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CORRESPONDENCE

Italian males recovering from mild COVID-19 show no evidence of SARS-CoV-2 in semen despite prolonged nasopharyngeal swab positivity

Carlo Pavone[1] · Giovanni M. Giammanco[2] · Davide Baiamonte[1] · Mirko Pinelli[1] · Celestino Bonura[2] · Maurizio Montalbano[3] · Giuseppe Profeta[4] · Loredana Curcurù[5] · Floriana Bonura[2]

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To the Editor:

The causative agent of COVID-19, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is able to infect humans and other animals, causing mainly respiratory, hepatic, gastrointestinal, and neurological symptoms in infected subjects. Droplets and fomites are generally considered the most important transmission factors, with social distancing as the main strategy to limit the actual pandemic, but little is known about the possibility of sexual transmission, including oral sex transmission. Recently, Angiotensin-converting enzyme 2 (ACE2), the receptor used by the virus to enter human cells, has been identified in human testis as it is highly expressed in Leydig, Sertoli, and seminiferous tubules cells, and new findings suggest a possible expression of ACE2 even in spermatocytes. At the time of this article, few studies looking for the presence of SARS-CoV-2 in human semen are available but have come to discordant conclusions [1–5]. In particular, while the detection of SARS-CoV-2 RNA in semen during the acute phase of severe symptomatic infections has already been demonstrated, weaker evidence has been shown of virus shedding through semen in the recovery phase or convalescence of COVID-19 and in patients with mild symptoms or in asymptomatic cases. Therefore, we tried to determine if SARS-CoV-2 is detectable in the semen of Italian patients showing mild or no symptoms of COVID-19 at the time of sampling, in order to better understand if sexual transmission is to be considered for the spread of SARS-CoV-2. Criteria for eligibility for our study were a positive nasopharyngeal swab PCR tests for SARS-CoV-2 (performed according to WHO guidelines) and diagnosis of a mild or asymptomatic COVID-19 infection, not requiring hospitalization (i.e., isolated in non-hospital setting; e.g., houses or hotels). Out of the 29 patients initially contacted and eligible, only 9 gave their written informed consent to participate and were enrolled to this study (approved by the ethical commission of *A.O.U. Policlinico "Paolo Giaccone"* University Hospital, Palermo, Italy). After consent was gained, qualified medical staff took enrolled patient's medical history, including information about comorbidities, therapy, and urological conditions. Data about the timing and results of nasopharyngeal SARS-CoV-2 tests, Computed Tomography (CT) scans, and COVID-19-correlated symptoms, both at the time of diagnosis and at the time of interview, were collected. Ejaculated semen specimens were collected and sent to the laboratory within one hour from collection for molecular testing. Nucleic acids were extracted from 0.5 ml of semen samples and detection of SARS-CoV-2 was performed using real-time RT-PCR protocols (performed according to WHO guidelines) targeting three different genes: viral RNA polymerase (R), envelope protein (E), and nucleocapsid protein (N).

Results of real-time RT-PCR in semen showed no evidence of SARS-CoV-2 RNA in the nine patients enrolled,

✉ Giovanni M. Giammanco
giovanni.giammanco@unipa.it

1 Section of Urology, Department of Surgical, Oncological and Oral Sciences, University of Palermo, Via del Vespro 129, Palermo, Italy

2 Section of Microbiology, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, University of Palermo, Via del Vespro 133, Palermo, Italy

3 Medical Direction "Azienda Sanitaria Provinciale di Palermo", Via G. Cusmano 24, Palermo, Italy

4 General Management, "Azienda Sanitaria Provinciale di Palermo", Via Pindemonte 88, Palermo, Italy

5 Prevention Department "Azienda Sanitaria Provinciale di Palermo", Via Enzo ed Elvira Sellerio 45, Palermo, Italy

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Table 1 Clinical characteristics and sampling times of patients positive at SARS-CoV-2 nasopharyngeal swab included in the study.

Patient	Group[a]	Age	BMI (Kg/m^2)	Date of first SARS-CoV-2-positive nasopharyngeal swab	Time lapse between first SARS-CoV-2-positive swab and semen collection (days)	Date of last SARS-CoV-2-positive nasopharyngeal swab	Time lapse between last SARS-CoV-2-positive swab and semen collection (days)	Time lapse between first and last SARS-CoV-2-positive swab (days)	Semen real-time RT-PCR result	Symptoms at diagnosis	Chest CT at diagnosis	Symptoms at semen collection	Comorbidity	Ongoing therapies	Smoker
1	C	42	30	10/04/20	39	14/05/20	4	34	NEG	Loss of taste and smell, muscle aches, diarrhea, fatigue headache and fever	Yes, suggestive of COVID-19	Muscle aches	Hypercholesterolemia	Statins	Yes
2	C	60	29,8	15/04/20	34	14/05/20	4	29	NEG	Cough	No	None	Hypertension, benign prostatic hyperplasia, cardiac valvulopathy	None	No
3	C	47	26,5	09/04/20	41	15/05/20	4	36	NEG	Loss of taste and smell, cough, headache, conjunctivitis and fever	No	None	Hypertension	None	No
4	C	28	23,5	13/04/20	36	14/05/20	5	31	NEG	Diarrhea and headache	No	None	None	None	Yes
5	C	52	27,7	22/04/20	48	01/06/20	8	40	NEG	Muscle aches, fatigue and fever	Yes, suggestive of COVID-19	None	Angina pectoris	ARBs	No
6	A	47	25,5	27/05/20	13	27/05/20	13	0	NEG	Fatigue	No	None	Acute myocardial infarction	ARBs, aspirin and clopidogrel	Yes
7	C	32	27	20/03/20	88	08/06/20	8	80	NEG	Diarrhea	No	Diarrhea	None	None	Yes
8	C	31	24	05/04/20	74	11/06/20	7	67	NEG	Loss of smell, fatigue and fever	No	None	Klinefelter syndrome	None	Yes
9	A	31	30,6	15/06/20	7	15/06/20	7	0	NEG	None	No	None	None	None	No

ARBs Angiotensin II receptor blockers, *CT* Computed Tomography scan.

[a]Group A (Acute) includes patients whose semen was sampled while in the canonical 14-day quarantine period; Group C (Convalescent) includes patients whose semen was sampled after the canonical 14-day quarantine period.

being their samples negative for the detection of all the three molecular targets used in duplicate repetitions. The nine patients enrolled for semen testing had all been positive at SARS-CoV-2 nasopharyngeal swabs at least once, but seven of them had been tested positive more than once. At the time they were first tested positive, all but one of the nine patients showed mild symptoms of COVID-19, including temperature, cough, fatigue, muscle aches, headache, loss of taste or smell, diarrhea or conjunctivitis, the ninth patient (patient no. 9) being asymptomatic (Table 1). None of our patients required hospitalization, but two of them had a chest CT at diagnosis that was suggestive of COVID-19 pneumonia. In this study most of the patients with SARS-CoV-2 infection (77.8%) had a BMI > 25 kg/m^2 that classified them as overweight and 55.6% had a past medical history of hypercholesterolemia, hypertension, and cardiovascular disease, but apparently this did not affect the severity of their illness and did not facilitate semen shedding of the virus. The complete clinical characteristics of patients are shown in Table 1. The seven patients having multiple positive SARS-CoV-2 nasopharyngeal swab results, had a time lapse between first and last SARS-CoV-2-positive swab of 29–80 days (median, 36 days), they were still kept in quarantine at home or at a COVID-hotel waiting for negative nasopharyngeal swabs, and could be therefore considered as convalescent patients (group C, Table 1). The two patients having a single SARS-CoV-2-positive swab before semen sampling were still attending their canonical 14-day quarantine period and were considered to be still in the acute phase of their infection (group A, Table 1). Semen sampling of all 9 patients was performed within 13 days of their last positive nasopharyngeal swab RT-PCR test result (range, 4–13 days; median, 7 days), and when they mostly had no symptoms. Only two patients had muscle aches or diarrhea at the time of semen collection. The median age of patients with SARS-CoV-2 infection was 42 years. Being relatively young patients and showing minor symptoms or having recovered from mild disease, they could be in the best conditions for transmitting the COVID-19 infection by sexual intercourse. Up to now a single study found SARS-CoV-2 in semen specimens but patients were in acute stage of infection (4/15; 26.7%) or recovering from severe symptoms (2/23; 8.7%) [5]. A few further studies showed no evidence of SARS-CoV-2 in semen of patients with mild COVID-19 symptoms or recovering from COVID-19 with mild-moderate symptoms at the time of testing [1–4]. Despite the limited size of the sampled population, our results seem to indicate that sexual transmission of SARS-CoV-2 by men recovering from mild symptoms of COVID-19 is highly unlikely. However, since severe acute COVID-19 cases were not included in the selection criteria of this study, we cannot rule out the presence of SARS-CoV-2 in the seminal fluid of such patients. Further larger scale studies, analyzing serial samples taken from the start of symptoms to complete recovery, are required to have a complete picture of the risk of sexual transmission of SARS-CoV-2. Studies on SARS-CoV-2 detection and persistence in semen will be beneficial both to clinical practice and public health strategies, especially considering the high morbidity and mortality of COVID-19.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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