Dermatitis during spaceflight Associated with HSV-1 reactivation - A case Study

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BACKGROUND

- Background: Human alpha herpesviruses, herpes-simplex-virus 1 & 2, and varicella-zoster-virus (VZV), establish latency in various cranial nerve ganglia, and often reactivate in response to stress.
- In astronauts, reactivation of Epstein-Barr-virus (EBV), VZV, HSV-1 and Cytomegalovirus (CMV) are typically asymptomatic, though live/infectious virus is recovered and its shedding rate increases with spaceflight duration.
- The risk of clinical disease, therefore, increases for crewmembers assigned to extended missions (>180 days.)
- We report for first time, HSV-1 skin rash (dermatitis) occurring during a long duration spaceflight.
- **Hypothesis:** Stress associated with spaceflight dysregulates the immune status and stress hormones of astronauts that causes reactivation of latent herpes viruses and therefore, some clinical conditions.

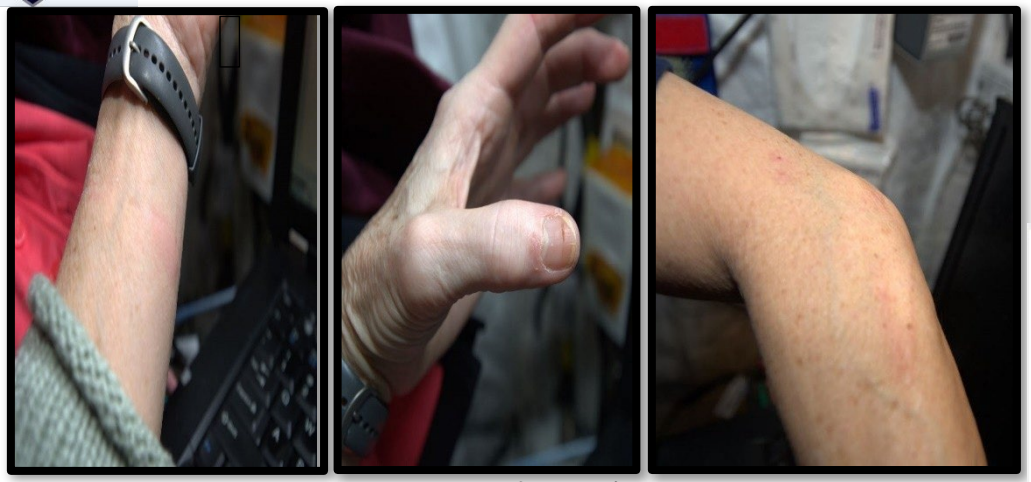
Results

- The crewmember reported a persistent dermatitis, which was treated in flight with antihistamines and topical/oral steroids. No HSV-1 DNA was detected in any pre-mission samples.
- Saliva and rash swab samples collected on flight day-82 yielded ~~a~~ high HSV-1 viral copies.
- Post-mission saliva samples yielded infectious HSV-1. HSV-1 from both rash and saliva samples had 99.4% genotype homology.
- Physiological stress biomarkers (cortisol, DHEA, and salivary amylase), immune markers (adaptive regulatory and inflammatory plasma cytokines) and biochemical profile markers including vitamin/mineral status and bone metabolism are also presented for this case.
- These data highlight an atypical presentation of HSV-1 and underscore the importance of viral screening during clinical evaluations of in-flight dermatitis to determine viral etiology.

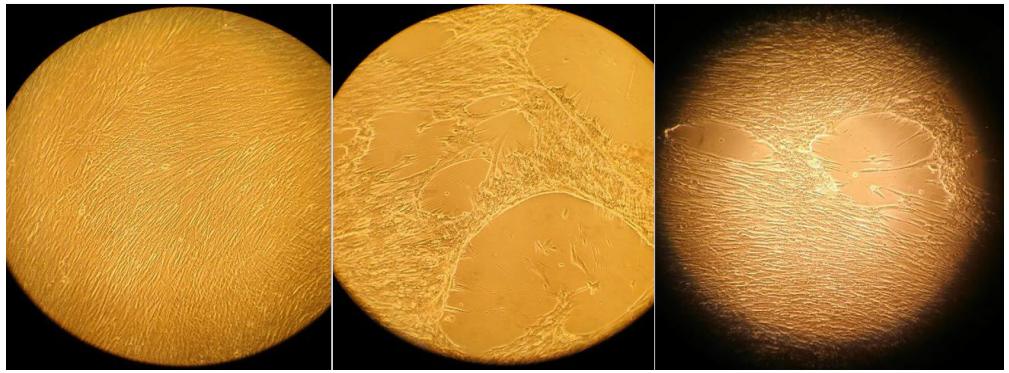
Results contd…

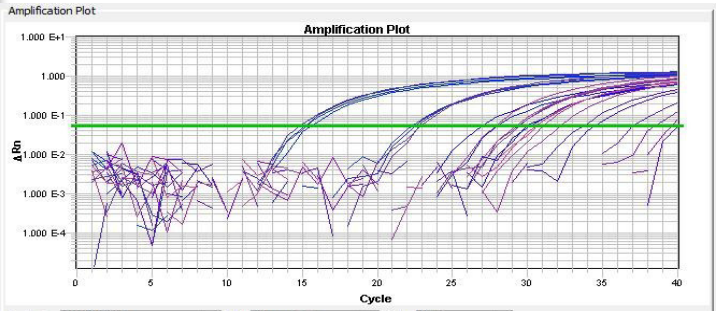
Viral DNA in Saliva

	EBV	CMV	HSV1	VZV
Pre	+	-	-	-
In	+	-	+	-
Post	+	-	+	-



Negative Control | R+0 Tertiary Indirect Culture 10^{-1} | 10^{-5}





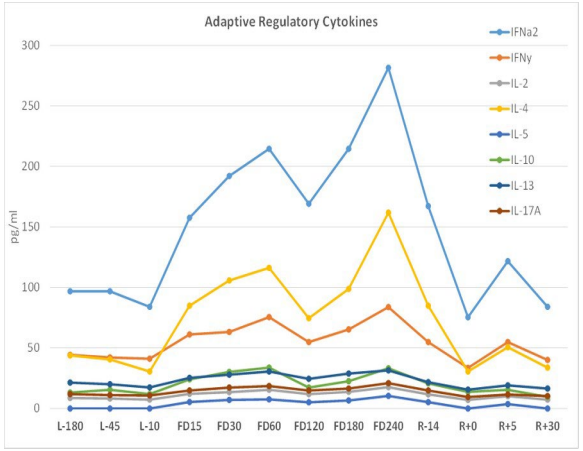
HSV1 in saliva and skin lesion before, during and after the spaceflight

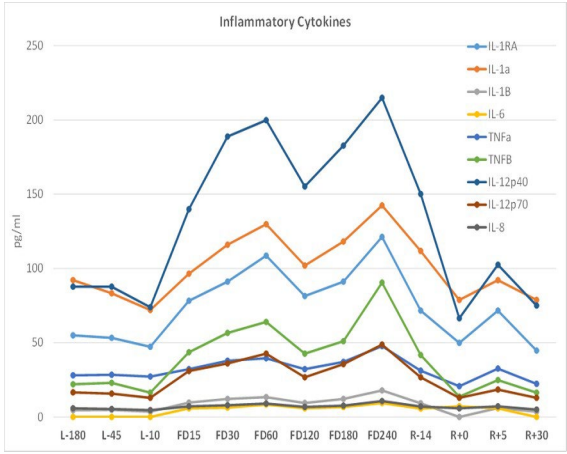
Sampling Time Point	Saliva		Skin Lesion	
	HSV1 DNA	HSV1 culture	HSV1 DNA	HSV1 culture
Pre flight (L-180)	0	not done	ND	not done
Pre flight ()	0	not done	ND	not done
Mid flight (FD-82)	28	+	530E+04	+
Landing (R+0)	1.67E+07	+	2.40E+04	+
Post flight (R+30)	0	not done	not done	not done
Post flight (R+90)	0	not done	not done	not done

Tertiary infection using the cells and media from the secondary infection. Negative control *(left),* Serial dilution 10^{-1} *(center),* and serial dilution 10^{-5} *(right).*

Results and conclusions

Plasma cytokines concentrations measured before, during and after the spaceflight showed a significant increase in some of the Inflammatory cytokines, and adaptive immunity cytokine suggesting a TH2 shift.





Dermatological lesions present during space flight and immediately after returning to Earth coincided with elevated circulating inflammatory cytokines, higher HSV-1 DNA shedding in saliva, and in the lesion swab. HSV-1 DNA recovered from both skin lesions and saliva samples were genome sequenced and found to be nearly identical at the consensus genome level. However, the in-flight rash sample contained a far more diverse population of viral genomes than the post-orbit saliva sample. The reasons for this are not known, but may include differences in immune activation state, exposure to ionizing radiation in space, or lesion vs. asymptomatic shedding. Astronaut saliva contains increasingly significant viral DNA, during and after spaceflight that can be infectious. For that reason, and in response to the data from the current astronaut subject indicating that the persistent skin rash may have a viral etiology, we recommend prophylactic (vaccine) treatment, where available, to the astronauts before they go into space as a countermeasure. Further, we have published a deep space countermeasures protocol to restore immune function. This protocol is scheduled by HHC to be ground validated in Palmer Antarctica and onboard ISS.

Conclusions

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viruses

MDPI

Article

Dermatitis during spaceflight associated with HSV-1 reactivation

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Abstract: Human alpha herpesviruses herpes simplex virus (HSV-1 or -2) and varicella zoster virus (VZV) establish latency in various cranial nerve ganglia, and often reactivate in response to stress-associated immune system dysregulation. Reactivation of Epstein Barr Virus (EBV), VZV, HSV-1 and Cytomegalovirus (CMV) is typically asymptomatic during spaceflight, though live/infectious virus has been recovered and the shedding rate increases with mission duration. The risk of clinical disease, therefore, may increase for astronauts assigned to extended missions (>180 days). Here, we report for the first time, a case of HSV-1 skin rash (dermatitis) occurring during a long duration spaceflight. The astronaut reported persistent dermatitis during flight, which was treated onboard with oral antihistamines and topical/oral steroids. No HSV-1 DNA was detected in 6-month pre-mission saliva samples, but on flight day 82, a saliva and rash swab both yielded 4.8 copies/ng DNA and 5.3×10^4 copies/ng DNA, respectively. Post-mission saliva samples continued to have high infectious HSV-1 load (1.67×10^7 copies/ng DNA). HSV-1 from both rash and saliva samples had 99.4% genotype homology. Additional physiological monitoring, including stress biomarkers (cortisol, dehydroepiandrosterone (DHEA), and salivary amylase), immune markers (adaptive regulatory and inflammatory plasma cytokines) and biochemical profile markers including vitamin/mineral status and bone metabolism are also presented for this case. These data highlight an atypical presentation of HSV-1 during spaceflight and underscore the importance of viral screening during clinical evaluations of in-flight dermatitis, to determine viral etiology and guide treatment.

Keywords: Herpes, Viral Reactivation, Spaceflight, Dermatitis, Stress, Immune Depression

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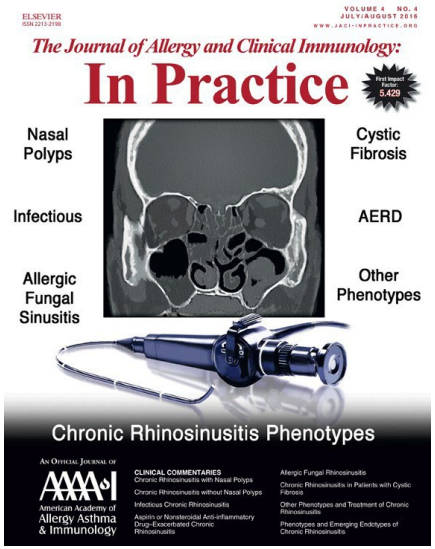
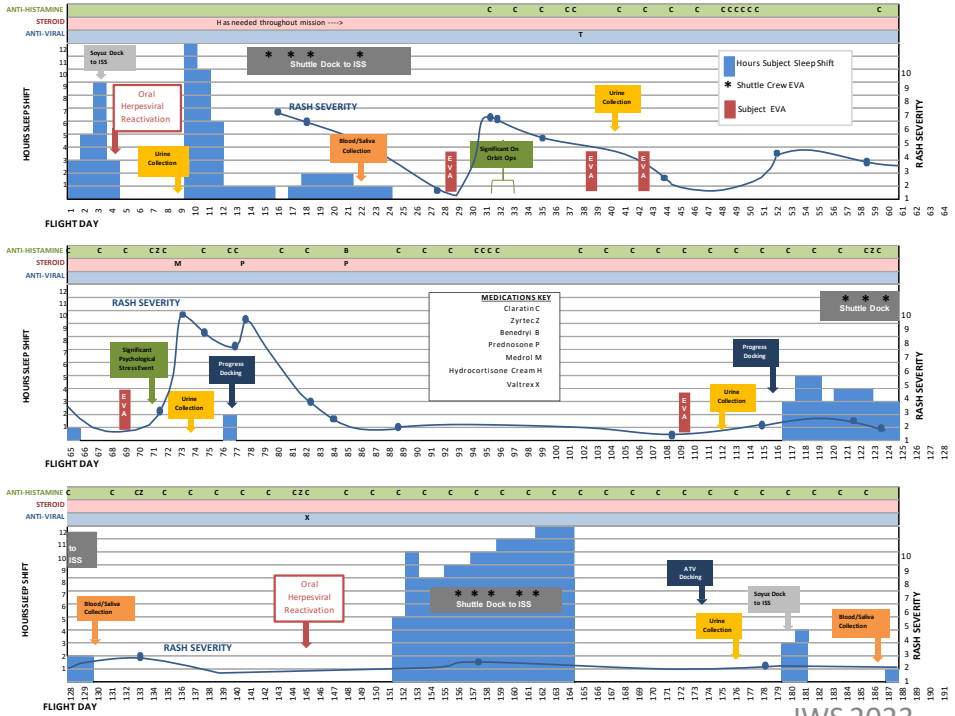
1. Introduction

Over the last two decades, our studies have shown that astronauts exhibit persistent immune system dysregulation due to stress and other unique features associated with spaceflight [1–3]. Further, we have illustrated that multiple herpesviruses persistently reactivate in astronauts during space missions. This is evidenced by shedding of viral DNA in body fluids, namely saliva, before, during and after both short (up to 16 days) and long (≥ 180 days) duration space missions [4,5]. About 50% of astronauts reactivate and shed viral DNA for one or more of the nine known human herpesviruses during and after spaceflight [6]. Four common herpes viruses that have been detected during space flight include Epstein-Barr Virus (EBV), Varicella Zoster Virus (VZV), Herpes Simplex Virus 1





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Clinical Communications

A case of persistent skin rash and rhinitis with immune system dysregulation onboard the International Space Station

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Clinical Implications

- Factors associated with spaceflight, including microgravity and stress, induce dysregulation of the human immune system. In some astronauts, this phenomenon may associate with adverse clinical outcomes observed during flight such as rashes or persistent rhinitis.

TO THE EDITOR:

There is now ample evidence to confirm that dysregulation of various immune system parameters, including leukocyte distribution, functional capacity of various cellular populations, and cytokine production profiles, is associated with spaceflight.[1] This phenomenon was recently found to persist for the duration of a 6-month deployment to the International Space Station (ISS).[2] In astronauts, the reactivation of latent herpesviruses has been correlated with immune system alterations.[3] There is a common perception that astronauts do not experience illness during flight. This may be due to the (appropriately) restricted nature of an astronaut's confidential medical information, or related to successful preflight quarantine and living in a quasi-isolation chamber. Nevertheless, astronauts do indeed experience varying degrees of illness.[4] For this case report, we track symptomology, medication use, and research immunology findings for an ISS astronaut during a typical 6-month flight onboard ISS. This particular crewmember experienced a chronic rash, which occurred early and never fully resolved during the course of the mission. We overlay observed symptoms with major mission events, to highlight a potential relationship between clinical outcomes and mission stress. Parallel data from a biomedical research investigation are presented in this article's Online Repository at www.jaci-inpractice.org.

This ISS mission consisted of 191 flight days from launch to landing. Occurring during this ISS deployment were the dockings of 3 Space Shuttle missions, 2 Soyuz vehicles, 2 Russian "Progress" cargo vehicles, and 1 European Space Agency "ATV" cargo vehicle. The crewmember participated in 5 EVAs (extravehicular activities—spacewalks). There were also 12 additional EVAs or spacewalks that occurred during Shuttle docked operations. These additional EVAs were performed by Shuttle crewmembers, but required support and guidance by ISS crewmembers. The crewmember also supported other significant on-orbit operations such as relocation of modules and hardware installation. All major mission events, including vehicle docking and/or undocking, and EVAs are represented in Figure 1. Crewmember on-orbit blood, saliva, and urine sample collections are also indicated, as are crewmember circadian rhythm shifts. Generally, these rhythm shifts are purposeful and preplanned by ground control to support mission operations. Other relevant medical data such as symptomatic incidents or periods of relevant medication usage are also represented. Using this information, clinical findings and research data may be interpreted in the context of the mission schedule and on-orbit events.

The case study crewmember experienced no unusual symptoms, other than those associated with normal adaptation to microgravity, before flight day 17. The crewmember then developed a rash, possibly dermatitis, on flight day 17. This corresponded to the first period of notable stress in the mission, coinciding with a Shuttle docking and an extremely high workload (Figure 1). The rash presented red, bumpy, and very itchy areas on the back and neck (Figure 2). Coinciding with the rash development was the appearance of eye and upper respiratory rhinitis symptoms, primarily sneezing and itchy, watery eyes. It is noteworthy that the crewmember does not experience terrestrial allergies of any kind and had never previously required any antihistamine medication. The occurrence of symptoms and rash severity over the general mission timeline is presented in Figure 1. Rash severity was tracked on a relative 1-10 scale between the crewmember and flight surgeon, with guidance having been provided to the crewmember to grade based on discomfort and operational impact. The crewmember treated the rash with hydrocortisone cream as needed at the crewmembers' discretion. The use of this medication was not recorded daily, but per the crewmember, it was used heavily for the duration of the mission. The crewmember was also prescribed fluconazole on mission day 22, on the possibility that the rash could have fungal component. The antifungal had no beneficial effect on the rash. Near to the Shuttle undocking on flight day 27, there was general improvement in the rash severity, and the rhinitis symptoms were treated with, and responded to, an oral antihistamine. A worsening of rash symptoms occurred around mission day 33, immediately after an EVA, and coinciding with a period of notable on-orbit operations. Terbinafine cream was prescribed for use as needed on flight day 34. The severity of the rash generally diminished to 1-2+ by mission day 48, after 2 more EVAs. On flight day 69, the most challenging EVA (per the crewmember description) occurred. On mission day 71, a crewmate received some distressing personal news regarding a death in the family. This event was a psychological stressor for the entire crew. On mission day 73, the rash flared to its worst point in the 6-month mission, described by the crewmember as 10+. We retrospectively anticipate, based on rash locations, appearance, and discomfort and/or itch, that this level of severity would correspond to approximately 30-37 on the Scoring Atopic Dermatitis scale. At this point, the hydrocortisone cream was exhausted. Triamcinolone acetonide cream was used and was found to be ineffective. A methylprednisolone steroid dosepack was prescribed, and the rash improved during the initial period of the 6-day treatment, with return of symptoms on the fifth day of the tapering. A 30 mg prednisone dose was initiated with a much


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