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## COVID ORCHITIS - A CASE REPORT

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### **ABSTRACT :**

Corona virus also known as COVID 19, is an ongoing worldwide pandemic caused by severe acute respiratory syndrome corona virus 2 (SARS – CoV 2)<sup>[1]</sup>. COVID 19 presents differently in different people with the most common symptoms being fever, dry cough and generalised fatigue. Although most patients develop only mild to moderate illness and recover without hospitalisation, it has also known to be associated with a wide range of multi-organ complications including pneumonia, ARDS, acute liver injury, acute cardiac injury, rhabdomyolysis, acute kidney injury, DIC, septic shock and MODS. However the effect COVID 19 on the Genito-urinary tract, especially the male reproductive system has still not been very well established. The male reproductive system is vulnerable to infection and patients with COVID 19 have found to have varied changes in their sex hormones and occurrences of orchitis suggesting gonadal impairment and possible infertility issues in the future.<sup>[2]</sup>

**Keywords** – COVID 19, SARS Cov 2, ACE 2, orchitis, hormones, Infertility.

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### **INTRODUCTION**

COVID 19 outbreak was initially identified in Wuhan, the capital of Hubei province, China in December 2019. <sup>[3][4]</sup>It was later declared a Public Health Emergency of International Concern in January 2020 and a pandemic in 11<sup>th</sup> March 2020 when human to human transmission became prevalent. <sup>[5][6]</sup> Human transmission was thought to be mediated through contact with zoonotic hosts at a wet market in Wuhan. However, due to the phylogenetic similarity between SARS CoV and SARS CoV 2 virus it is

postulated that bats, racoons, dogs or civet cats, which are commonly used food sources in China, could be the possible reservoirs. More than 188 countries and territories have been affected, with over 19.8 million cases of COVID 19 been reported as of August 2020 resulting in a death rate of over 7 lakhs<sup>[7]</sup>. Although the prevalence of COVID 19 in men and women are similar, the severity of the disease and mortality rates in men appear to be higher. It has been confirmed that the main mode of transmission of COVID 19 in humans are through respiratory droplets

and close contact, even though SARS CoV-2 has also been detected in saliva, stools, urine and semen samples.<sup>[8]</sup> However, there is no current evidence of viral transmission via semen or vaginal fluids .

Several viruses such as mumps virus, HIV, Epstein-Barr virus, Cytomegalovirus, Hepatitis B & C, Rubella and members of the Corona virus family can cause viral orchitis. However, the exact incidence and prevalence of orchitis due to members of the Corona virus family have not been established yet. The association between members of the corona virus family and orchitis were first demonstrated through a study conducted by Xu J et al in 2006. The study analysed the pathological changes of testis from 6 patients who died from SARS CoV 1 virus (similar to the SARS CoV -2) and noticed widespread germ cell destruction, few spermatozoon in the seminiferous tubule, thickened basement membrane and leukocyte infiltration.<sup>[9]</sup> Due to the presence of significant involvement of the seminiferous tubules and germ cell destruction, it is believed that SARS CoV 2 could also be potentially transmitted by semen. Here we present a case report of orchitis in a COVID 19 positive patient.

#### **CASE REPORT**

A 26 years old male patient, initially diagnosed with Classical Hodgkin's lymphoma in March 2013 and was treated with chemotherapy (ABVD regimen). He was thereafter on regular follow up and remained in remission. He recently presented with complaints of fever for the past 1 week associated with scrotal pain for the past 3 days in August 2020 and was further evaluated. Routine blood investigations showed mild leucocytosis and hyponatremia. COVID 19 by RT PCR done on 03.08.2020 was found to be

Positive. Chest X ray showed no significant abnormality. Ultrasound Scrotum showed an enlarged right epididymis with heterogeneous echotexture, increased echogenicity in right testis and minimal hydrocele suggestive of Right Epididymo Orchitis. Blood and urine culture revealed no bacterial growth. IL -6 levels were elevated at 19.9pg/ml. Other inflammatory markers like D dimer, procalcitonin and serum ferritin levels were within normal limits. Luteinizing hormone and testosterone levels were also found to be within normal limits. Repeat ultrasound done 2 days later showed mildly enlarged right testis with diffusely increased echoes and persistently enlarged right epididymis with heterogeneous echotexture suggestive of right epididymo orchitis. He was treated with wide spectrum antibiotics, prophylactic anticoagulants and other supportive medications. He became symptomatically better and was discharged after a week in a stable condition.

#### **DISCUSSION**

There are a number of factors that have been described in the pathogenesis of SARS CoV 2 orchitis, of which the role of ACE 2 receptors are very significant. SARS CoV 2 enters the human cell through the strong interaction of its spike protein S with the ACE 2 receptors and the priming of its S protein by the host cell serine proteases TMPRSS2.<sup>[9,10]</sup> ACE 2 receptors are endogenous counter regulator that deactivated the angiotensin II in the Renin angiotensin aldosterone system<sup>[11]</sup>. These receptors have a widespread tissue distribution throughout the body with a relatively higher expression in the oral cavity, alveolar cell I and II, respiratory epithelial cells, kidney, intestines and testis.<sup>[9,12-13]</sup> Moreover both ACE 2 receptors and TMPRSS2 are highly

expressed in the urogenital tract substantiating the susceptibility of these organs. Further studies conducted by Fan et al and Shen et al discussed the age dependant levels of mRNA ACE 2 expression in both somatic and germ cells of testis with the highest levels of expression in middle aged men (approximately 30 years). They also discussed the prevalence of higher positive rates of ACE 2 in infertile men in comparison to healthy men, indicating the role of ACE 2 in the future reproductive health of COVID 19 positive male patients.<sup>[14-15]</sup>

Possible secondary autoimmune reaction due to persistent fever may also be considered in the pathogenesis of SARS CoV 2 orchitis. Elevated body temperatures due to viral infection have known to result in meiotic germ cell apoptosis, eventually resulting in germ cell degeneration and destruction. This has been attributed to the high sensitivity of germ cells to temperature changes.<sup>[16]</sup>

The significant hormonal changes in COVID 19 male patients have also been widely noticed. These hormonal changes occur as a consequence of multiple factors like direct testicular damage due to the virus, elevated body temperature, inflammation and dysregulation of the neuroendocrine signalling system (Hypothalamic Pituitary Adrenal axis).<sup>[17,18]</sup> A recent study of 81 COVID 19 patients conducted by Ma et al further showcased the first direct evidence of male hormonal variations in COVID 19 patients. It revealed that the levels of Luteinizing hormone was significantly increased but the testosterone to LH ratio and FSH to LH ratio were significantly reduced in comparison to similar healthy counterparts.<sup>[2]</sup> Several statistical regression analysis have also shown the

negative association of testosterone to LH ratio with C reactive protein and white blood cells levels in COVID 19 patients.

On the other hand, in women the sex hormonal levels and non menopausal status have been associated with their better prognosis. Estradiol or E2 results in the production of higher levels of antibodies by stimulating the humoral immune response to viral infection.<sup>[20-23]</sup> It also down regulates the expression of ACE 2 receptors which are the primary receptors in the pathogenesis of SARS CoV 2 infection.<sup>[19]</sup> Several regression analyses showed that the levels of E2 and Anti Mullerian Hormone in non-severe group were significantly higher than that of the severe group, probably due to their regulation of immune related cytokines.

## CONCLUSIONS

These above observations in COVID 19 positive patients have led to a possible concern on the impact of male fertility worldwide despite the lack of concrete evidence to support these findings. Multiple research studies on the sexual transmission of COVID 19 are still underway. As a result of which the European Society of Human Reproduction and Embryology has advised that "all fertility patients considering or planning treatment, even if they do not meet the diagnostic criteria of COVID-19 infection, should avoid becoming pregnant at this time." Several potential treatment options like TMPRSS2 inhibitors Bromhexine, Nafamostat, Aprotinin, Camostat and the use of exogenous estrogen therapy in COVID 19 male and female patients to improve immunity, are also being currently explored.

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