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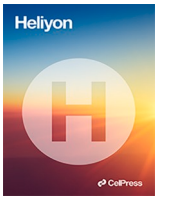

Persistent oligonecrozoospermia after asymptomatic SARS-CoV-2 infection. A case report and literature review

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ABSTRACT

COVID-19 is known to have deleterious effects on different systems such as the respiratory, cardiovascular, central nervous, and gastrointestinal. However, conflicting data about the possible implications for male reproductive health and fertility have been reported. In addition, the long-term consequences of SARS-CoV-2 infection remain unclear. Herein, we report a case of a 42-year-old man with no known co-morbidities and normal baseline semen quality, who subsequently suffered an asymptomatic SARS-CoV-2 infection. Shortly after, the patient developed sudden oligoasthenozoospermia, even reaching azoospermia, which gradually evolved into persistent severe oligonecrozoospermia, accompanied by semen inflammation and oxidative stress. Remarkably, the latter occurred in the absence of urogenital infections, hormonal imbalances, tissue/organ obstruction/damage, medication or drug treatment, smoking, or exposure to toxins/pollutants, radiation, or high temperature. This case constitutes valuable clinical evidence that adds to the current knowledge in the field and highlights the need for further and longer follow-up studies to better understand the putative long-term consequences of SARS-CoV-2 infection on male fertility.

1. Introduction

From the beginning of the global pandemic until January 2023, more than 600 million cases of COVID-19 and more than 6 million fatalities have been reported [1]. Although COVID-19 affects individuals of both sexes, it has a disproportionately greater impact on males, resulting in greater severity and high mortality rates [2]. COVID-19 can present with a wide range of clinical manifestations, from asymptomatic infection to fatal disease. In addition, although its long-term consequences remain uncertain, it is increasingly known that many patients experience heterogeneous, long-term, post-acute sequelae of COVID-19, also known as long COVID-19 [3].

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Table 1
Semen quality.

Semen analysis	Date of analysis														Lower reference limit[a]
Variable	11-Feb-14	01-Apr-15	06-Apr-16	17-Jul–18	09-Sep-19	26-Jan-21	25-Feb-21	15-Apr-21	21-Apr-21	13-May-21	01-Jun-21	05-Jul-21	14-Jan-22	08-Feb-23	
Volume (mL)	5.8	6.8	6.9	6.9	6.2	4.6	Confirmation of SARS-CoV-2 infection	2.6	4.7	8.2	5.4	5.6	5.4	7.2	≥1.5
pH	7.7	7.8	7.6	7.8	7.6	7.6		7.6	7.7	7.6	7.4	7.6	7.5	7.6	≥7.2
Sperm concentration ($x10^6$/mL)	9.33	31.22	47.28	15.51	24.33	41.82		6.67	0.85	0.27	0.15	0.27	0.00	0.83	≥15.00
Total sperm count (millions)	54.1	212.3	326.2	107.0	150.8	192.4		17.3	4.0	2.2	0.8	1.5	0.0	5.9	≥39.0
Sperm total motility (%)	34.0	15.0	20.0	46.0	30.0	46.0		0	0	0	0	0	0	0	≥40.0
Sperm progressive motility (%)	19.0	11.0	12.0	30.0	23.0	33.0		0	0	0	0	0	0	0	≥32
Sperm viability (%)	88	86	60	76	90	79		4	8	0	0	0	0	0	≥58
Peroxidase (+) cells ($x10^6$/mL)	0.02	0.07	0.11	0.29	0.73	0.27		0.16	0.09	0.08	0.15	0.08	0.27	0.01	≤1.00
Anti-sperm IgG antibodies (direct MAR test, %)	1	3	2	ND	2	1		ND	ND	ND	ND	ND	ND	ND	<10
Anti-sperm antibodies (IgG, IgA) in seminal plasma (indirect MAR test, %)	ND	ND	ND	ND	ND	ND		3, 1	ND	ND	ND	ND	ND	ND	<10
Fructose (mg/dL)	ND	ND	ND	ND	ND	ND		ND	156	ND	ND	ND	258	ND	150–450
Citric acid (mg/dL)	ND	ND	ND	ND	ND	ND		ND	680	ND	ND	ND	365	ND	350–670
Alpha-glucosidase (mU/ejaculate)	ND	ND	ND	ND	ND	ND		ND	58.6	ND	ND	ND	29.5	ND	>20.0

(a) Lower reference value according to the Semen Analysis Manual of the World Health Organization, 5th Ed., 2010 [9]. ND: Not determined. MAR: Mixed antiglobulin reaction.

The term "long COVID-19″ defines a multifaceted syndrome that encompasses ongoing, recurrent, or new manifestations or additional health consequences that persist or arise beyond four weeks following the initial SARS-CoV-2 infection [3,4]. Although the natural progression of long COVID-19 has not yet been fully unraveled, it has been shown to affect individuals of different ages, especially among patients aged 36–50 years, who have experienced acute symptomatic or asymptomatic infections, characterized predominantly by mild, non-hospitalized disease [4]. Currently available data indicate that more than 65 million people worldwide experience the consequences of long COVID-19 [3,5]. However, the actual prevalence is likely to be significantly higher due to the high number of subclinical and unreported cases.

In this context, reported evidence suggests that SARS-CoV-2 infection can alter sperm quality and also exert long-term effects on male fertility potential. In this regard, an inverse association has been described between the infection and sperm quality parameters such as volume, concentration, motility, and viability, with the degree of these alterations correlating with disease severity [6,7]. It is worth noting that a recent meta-analysis has revealed that even mild or asymptomatic cases of COVID-19 have adverse effects on sperm quality, reducing sperm concentration, total sperm count, sperm motility, and normal sperm morphology [8]. Nevertheless, there is substantial heterogeneity among reported studies, resulting from non-standardized diagnostic criteria, diverse laboratory methods used, and different medical centers and research institutions. All of that, together with the absence of data on semen quality before the infection, may introduce some bias in the results of the analysis regarding the impact of COVID-19 on sperm quality. Moreover, there is scarcely documented data about the precise association between the onset of infection and the occurrence of alterations in sperm quality. In addition, the lack of long-term assessment cohort studies raises many questions about the possible long-term consequences of SARS-CoV-2 infection on sperm quality and male fertility potential [4],[8]. Herein, we report the case of a male individual known to have normal sperm parameters who subsequently suffered asymptomatic SARS-CoV-2 infection. Shortly after the infection was confirmed, the patient developed sudden oligoasthenozoospermia, even reaching azoospermia, which gradually evolved into persistent severe oligonecrozoospermia.

2. Case presentation

A 42-year-old man with no known co-morbidities, taking no medications or dietary supplements, presented on January 25th, 2021 to the Reproductive outpatient clinic with his 42-year-old female partner, who had a low ovarian reserve and poor oocyte quality, seeking care for the couple's primary infertility. Neither the patient nor his wife have had children. He has been attending the clinic for regular controls during the preceding 7 years. He was 190 cm tall and weighed 94 kg, indicating a body mass index of 26.0 kg/m^2. His medical record revealed a history of varicocelectomy (varicocele grade 3) in 2010 and no other condition including orchitis, parotiditis, or urogenital infection in the last 3 years. He was not taking any medication or supplements. He reported drinking alcohol occasionally (social drinker) and not smoking or taking drugs. In addition, he referred not to be life or occupationally exposed to toxins or pollutants, radiation, or high temperatures. A baseline semen analysis performed on January 26th, 2021, revealed an overall normal sperm quality, with semen volume of 4.6 mL, sperm concentration of 41.82x10^6/mL, total sperm count of 192.4 x10^6 spermatozoa, total motility of 46%, and viability of 79%, and the absence of leukocytospermia and anti-sperm antibodies (Table 1). Interestingly, as the patient attended the clinic for regular controls since February 2014, extensive background data on his semen quality are available, which showed a history of good overall sperm quality in the previous 7 years (Table 1).

Following the couple's counseling, the treatment plan was to perform ICSI followed by intrauterine embryo transfer to attempt conception. On April 15th, 2021, when the first ICSI was going to be performed, a new semen analysis surprisingly revealed a sperm

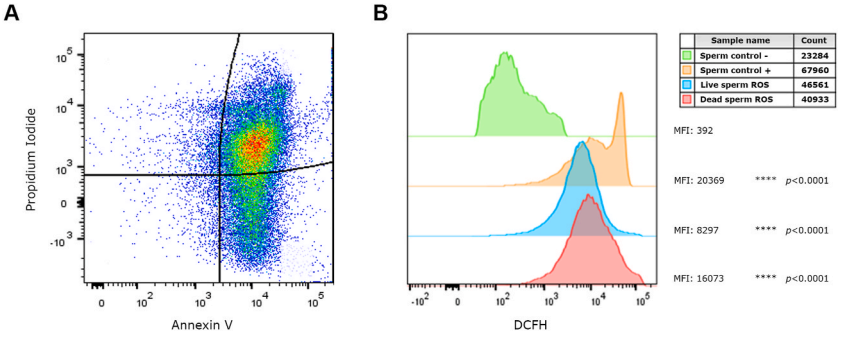

Fig. 1. *Assessment of intracellular sperm ROS production* by flow cytometry using the probe DCFH-DA that fluoresces to DCFH when oxidized as previously described [11]. **(A)** Representative dot plot of the analysis of sperm apoptosis/necrosis by Annexin V (A)/propidium iodide (PI) staining showing the subsets of live (A-/PI-), early apoptotic (A+/PI-), late apoptotic (A+/PI+) and necrotic (A-/PI+) patient spermatozoa. **(B)** Representative histograms showing ROS production levels (MFI) from the patient live (A-/PI- and A+/PI-) and dead (A+/PI+ and A-/PI+) spermatozoa. The negative and positive controls consisted in spermatozoa alone (not incubated with DCFH-DA) or spermatozoa exposed to DCFH-DA in the presence of H_2O_2 (1 mM), respectively. Data are shown as mean ± SD. Fractions of sperm samples (n = 3) were tested separately and maintained at 37 °C throughout all procedures. Data were collected on FACS-CANTO II flow cytometer (BD Biosciences) and analyzed using FlowJo software (version 7.6.2). Statistical analysis was performed using one-way ANOVA with Bonferroni post hoc test analysis. A $p < 0.05$ (versus the negative control) was considered statistically significant.

volume of 2.6 mL, sperm concentration of 6.67 x10^6/mL, total sperm count of 17.3x10^6 spermatozoa, 0% motility, and 4% viability. In addition, normal leukocyte counts and no anti-sperm antibodies were detected (Table 1). After exhaustive anamnesis, the patient referred his wife suffered from mild COVID-19 and he had an asymptomatic SARS-CoV-2 infection confirmed on February 25th, 2021, which did not require hospitalization or any medication. He was unvaccinated against COVID-19. Besides, the patient reported no other recent apparent event or significant lifestyle change during the preceding 3 months. Six days later, on April 21st, 2021, a new semen analysis confirmed sperm quality alterations further showing marked oligoasthenozoospermia and necrozoospermia (Table 1). Remarkably, magnetic resonance imaging (MRI) of the pelvis and scrotum revealed the absence of any obstruction, or alteration in any tissue or organ including the testicles, epididymides, vas deferens, seminal vesicles, or the prostate. Three weeks later, on May 13th, 2021, the patient provided a new semen specimen. Semen analysis revealed persistent oligoasthenozoospermia and necrozoospermia (Table 1, Fig. 1A). Furthermore, elevated concentrations of TNF, IL-1β, and IL-6 were detected in semen (Table 2). Noteworthy, highly increased levels of sperm ROS production were detected in the fraction of viable sperm by flow cytometry (Fig. 1B). Remarkably, high levels of ROS were also detected in the fraction of late apoptotic/necrotic spermatozoa suggesting oxidative stress as the underlying cause of the observed necrozoospermia. In parallel, negative results were obtained when assessing semen infection of 17 known uropathogens including viruses, bacteria, fungi, and parasites using either culture methods or PCR [10]. Besides, the quantification of serum levels of different hormones showed results within reference values, indicating no endocrine alterations (Table 2). Considering that the patient presented markedly decreased sperm quality, semen inflammation, and sperm oxidative stress, in the absence of detectable urogenital infection, anatomical obstruction, or hormonal imbalances, treatment with antioxidant supplementation was prescribed, which consisted of vitamin C and E (both 1g/day) during 6 months. The patient accepted and immediately started the treatment, which was well tolerated.

In the following two months, on June 1st and July 5th, 2021, the analysis of new semen specimens indicated the persistence of severe oligozoospermia and total necrospermia (Table 1) despite strict adherence to the treatment. Strikingly, the latter progressed to azoospermia, detected on January 22nd, 2022 (Table 1). Moreover, the patient's sperm quality has not recovered nearly 2 years after infection, as a recent semen analysis showed severe oligozoospermia and complete necrozoospermia (Table 1).

Altogether, these findings revealed the development of persistent severe oligonecrozoospermia following an episode of asymptomatic SARS-CoV-2 infection.

3. Discussion

Cumulative epidemiological evidence shows that men are more vulnerable to the development of COVID-19, with higher morbidity and mortality rates than women [14]. Although substantial knowledge about the pathophysiology of COVID-19 has been gained since the onset of the SARS-CoV-2 pandemic, several aspects of COVID-19 remain to be elucidated, particularly those related to the long-term sequelae of the disease [3,4,15]. Although it is known that COVID-19 can exert pathogenic implications on the respiratory, cardiovascular, central nervous, and gastrointestinal systems, it is still uncertain whether the pathology exerts deleterious effects on the urogenital tract and reproduction [3],[4],[15]. As shown in Table 3, some reported evidence indicates that semen quality and male fertility potential would be affected by SARS-CoV-2 infection. Such studies have shown that both clinically severe and mild COVID-19, as well as asymptomatic SARS-CoV-2 infections, were associated with alterations in semen quality such as reductions in total sperm count, sperm concentration, sperm motility, and/or sperm viability [6,16–20], being this effect potentially reversible after disease recovery [7,21,22]. On the contrary, several other studies have reported that SARS-CoV-2 infection does not have a substantial impact on sperm quality (Table 3) [23–29]. Therefore, available reported data is conflicting and heterogeneous. In addition, and most importantly, most studies lack information on the seminal quality of individuals before and in the early and late periods after infection,

Table 2
Assessment of inflammatory and endocrine biomarkers.

		13-May-2021	Reference values
Cytokines in semen	TNF	30.6	0.0–2.0[a]
(pg/mL)	IL-1β	24.0	0.0–12.0[a]
	IL-6	99.2	2.0–20.0[a]
	IL-8	2120.9	850.0–1910.0[a]
	IFNγ	0.00	0.0–10.0[a]
	IL-10	0.00	0.0–10.0[a]
	IL-17	8.2	0.0–19.8[a]
Serum/plasma hormones	Total testosterone (ng/dL)	403	245–1500[b]
	Bioavailable testosterone (ng/dL)	245	91–337[b]
	Free testosterone (ng/dL)	9.10	5.71–17.90[b]
	FSH (mUI/mL)	4.8	1.0–12.0[b]
	LH (mUI/mL)	4.4	1.5–9.2[b]
	Prolactin (ng/mL)	8.1	4.5–21.5[b]
	17β-Estradiol (pg/mL)	18	10–60[b]
	Cortisol 8.00 a.m. (μg/dL)	15.4	5.0–25.0[b]
	Post-Dexamethasone Cortisol (μg/dL)	0.53	≤1.70[b]
	TSH (μUI/mL)	1.57	0.4–4.0[b]

[a] Reported reference values for cytokine levels in semen [12]. Cytokines levels in semen were assessed as previously described [13].
[b] Reference normal values according to patient age and sex currently established and used in the local setting.

Table 3
Basic characteristics of the reviewed literature.

Study	Type	Country	Year	Subjects	Severity	Main findings
Holtmann 2020 [17]	Prospective cohort study	Germany	2020	18 patients/10 controls	Asymptomatic/Mild/ Moderate	No virus detection in semen ↓ sperm concentration ↓ sperm motility
Li 2020 [33]	Observational	China	2020	23 patients/22 controls	Asymptomatic/Mild/ Moderate	No virus detection in semen Inflammatory histopathological findings and impaired spermatogenesis in testis/ epididymis ↑ IL-6, TNF, MCP-1 and leukocytes in semen ↓ sperm concentration irrespective of disease severity/fever
Yang 2020 [34]	Observational	China	2020	12 patients	Severe	No virus detection in testis Inflammatory histopathological findings and impaired spermatogenesis in testis/ epididymis
Gacci 2021 [6]	Prospective and cross-sectional	Italy	2021	43 patients	Moderate /Severe	↓ sperm concentration ↑ frequency of oligo/azoospermia ↑ IL-8
Pazir 2021 [18]	Prospective cohort study	Turkey	2021	24 patients	Asymptomatic/Mild	↓ sperm motility
Koc 2021 [19]	Prospective cohort study	Turkey	2021	21 patients	Mild	↓ sperm volume ↓ sperm motility ↓ sperm normal morphology
Erbay 2021 [20]	Multicenter cohort study	Turkey	2021	69 patients	Mild/Moderate	↓ sperm volume ↓ sperm concentration ↓ sperm motility ↓ sperm viability
Guo 2021 [7]	Prospective cohort study	China	2021	41 patients/50 controls	Moderate /Severe	↓ sperm concentration ↓ sperm motility Potentially reversible
Ruan 2021 [23]	Prospective cohort study	China	2021	74 patients	Asymptomatic/Mild/ Moderate/Severe	No virus detection in semen No major effects on sperm quality
Gul 2021 [26]	Prospective and cross-sectional	Turkey	2021	29 patients	Mild/Moderate/Severe	No effects on sperm quality
Ma 2021 [27]	Prospective cohort study	China	2021	12 patients	Mild/Moderate	No virus detection in semen No major effects on sperm quality
Temiz 2021 [29]	Prospective and cross-sectional	Turkey	2021	10 patients/10 controls	ND	No virus detection in semen No major effects on sperm quality
Paoli 2021 [35]	Observational	Italy	2021	4 patients/2 controls	Mild/Moderate	No virus detection in semen
Hajizadeh Maleki 2021 [36]	Prospective cohort study	Iran	2021	84 patients/ 105 controls	Mild/Moderate/Severe	↑ IL-1β, IL-6, IL-8, IL-10, TGF-β, INF-α, INF-γ and oxidative stress in semen ↓ sperm volumen ↓ sperm concentration ↓ sperm motility ↓ sperm normal morphology
Morselli 2022 [37]	Prospective cohort study	Italy	2022	43 patients	Mild/Moderate/Severe	↑ frequency of oligo/azoospermia ↑ IL-1β in semen Semen IL-1β and TNF levels negatively correlated with sperm concentration
Aksak 2022 [16]	Prospective cohort study	Turkey	2022	100 patients/ 100 controls	Mild	↓ sperm concentration ↑ frequency of azoospermia
Wang 2022 [38]	Cross-sectional	China	2022	3 patients/3 controls	ND	COVID-19 inhibits spermatogenesis by inducing testicular cell senescence
Donders 2022 [21]	Prospective cohort study	Belgium	2022	118 patients	Mild/Moderate/Severe	No virus detection in semen ↑ frequency of oligozoospermia ↓ sperm motility ↓ sperm normal morphology Reversible and irrespective of disease severity
Tufveson 2022 [22]	Meta-analysis	Denmark	2022	9 studies	Asymptomatic/Mild/ Moderate/Severe	SARS-CoV-2 infection reversibly impairs spermatogenesis
Hu 2022 [24]	Prospective cohort study	China	2022	36 patients/45 controls	Asymptomatic/Mild/ Moderate/Severe	No effects on sperm quality
Shcherbitskaia 2022 [28]	Prospective cohort study	Russia	2022	17 patients/22 controls	ND	No effects on sperm quality
Seckin 2022 [39]	Case Report	USA	2022	1 clinical case	Moderate	Development of full asthenozoospermia that progressively reversed after recovery

(*continued on next page*)

Table 3 (*continued*)

Study	Type	Country	Year	Subjects	Severity	Main findings
Gharagozloo 2022 [40]	Case Report	USA	2022	1 clinical case	Moderate	Development of azoospermia that progressively reversed after recovery
Paoli 2023 [25]	Prospective cohort study	Italy	2023	80 patients/98 controls	Mild/Moderate/Severe	No effects on sperm quality
Che 2023 [8]	Meta-analysis	China	2023	13 studies	Asymptomatic/Mild	↓ sperm concentration ↓ sperm motility ↓ sperm normal morphology irrespective of fever and disease severity No hormonal dysregulation

ND: No data.

which would allow for a comprehensive interpretation of the data and appropriate conclusions to be drawn [8],[22],[30–32]. Therefore, it is still unknown whether SARS-CoV-2 infection would have long-lasting deleterious effects on seminal quality and male fertility potential [3,4]. Consequently, conclusive evidence is urgently needed to accurately understand the pathophysiology of SARS-CoV-2 infection and its potential effects on sperm quality and male fertility.

We are herein reporting a rare case of a normospermic 42-year-old man who suddenly developed progressive oligoasthenozoospermia that evolved to persistent severe oligonecrozoospermia after an asymptomatic SARS-CoV-2 infection. The peculiarity of this case is that 1 month before the infection, the patient presented a completely normal semen quality. Noteworthy, and different from most reported data, we have retrospective yearly data from the patient indicating an overall normal semen quality up to 7 years preceding the infection, which then suddenly deteriorated shortly after being diagnosed with asymptomatic SARS-CoV-2 infection and without any other apparent cause. Furthermore, the speed with which the patient became oligozoospermic and even azoospermic is remarkable. Two months after the infection was confirmed, the total count of spermatozoa dropped to less than 10% of the previously observed value (192.4 million on January 26th, 2021, to 17.3 million on April 15th, 2021, Table 1). Most impressive, total sperm motility and viability decreased much more suddenly and even reached null values shortly after the infection (Table 1). Strikingly, these alterations have not reversed after almost 2 years from the infection episode having rendered the patient oligonecrozoospermic up to date, which is another peculiarity of this rare case. Although very scarce, reported data in that regard is consistent with our findings. Aksak et al. detected azoospermia in 4 out of 100 patients who recovered from COVID-19 while none of the control individuals [16]. Moreover, Gacci et al. found that 18.6% and 7% of sexually active men recently recovered from COVID-19 were azoospermic and oligospermic, respectively, indicating that 25% of patients had severely reduced sperm counts after an episode of acute SARS-CoV-2 infection [6]. Besides, Li et al. reported oligozoospermia in a significant fraction (39.1%) of patients recovered from COVID-19 [33]. Noteworthy, oligozoospermia prevalence was irrespective of symptomatic/asymptomatic infection, disease severity, and the presence or absence of fever [33]. However, these authors did not have the baseline semen quality parameters data before the infection to distinguish infection consequent from pre-existing conditions [6,16,33]. Nonetheless, the prevalence of azoospermia found in patients recovered from COVID-19 exceeds that reported for the regular population [41], strongly supporting a negative effect of the infection on sperm counts. In agreement, Seckin et al. reported a case of a 48-year-old male, unvaccinated, who developed asthenozoospermia after a moderate episode of COVID-19 [39]. Interestingly, the patient showed all normal semen parameters 3 weeks before the infection [39]. Moreover, Gharagozloo et al. reported a longitudinal study that showed the state of azoospermia after an episode of moderate COVID-19 that did not require hospitalization in a 55-year-old man [40]. The patient was a previously fit and healthy man, with no other comorbidities and not taking any medication or supplements. He experienced a surprisingly rapid decline in sperm count leading to azoospermia, detected two weeks after resolving a moderate and shortly symptomatic SARS-CoV-2 infection [40]. In agreement with our data, it is striking how fast these patients developed astheno- or azoospermia after suffering from SARS-CoV-2 infection [6],[7],[39],[40]. Nevertheless, and although scarce, reported studies containing pre-infection semen quality data show that the observed deterioration in semen quality after symptomatic SARS-CoV-2 infection, even to the point of azoospermia, progressively reverses after 2 or 3 cycles of spermatogenesis [21],[22],[39],[40]. On the contrary, the case presented herein shows the sudden development of severe oligoasthenozoospermia, even reaching azoospermia, which led to persistent oligonecrozoospermia after an acute episode of asymptomatic SARS-CoV-2 infection.

The sperm alterations and impaired spermatogenesis observed in our patient could be due to different effects of SARS-CoV-2 infection, either direct and/or indirect. Firstly, the infection could alter testicular function. Histopathological alterations have been described in the testes of patients with COVID-19, such as thinning of the seminiferous tubules, detachment of Sertoli cells, loss of Leydig cells, leukocyte infiltrates, deposits of IgG, destruction of germ cells, increased number of apoptotic cells, and decreased number of spermatozoa in the seminiferous tubules [33,34]. To bind to the cell and fuse and enter the cell, the SARS-CoV-2 virus uses the angiotensin-converting enzyme 2 (ACE2) as a receptor and the cellular type II transmembrane serine protease (TMPRSS2) as a co-receptor [42]. In this regard, the testicle has been proposed as a potential target organ highly susceptible to SARS-CoV-2 infection because high levels of ACE2 and TMPRSS2 expression have been described in spermatogonia, peritubular myoid cells, and Leydig and Sertoli cells [43–45]. However, this is controversial as it has been shown that ACE2 and TMPRSS2 are not co-expressed at the cellular level in testicular tissue [46–48], suggesting that the testis would not be susceptible to infection. Accordingly, the vast majority of accumulated evidence has shown negative results for the detection of SARS-CoV-2 viral RNA or proteins in semen from infected individuals [35,49]. In addition, sexual transmission of SARS-CoV-2 infection has not been demonstrated [49]. Nevertheless, other receptors such as CD147 or Basigin (BSG), and coreceptors, such as cysteine protease cathepsin L (CTSL), have been identified by which

SARS-CoV-2 could invade the host cell [50,51]. However, the possibility of testicular infection and impaired spermatogenesis by SARS-CoV-2 cannot be dismissed because the coexpression of BSG and CSTL has been described in primary spermatocytes [46].

Besides, testicular damage and spermatogenesis impairment may be caused by infection and/or inflammation [52,53]. However, we obtained negative results when screening a panel of 17 common uropathogens including bacteria, viruses, fungi and parasites. Nevertheless, the patient showed significantly increased seminal concentrations of TNF, IL-6, and IL-1β together with markedly high levels of sperm ROS production indicating semen inflammation and oxidative stress. These findings are supported by reported evidence indicating elevated seminal concentrations of inflammatory cytokines and decreased semen antioxidant capacity, in conjunction with impaired spermatogenesis, in men with COVID-19 [6],[28],[33],[36],[37]. Increased seminal levels of inflammatory cytokines are considered to be resultant of the so-called cytokine storm, a phenomenon usually presented by patients with COVID-19 [54], which may induce harmful side effects in the testis and epididymis through the stimulation of local inflammation and oxidative stress. It is well known that inflammatory cytokines, in particular IL-6, TNF, and IL-1β, and oxidative stress are deleterious to spermatogonia and spermatozoa as they trigger deregulated ROS production and elicit apoptosis [11,55–58]. In addition, a negative correlation has been demonstrated between seminal IL-1β and TNF concentrations and sperm concentration and total sperm count in SARS-CoV-2 infected patients, with the highest IL-1β levels detected in the group of patients with crypto-azoospermia [37]. Furthermore, recently reported evidence has revealed that the infection with SARS-CoV-2 would be able to suppress spermatogenesis by inducing senescence in testicular cells through the MAPK pathway, which is mainly elicited by stress responses such as inflammation and oxidative stress [38]. Noteworthy, the production of exaggerated levels of cytokines and chemokines could also trigger an autoimmune reaction with pathological consequences in the testis like inflammation-induced inhibition of spermatogenesis [31],[59].

Additional potential effects of the infection contributing to the observed sperm impairment could be anatomical obstructions and/or hormonal imbalances affecting sperm production. Remarkably, NMR imaging showed the absence of any obstruction or alteration in the urogenital tract organs of the patient ruling out the former possibility. Regarding the latter, our patient presented testosterone, FSH, LH, prolactin, and estradiol serum levels within normal range values indicating the absence of disturbances of the hypothalamus-pituitary-gonads axis. Accordingly, a recently published systematic meta-analysis found no significant differences in serum sex hormone levels before and after infection, strongly suggesting that hormone deregulation may not be a result of SARS-CoV-2 infection [8]. Finally, fever, medications, smoking, and toxins/pollutant exposure are other known factors to alter spermatogenesis and decrease sperm quality [60,61]. Nevertheless, our patient does not smoke and was neither under any medication therapy nor had fever, or has been knowingly exposed to toxins/pollutants, radiation, or high temperatures. Remarkably, accumulated evidence has shown that fever has a negligible effect on semen quality in SARS-CoV-2 infected patients [6],[18],[25]. Moreover, and in agreement with our findings, mild/asymptomatic COVID-19 has also been shown to exert deleterious consequences on semen quality, mostly affecting sperm concentration and motility, and independent of the severity of symptoms, variations in sex hormone levels, or fever [8].

Although we cannot discard any other possible cause for the sudden deterioration of the patient's sperm quality, the asymptomatic SARS-CoV-2 infection emerged as the only apparent event timely associated with the sudden development of persistent oligonecrozoospermia. A wide range of inquiries and tests were undertaken to assess the most probable causes: known infections, toxics or pollutants, radiation, high temperatures, endocrine alterations, andropause, trauma, and sperm-autoantibodies. Nevertheless, our study has some limitations since we did not assess rare or uncommon urogenital infections (not routinely assessed in clinical practice) or toxic/pollutant levels in serum or urine specimens from the patients to ascertain an unknowingly toxic/pollutant exposure.

4. Conclusion

Our study identified a unique case of a male individual of childbearing age, with no other co-morbidities and normal baseline semen quality, who suddenly developed oligoasthenozoospermia, even reaching azoospermia, associated with semen inflammation and oxidative stress after an asymptomatic SARS-CoV-2 infection. Strikingly, the patient remains with severe oligonecrozoospermia up to date, nearly 2 years after the infection. To our knowledge, there are no other reported cases of persistent severe oligonecrozoospermia following SARS-CoV-2 infection, with a documented normal semen quality before the infection and no other putative underlying cause including infections, hormonal alterations, tissue obstruction, drugs or medication treatment, smoking, or exposure to toxins, pollutants, radiation, or high temperatures. Although growing evidence indicates that SARS-CoV-2 infection may have detrimental effects on spermatogenesis, the impairment seems to resolve after a few months [49]. However, whether such effects can persist long after healing is currently unknown. The case presented herein adds to the current knowledge in the field. Our results highlight the need for more and longer follow-up studies including large patient populations (comparative before and after the infection) to verify our results and better understand the putative long-term consequences of SARS-CoV-2 infection on male fertility.

Patient perspective

The patient has remained with persistent severe oligonecrozoospermia up to the time this report was submitted (February 2023) with no further complications. After medical counseling, the couple decided to undergo assisted reproduction (ICSI) with oocytes and spermatozoa both from donors. The patient is committed to maintaining medical care and regularly attends to periodic controls.

Ethics statement

The present study protocol was reviewed and approved by the institutional review board of the Hospital Nacional de Clínicas, Universidad Nacional de Córdoba (Reg. No. RePIS #3512). The study was carried out according to the Code of Ethics of the World

Medical Association, the 1964 Declaration of Helsinki, and the Argentinian law of personal data protection (Ley Nacional 23526). Written informed consent to participate in this study was provided by the patient and for the publication of any potentially identifiable images or data included in this article.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

Data will be made available on request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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