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CHARACTERISTICS OF SARS-COV-2 INFECTION IN PATIENTS WITH PROSTATE NEOPLASM: CASE REPORT

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Abstract: *Oncological patients are a vulnerable group to SARS-CoV-2 infection, which is caused by a decrease in the functionality of the immune system through its fight against cancer cells, but also through treatment. This article aims to a better understanding of the pathogenetic mechanism by which these events occur, in particular the connection between TMPRSS2 protein, antiandrogenic therapy, and repeated SARS-CoV-2 infections. The deepening of the possible mechanisms underlying the interaction between COVID-19 and prostate cancer alludes to a potential association between SARS-CoV-2 receptors on host epithelial cells, but also to how anti-androgenic therapy influences the course of the disease.*

INTRODUCTION

SARS-CoV-2 infection was first identified in the Chinese city of Wuhan in December 2019, the first case in Romania occurring on February 26th 2020. SARS-CoV-2 is a virus that belongs to the coronavirus family, which has caused an ongoing global pandemic. It has developed several variants, including Alpha, Beta, Gamma, Delta and Omicron, the last two being the most virulent. Most patients have mild to moderate symptoms. The most common symptoms are fever, dry cough, fatigue, neuralgia and myalgia.(1) The pandemic has been a major international challenge, especially among immunocompromised cancer patients.

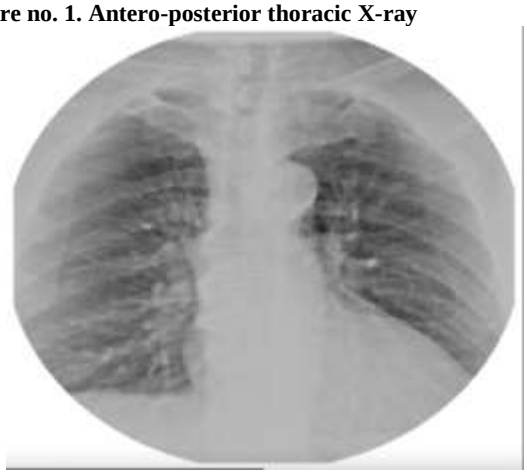
In this article we present the case of a patient with prostate adenocarcinoma who underwent reinfection with SARS-CoV-2, but also the pathophysiological and pharmacological features that make the connection between the two pathologies. The severity of SARS-CoV-2 disease and its progression are about 3 times higher in males (2), which requires a deepening of the discussion given the involvement of androgen hormones and prostate cancer.

CASE REPORT

We present the case of a 68-year-old patient who was diagnosed in 2017 with Gleason 3+3 prostate adenocarcinoma (undergoing hormone therapy) with stable disease and high blood pressure, who presented on September 22nd, 2020, in the emergency service of Sibiu County Clinical Hospital for: dry cough, fever and asthenia. The objective examination at the time of hospitalization revealed: pale skin, sweating and sabural tongue. Pulmonary auscultation revealed bilateral basal stiffened vesicular murmur with bilateral basal crackling rales. Laboratory tests showed: K (potassium) = 3.42mEq / L, aspartate-amino-transferase (AST) = 84 mg / dL, Leuk (leukocytes) = 11000 / mm, Neutrophils = 78%, Lymphocytes = 14.4 %, erythrocyte sedimentation rate (ESR) = 19mm / h, Ferritin = 474ng / ml. SARS-COV-2 testing (2 determinations), both positive, was performed.

Chest radiography showed multiple bilateral opacities present in the lung hilum, but also peripheral, with accentuated bronchovascular pattern. The mediastinum was enlarged, with the left contour of the heart accentuated.

Figure no. 1. Antero-posterior thoracic X-ray



Following clinical and paraclinical investigations, the diagnosis of SARS-COV 2 infection was made and antiviral treatment was chosen (Lopinavir / Ritonavir 200 mg/ 0 mg), but also corticotherapy (Dexamethasone phosphate 8mg/2ml solution for injection), Hydroxychloroquine sulphate 200 mg, as a result of which the patient's condition improved.

On the 20th of May 2021, he presented again at the emergency unit for high fever (39^0 C), dry cough, myalgias and altered general condition. Testing was performed again for SARS-CoV-2 virus with a positive result (possible reinfection) and chest CT examination showed multiple areas of condensation in the matte glass disseminated bilaterally in the lung, associated with fine retractile bands more evident

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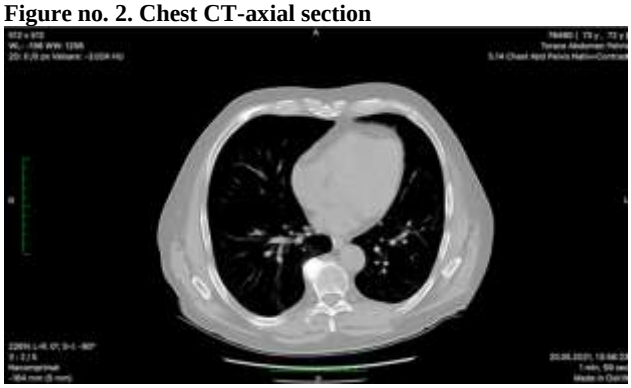
bilaterally - lesions suggestive for the infectious substrate.

In this case, we opted for the same treatment with antivirals and corticosteroids, which triggered a favourable evolution, along with the recommendation to be admitted to the department of pneumology for pulmonary recovery.

Figure no. 2. Chest CT-axial section



DISCUSSIONS

The interaction of the virus with the renin-angiotensin-aldosterone system is a key factor for infectivity. According to studies, the binding site of SARS-Cov-2 virus is the angiotensin 2 conversion enzyme (ECA-2). When the virus invades the body, invariant T cells and γδ cells of the bronchial mucosa respond quickly to the presence of the antigen and trigger cytokines, which are essential for its destruction. The conversion enzyme is found in countless tissues, but the lung alveolar epithelial cells are predominant. By testicular RNA sequencing, ECA-2 was identified in spermatogonia and Leydig and Sertoli cells, but with low expression in spermatocytes, spermatids, and other somatic cells. These findings suggest that the testis is a vulnerable organ to SARS-CoV-2 infection that could lead to spermatogenic insufficiency. ECA-2 levels have been shown to be highly stimulated in stressful situations, such as high blood pressure.(3) An example on this point, including the case report, is the radiological appearance of enlarged heart, along with the diagnosis of hypertension which can be found in the patient history. Elevated serum ACE-2 levels lead to increased blood pressure and, implicitly, heart hypertrophy. This would explain the increased mediastinal size.

Cancer patients are mainly older people with a higher expression of the conversion enzyme, but also countless comorbidities, so the immune system is significantly lower. That puts them at a much higher risk of infection and complications with increased mortality.

TMPRSS2 is a cellular protease belonging to the transmembrane serine protease family that allows easy access of viruses, including SARS-CoV-2, to host cells and develops especially during carcinogenesis. This protease is found mainly in tissues, such as the prostate and seminal vesicles, specifically in the secretory epithelial cells. Their action is promoted by androgen hormones, which would explain the increased susceptibility of severe cases in males compared to females.

SARS-CoV-2 virus binds to angiotensin 2 converting enzyme for cell entry, followed by proteolytic cleavage of S protein by TMPRSS2, allowing viral and cell membranes to fuse. S protein mediates virus attachment and membrane fusion during infection.(1) In addition to the presence of this enzyme in the prostate, it is also found in the lung parenchyma, also under the control of androgens. Thus, a high level of this protease could be associated with an increased risk of infection in patients with prostate adenoma.(4,5)

Administration of antiandrogenic therapy may also influence the risk of infection and the severity of COVID-19 disease. Some studies have shown that antiadrogenic treatment may have beneficial effects in this regard.

Androgen therapy has been developed to stop the intracellular cascade of androgen activation that increases the aggressiveness and progression of the tumour. Studies have been carried out on the premise that patients with this type of treatment have a lower risk of becoming infected with COVID-19 and will experience a less aggressive form of the disease. However, research has shown that there is no link between them. In addition, patients with metastatic disease have an increased risk of severe side effects such as heart disease. Certain drugs, which inhibit androgens by inhibiting the enzymes that cause androgen secretion, increase the expression of TMPRSS2 in the lung parenchyma.(2,6)

The efficacy of glucocorticoids in the treatment of COVID-19 is highly controversial. Although glucocorticoids are associated with good prevention of acute respiratory distress syndrome, dyspnea, and severe pneumonia, some studies have shown that there are no benefits in patients with mild illness. For severe COVID-19 treatment, dexamethasone increases the survival rate of patients in need of respiratory support such as invasive mechanical ventilation or simply oxygen therapy.(6)

Lopinavir/ ritonavir are substances used against the HIV virus, but they have also been shown to be effective in combating SARS-CoV-2, with inhibitory activity in vitro.(7)

CONCLUSIONS

There is a close link between the SARS-CoV-2 receptor, ECA-2 and the TMPRSS2 enzyme, which explains the cascade of pathogenetic mechanisms, as well as the initiation of antiandrogenic therapy that would aggravate the progression of COVID-19 disease.

The expression of ECA-2 and TMPRSS2 in different organs and at different stages of prostate cancer in patients treated with antiandrogen therapy may help to discover the basis of the biological mechanism in the future.

Compared to the case presentation, we can offer several explanations for repeated SARS-CoV-2 infections, this being the result of a combination of factors. First of all, the patient was given antiandrogenic therapy to fight prostate cancer, which would have increased the expression of TMPRSS2 in the body, thus the virus having a better penetrability of the cells. Secondly, the advanced age along with the patient's immune depression and the stressful conditions that led to the increase in ECA-2 explain both the easy access of the virus in the body and the occurrence of cardiovascular problems such as high blood pressure and ventricular cardiac hypertrophy.

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