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Testicular pain as unusual presentation of COVID-19. A brief review of SARS-CoV-2 and the testis

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Abstract

Research Question: Can SARS-CoV-2 induce testis damage and dysfunction?

Design: Description of the case of a young man presenting with heavy testicular pain as the first symptom of COVID-19. A review of the literature is also presented

Results: SARS-CoV-2 may enter into the host cell by binding to ACE2. This receptor seems to be widely expressed in different testicular cell types making possible the occurrence of orchitis in male COVID-19 patients. From a review of the literature, it seems that there is no evidence at this moment of sexual transmission of SARS-CoV-2, however the possibility of the virus induced testis damage and dysfunction could not be excluded.

Conclusions: Further studies are necessary on the pathological effect of SARS-CoV-2 in male reproductive system and to insure a proper andrological follow-up to male patients.

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Since the beginning of the SARS-CoV-2 pandemic up to May 30 there have been over 5,8 millions cases worldwide and over 230,000 cases in Italy (www.salute.gov.it). At the beginning of March, before the national lockdown, some regions in Northern Italy were declared as “red zone” ; among these our region, , Emilia-Romagna, in the middle of which Modena is located. Here, almost 200 cases per day were registered during the epidemic peak.

In mid-April, a 43-year-old man with medical history of Type 1 diabetes presented to the Emergency Department (ED) of our University Hospital with low-grade fever and severe bilateral

testicular pain that had started three days earlier. When asked in ED, he reported not having unsafe sex for years and not having suffered from previous venereal diseases. At ED admission, no evidence of inguinal hernia or urinary tract infections were instrumentally or clinically detected. Thus, given the stability of the clinical outlook, the patient was discharged at home with paracetamol therapy.

Twelve hours later, due to the onset of dyspnea, the patient returned to the ED complaining again of uncontrollable testicular pain, prevalent on the left side. He performed a chest X-ray showing multiple thickening concomitant with bilateral consolidations. Oropharyngeal swab tested positive for SARS-CoV-2, thus the patient was transferred to Infectious Disease (ID) department with the diagnosis of COVID-19 pneumonia associated with testicular pain. At ID admission, testicles examination performed by the attending urologist showed absence of redness and palpable swelling, but presence of pain in the scrotum and inguinal lymph nodes. Urine microbiological investigations were performed not showing any kind of infection. However, antibiotic therapy was started with Amoxicillin/Clavulanic Acid and Azithromycin.

The following day, due to a progressive worsening of oxygenation, with the need to upgrade O_2 therapy up to 15 L/min, interleukin-6 blocking agent Tocilizumab 8 mg/kg was prescribed. Shortly before Tocilizumab administration, blood chemistry tests showed an increase in LDH 1213 U/L, D-dimer 1150 ng/ml and C-reactive protein 23.80 mg/dl. In the meanwhile, a CT scan of the lung and abdomen was performed alongside with some scans on the testicles that demonstrated regular and symmetrical enhancement of testis, epididimys, testicular artery and pampiniform plexus (Figure 1); to complete the CT scan examination, an ultrasound was performed due to the persistence of severe pain. The ultrasound report showed a slightly inhomogeneous aspect of the left didymus, mild accentuation of vascularisation pattern and slight swelling of the left epididymis. Thus, ultrasound picture was compatible with epididymitis.

On day 2, further worsening of the oxygenation (PaO_2/FiO_2 ratio lower than 70 mmHg) developed concomitant with severe tachypnea and dyspnea. Patient was discharged from ID

department and admitted to our Intensive Care Unit (ICU) for non-invasive ventilation strategy. In ICU, a new testicular ultrasound was performed confirming the previous findings and conserved vascular flows.

On day 3, due to the persistence of poor oxygenation unresponsive to non-invasive strategies, the patient was intubated, mechanically ventilated and rescue therapy with prone position was implemented.

On day 4, a severe cardiogenic shock developed giving way to inotropes and vasopressors infusion. Unfortunately, 3 days later the patient died because of irreversible cardiogenic shock following myocarditis of unknown origin.

At autoptic examination, the attention of the pathologists focused on the myocardium which revealed very sclerotic and stenotic coronary vessels with marked thickening of the left ventricular wall; no positive immunoreactivity to SARS-CoV-2 antibody was detected in myocytes. Unfortunately, testicles were only macroscopically examined and no noteworthy morphological alterations were described.

We asked the patient's relatives the permission to publish this case report since it is suggestive that even in the absence of a histo-pathological confirmation, given the fulminant evolution of the COVID-19 disease, the testicular pain could be related to epididymitis following SARS-CoV-2 infection.

Similar to severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS), SARS-CoV-2 infection can cause a respiratory syndrome of different magnitude with a variable spectrum of symptoms such as fever, cough and dyspnea; this points out

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that SARS-CoV-2 has the respiratory tract as its main target . In addition, several studies have provided evidence of potential infection of SARS-CoV-2 in cardiovascular, digestive and urinary systems (Behzad et al., 2020). However, the relationship between SARS-CoV-2 and reproductive system has not been clarified yet.

It is known that viruses like HIV, HBV, and mumps can enter the testis andcause viral orchitis that may result in male infertility and testicular tumor (Dejucq *et al.*, 2001). During the past SARS epidemic, several studies have demonstrated the relationship between members of the coronavirus family (SARS-CoV) and orchitis. Even if SARS-CoV virus has not been detected in testicular tissue (Ding *et al.*, 2004), testicular damage and germ cell destruction was clearly observed in these cases (Xu *et al.*, 2006).

Like previous coronaviruses, with which it shares 78% genetic homology, SARS-CoV-2, seems to have a strong interaction capacity for angiotensin-converting enzyme 2 (ACE2) and belongs to the angiotensin-converting enzyme family of dipeptidyl carboxydipeptidases, which is homologous to human angiotensin 1 converting enzyme. This receptor, which is mainly found in pulmonary epithelium but also in other tissues such as intestines, kidneys and testes (Li MY *et al.*, 2020), mediates the entrance into human cell of SARS-CoV-2, which completes intracellular replication, virus release and induces cytotoxicity. This explains why the route of virus infection depends on the expression and distribution of the corresponding receptor (Jayawardena *et al.*, 2019)

Recent studies have demonstrated the highly expression of ACE2 in kidney and testicular tissue, in particular in spermatogonia, Sertoli, Leydig cells, suggesting the possible effects in spermatogenesis and the possible occurrence of orchitis in male SARS-CoV-2 patients. (Cardona Maya *et al.*, 2020; Fan *et al.*, 2020; Liu *et al.*, 2020; Wang *et al.*, 2020).

In order to clarify this possibility, Song *et al*. (2020) have employed real-time polymerase chain reaction testing (RT-PCR) to detect SARS-CoV-2 in semen or testicular biopsy specimen of 13 hospitalized male patients, but no positive RT-PCR result was found. In line with the previous study, Paoli *et al*. (2020) have investigated the presence of SARS-CoV-2 in semen and urine

samples of a volunteer with positive naso-pharyngeal swab, but both these samples were found negative for the viral mRNA. A very recent study included 18 semen samples from recovered males obtained 8 to 54 days after absence of symptoms and 2 samples from patients with an active COVID-19 infection. No RNA was detected by RT-PCR in the semen including semen samples from two patients with an acute COVID-19 infection. Of note, subjects with a moderate infection showed an impairment of sperm quality (Holtmann et al., 2020). These results show that there is no evidence at this moment of SARS-CoV-2 sexual transmission, but the possibility of the virus-induced testis damage and dysfunction could not be excluded (Chen et al., 2020). Like in previous coronaviruses, viral binding to the ACE2 receptor in testis may lead to tissue inflammation and development of orchi-epididymitis with testicular pain, thus allowing us to identify SARS-CoV-2 , which is believed to induce a systemic vasculitis - in particular of small vessels - as another possible cause of testis damage and orchitis (Corona et al., 2020). .

To our knowledge, apart from this case, testicular pain was correlated with COVID-19 only in the report of Kim et al. (Kim et al., 2020); they described an atypical clinical presentation of SARS-CoV-2 infection with abdominal and testicular pain in a 42-year-old man. However, the clinical course of the patient described by Kim et al. was benign, while unfortunately our patient died due to a fulminant evolution. Paying the utmost attention to the clinical manifestation of testicular pain in the SARS-Cov-2 pandemic era, in addition to preserving health-care workers from possible contagion, allows proper early identification of a patient who could rapidly deteriorate.

The frequency of such an atypical presentation in SARS-CoV-2 infection is unknown, it should however be considered for every patient who comes to Emergency Department. Further studies are necessary in order to investigate the possible short- and long-term effects of SARS-CoV-2 in male reproductive system and to insure a proper andrological follow-up to swab-positive male patient even in absence of pulmonary symptoms.

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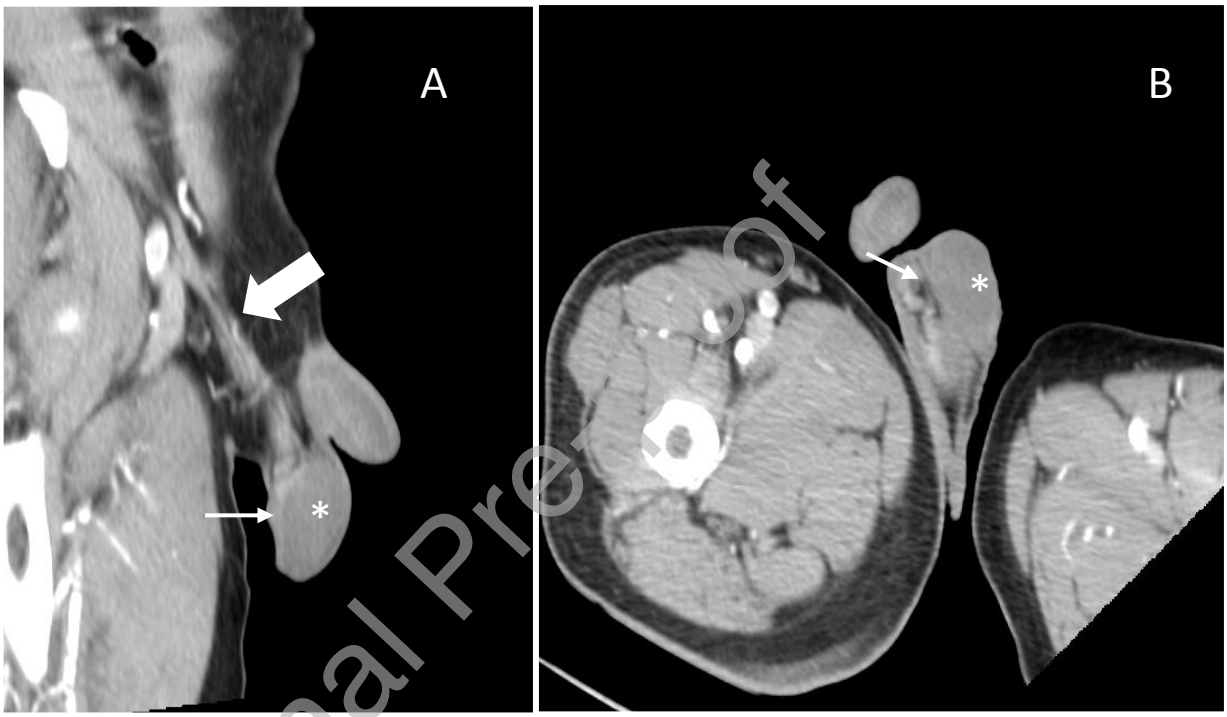
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Legend of Figure

Figure 1: Contrast enhanced CT scan demonstrates regular and symmetrical enhancement of testis (*), epididimys (arrow), testicular artery and pampiniform plexus (thick arrow). There is also no evidence of testis enlargement or scrotal fluid collection. Panel A: multiplanar reformat on right didimus long axis. Panel B: multiplanar reformat on left didimus long axis.



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Fig 1 Contrast enhanced CT scan demonstrates regular and symmetrical enhancement of testis (*), epididimys (arrow), testicular artery and pampiniform plexus (thick arrow). There is also no evidence of testis enlargement or scrotal fluid collection. Panel A: multiplanar reformat on right didimus long axis. Panel B: multiplanar reformat on left didimus long axis.



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Antonio La Marca is Professor of Obstetrics and Gynecology at the University of Modena and Reggio Emilia, Italy. His clinical activity covers all fields of reproductive medicine and surgery.
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