American Journal of Ophthalmology Case Reports 20 (2020) 100843

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Novel case of an adult with toxic shock syndrome following COVID-19 infection

Yilin Feng [a], Stephen T. Armenti [a], Owen R. Albin [b], Shahzad I. Mian [a,*]

[a] University of Michigan, Kellogg Eye Center, Department of Ophthalmology and Visual Sciences. 1000 Wall St, Ann Arbor, MI, 48105, USA
[b] University of Michigan, Department of Infectious Disease. 1500 E Medical Center Drive, Ann Arbor, MI, 48109, USA

ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Conjunctivitis
Toxic shock syndrome

ABSTRACT

Purpose: To report a case of an adult who developed toxic shock syndrome following COVID-19 infection.
Observations: A 28-year-old female tested positive for COVID-19. 19 days later, she developed a fever, rash and a burning sensation in both eyes. Her examination revealed mild ocular inflammation with bilateral eyelid and conjunctival involvement. Skin biopsy favored a diagnosis of toxic shock syndrome. She was initiated on corticosteroid eye drops and her ocular symptoms resolved three days later.
Conclusion and importance: Toxic shock syndrome is almost always associated with conjunctival inflammation. To our knowledge, this is the first report of an adult patient with toxic shock syndrome following COVID-19 infection. The association between toxic shock syndrome and COVID-19 is unclear; however, patients should be vigilant for symptoms as toxic shock syndrome can progress rapidly and cause multi-organ failure.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has caused significant morbidity and mortality worldwide. The pathogen causing COVID-19, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can cause significant respiratory as well as multi-organ failure. Recently, studies have shown that patients with COVID-19 can also have ocular involvement. The most common ocular manifestation is conjunctivitis, with rates ranging from 0.8 to 31.6%.[1,2] In addition, there have been cases of retinal pathology reported in the setting of COVID-19, with hemorrhages and cotton wool spots on clinical exam, and hyper-reflective lesions of the inner retina on optical coherence tomography (OCT).[3] However, the significance of these findings and possible relationship to other neurologic consequences of COVID-19 has yet to be determined.

In addition to primary ocular infection related to SARS-CoV-2, patients can develop indirect ocular complications related to COVID-19, especially those who are critically ill. ICU patients are at high risk for ocular surface diseases, such as exposure keratopathy, with rates of up to 40%.[4] In ventilated patients with acute respiratory distress syndrome, prone positioning is often used to improve gas exchange. This practice not only can cause ocular surface disease, but can also be associated with increased intraocular pressure and ischemic optic neuropathy, threatening vision in at-risk patients.[5]

Recently, children have been reported to develop a rare COVID-related inflammatory disease, now named Pediatric Multi-System Inflammatory Syndrome. One center in Italy recently saw a 30-fold increase in the incidence of Kawasaki-like disease in children over one month, most of whom tested positive for COVID-19 nasopharyngeal PCR or SARS-CoV-2 serology.[6] These children exhibit symptoms similar to those seen in Kawasaki disease and toxic shock syndrome (TSS) and present with fever, conjunctivitis, abdominal pain, and rash.[7] Here, we describe a case of an adult patient with recent diagnosis of COVID-19 who developed TSS.

2. Case report

A 28-year-old female presented with rash, fever, and hypotension. Her past medical history was significant for end-stage renal disease, type 2 diabetes mellitus, and hypertension. She had no past ocular history. 19 days prior to this admission, she tested positive for COVID-19 and was admitted for hypoxic respiratory failure and required non-invasive positive pressure ventilation (NIPPV). At that time, she was treated with a course of hydroxychloroquine, steroids, and antibiotics. She was discharged 14 days later. 5 days following her discharge, she developed generalized weakness, poor appetite, fever, and desquamating rash and

* Corresponding author. Professor of Ophthalmology and Visual Sciences, University of Michigan, Kellogg Eye Center, 1000 Wall St, Ann Arbor, MI, 48105, USA.
E-mail address: smian@med.umich.edu (S.I. Mian).

https://doi.org/10.1016/j.ajoc.2020.100843
Received 25 May 2020; Received in revised form 6 July 2020; Accepted 11 July 2020
Available online 29 July 2020
2451-9936/© 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

re-presented for evaluation. Upon arrival, she was febrile to 38.8 °C. Her blood pressure was 90/43. Her skin exam demonstrated diffuse erythematous and dusky colored plaques with bullae and superficial flaking, yellow crusting, scaling, and widespread erosions that involved 40% of her total body surface area. A gynecologic exam revealed no vulvar or vaginal involvement. Initial laboratory workup was notable for leukocytosis of 29,600/mm^3. Respiratory virus panel, COVID-19 nasopharyngeal PCR, and blood cultures were negative. Chest x-ray revealed bibasilar infiltrates. Due to concern for septic shock, she was started on broad spectrum antibiotics (vancomycin, ceftazidime, and clindamycin).

Two days following her admission, she reported a burning sensation in both eyes and oral pain. Ophthalmic examination revealed that her visual acuity without pinhole was 20/40 in the right eye and 20/50 in the left eye. Her slit lamp exam was notable for areas of hyperpigmented skin with patchy lower eyelid desquamation and fluorescein staining involving less than 1/3 of the right eyelid margin and patchy lower left eyelid involvement with fluorescein staining involving the lateral 1/4 eyelid margin. Her conjunctiva exam revealed mild (1+) injection in both eyes with patchy palpebral conjunctival staining of the left eye. The remainder of her eye exam was unremarkable.

She was initiated on prednisolone acetate 1% eye drops every 2 hours in both eyes, preservative free artificial tears every 2 hours in both eyes, and erythromycin ointment four times a day in both eyes. On follow up 3 days later, she reported resolution of ocular symptoms. Repeat examination at that time was notable for only trace injection in both eyes without cicatrization. She was started on a taper of prednisolone acetate 1% eye drops and she did not report further ocular symptoms.

The patient's clinical presentation was initially suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) due to recent hydroxychloroquine use[8,9]; however, the superficial flaking of her skin raised concern for TSS. She underwent a punch biopsy which demonstrated "subcorneal split with parakeratosis, rare intraepidermal dyskeratosis, and superficial perivascular inflammation with neutrophils and eosinophils." The tissue sample was negative for a specific direct immunofluorescence pattern using monospecific fluorescein isothiocynanate (FITC)-conjugated anti-human IGG, IgA, IgM, C3, and fibrin. These histopathologic findings favored toxic shock syndrome and excluded Steven's Johnson syndrome and toxic epidermal necrolysis. However, the patient denied recent wounds, tampon use, or nasal packing, and there was no obvious infectious source on the patient's clinical exam or imaging tests. Thus, it is possible that her presentation of toxic shock may have instead been due to a primary immune-mediated post-COVID-19 phenomenon, similar to that described in pediatric patients.

3. Discussion

TSS is a rare, multi-system, toxin-mediated disease that often presents with shock and progresses to multi-organ system failure. Diagnosis of TSS can be challenging as it is a clinical diagnosis. According to the Center for Disease Control, TSS is considered in a patient with the following clinical manifestations: fever, rash, desquamation, hypotension, and multisystem (three or more) involvement.[10] Our patient presented with fever, rash, desquamation, and hypotension. Her symptoms also indicated multisystem involvement, such as generalized weakness, poor appetite, as well as mucous membrane involvement. Given her recent use of hydroxychloroquine which can be associated with SJS/TEN, she underwent a skin biopsy. While a biopsy is not necessary to diagnose TSS, it is often helpful to differentiate TSS from SJS/TEN due to its similarities in clinical presentations. For example, compared to SJS/TEN, TSS is more likely to demonstrate perivascular dermatitis and have neutrophil involvement.[11,12] The histopathologic findings of TSS can be specific and diagnostic for the condition,[13] which can greatly aid in the diagnosis and treatment of patients.

The causes of TSS most commonly include toxin-producing strains of *Staphylococcus aureus* and *Streptococcus pyogenes*, which release bacterial toxins that trigger excessive T-cell activation and downstream cytokine storm.[13] Staphylococcal TSS may present following influenza infection with symptoms of fever, abdominal pain, and myalgia early in disease, followed by confusion and lethargy. Desquamating rash occurs later, often around 10–21 days after disease onset.[13] Other causes of staphylococcal TSS classically include wounds, prolonged tampon use or nasal packing. Streptococcal TSS, on the other hand, frequently presents following overt invasive soft-tissue infections such as necrotizing fasciitis or cellulitis.[13]

Post-influenza TSS has been well-described in the literature, with the etiology attributed to a secondary bacterial pneumonia caused by *Staphylococcus aureus*. Impaired polymorphonuclear leukocyte chemotaxis and decreased tracheobronchial clearance following influenza infection increase the susceptibility of developing a secondary bacterial pneumonia.[14,15] The patient we present in this case developed symptoms of TSS approximately 19 days following her diagnosis of COVID-19. Secondary bacterial pneumonia has been reported in COVID-19 patients and it is conceivable that her presentation of toxic shock was secondary to a staphylococcal pneumonia.[16,17] Alternatively, SARS-CoV-2 can elicit a strong immune response in the host,[6] and her TSS may have been a primary immune-mediated post-COVID-19 phenomenon, similar to that increasingly recognized in the pediatric population.

Conjunctival inflammation is an important feature of TSS and is almost always present early in the disease course.[18,19] The conjunctival inflammation in TSS is likely triggered by bacterial superantigens that cross mucosal barriers.[20] Albeit less commonly, there have been rare reports of additional ocular consequences of TSS, including optic neuropathy, necrotizing anterior scleritis, and keratitis in streptococcal TSS, and vertical gaze palsy in the setting of staphylococcal TSS.[21,22]

4. Conclusion

To our knowledge, this is first case of TSS in an adult following COVID-19 infection. The etiology may be due to a bacterial pneumonia from *Staphylococcus aureus*, though reports of Pediatric Multi-System Inflammatory Syndrome describe a similar illness associated with COVID-19 infection occurring in children. Additional research is needed to investigate the relationship between multi-system inflammatory conditions and COVID-19.

Patient consent

Verbal consent was obtained from the patient to publish this report. This report does not contain any personal information that could lead to identification of the patient.

Funding

No funding or grant support.

Authorship

All authors attest they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

There are no conflicts of interest.

Acknowledgements

None.

References

1. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708–1720.
2. Wu P, Duan F, Luo C, et al. Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in hubei province, China. *JAMA Ophthalmol*. 2020;138(5):575–578.
3. Marinho PM, Marcos AAA, Romano AC, Nascimento H, Belfort R. Retinal findings in patients with COVID-19. Lancet Lond Engl. doi:10.1016/S0140-6736(20)31014-X.
4. Hernandez EV, Mannis MJ. Superficial keratopathy in intensive care unit patients. *Am J Ophthalmol*. 1997;124(2):212–216.
5. Saran S, Gurjar M, Kanaujia V, et al. Effect of prone positioning on intraocular pressure in patients with acute respiratory distress syndrome. *Crit Care Med*. 2019;47(9):e761–e766.
6. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet Lond Engl. doi:10.1016/S0140-6736(20)31103-X.
7. Jones V, Mills, M, Suarez, D, Hogan, C. COVID-19 and Kawasaki disease: novel virus and novel case. Hosp Pediatr. doi: 10.1542/hpeds.2020-0123.
8. Leckie MJ, Rees RG. Stevens-Johnson syndrome in association with hydroxychloroquine treatment for rheumatoid arthritis. *Rheumatol Oxf Engl*. 2002;41(4):473–474.
9. Sharma AN, Mesinkovska NA, Paravar T. Characterizing the adverse dermatologic effects of hydroxychloroquine: a systematic review. J Am Acad Dermatol. doi:10.1016/j.jaad.2020.04.024.
10. *Toxic Shock Syndrome (Other than Streptoccal) TSS 2011 Case Definition*. Centers for Disease Control and Prevention website; 2011. https://wwwn.cdc.gov/nndss/conditions/toxic-shock-syndrome-other-than-streptococcal/case-definition/2011/. Accessed July 5, 2020.
11. Hurwitz RM, Rivera HP, Gooch MH, Slama TG, Handt A, Weiss J. Toxic shock syndrome or toxic epidermal necrolysis? Case reports showing clinical similarity and histologic separation. *J Am Acad Dermatol*. 1982;7(2):246–254.
12. Hurwitz RM, Ackerman AB. Cutaneous pathology of the toxic shock syndrome. *Am J Dermatopathol*. 1985;7(6):563–578.
13. Lappin E, Ferguson AJ. Gram-positive toxic shock syndromes. *Lancet Infect Dis*. 2009;9(5):281–290.
14. Abramson JS, Lyles DS, Heller KA, Bass DA. Influenza A virus-induced polymorphonuclear leukocyte dysfunction. *Infect Immun*. 1982;37(2):794–799.
15. Camner P, Jarstrand C, Philipson K. Tracheobronchial clearance in patients with influenza. *Am Rev Respir Dis*. 1973;108(1):131–135.
16. Tian S, Xiong Y, Liu H, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. Mod Pathol. doi:10.1038/s41379-020-0536-x.
17. Rasmussen SA, Smulian JC, Lednicky JA, Wen TS, Jamieson DJ. Coronavirus Disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. *Am J Obstet Gynecol*. 2020;222(5):415–426.
18. Bach MC. Dermatologic signs in toxic shock syndrome—clues to diagnosis. *J Am Acad Dermatol*. 1983;8(3):343–347.
19. Fisher CJ, Horowitz BZ, Nolan S. The clinical spectrum of toxic shock syndrome. *West J Med*. 1981;135(3):175–182.
20. Rajagopalan G, Smart MK, Murali N, Patel R, David CS. Acute systemic immune activation following vaginal exposure to staphylococcal enterotoxin B–implications for menstrual shock. *J Reprod Immunol*. 2007;73(1):51–59.
21. Papageorgiou KI, Ioannidis AS, Andreou PS, Sinha AJ. Optic atrophy, necrotizing anterior scleritis and keratitis presenting in association with Streptococcal Toxic Shock Syndrome: a case report. *J Med Case Rep*. 2008;2:69.
22. Dick DJ, Harvey RD, Hudson SJ, Walls TJ. Conjugate deviation of downgaze in the toxic shock syndrome. *Postgrad Med*. 1985;61(721):995–996.