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COVID-19–Associated Genitourinary Lesions: A Literature Review.

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Abstract

Background: Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), is now recognized as a multisystem disorder extending far beyond the respiratory tract. The genitourinary (GU) system represents an important target because of the widespread expression of angiotensin-converting enzyme-2 (ACE2) receptors and transmembrane serine protease-2 (TMPRSS2) in renal, urothelial, testicular, prostatic, and penile tissues. Emerging evidence has demonstrated a broad spectrum of GU manifestations ranging from acute kidney injury and lower urinary tract symptoms to orchitis, epididymitis, erectile dysfunction, Penile Mondor Disease, and hemorrhagic cystitis. The pathogenesis appears multifactorial and involves direct viral cytotoxicity, endothelial injury, cytokine-mediated inflammation, microvascular thrombosis, and immune dysregulation. Renal involvement remains the most frequently reported GU complication, whereas penile vascular thrombosis and hemorrhagic cystitis are uncommon but clinically significant manifestations. Although much of the available evidence is derived from observational studies and case reports, increasing recognition of these lesions has important implications for diagnosis, management, and long-term follow-up. This review summarizes the current understanding of COVID-19-associated genitourinary lesions, including their pathophysiology, clinical presentation, investigation, management, and future research directions.

Keywords: COVID-19, SARS-CoV-2, Genitourinary lesions, Acute kidney injury, Orchitis, Erectile dysfunction, Hemorrhagic cystitis, Penile Mondor disease.

INTRODUCTION

Since its emergence in late 2019, COVID-19 has evolved from a respiratory infection into a complex systemic disease with widespread extrapulmonary manifestations. More than 775 million confirmed cases have been reported globally, and increasing evidence indicates that SARS-CoV-2 can affect virtually every organ system in the human body.[1] Among the extrapulmonary systems affected, the genitourinary tract has attracted growing attention because of its susceptibility to both direct viral injury and secondary inflammatory and thrombotic complications.[2]

The biological basis for genitourinary involvement lies in the expression of ACE2 receptors and TMPRSS2 proteins, which facilitate viral entry into host cells. These molecules are highly expressed in renal tubular epithelium, bladder urothelium, prostatic tissue, Sertoli cells, Leydig cells, seminiferous tubules, and penile vascular endothelium.[3,4] Consequently, SARS-CoV-2 infection may produce pathological changes throughout the urinary and male reproductive systems.

Current literature suggests that COVID-19-associated genitourinary lesions encompass a broad spectrum of conditions including acute kidney injury (AKI), proteinuria, hematuria, lower urinary tract symptoms (LUTS), COVID-associated cystitis, hemorrhagic cystitis, orchitis, epididymitis, infertility-related changes, erectile dysfunction, priapism, and penile vascular thrombosis.[5,6] Although renal complications are the most prevalent manifestations, emerging reports indicate that the reproductive and lower urinary tracts may also be significantly affected during both acute infection and the post-COVID period.[7]

Pathophysiology of Genitourinary Involvement

The mechanisms underlying genitourinary injury in COVID-19 are multifactorial and incompletely understood. Direct viral invasion remains one of the principal proposed mechanisms. Following attachment of the viral spike protein to ACE2 receptors, SARS-CoV-2 enters susceptible cells and initiates intracellular replication, leading to cellular dysfunction and tissue injury.[3]

In addition to direct cytopathic effects, endothelial dysfunction has emerged as a central pathological feature of COVID-19. Viral-induced endothelial injury promotes activation of inflammatory pathways, platelet aggregation, and thrombin generation, resulting in a hypercoagulable state capable of affecting both macrovascular and microvascular circulation.[8,9] This phenomenon may explain the occurrence of unusual vascular manifestations such as penile Mondor disease and priapism.

Another important mechanism involves cytokine-mediated inflammation. Elevated levels of interleukin-6, tumor necrosis factor-alpha, and other pro-inflammatory mediators contribute to tissue edema, vascular permeability, and organ dysfunction.[10] In the urinary bladder, these inflammatory pathways may produce lower urinary tract symptoms even in the absence of detectable viral particles within urine. Similarly, inflammatory injury to the testes and epididymis may contribute to impaired spermatogenesis and hormonal disturbances.[6]

Renal Lesions

Renal involvement represents the most frequently reported genitourinary manifestation of COVID-19. Early studies from hospitalized cohorts demonstrated proteinuria in up to 44–65% of patients and hematuria in approximately 26–44% of cases at presentation.[11] The incidence of acute kidney injury varies considerably depending on disease severity and patient population, ranging from approximately 5% in mild disease to more than 40% among critically ill patients requiring intensive care admission.[12]

Histopathological studies have identified acute tubular injury as the predominant lesion, although collapsing glomerulopathy, thrombotic microangiopathy, and acute interstitial nephritis have also been described.[13] The development of AKI is associated with prolonged hospitalization, increased need for renal replacement therapy, and significantly higher mortality rates. Consequently, renal dysfunction remains one of the most important prognostic indicators among hospitalized COVID-19 patients.[12]

Bladder Lesions

Bladder involvement has increasingly been recognized during the course of COVID-19 infection. Patients frequently present with urinary frequency, urgency, nocturia, dysuria, and sterile pyuria despite negative urine cultures.[14] This clinical entity, termed COVID-associated cystitis (CAC), is believed to result from inflammatory cytokine release within the bladder rather than direct viral replication.[15]

A systematic review evaluating lower urinary tract involvement reported that de novo urinary symptoms and worsening of pre-existing LUTS are among the most common urinary manifestations of COVID-19.[5] Elevated urinary concentrations of inflammatory cytokines have been demonstrated in affected individuals, supporting the concept of cytokine-mediated bladder injury.[15]

Hemorrhagic cystitis represents a much rarer manifestation. Published reports describe patients presenting with gross hematuria, clot retention, suprapubic discomfort, and irritative urinary symptoms during or shortly after SARS-CoV-2 infection.[16] Because hematuria may result from multiple causes, including urinary tract infection, anticoagulant therapy, malignancy, nephrolithiasis, BK virus infection, or catheter-related trauma, thorough evaluation is essential before attributing hemorrhagic cystitis solely to COVID-19.[16]

Testicular and Epididymal Lesions

The male reproductive system appears particularly vulnerable to COVID-19 because of the high expression of ACE2 receptors within Sertoli and Leydig cells.[4] Clinical manifestations include scrotal pain, orchitis, epididymitis, and epididymo-orchitis.[5]

A systematic review of genitourinary manifestations identified scrotal discomfort, swelling, and pain as common reproductive symptoms among hospitalized male patients with COVID-19.[5] Ultrasonographic studies have demonstrated findings consistent with orchitis, epididymitis, and epididymo-orchitis in a subset of affected individuals. Histopathological examinations have further revealed seminiferous tubular injury, reduced Leydig cell numbers, interstitial edema, and inflammatory cell infiltration.[17]

These findings have raised concerns regarding male fertility. Several studies have reported transient reductions in sperm concentration, total sperm count, motility, and testosterone levels following infection.[6] Although current evidence suggests that many of these abnormalities improve over time, the long-term reproductive consequences of COVID-19 remain incompletely understood.

Prostatic Lesions

Prostatic involvement has been reported less frequently than renal or testicular manifestations. Nevertheless, several patients develop prostatitis-like symptoms characterized by pelvic discomfort, urinary frequency, dysuria, and perineal pain during acute infection.[18]

Because both ACE2 and TMPRSS2 are expressed within prostatic tissue, direct viral involvement remains biologically plausible. However, current evidence favors inflammatory and immune-mediated mechanisms rather than substantial viral replication within the prostate itself.[18] Additional research is required to determine whether COVID-19 contributes to chronic prostatic inflammation or long-term lower urinary tract dysfunction.

Penile and Vascular Lesions

Among the most intriguing genitourinary manifestations of COVID-19 are penile vascular complications. Erectile dysfunction has emerged as an increasingly recognized consequence of SARS-CoV-2 infection. Multiple studies have demonstrated a significantly increased risk of erectile dysfunction among men recovering from COVID-19, likely resulting from endothelial dysfunction, cavernosal fibrosis, impaired nitric oxide signaling, hormonal disturbances, and psychological stress.[19,20]

Histopathological evidence has strengthened this association. Viral particles and viral RNA have been identified within penile tissue months after infection, accompanied by reduced endothelial nitric oxide synthase expression and evidence of endothelial injury.[21] These findings support a biological link between COVID-19 and subsequent erectile dysfunction.

Penile Mondor Disease, a superficial thrombophlebitis of the dorsal penile vein, has also been reported following COVID-19 infection.[22] Patients typically present with a painful cord-like induration along the dorsal aspect of the penis. Doppler ultrasonography demonstrates thrombosis of the superficial dorsal penile vein and confirms the diagnosis. Although uncommon, these cases further support the role of COVID-19-associated hypercoagulability in the development of unusual vascular lesions.[22]

Investigation

Evaluation of COVID-19-associated genitourinary lesions should be guided by clinical presentation and suspected organ involvement. Laboratory investigations typically include complete blood count, inflammatory markers, coagulation profile, renal function tests, urinalysis, and urine culture. Imaging studies may involve renal ultrasonography, Doppler ultrasonography of penile or scrotal structures, computed tomography urography, or magnetic resonance imaging when indicated.[16,22]

Patients presenting with significant hematuria require cystoscopic evaluation to identify the source of bleeding and exclude malignancy or alternative causes of hemorrhage. Similarly, persistent reproductive symptoms may warrant hormonal profiling and semen analysis, particularly in younger patients concerned about fertility.[17]

Management

Management of COVID-19-associated genitourinary lesions is largely supportive and directed toward the affected organ system. Acute kidney injury requires optimization of fluid balance, avoidance of nephrotoxic agents, and renal replacement therapy when necessary.[12]

Patients with COVID-associated cystitis are generally managed with hydration, symptom control, and observation. Severe hemorrhagic cystitis may require bladder irrigation, catheterization, endoscopic clot evacuation, or cystoscopic coagulation of bleeding vessels.[16]

Orchitis and epididymitis are usually treated conservatively with analgesics, anti-inflammatory medications, and scrotal support. Most cases demonstrate gradual clinical improvement without long-term complications.[17]

Penile Mondor Disease is generally self-limiting and responds well to nonsteroidal anti-inflammatory drugs, temporary sexual abstinence, and clinical follow-up. Anticoagulation may be considered in selected patients with extensive thrombosis or concurrent thromboembolic disease.[22] Erectile dysfunction following COVID-19 should be managed according to established guidelines, including cardiovascular risk assessment, phosphodiesterase-5 inhibitors, lifestyle modification, and psychological support where appropriate.[19].

DISCUSSION

The expanding spectrum of COVID-19-associated genitourinary lesions underscores the systemic nature of SARS-CoV-2 infection. While acute kidney injury remains the most common manifestation, increasing evidence suggests that

inflammatory and thrombotic complications can involve nearly every component of the genitourinary tract. Endothelial dysfunction appears to be the unifying pathological mechanism linking many of these lesions, particularly those affecting penile vascular structures and erectile function.[8,21]

Current evidence also indicates that lower urinary tract symptoms and reproductive abnormalities may persist beyond the acute phase of infection, forming part of the broader post-COVID syndrome.[15] Although most reported lesions are self-limiting, their potential impact on quality of life, fertility, and sexual health warrants continued investigation.

A major limitation of the available literature is the predominance of observational studies, retrospective analyses, and case reports. Consequently, the true incidence of many genitourinary manifestations remains uncertain. Large prospective multicenter studies are needed to establish causality, identify risk factors, and determine long-term outcomes

CONCLUSION

COVID-19 is associated with a diverse range of genitourinary lesions involving the kidneys, bladder, prostate, testes, epididymis, and penis. Renal injury remains the most frequently encountered manifestation, whereas hemorrhagic cystitis and Penile Mondor Disease are uncommon but increasingly recognized complications. The underlying pathogenesis appears multifactorial, involving direct viral invasion, endothelial dysfunction, inflammation, and thrombosis. Awareness of these manifestations is essential for timely diagnosis and appropriate management. Further prospective studies are required to clarify long-term genitourinary outcomes and optimize patient care.

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