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Case Report

Management of Persistent Erectile Dysfunction after COVID-19 Infection: An 18-Month Follow-Up Case Report

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Abstract: The coronavirus disease 2019 (COVID-19) is an emerging pandemic caused by a novel coronavirus (SARS-CoV-2). Since December 2019 the new virus has spread all over the world and has become a major health problem also because of the public measures that could affect people's sexual activity. We report a case of a 35-year-old married male admitted to the andrology outpatient clinic in July 2021 because of sudden onset erectile dysfunction (ED). The diagnostic workup showed no risk factor for ED, normal levels of testosterone, increased levels of endothelial dysfunction markers, such as CRP (C-Reactive Protein) and Endothelin-1, and reduced Vitamin D (VD) levels. Dynamic penile duplex ultrasound (D-PDU) revealed dysfunctional penile arterial flow. The five-item International Index of Erectile Function (IIEF-5) and the Short-Form Health Survey (SF-36) showed a reduction in all domain scores. The patient, initially unresponsive to the high dose oral phosphodiesterase 5 inhibitors (PDE-5is), was treated with vitamin-D and then submitted to LI-SWT (low intensity shockwave treatment), with a progressive clinical benefit at the 12-month follow-up. After 18 months, hormone levels persisted in normal ranges, with a consistent reduction in CRP and Endothelin-1. Additionally, IIEF-5, SF-36 and arterial flow significantly improved over the follow-up period. Thus far, the erectile function was restored and the patient is no more treated with PDE-5i.

Keywords: erectile dysfunction; pandemic; COVID-19; case report; LI-SWT; PDE-5i; IIEF-5

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1. Introduction

Since 2019, COVID-19 has become a major public health concern. In most cases the respiratory symptoms of COVID-19 include fever, cough and shortness of breath [1]. The disease could involve the lungs and progress to severe forms, including acute respiratory distress syndrome (ARDS) and respiratory failure [2].

COVID-19 has been related to many long-term consequences due to endothelial dysfunction [3]. The pathophysiological mechanisms behind endothelial dysfunction in COVID-19 are still not entirely understood. Viral infection by SARS-CoV-2 occurs first in airway epithelial cells and vascular endothelial cells, causing endothelial dysfunction either directly through endothelial cell infection, or indirectly through other susceptible types of cell infection, which provoke hyperinflammation [4]. Endothelial dysregulation promotes vasoconstriction, vascular leakage, thrombosis and hyperinflammation, involving, consequently, an elevated prothrombin time, increased D-dimers and fibrin degradation products, augmented levels of C-reactive protein (CRP) and interleukin-6 (IL-6) [5].

Thrombotic and inflammatory processes are involved in developing ARDS and extrapulmonary complications. However, even asymptomatic forms of COVID-19 could lead to microvascular involvement [6].

In 2020, due to the absence of vaccines and effective treatments, social distancing and self-isolation were implemented in many countries in order to minimize disease

transmission. During the pandemic, many people experienced psychological discomfort and symptoms such as depression and anxiety [7]. Moreover, because of these unusual circumstances and emotional damage, people changed their sexual behaviors [8–10].

Erectile dysfunction (ED) is defined as the inability to attain or maintain an erection sufficient to allow sexual satisfaction [11]. Even if ED could be determined by psychogenic disorders, in most cases it recognizes an organic etiology [12].

Data from recent studies suggest a statistical association between COVID-19 and ED [13–16]. These results also suggest the possible role of the infection in the development of ED: the removal of the possible influence of anxiety and depression confirmed that the prevalence of ED among COVID-19 patients is not only a consequence of stress and psychological factors due to the lockdown, but it is also related to other organic factors [17]. On the other hand, it is now clear that it is hard to fully separate organic and psychogenic conditions, which in most cases coexist and contribute to the pathogenesis of ED [18].

A potential association between organic ED and COVID-19 has been postulated since the beginning of the pandemic [8] and a 2021 study found SARS-CoV-2 in the vascular endothelial cells of the corpus cavernosum in penis biopsies in men who developed severe ED, with a reduced expression of endothelial nitric oxide synthase (eNOS) [5,14].

Endothelial dysfunction is one of the most frequent mechanisms that can lead to ED [19]. The vascular tone results from the balance between vasoconstrictors (i.e., endothelin-1 or angiotensin 2), and vasodilators (i.e., nitric oxide (NO) or prostacyclin) agents. In the latter, NO is synthesized by eNOS [20]. The damaged endothelium attracts pro-inflammatory cells and expresses factors limiting NO availability (causing vessel and smooth muscle contraction). Another pathway involved is the augmented production of tumor necrosis factor alpha (TNF-α) in response to increased inflammatory conditions, which induces reactive oxygen species (ROS) generation and a drop in NO levels, apart from suppressing (eNOS) expression [21]. For these reasons, ED is considered a characteristic consequence of endothelial dysfunction.

In addition to endothelial damage, other mechanisms resulting from the COVID-19 infection could determine ED. SARS-CoV-2 may affect the testicles because the Leydig cells express ACE2, possibly leading to the development of a form of hypergonadotropic hypogonadism [22,23]. Moreover, complications of the post-acute phase of COVID-19 (the so-called "long COVID") that interests many patients should not be overlooked. These include dyspnea, fatigue, anxiety, sleep disorders, myocarditis and cardiomyopathy [24] and pulmonary fibrosis (which causes hypoxia in the penile vascular bed) [25]; all factors contribute to potentially determining ED [26]. As observed by Romano et al., sexual function could be impaired in patients affected by chronic conditions such as gastrointestinal diseases [27].

Major possible underlying mechanisms involved in COVID-19-related erectile dysfunction are summarized in Figure 1.

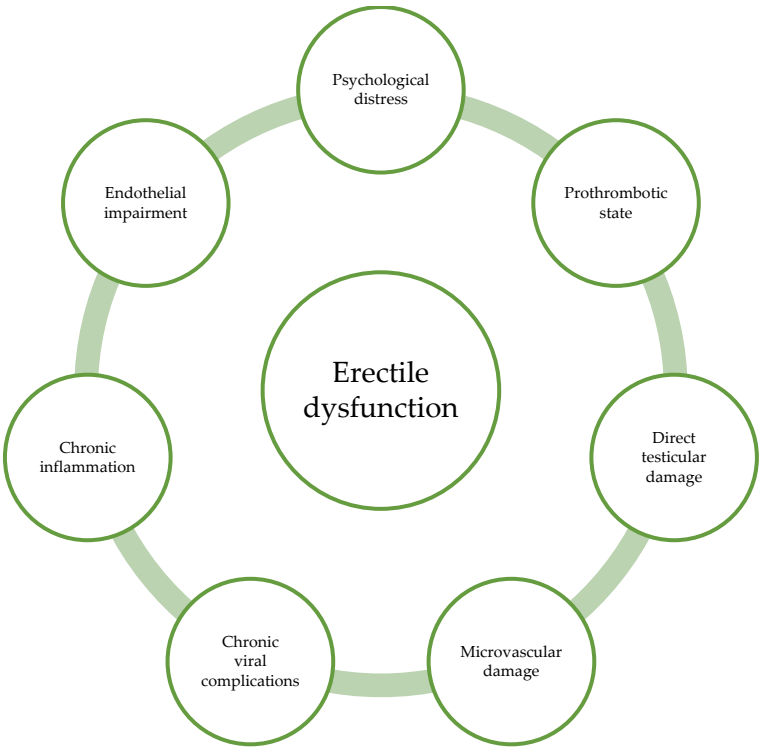

Figure 1. Different pathogenetic mechanisms by which COVID-19 could affect erectile function.

2. Patients and Methods

A 35-year-old nonsmoker man was admitted in January 2021 to our andrology day hospital for newly onset ED. He had been married since 2015 and never suffered ED. A review of his medical history did not reveal any disorder. There were no prior surgeries or accidents. Moreover, the patient did not take any drug and his BMI was 22.4 kg/m^2.

He reported poorly symptomatic COVID-19 four months before. He only suffered cough and fever (lower than 38 °C). Olfaction and taste were not involved (data not shown). Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) were used to treat the SARS-CoV-2 infection. Three weeks after his remission he reported his first sudden episode of ED with inability to achieve erection during climax (three out four sexual intercourses during the last 8 weeks). During the first admittance a complete clinical and biochemical exam was carried out, with no significant findings except the detection of Vitamin D deficiency (VDD) and the presence of positive markers of inflammation and endothelial damage; endocrinological laboratory testing was executed, showing a state of eugonadism. Results are summarized in Tables 1 and 2.

Table 1. Hormone levels during follow-up period.

Hormone	Normal Range (Age Related)	T0	T1 (6 Months)	T2 (12 Months)	T3 (18 Months)
Total Testosterone	13–33 nmol/L	21.1	19.9	19.8	20.2
Free Testosterone	0.17–0.66 nmol/L	0.65	0.60	0.60	0.62
Luteinizing Hormone (LH)	1.8–12.0 mUI/mL	6.3	7.1	6.9	7.6
Follicle-stimulating Hormone (FSH)	1.4–15.4 UI/L	7.2	6.3	6.2	6.7
Estradiol	10–45 pg/mL	12.0	13.2	12.7	13.2
Sex-hormon binding-globulin (SHBG)	10–57 nmol/L	15.0	16.2	15.9	15.4
Vitamin D	30–150 ng/dL	14.2	23.2	33.4	47.2

Table 2. Inflammatory markers during follow-up period.

Marker	Normal Range	T0	T1 (6 Months)	T2 (12 Months)	T3 (18 Months)
Endothelin-1	0.87–1.61 pg/ml	1.8	1.6	1.2	1.0
C-Reactive Protein (CRP)	<5.0 mg/L	8.8	6.2	<5.0	<5.0

To complete our diagnostic process, two different questionnaires were administered to the patient: SF-36 [28], IIEF-5 [29,30] (results are summarized in Table 3).

Table 3. Questionnaires scores during follow-up period.

Questionnaire		Normal Scores (%)	T0	T1 (6 Months)	T2 (12 Months)	T3 (18 Months)
SF-36	Vitality	100	70	70	80	85
	Social functioning	100	37.5	62.5	100	100
	Role-emotional	100	100	100	100	100
	Mental Health	100	72	76	88	96
	Physical functioning	100	90	95	100	100
	Role-Physical	100	75	100	100	100
	Bodily pain	100	77,5	77,5	100	100
	General Health	100	65	70	75	90
IEEF-5		≥22	13	17	20	23

Oral supplementation with cholecalciferol 25,000 UI every two weeks and sildenafil 50 mg on demand were initially started. After 4 weeks, the patient reported modest clinical benefits so that the dose of sildenafil was titrated to 100 mg on demand. Although increasing the dose of sildenafil can ameliorate both the sexual success rate and the sexual attempts' frequency [31], the patient still failed with sexual attempts.

Because of a persisting incomplete response to PDE-5i, after 30 days with sildenafil 100 mg on demand, a penile duplex ultrasound was performed (8 weeks since the patient's first visit) to assess potential penile vascular impairment [32]. After injection of Alprostadil 20 mcg, a mild reduction in systolic peak flow velocity was found (Figure 2).

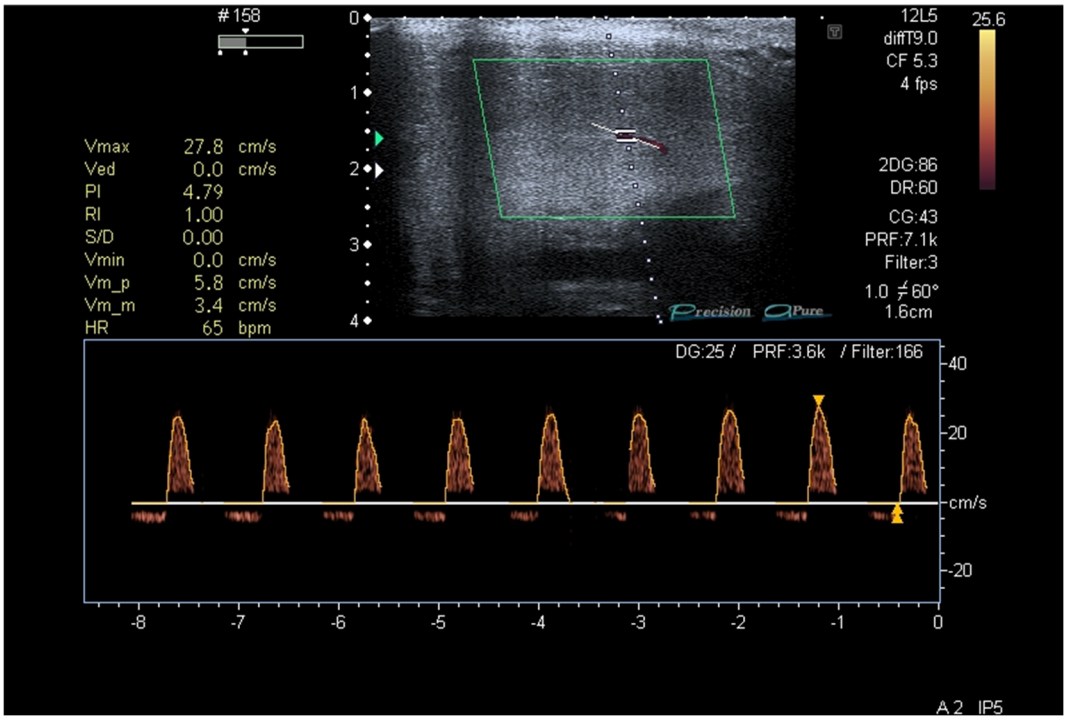

Figure 2. Penile duplex ultrasound at baseline (2 months since patient's first visit).

However, after 60 days, the patient still reported no improvement in his sexual intercourses.

Since the patient firmly refused to use a vacuum device and second-line therapies (intra-cavernous injections) to improve his erectile function, we decided to apply low intensity shockwave treatment (LI-SWT).

The patient underwent six consecutive weekly LI-SWT sessions of 20 min consisting of 4000 pulses with an energy density of 0.09 mJ/mm^2 and a frequency of 8 Hz. We used linear-focused piezo shockwaves (Linear Shockwave Tissue Coverage-Erectile Dysfunction, LSTC-ED, Richard Wolf GmbH, Knittlingen, Germany). Therapy with tadalafil daily 5 mg was started for four months according to a previously published procedure [33].

3. Results

After 6 months from the first visit (T1 in the tables), the patient came back to our outpatient clinic and reported no adverse events and a good improvement in the frequency and quality of his erections (as highlighted by the better scores on the questionnaires administered), even though he did not turn back to his pre-COVID state (see Table 1; IIEF5 +4 points). The hormonal balance at T1 remained normal, while we observed a reduction in the Endothelin-1 and CRP levels (see Tables 1 and 2). Therapy with tadalafil was carried on. An improvement in Vitamin D levels was found so we decided to shift Cholecalciferol supplementation to a monthly dose of 25,000 UI.

After a 12-month follow-up (T2 in the tables), the subject significantly improved his IIEF5 score (IIEF5 + 3 points). Vitamin D and inflammation indices were within the normal ranges. In agreement with the patient, we proposed to start daily tadalafil titration at an alternate-day intake until the suspension of the drug two months later.

In July 2022 (T3, four months after tadalafil was withdrawn), the patient was re-evaluated, confirming the clinical remission of ED (IIEF5 +2 points) without therapy and the normalization of the inflammation and vascular damage indices. Lastly, a penile duplex ultrasound was repeated after 18 months and a recovery of the penile vascular function was found (Figure 3).

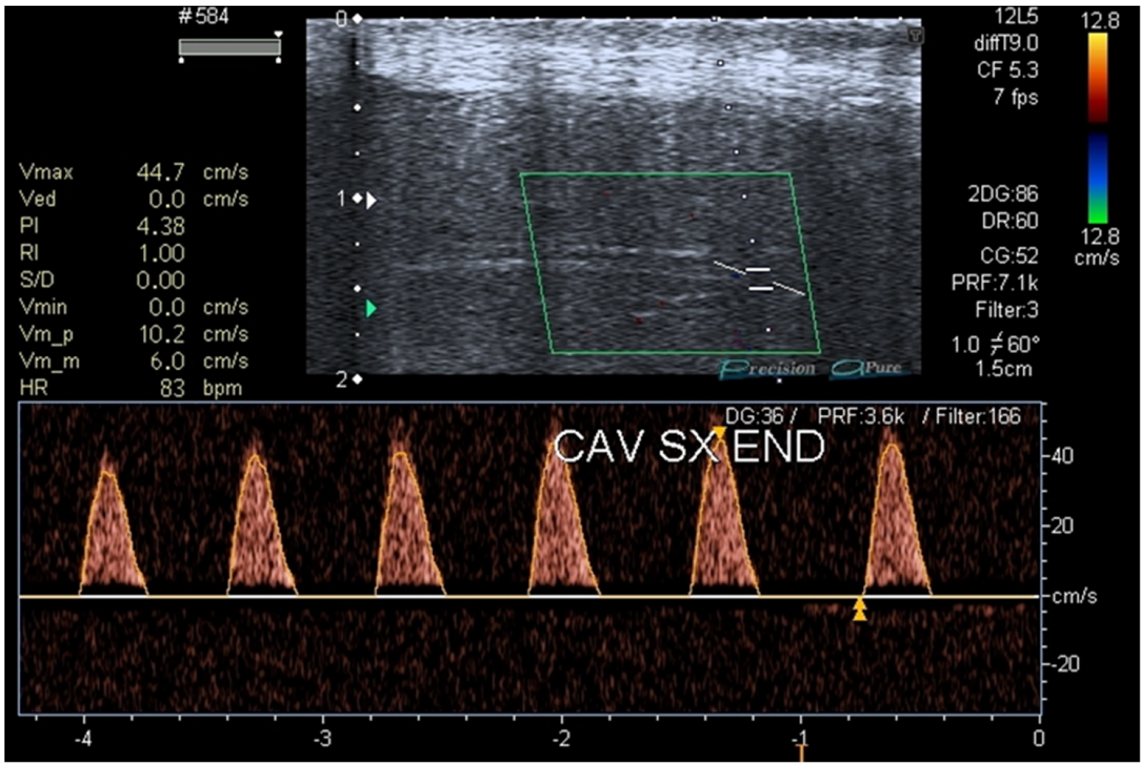

Figure 3. Penile duplex ultrasound at T3 (18 months after patient's first visit).

4. Discussion

Because of COVID-19's continuous spreading, clinicians should be prepared to treat long COVID and its consequences that are common in recovered patients [34]. In particular, the understanding of the physio-pathological mechanisms ranging from SARS-CoV-2 infection to its poly-district clinical manifestations is increasingly necessary to be able to orient, even if empirically, on their therapeutic management.

With relation to the new evident emergence of ED as a potential complication, although rare, the most plausible etiological hypothesis seems to be the vascular one [5]. Moreover, physical and mental stress related to quarantine might worsen ED [9].

In the case here reported by our group, at first, we had no clinical explanation for the etiology of ED other than the possibility of endothelial damage in the penile vascular tissue. This hypothesis was confirmed by the first penile ultrasound performed after two months of poor responsiveness to PDE-5is.

Even if PDE-5is are recognized as a first-line treatment for ED [35], approximately 30–35% of patients are considered non-responders [36]. Many comorbidities could affect the efficacy of PDE-5is [37]. These patients suffer from histopathological changes in penile tissues due to persistent hypoxia with related arterial insufficiency [38]. It has been suggested to optimize treatment with increasing doses of medications [39]. About 50–70% of patients still do not have an adequate response after restoring correct use of PDE-5is [40]. However, 8–12% of PDE-5is non-responders could benefit from a second PDE-5i so we decided to shift sildenafil to tadalafil 5 mg daily [41].

Considering its long half-life (18h) [42], tadalafil could be taken long before sexual intercourse increasing spontaneity [43] and compared to on-demand sildenafil, daily tadalafil has a broader period of opportunity for sexual activity, more sexual attempts, reducing sex time concerns and a more satisfying erection hardness [44]. Moreover, the daily dosing regimen of tadalafil could be considered a salvage therapy in previous PDE-5is non-responders [45].

In recent decades, "penile rehabilitation" (restoring penile function) has been debated, even if only minor studies suggest clinical benefit [46]. It has been postulated that the chronic daily use of tadalafil could contribute in repairing endothelial injury. Moreover, daily tadalafil leads to significantly lower levels in C-reactive protein and endothelin-1, which are known to be associated with inflammation and also to COVID-19 [47].

Shockwave therapy has been proposed as a therapeutic option in patients with vasculogenic ED who are poor responders to PDE-5is and who are not fit for second-line therapies [11,33]. LI-SWT proved to be safe and effective with a significant improvement of penile hardness. An improvement in cell proliferation and NO release has been observed because of nitric oxide synthase (eNOS) activation [48].

Regardless of the pathophysiological mechanism behind endothelial damage, there is no question that multiorgan endothelial dysfunction is a characteristic of COVID-19, especially in its severe form [49]. Endothelial damage in acute COVID-19 causes endothelin-1, acute phase proteins (such as CRP) and inflammatory cytokine elevation [50]; the endothelial cell involvement seems to be able to continue even beyond the acute phase of illness [51]. Moreover, in a recent study by Perri et al., it has been suggested that SARS-CoV-2 could activate the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome determining a chronic pro-inflammatory state [52].

In fact, as seen in many other studies about COVID-19 [50,53], in the case here reported, inflammation markers, such as Endothelin-1 and CRP, were elevated at baseline (four months after COVID-19 remission). We observed a consistent reduction in Endothelin-1 and CRP values after six months and throughout the follow-up period (Table 2). The same improvement was observed in IIEF-5 and SF-36 scores (Table 3) and in the dynamic penile ultrasound performed after 18 months from the first visit (Figure 3).

A recent study by Harirugsakul et al. investigated erectile function three months after COVID-19 in a cohort of 129 subjects. They concluded that the ED course was

persistent and self-remitted, similar to other COVID-19 sequelae. Particularly, improvement of anosmia and ageusia could explain transitory ED [54]. Anosmia and ageusia may contribute to the reduction of sexual interest, probably because of the reduced perception of pheromones [55–57].

Vitamin D, a steroidal hormone produced by the skin, has been correlated with multiple metabolic and cardiovascular outcomes [58]. Since 2020, the possible relation between COVID-19 and Vitamin D (VD) levels has been widely studied. A meta-analysis from 2021 concluded that VD levels were significantly lower in patients infected with COVID-19 and in patients with severe disease [59].

Endothelial damage in COVID is a phenomenon that seems to be reversible, although in unpredictable times; the improvement of endothelial damage, accompanied in this case by the increase in the quality of the patient's erections, may have been helped, as mentioned by the repairing effect on the endothelium of tadalafil, but we also hypothesized possible actions on the VD receptor as derived by a high-dose vitamin D supplementation. It has become clear that Vitamin D supplementation could improve some cardiovascular risk factors [60]. In fact, it is directly involved in endothelial function and integrity [61] through its anti-inflammatory and immunomodulatory effects [58]. It seems that vitamin D supplementation could also have a positive effect on inflammatory markers [62], reducing CRP levels [63]. Moreover, Vitamin D induces a shift from inflammatory Th1 to anti-inflammatory Th2 response [64].

The therapeutic strategy we have applied to this case, including LI-SWT, should not be considered a univocal approach to COVID-19-related ED, but has proved to be effective in our clinical context. In particular, since the remission of erectile dysfunction is not foreseeable, it is not yet possible to suggest a specific therapeutic strategy and the time to suspend therapy; however, we speculated that the clinical use of basic markers of inflammation and vascular damage could be helpful to determine the right time to attempt a dose reduction.

5. Conclusions

We reported a single case of ED with an abrupt onset of manifestations four months after poorly symptomatic COVID-19 with progressive responsiveness to LI-SWT and then to PDE-5is. In addition, we may speculate that the daily use of tadalafil and vitamin D supplementation contributed to the reduction in inflammatory markers observed throughout the follow-up period. However, due to the fact that our study reports on a single case, further research with a larger sample size is needed to support our hypothesis.

Even if COVID-19 has been deeply investigated, only a few studies have focused on ED as its consequence [65]. Our data suggest a good prognosis for COVID-19-related ED, although future studies are needed to better understand the physio-pathological effects of the SARS-CoV-2 infection and the underlying mechanisms by which erectile dysfunction may be determined.

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Conflicts of Interest: The authors declare no conflict of interest.

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