COVID-19 infection in a patient with Behçet's Disease

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ABSTRACT

Background: We are continually learning how to best manage patients testing positive for SARS-CoV-2 [coronavirus disease 2019 (COVID-19)]. This is particularly challenging in rare autoimmune conditions, where immune system dysfunction, whether by disease or treatment, has the potential to impact on the course of COVID-19 in several ways.

Case Presentation: We present the case of a 52-year-old female with Behçet's Disease, treated by immunosuppressive drugs, who tested positive for COVID-19 during the first month of the pandemic in the United Kingdom. In this case a multidisciplinary team approach, involving gynecological, rheumatological, microbiological, and respiratory teams was essential in ensuring the best outcome for the patient.

Conclusion: Our patient had a favorable outcome; she did not require intensive care admission and has recovered. This case supports the hypothesis that the chronic immunosuppression may confer a degree of protection against severe COVID-19 disease, potentially by mitigating the pro-inflammatory cytokine responsible for the respiratory failure seen in severe cases of the disease.

Keywords: Case report, Behçet's Disease, COVID-19, immunosuppression, autoimmune disease, multidisciplinary team.

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Background

The outbreak of coronavirus disease 2019 (COVID-19) has been declared as a global pandemic [1]. The spectrum of disease severity associated with this virus varies from mild symptoms to respiratory failure with shock or multi-organ dysfunction that may be fatal [2].

Respiratory failure due to COVID-19 is thought to be the result of an unregulated cytokine storm that may rapidly provoke acute respiratory distress syndrome [3]. COVID-19 has also unfortunately further exposed the longstanding social determinants of health that exist globally; with poverty, ethnicity, education level, malnutrition, and crowded living conditions being shown to have adverse effects on COVID-19 outcomes [4,5]. Given the pandemic remains in its infancy, there are little data on the effect of COVID-19 on immunosuppressed patients with chronic rheumatological diseases, with Behçet's Disease (BD) being no exception. We present a case of a patient with BD who tested positive for COVID-19 and survived.

Case Presentation

A 52-year-old women with a longstanding history of BD, was admitted to hospital with malaise and fever. The patient had multiple medical comorbidities including previous infective endocarditis, arm thrombosis, gastrointestinal bleeds, and a gynecological history of endometrial ablation and recurrent Bartholin's cyst abscesses requiring drainage. At the time, with relatively low numbers of COVID infections compared to neighboring hospitals, testing for COVID-19 on admission was reserved for patients who were displaying classical symptoms of the disease, i.e., new persistent cough or fever. Initially, she tested COVID-19 negative. Acute treatment for sepsis of unknown origin and a flare up of BD was initiated with broad spectrum intravenous (IV) antibiotics (meropenem & teicoplanin), anti-fungals (anidulafungin), and IV hydrocortisone. Given the patient's complex background, all antimicrobial decisions were taken based on local guidelines alongside discussion with consultant microbiologist. A gynecological oncological opinion was sought as the patient had a large, chronically infected, horseshoe shaped vulval ulcer. Surgery is only very exceptionally performed for ulcers in BD - however, as the chronic infection with necrotic tissue had not responded to long courses of antibiotics and prevented the definitive treatment with

increased immunosuppression by tumor necrosis factor inhibitor, this was now required. The patient underwent an anterior hemivulvectomy with resection of both labia and the anterior introitus. Histopathological assessment of the resected specimen showed "extensive non-specific epidermal ulceration with neutrophilic infiltration, scar and fibrosis in keeping with BD". There were no post-operative complications and 2 days later the patient was clinically well and discharged home with oral antibiotics and a tapering steroid regime as guided by her rheumatologist. Six days later the patient became unwell at home with high fevers and vomiting. She was admitted, blood cultures taken and commenced on broad spectrum IV antibiotics (meropenem & teicoplanin) and antifungal (fluconazole) agents. The initial clinical suspicion from microbiology was that of a peripherally inserted central catheter line infection, which had been inserted 3 days prior to her anterior hemivulvectomy due to poor venous access. However, later that evening, the patient developed a new oxygen requirement of 2 l as well as bibasal crackles on auscultation of the chest. Blood tests were unremarkable with inflammatory markers, renal function, liver function and lactate all within the normal range. A chest X-ray was performed which demonstrated no acute pathology. An urgent swab using cobas® RT-PCR for COVID-19 was repeated, which was positive. She subsequently also tested positive for the antibody to COVID-19 (Anti-SARS-CoV-2). The patient was transferred to the respiratory ward of the neighboring trust for a medical review. This case pre-dated the evidence that later emerged for the use of dexamethasone and remdesivir for use in selected patients with COVID-19. Over the next 2 days her condition stabilized, with no further temperature spikes nor an increase in her oxygen demand. On day 3, she no longer required oxygen and was deemed medically fit for discharge. The patient was discharged to self-isolate at home for 7 days with a steroid reducing regime. Follow up was organized with gynecological and rheumatology parent teams. Following discharge, the patient made a steady recovery from COVID-19, with no ongoing respiratory symptoms. She had a very severe flare up of Behçet's, however, and following exclusion of ongoing infection was commenced on certolizumab with significant improvement in her Behcet's related symptoms. It is unclear how the patient contracted COVID-19, especially given that at the time, routine PCR testing was not being performed prior to discharge. However, given how careful the patient had been with her self-isolation, it is both our clinical suspicion and the patient's belief that it was a hospital acquired infection during her first admission.

Discussion

BD is a rare, multisystem, variable vessel vasculitiides [6]. It was originally described in 1937 as a triad of oral apthae, genital ulcers, and uveitis [7]. Recurrent inflammatory episodes involving the gastrointestinal tract, the central nervous system along with manifestations in the articular and peripheral vasculature are typical of BD [8,9]. Presentation generally occurs between the ages of 20 to 30 years [7]. There is a significant morbidity and mortality associated with BD, particularly in males who have early onset disease. BD is epidemiologically complex, with cases clustering along the historical "Silk Road" which extends from Eastern Europe to Japan [8,9]. The prevalence of BD in the UK is 0.64 per 100, 000 [7,8]. Turkey has the highest prevalence worldwide 0.8-4.2 per 100,000. The etiology underpinning this geographical distribution is unknown, but genetic factors have been proposed, most notably the HLA-B51 allele [7-10].

The pathogenesis of BD is poorly understood. It is considered that the autoimmune dysregulation following exposure to environmental factors leads to hyperactivation of neutrophils and T cells [10,11], especially in genetically susceptible individuals [10,11]. There is no single test for diagnosing BD. Obtaining a focused history, thorough examination coupled with investigations is critical, while simultaneously excluding other differentials [12]. Diagnosis can be supported based on a criterion set out by the International Study Group for BD. Patients who have at least three episodes of mouth ulcers in a 12-month timeframe, plus at least two of the following: genital ulcers, eye inflammation, skin lesions or pathergy [13,14]. The management of BD is multifactorial, the severity of disease and organs affected, coupled with patient factors such as age and sex [14]. Initial treatment is usually medical involving topical/oral steroids [15] and in recent years biologic agents [16]. Surgical intervention can be indicated in certain patients, as in this case [14].

Outcomes in patients with COVID-19 appear to be determined by the extent (or lack thereof) of the exaggerated immune system response [3]. There are currently no specific treatment strategies that have been proven to prevent or mitigate the cytokine storm associated with COVID-19. However, several anti-rheumatic agents have been postulated to be of potential use given their immunomodulatory properties, such as chloroquine, anti-TNF, anti-IL1, JAK inhibitors and systemic corticosteroids [3,17]. Most notably, the RECOVERY et al. [18] trial demonstrated that in hospitalized patients with COVID-19, the use of dexamethasone for up to 10 days reduced deaths by one-third in ventilated patients and by one-fifth in patients requiring oxygen only. However, no benefit of dexamethasone was seen in patients who required no respiratory support, and the results were consistent with possible harm in this group [18]. With immunosuppressant medications like dexamethasone showing some promise, it remains to be seen whether patients with chronic rheumatic disorders like BD, whose long-term immunosuppressant regimes may actually confer a degree protection against the aberrant immune response seen in COVID-19 [15]. There

are provisional data on this topic emerging from areas of Europe. A French study considered 694 patients with a diagnosis of inflammatory rheumatic and musculoskeletal diseases (iRMD) [19]. The death rate of hospitalized patients with iRMD-COVID-19 (moderate-severe) was compared with a subset of patients with non-iRMD-COVID-19 from a French hospital matched for age, sex, and comorbidities. This study reported that as already identified in the general population, older age, male gender, obesity, and hypertension were found to be associated with severe COVID-19. However, patients treated with corticosteroids, but not methotrexate, or tumor necrosis factor alpha and interleukin-6 inhibitors, were considered as more likely to develop severe COVID-19. This paper concluded that unlike common comorbidities such as obesity, and cardiovascular or lung diseases, the risk of death is not significantly increased in patients with iRMD. Given the small sample size of patients with BD in this study (7 out of the 694 total), is it unclear how translational these findings are to the case we present here.

In a cross-sectional study based in Tuscany (an area with COVID-19 rates comparable to other European countries), patients with systemic autoimmune diseases ($N = 458$) did not appear to carry an increased risk of infection of COVID-19 compared to the general population ($N = 3,729,641$) [20]. Of the 458 patients analyzed, 41 had BD and many were receiving immunosuppressive medications in isolation or combination [56% on corticosteroids, 44% traditional disease-modifying antirheumatic drugs (DMARDs), and 41% biologic DMARDs]. Just one patient in the autoimmune disease group tested positive for COVID, compared to 7,527 in the general population. This gave a comparable infection prevalence of 0.22% (95% CI 0.01%-2.21%) in the cohort group versus 0.20% (95% CI 0.20%-0.21%) in the general population which was not statistically significant ($p = 0.597$). Though this paper supports the notion that immunosuppression in patients with autoimmune diseases (including BD) may at the very least not be harmful to patients with COVID-19, the singular positive case in the cohort group makes the results difficult to interpret. Monti et al. [21] studied the clinical course of COVID-19 in 320 Italian patients with chronic arthritis, of which 57% had rheumatoid arthritis and 43% with spondyloarthritis. All patients were receiving immunosuppressive medications; 52% with anti-TNF, 40% with biologic DMARDs and 8% with targeted DMARDs. Of the four confirmed COVID-19 cases and the four highly suggestive of infection, nobody developed severe complications or died. Only one patient, aged 65, was admitted to hospital for a few days of low-flow supplementary oxygen, which is similar to the clinical course of COVID-19 shown by our patient with BD.

Conclusion

The current COVID-19 guidance for patients with BD is to continue taking their immunosuppressive medications unless specifically told not to by their consultant. Any theoretical protection must of course be balanced with the increased risk of catching and then spreading the COVID-19 infection by these immunosuppressed patients. The case we present here is just one example of where the long-term immunosuppressive treatment for BD may have led to a more favorable outcome for a patient who became infected with COVID-19. It remains unclear whether the presence of Anti-SARS-CoV-2 (as in this case) confers any long-term protection to secondary infections with COVID-19. Our case supports the findings of Espinosa et al. [22], who also reported mild clinical courses of COVID-19 infections in four female patients aged between 37 and 51 with BD in one hospital in Barcelona. We suggest the following learning points:

1. Have a high index of suspicion for COVID-19 in patients with the relevant symptoms.
2. Have a low threshold to re-swab patients for COVID-19, particularly if a patient's clinical state deteriorates.
3. Decisions regarding starting/stopping immunosuppressive drugs in COVID-19 patients with BD should be made on a case-by-case basis.
4. Multidisciplinary team management of BD patients is essential.

What is new?

Given the pandemic remains in its infancy, there are little data on the effect of COVID-19 on immunosuppressed patients with chronic rheumatological diseases, with BD being no exception. The authors present a case of a patient with BD who tested positive for COVID-19 and survived.

List of Abbreviations

COVID-19	Coronavirus disease 19
BD	Behçet's Disease
IV	Intravenous
RT-PCR	Reverse transcriptase PCR
i-RMD	Inflammatory rheumatic and musculoskeletal diseases

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for publication

Written informed consent was obtained from the patient in this case.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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References

1. The World Health Organization. WHO: WHO announces COVID-19 outbreak a pandemic. Geneva, Switzerland: The World Health Organization; 2020.
2. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–9. https://doi.org/10.1001/jama.2020.1585
3. Sarzi-Puttini P, Giorgi V, Sirotti S, Marotto D, Ardizzone S, Rizzardini G, et al. COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? Clin Exp Rheumatol. 2020;38(2):337–42.
4. Paremoer L, Nandi S, Serag H, Baum F. COVID-19 pandemic and the social determinants of health. BMJ. 2021;372:n129. https://doi.org/10.1136/bmj.n129
5. Abrams EM, Szefler SJ. COVID-19 and the impact of social determinants of health. Lancet Respir Med. 2020;8(7):659–61. https://doi.org/10.1016/S2213-2600(20)30234-4
6. Nair JR, Moots RJ. Behcet's disease. Clin Med (Lond). 2017;17(1):71–7. https://doi.org/10.7861/clinmedicine.17-1-71
7. Hatemi G, Seyahi E, Fresko I, Talarico R, Hamuryudan V. One year in review 2019: Behçet's syndrome. Clin Exp Rheumatol. 2019;37 Suppl 121(6):3–17.
8. Yazici H, Fresko I, Yurdakul S. Behçet's syndrome: disease manifestations, management, and advances in treatment. Nat Clin Pract Rheumatol. 2007;3(3):148–55. https://doi.org/10.1038/ncprheum0436
9. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. N Engl J Med. 1999;341(17):1284–91. https://doi.org/10.1056/NEJM199910213411707
10. Zeidan MJ, Saadoun D, Garrido M, Klatzmann D, Six A, Cacoub P. Behçet's disease physiopathology: a contemporary review. Auto Immun Highlights. 2016;7(1):4. https://doi.org/10.1007/s13317-016-0074-1
11. Türsen U. Pathophysiology of the Behçet's disease. Patholog Res Int. 2012;2012:493015. https://doi.org/10.1155/2012/493015
12. Hng M, Zhao SS, Moots RJ. An update on the general management approach to common vasculitides. Clin Med. 2020;20(6):572–9 https://doi.org/10.7861/clinmed.2020-0747
13. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. Lancet. 1990;335(8697):1078–80.
14. Rokutanda R, Kishimoto M, Okada M. Update on the diagnosis and management of Behçet's disease. Open Access Rheumatol. 2014;7:1–8.
15. Benson RM, Kirwan J, Moots RJ. A novel treatment in the management of genital ulceration in Behçet's disease. Clin Exp Rheumatol. 2019;121(6):158.
16. Moots RJ, Fortune F, Situnayake D. The Behçet's centres of excellence. Rheumatology. 2018;57(4):594–5. https://doi.org/10.1093/rheumatology/kex037
17. Ferro F, Elefante E, Baldini C, Bartoloni E, Puxeddu I, Talarico R, et al. COVID-19: the new challenge for rheumatologists. Clin Exp Rheumatol. 2020;38(2):175–80.
18. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with COVID-19 - preliminary report. N Engl J Med. 2021;384(8):693–704.
19. FAI2R /SFR/SNFMI/SOFREMIP/CRI/IMIDIATE consortium and contributors. Severity of COVID-19 and survival in patients with rheumatic and inflammatory diseases: data from the French RMD COVID-19 cohort of 694 patients. Ann Rheum Dis. 2020;80(4):527–38.
20. Emmi G, Bettiol A, Mattioli I, Silvestri E, Di Scala G, Urban ML, et al. SARS-CoV-2 infection among patients with systemic autoimmune diseases. Autoimmun Rev. 2020;19(7):102575. https://doi.org/10.1016/j.autrev.2020.102575
21. Monti S, Balduzzi S, Delvino P, Bellis E, Quadrelli VS, Montecucco C. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. Ann Rheum Dis. 2020;79(5):667–8. https://doi.org/10.1136/annrheumdis-2020-217424
22. Espinosa G, Araujo O, Amaro S, Bodro M, Moreno PJ, Moreno R, et al. COVID-19 and Behçet's disease: clinical case series. Ann Rheum Dis 2021; 80:e41. https://doi.org/10.1136/annrheumdis-2020-217778.

Summary of the case

1	**Patient (gender, age)**	Female, 52-year-old
2	**Final diagnosis**	COVID-19 infection
3	**Symptoms**	Fever and vomiting
4	**Specialty**	Rheumatology and Gynaecology
5	**Background**	There is little data on the effect of COVID-19 on immunosuppressed patients with chronic rheumatological disease
6	**Case report**	COVID-19 infection in a patient with BD
7	**Conclusions**	Long term immunosuppressant medication may confer protection to severe COVID-19 infections