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Testicular Changes Associated With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

To the Editor.—It has been established that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as coronavirus disease 2019 (COVID-19), primarily infects cells of the respiratory tract,[1] leading to diffuse alveolar damage, pulmonary vascular injury, and thrombosis.[2] However, characterization of its effects on testes is still not well defined. Here, we present our analysis of the morphologic features seen in testes obtained from patients with COVID-19.

We analyzed testes and epididymis specimens from a series of 10 autopsies of patients with proven SARS-CoV-2 infection who died at our institution. Autopsies were conducted according to published US Centers for Disease Control and Prevention guidelines.[3]

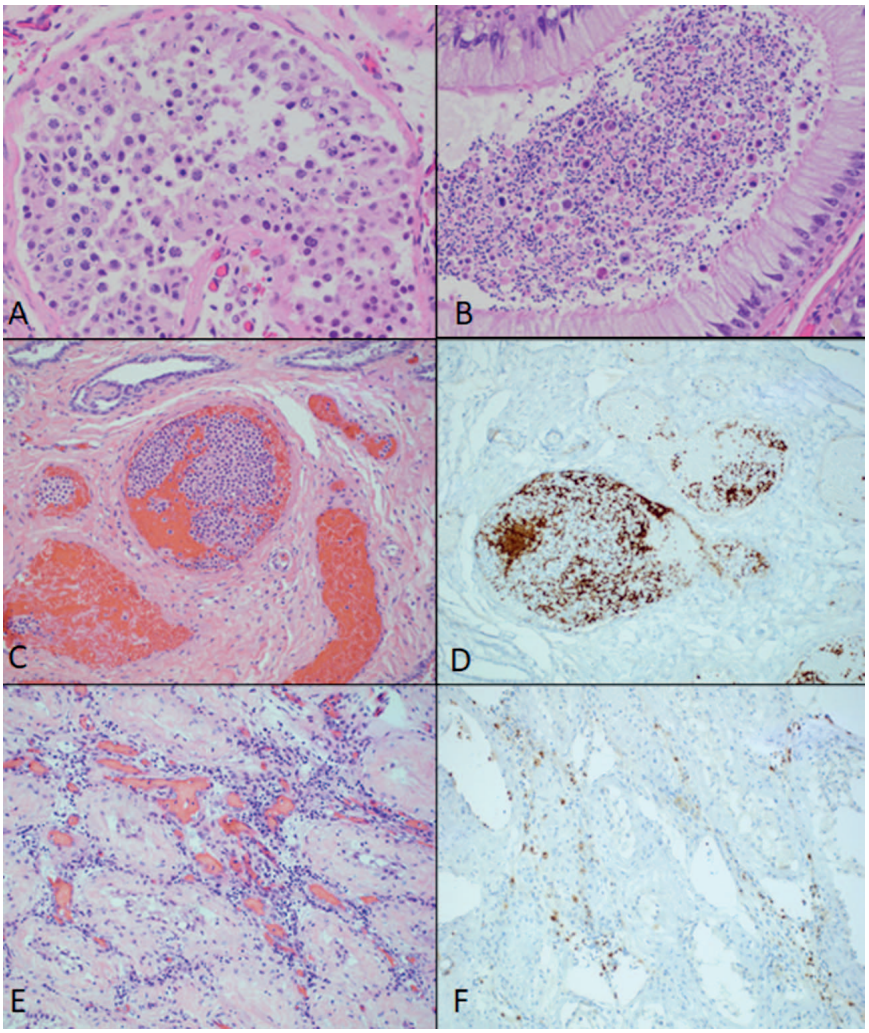
Six testes samples were tested by reverse transcription–polymerase chain reaction for 3 regions of the COVID-19 virus gene, *ORF1abb*, *N* gene, and *E* gene.

The median age was 49.5 years (range, 22–83 years). All cases tested positive for SARS-CoV-2 by nasopharyngeal swab at time of hospital admission. The median duration from admission to death was 15 days (range, 7–27 days). Patients had multiple reported preexisting comorbidities (median, 3; range, 0–6), the most frequent being type 2 diabetes mellitus and hypertensive disease.

At autopsy COVID-19 was detected in the respiratory tracts of all patients; however, all testicular samples tested for COVID-19 were negative.

A total of 7 of 10 cases showed morphologic alterations attributable to oxidative stress, seen at different stages of the spermatocyte cycle, including chromatin condensation, acidophilic cytoplasm, and nuclear fragmentation. Sloughing of spermatocytes into the tubular lumen and accumulation in the head of epididymis was seen. Elongation of spermatids and swelling and vacuolization of the Sertoli cells were also noted (Figure, A and B). These changes were similarly observed in the orchiectomy specimen from 1 living patient presenting with testicular cancer. Total loss of intratubular cell mass and tubular basement thickening were seen in cases with longer course. A notable finding was the presence of multifocal microthrombi in 2 cases. A CD61 stain highlighted increased platelets in testicular vessels associated with cluster and occasional thrombus formation (Figure, C and D). One case showed increased mononuclear inflammatory infiltrate ($CD8^+$ dominant) in the interstitial space, compatible with orchitis (Figure, E and F).

In this analysis, evidence of acute testicular injury is seen and is particularly related to oxidative stress, which has previously been reported in animal models in association with type 2 diabetes mellitus.[4] We compared our findings to a control group of 7 testes obtained during autopsy from patients who had similar comorbidities and



A, Changes associated with seminiferous tubule injury include chromatin condensation, acidophilic alteration of the cytoplasm of spermatocytes, and swelling with vacuolization of the Sertoli cells. B, Accumulation of sperm and immature spermatocytes in the epididymis. C, Multifocal platelet aggregation and microthrombi. D, CD61 immunostain highlights platelet clusters within testicular vessels. E, Mononuclear inflammatory infiltrate in the testicular interstitium, atrophic seminiferous tubules consistent with orchitis. F, Immunohistochemical studies reveal a predominant $CD8^+$ infiltrate (hematoxylin-eosin, original magnifications ×400 [A and B] and ×200 [C and E]; CD61, original magnification ×200 [D]; CD8, original magnification ×200 [F]).

age distribution but were negative for COVID-19. The observed testicular changes in our control group were mainly related to chronic processes (decreased spermatogenesis, reduced Leydig cells, and hyalinization of seminiferous tubules), whereas the changes in COVID-19–positive patients were acute (sloughing of spermatocytes, elongation of spermatids, and swelling of Sertoli cells). Similar findings have been reported in biopsies of testes of COVID-19 patients[5]; however, analyzing sections of testes with adjacent epididymis allowed us to further characterize the microenvironment and vascular changes that may be the essence of this oxidative stress. We show striking evidence of microthrombosis in the testicular vasculature similar to that previously described in lung tissue.[2,6] Further, we did not detect the virus in the testes, which suggests that direct testicular injury by SARS-CoV-2 infection is unlikely. The observed morphologic alterations in testes are thus likely to be a consequence of a coagulation disease leading to microthrombi and hypoxic injury. Toxic metabolic effects of prolonged illness and possibly the cytokine storm that characterizes severe COVID-19 may also explain these changes. The type and extent of testicular injury we observed here suggest that the testes could heal from COVID-19.

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