissue disease with Sjögren syndrome and seronegative arthritis) or, combinedly, rheumatological and oncohaematological disorders (M, 64 years; ankylosing spondylitis and chronic lymphatic leukemia), undergoing anti-CD20 therapy (rituximab).
- The two subjects exhibited a long-term positivity (months) of SARS-CoV-2 nasopharyngeal swabs, with radiological findings of severe persisting lung alterations, but with a largely compensated clinical presentation, due to a slow adaptation. Both developed orolabial painful herpes-like lesions (Figure), in the presence of CMV-DNA on blood samples, documented by PCR. Bioptic sampling of the lesions was rejected by the patients.
- In both cases, the administration of valganciclovir correlated with rapid relief and a regression of the lesions, with a comparable timing of about 5 days;
- Our observations are clearly limited by their "*ex adiuvantibus*" nature and by the availability of a limited sample. Nevertheless, literature evidence for CMV role in non-severe COVID-19 patients is drastically scarce. Thus, we suggest that a quantity of orolabial ulcers may be due to a low-level replication of CMV, rather than SARS-CoV-2 itself, and it would be ideal to understand the targets of CMV-specific therapies.

CASES	1	2
SEX	F	M
AGE	48	64
RPA	Mixed connective tissue disease, Sjögren syndrome and seronegative arthritis, Long QT syndrome, osteoporosis, multifactorial anaemia, polycystic ovary, endometriosis, thyroid nodules, bilateral cataract, ulnar neuropathy	CLL (2015), ankylosing spondylitis, OSAS (nocturnal CPAP therapy, at home), BPH, hypertension, AMI (2022), carpal tunnel syndrome
IMMUNOSUPPRESSIVE DRUGS	CCS Rituximab	Rituximab Infliximab (discontinued, due to ADR, remotely) Methotrexate (discontinued, 1 month earlier)
SARS-COV-2 VACCINATION STATUS	3 DOSES, mRNA-based	3 DOSES, mRNA-based
PPA	(July, 2023) - paucisymptomatic COVID-19 (10/11/2022) - I hospital admission (due to respiratory failure); already known COVID-19; Chest CT (10/11/2022): diffuse GGOs, wide crazy paving areas	(28/2/2023) - I hospital admission (due to respiratory failure) concurrent COVID-19 diagnosis; Chest CT: typical, CT severity score 12/25; Therapy: CCS, oxygen, antivirals (see below) (20/3/2023) - II hospital admission (due to respiratory failure, P/F nadir 162); Chest CT: typical, CT severity score 20/25; Therapy: CCS, oxygen, early therapies (see below)
1st POSITIVE SARS-CoV-2 NPS	2/11/2022	28/2/2023
CMV DNA (WHOLE BLOOD) (PCR)	(12/11/2022) : 202 UI/mL (2/12/2022): 1761 UI/mL (30/12/2022): 10507 UI/mL	(11/4/2023): 1360 UI/mL - (28/4/2023): 170 UI/mL
SARS-CoV-2 RNA (NPS) (RT-qPCR for genes E, N, and Orf1ab)	(14/11/2022): CT 20, 21, 20 (2/12/2022): CT 19, 19, 19 (2/1/2023): CT 29, 30, 29	(11/4/2023): CT 31,31,31 (28/4/2023): CT 31,31,31 (11/5/2023): CT 23, 21, 21
ADDITIONAL INFO	(10/11/2022) UATs (Legionella, S. pneumoniae): negative HSV 1-2 IgM/IgG: negative (12/11/2022) serum BDG: 41.82 pg/mL (12/11/2022) serum EBV DNA: negative (12/11/2023) HBV, HCV, HIV screening, and QTF: negative	(March 2023) UATs (Legionella and S. pneumoniae): negative (11/4/2023) HBV, HCV, HIV screening, and QTF: negative; serum BDG and GM: negative serum inflammatory markers: stably negative (28/4/2023) serum protein electrophoresis: hypogamma 0.3 g/dL (total proteins 4.3, albumin 2.7) (4/5/2023) lymphocytes subtyping: CD4+ 386 cell/uL, CD8 369, CD4/CD8 1.00, (7/4/2023) PLT nadir 100000/µL (basal ~300000/µL)
GENERAL CLINICAL PRESENTATION - GENERAL MANAGEMENT	Low-grade fever, dyspnea (on exertion) - Therapy: ATB, CCS, oxygen (27/11/2022) topical nistatin, oral (escalation to IV fluconazole, 2 days later)	Fever, cough, dyspnea (on exertion), epistaxis - Therapy: ATB, CCS, oxygen
COVID-19 EARLY THERAPIES	CONTRAINDICATED/REJECTED	(28/2/2023): RDV (5 days) - (20/3/2023) RDV (10 days), TCZ, (21/3/23) Sotrovimab
DERMATOLOGICAL CLINICAL FEATURES	(1/12/2022): appearance of 2 small tongue ulcers (~ 7-8mm, painful), upon oral candidiasis (nistatin) (3/1/2023) burning, worsening nasopharyngeal pain; appearance of additional painful ulcers: 2 on the lower lip (~10 mm each, partially confluent, extending to the surrounding skin), one on the tongue (~ 8mm), and 2 on the face (one irregularly shaped, dmax ~ 18mm, with a small round satellite lesion, ~ 5mm)	(7/4/2023): burning oropharyngeal pain *sine materia*, glossitis (whitened tongue with an erytematous tip), multiple painful ulcers (~ 10 mm) located at the cheek mucosa and the transitional orolabial mucosa (vermillion zone), sore throat, dysphagia
CMV THERAPY (START)	5/1/2023	17/4/2023
CLINICAL-VIROLOGICAL IMPROVEMENT	5-7 days (clinical. Virological improvement was not reassessed due to patient's opposition)	5-7 days

Abbreviations: ADR (Adverse Drug Reaction); Ag (antigens); AMI (Acute Myocardial Infarction); RPA/PPA (Remote/Proximate Pathological Anamnesis); ATB (antibiotics); BDG (Beta-D-Glucan); BPH (Benign Prostatic Hypertrophy); CCS (corticosteroids); CPAP (Continuous Positive Airway Pressure); CT (cycle threshold); GGO (Ground-Glass Opacities); GM (galactomannan); IV (intravenous); NPS (nasopharyngeal swab); OSAS (Obstructive Sleep Apnea Syndrome); P/F (PaO2/FiO2 Ratio); PCR (Polymerase Chain Reaction); PLT (platelets); QFT (Quantiferon Test); RDV (remdesivir);TCZ (tocilizumab); UAT (Urinary Antigen Tests). Dates are espressed as dd/mm/yyyy.

Table- Schematic presentation of the cases

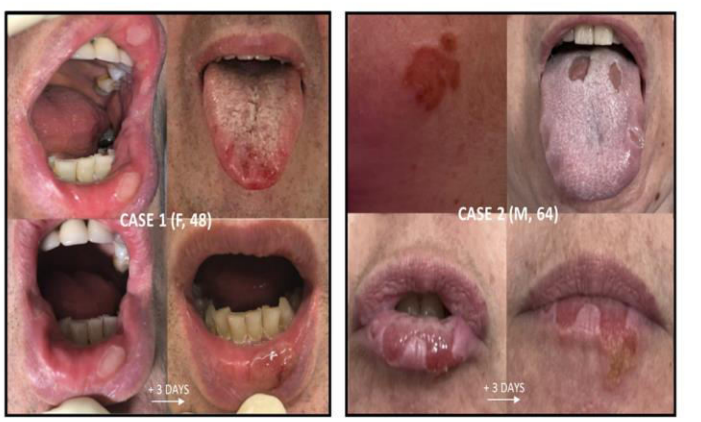

Figure- Photographs of the described dermatological findings

Conclusions

- COVID-19 patients with aphtous oral-perioral mucocutaneous lesions and a documented systemic replication of CMV (even low-grade), are likely to benefit from CMV-specific therapies.
- When feasible and accepted, bioptic studies may support the definition of the pathogenetic role of CMV in these patients, to offer therapeutic responses to a likely underestimated and undertreated subgroup of patients with mild CMV manifestations in mild COVID-19.

References

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