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Case Report

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Premature Ovarian Failure Related to SARS-CoV-2 Infection

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is known to have a wide spectrum of effects on the respiratory, cardiac, neurological, hematopoietic, gastrointestinal, ocular and urological systems, but there is very little information on its effects on the human ovary. Our aims are to describe a unique case that developed amenorrhea during and after SARS-CoV-2 infection and to push researchers to do more researches to understand the effects of SARS-CoV-2 infection on the ovaries. A 27-year-old female patient presented with amenorrhea. She had fever on the second day of the menstrual cycle, and her cycle had been interrupted on the same day. The patient had a sub-febrile temperature, myalgia, fatigue, sweating, loss of appetite, and mild sleep disorder. Based on clinical, laboratory, and reverse transcription polymerase chain reaction (RT-PCR) data of a nasopharyngeal swab sample, she had a positive result for SARS-CoV-2 infection. Till now there are limited publications on the effect of SARS-CoV-2 infection on the ovaries. In particular, the potential adverse effects of SARS-CoV-2 infection on fertility are unclear. Coronavirus disease 2019 (COVID-19) patients need to be followed up for a long time, and clinicians need to pay attention to menstrual disturbances, especially in young female patients. More evidence, through both epidemiologic and clinical studies, as well as long-term follow-up studies, is needed to understand the impact of this infection on the human ovary, especially in reproductive-aged women.

Keywords: SARS-CoV-2 infection; Premature ovarian; Ovary; Women fertility; Atypical manifestations

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus infection was an unprecedented pandemic that spread rapidly and widely across the globe. The symptoms and manifestations of this infection are complicated and vary widely, and have posed a huge challenge. SARS-CoV-2 has spread worldwide and in the end of 2021 more than over 278 million cases and just under 5.4 million deaths have been reported globally, while the number of both confirmed and fatal cases is continually increasing [1]. Although SARS-CoV-2 infection is primarily a respiratory disease, it affects various systems and organs throughout the body. Its effects on the respiratory, cardiac, neurological, hematopoietic, gastrointestinal, muscle-skeletal, cutan, ocular, and urological systems are now well known [2-13]. In addition to the typical cases, there have been a large number of reports on atypical forms or presentations of the disease and related complications [11, 14-18]. However, there are only a limited number of publications on the effect of SARS-CoV-2 infection on the ovaries. According to a PubMed search with the keywords "ovarian insufficiency, COVID-19" and literature review conducted on September 28, 2021, limited clinical cases have been published on the effects of the virus on the female reproductive system [5, 18]. SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor for entry into cells. There is evidence that the renin-angiotensin-aldosterone system is involved in female reproductive processes such as folliculogenesis, steroidogenesis, oocyte maturation, and ovulation [18-23]. However, the expression of ACE2 is very low in stromal and perivascular cells of the ovarian cortex, while its expression is highest in the endothelium, lungs, kidney, and the heart [2, 3, 10, 19-21, 24]. The purposes of this paper are to present a case of a 27-year-old woman who developed amenorrhea after recovering from SARS-CoV-2 infection and to draw attention to clinicians to follow COVID-19 patients for a long time, and they need to pay attention to menstrual disturbances, especially in young female patients.

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Case Report

Investigations

A 27-year-old female patient presented with amenorrhea. She had been diagnosed with COVID-19 eight months ago, and she had missed eight menstrual cycles since then. The patient had fever on the second day of the menstrual cycle and, on the same day, her cycle had been interrupted. There were no signs of metrorrhagia. The patient had a sub-febrile temperature of 37.5 - 37.8 °C for 2 - 3 days. She also had myalgia, fatigue, sweating, loss of appetite, and mild sleep disorder.

Diagnosis

Based on the clinical, laboratory, and reverse transcription

polymerase chain reaction (PCR-RT) data of a nasopharyngeal swab sample, she had a positive result for SARS-CoV-2 infection. Other members of her family had also tested positive for SARS-CoV-2 infection around the same time. As the patient had a mild form of the disease, she was treated only with vitamin supplements. She reported that she had a healthy lifestyle and did not have any health-related problems. Her first menstrual cycle had been at the age of 12 years, and since then, up to 8 months ago, her cycles had been regular. She had not taken any oral contraceptives prior to the infection, and she had not undergone chemotherapy or radiotherapy in the last 12 months. She mentioned that she was not worried and hoped that her menstrual cycle would resume in the near future. An objective structured clinical examination did not reveal any remarkable findings. As the patient had amenorrhea for more than 3 months, a hormonal evaluation was recommended. These were the findings of the evaluation: follicle-stimulating hormone 57.7 mIU/mL (menopausal range: 26.7 - 133.4); luteinizing hormone 26.21 mIU/mL (menopausal range 5.16 - 61.1); progesterone 0.4 ng/mL (0.1 - 0.3 on follicular phase and 1.2 - 15.9 on luteal phase); estradiol 10 pg/mL (menopausal level < 28 pg/mL); anti-Mullerian hormone 0.01 ng/mL (menopausal level < 0.2 ng/mL). The levels of thyroid-stimulating hormone, free thyroxine, free triiodothyronine, and prolactin were within the normal ranges, and liver enzyme and renal function results were also normal. Pregnancy was excluded as a possibility.

Treatment

The patient was referred to a gynecology specialist and started on estro-progesterone therapy.

Follow-up and outcomes

After 1 month, she referred that menstrual cycle was returned.

Discussion

This report describes a rare case of amenorrhea as a post-COVID-19 complication in a 27-year-old woman. While pre- and post-natal COVID-19-related complications have been reported in pregnant women, none of them were related to the absence or even interruption of the menstrual cycle. It is possible that similar cases of amenorrhea have been overlooked in clinical practice because of the non-disturbing effects of menstrual interruption. Additionally, female patients are probably reluctant about consulting a doctor about this issue and prefer to wait until their menstrual cycle returns to normal. This is a reason why COVID-19 patients need to be followed up for a long time, especially in young female patients. According to Li et al, psychological factors could play a role in such conditions; however, the patient in this case did not have any psychological symptoms [25]. She had a clinically mild form of the disease, with no pulmonary involvement, no difficulty in breathing, or other life-threatening complications. She did not have any signs of depression during or even after the SARS-CoV-2 infection. To gather more relevant information regarding our case, we searched PubMed and other medical websites, but we found a very limited number of papers. In one such paper, Somasundaram et al pointed out that men are more likely to be affected by SARS-CoV-2 infection due to the presence of SARS-CoV-2 receptors on spermatogonia and somatic (Leydig and Sertoli) cells in the testis, but similar studies in females have not found the presence of ACE2 receptors in ovaries or the effect of this virus on the ovaries. ACE2 was also expressed in the endometrium, to a greater extent in epithelial cells than stromal cells, and moreover, the expression of ACE2 changed with the menstrual [20, 23, 26]. Li et al reported that apart from the renin-angiotensin-aldosterone system that is involved in the reproductive and ovulatory processes, SARS-CoV-2 may affect female infertility through direct invasion of ovarian tissue and granular cells or may even cause direct endometrial damage. Renin-angiotensin (Ang)-aldosterone system (RAS) is involved in female reproductive processes such as folliculogenesis, steroidogenesis, oocyte maturation and ovulation [25]. Reis et al detected ACE2 mRNA transcripts in ovaries from reproductive-age women and postmenopausal women [25-27]. Additionally, data obtained from Bgee showed that the expression level of ACE2 in oocytes is relatively high. Therefore, the ovary and oocytes might be potential targets of SARS-CoV-2 [3, 10]. Li et al to suggest that SARS-CoV-2 might attack ovarian tissue and granulosa cells, and decrease ovarian function and oocyte quality, leading to female infertility or miscarriage or damage endometrial epithelial cells and affect early embryo implantation to affect the female fertility. However, there is still a lack of evidence on the effect of SARS-CoV-2 on the Fallopian tube, which should be paid greater attention in the future.

On the other hand, this is one case of amenorrhea associated with SARS-CoV-2 infection, and may well be a coincidence. However, based on the data currently, the exact effects of SARS-CoV-2 on the ovaries and its potential mechanisms are unclear. More evidence, including both epidemiologic and clinical studies, as well as long-term follow-up studies, is needed to verify the impact of SARS-CoV-2 infection on the human ovary, especially in reproductive-aged women.

Learning points

The pandemic of COVID-19 is continuing spreading all over the world. SARS-CoV-2 infection is a multisystemic disease, and it is important for physicians to understand its various complications. Clinicians and health workers are very concerned about its impact on reproductive health. For us as health workers, it is essential to protect the human reproductive system, as it is vital to the survival of humans. In particular, the potential adverse effects of SARS-CoV-2 infection on fertility are unclear, and more research and clinical studies are needed to understand if SARS-CoV-2 infection has direct or indirect effects on the ovaries.

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Conflict of Interest

The authors have no conflict of interest to disclose.

Informed Consent

Written informed consent for publication of his clinical details and/or clinical images was obtained from the patient.

Author Contributions

Entela Puca reviewed the literature and drafted the manuscript, conceived and designed this case report and revised the manuscript; Edmond Puca contributed to the literature review and manuscript drafting; both authors read and approved the final version of the submitted manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

References

1. WHO. COVID-19 Weekly Epidemiological Update. Edition 72, published December 28, 2021.
2. Tajbakhsh A, Gheibi Hayat SM, Taghizadeh H, Akbari A, Inabadi M, Savardashtaki A, Johnston TP, et al. COVID-19 and cardiac injury: clinical manifestations, biomarkers, mechanisms, diagnosis, treatment, and follow up. Expert Rev Anti Infect Ther. 2021;19(3):345-357.
3. Aggarwal S, Garcia-Telles N, Aggarwal G, Lavie C, Lippi G, Henry BM. Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): Early report from the United States. Diagnosis (Berl). 2020;7(2):91-96.
4. Brouwer MC, Ascione T, Pagliano P. Neurologic aspects of covid-19: a concise review. Infez Med. 2020;28(suppl 1):42-45.
5. Canning D, Karra M, Dayalu R, Guo M, Bloom DE. The association between age, COVID-19 symptoms, and social distancing behavior in the United States. medRxiv. 2020.
6. Chung MK, Zidar DA, Bristow MR, Cameron SJ, Chan T, Harding CV, 3rd, Kwon DH, et al. COVID-19 and Cardiovascular Disease: From Bench to Bedside. Circ Res. 2021;128(8):1214-1236.
7. Dhama K, Khan S, Tiwari R, Sircar S, Bhat S, Malik YS, Singh KP, et al. Coronavirus disease 2019-COVID-19. Clin Microbiol Rev. 2020;33(4):e00028-20.
8. Kolifarhood G, Aghaali M, Mozafar Saadati H, Taherpour N, Rahimi S, Izadi N, Hashemi Nazari SS. Epidemiological and clinical aspects of COVID-19; a narrative review. Arch Acad Emerg Med. 2020;8(1):e41.
9. Lu R, Qin J, Wu Y, Wang J, Huang S, Tian L, Zhang T, et al. Epidemiological and clinical characteristics of COVID-19 patients in Nantong, China. J Infect Dev Ctries. 2020;14(5):440-446.
10. Ortiz-Prado E, Simbana-Rivera K, Gomez-Barreno L, Rubio-Neira M, Guaman LP, Kyriakidis NC, Muslin C, et al. Clinical, molecular, and epidemiological characterization of the SARS-CoV-2 virus and the Coronavirus Disease 2019 (COVID-19), a comprehensive literature review. Diagn Microbiol Infect Dis. 2020;98(1):115094.
11. Puca E, Puca E, Pipero P, Kraja H, Como N. Severe hypocalcaemia in a COVID-19 female patient. Endocrinol Diabetes Metab Case Rep. 2021;2021:20-0097.
12. Synowiec A, Szczepanski A, Barreto-Duran E, Lie LK, Pyrc K. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): a Systemic Infection. Clin Microbiol Rev. 2021;34(2):e00133-20.
13. Wong JEL, Leo YS, Tan CC. COVID-19 in Singapore-Current Experience: Critical Global Issues That Require Attention and Action. JAMA. 2020;323(13):1243-1244.
14. Guillen E, Pineiro GJ, Revuelta I, Rodriguez D, Bodro M, Moreno A, Campistol JM, et al. Case report of COVID-19 in a kidney transplant recipient: Does immunosuppression alter the clinical presentation? Am J Transplant. 2020;20(7):1875-1878.
15. Parsova KE, Pay L, Oflu Y, Haciyev R, Cinier G. A rare presentation of a patient with COVID-19: Cardiac tamponade. Turk Kardiyol Dern Ars. 2020;48(7):703-706.
16. Haghighi-Morad M, Alavi Darazam I, Bahrami-Moltagh H, Amerifar M, Zamani N, Hassanian-Moghaddam H. Atypical presentation of COVID-19; an observational retrospective study. BMC Infect Dis. 2020;20(1):870.
17. Kandasamy S. An unusual presentation of COVID-19: Acute pancreatitis. Ann Hepatobiliary Pancreat Surg. 2020;24(4):539-541.
18. Wilkins J, Al-Inizi S. Premature ovarian insufficiency secondary to COVID-19 infection: An original case report. Int J Gynaecol Obstet. 2021;154(1):179-180.
19. Moin ASM, Sathyapalan T, Atkin SL, Butler AE. COVID-19 biomarkers for severity mapped to polycystic ovary syndrome. J Transl Med. 2020;18(1):490.
20. Moradi F, Enjezab B, Ghadiri-Anari A. The role of androgens in COVID-19. Diabetes Metab Syndr. 2020;14(6):2003-2006.
21. Sharma I, Kumari P, Sharma A, Saha SC. SARS-CoV-2 and the reproductive system: known and the unknown..!! Middle East Fertil Soc J. 2021;26(1):1.
22. Muniangi-Muhitu H, Akalestou E, Salem V, Misra S, Oliver NS, Rutter GA. Covid-19 and Diabetes: A Complex Bidirectional Relationship. Front Endocrinol (Lausanne). 2020;11:582936.
23. Johari YB, Jaffe SRP, Scarrott JM, Johnson AO, Mozzanino T, Pohle TH, Maisuria S, et al. Production of

trimeric SARS-CoV-2 spike protein by CHO cells for serological COVID-19 testing. Biotechnol Bioeng. 2021;118(2):1013-1021.
24. de Lusignan S, Dorward J, Correa A, Jones N, Akinyemi O, Amirthalingam G, Andrews N, et al. Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study. Lancet Infect Dis. 2020;20(9):1034-1042.
25. Li R, Yin T, Fang F, Li Q, Chen J, Wang Y, Hao Y, et al. Potential risks of SARS-CoV-2 infection on reproductive health. Reprod Biomed Online. 2020;41(1):89-95.
26. Viana GE, Pereira VM, Honorato-Sampaio K, Oliveira CA, Santos RA, Reis AM. Angiotensin-(1-7) induces ovulation and steroidogenesis in perfused rabbit ovaries. Exp Physiol. 2011;96(9):957-965.
27. Reis FM, Bouissou DR, Pereira VM, Camargos AF, dos Reis AM, Santos RA. Angiotensin-(1-7), its receptor Mas, and the angiotensin-converting enzyme type 2 are expressed in the human ovary. Fertil Steril. 2011;95(1):176-181.