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CASE SERIES

Healing of Peyronie's disease after multimodal antioxidant treatment. A case series

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Summary ***Introduction: Peyronie's disease (PD) is characterized by fibrosis of the penile tunica albuginea. Conservative treatment options may involve oral and/or injectable medications.***
Materials and methods: This case series includes four patients with PD in the first phase. The diagnosis of PD included a medical history; penile palpation; a physical examination of the penis, documenting penile deformity (Kelâmi method); penile dynamic Doppler ultrasound (PDDU) + elastography, measuring the plaque and calculating its volume (cm^3), and the deformation index (strain ratio); and the completion of the following questionnaires: IIEF to assess erectile function, VAS to assess pain, and Peyronie's Disease Questionnaire (PDQ) symptom bother to evaluate the psychosexual impact of the disease. Diagnostic follow-up evaluations were conducted before and every 6-12 months throughout the conservative treatment.
The four patients were treated at our andrology clinic between January 2019 and November 2023. Our treatment included the following: bilberry, propolis, ginkgo biloba, silymarin, L-carnitine, coenzime Q-10, Boswellia, superoxide dismutase, vitamin E, vitamin C, topical diclofenac gel, propolis cream, and perilesional penile injections with pentoxifylline for cases involving penile plaques with volumes of > 0.100 cm^3.
Results: Complete resorption of the PD plaque after treatment occurred in all cases. The disappearance of Peyronie's plaque occurred over a period ranging from 18 to 36 months, in relation to the volume of the plaque.
Conclusions: Despite the limited sample size in our study, these patients verifiably achieved the complete resorption of the affected disease area. Our results will provide useful insights for uroandrological clinical practice. Nevertheless, randomized controlled trials with a larger number of PD patients are needed to demonstrate the effectiveness of multimodal antioxidant treatment.

KEY WORDS: Peyronie's disease; Oxidative stress; Antioxidants; Pentoxifylline.

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INTRODUCTION

PD is a genetically based chronic inflammatory condition that affects the tunica albuginea of the penile corpora cavernosa in genetically predisposed males, leading to the formation of an inelastic and fibrous penile plaque that inevitably causes various types of penile deformation. Its prevalence ranges from 3.2% to 13.1% and is less common in Asian countries (0.6-5.0%) and among populations of black African descent (0.1-3.5%) (1-8). PD typically affects middle-aged men, but cases have increased among younger patients in recent years. In 2001, two authors reported the prevalence of PD in young people under the age of 40 as 1.5% and 4.8% (2, 9). Some authors have noted an increase in the incidence of PD in younger patients, with their study showing an 18.6% incidence in individuals under 40 compared with the 24.2% incidence found in our most recent study (10, 11). PD symptoms include penile deformity (in more than 90% of cases), penile pain (in between 20% and 70% of cases), erectile dysfunction (in over 30% of cases), and psychological distress, such as anxiety and depression (in approximately 48% of cases) (12, 13). Penile deformities can manifest as curvature, shortening, twisting, indentations, hourglass deformities, and in more severe cases, "*flail penis*".
Traumatic theory appears to be the most widely accepted of the several etiopathogenetic hypotheses. According to this theory, the local accumulation of fibrin resulting from trauma (whether micro- or macro-trauma) is believed to initiate the disease process by triggering the production of free radicals (oxidative stress) and fibrogenic cytokines, leading to excessive collagen production and deposition (plaque) (14-22). The disease progresses in two phases: The inflammatory ("*active*") phase comes first, lasting for approximately 12-18 months, during which plaque formation and remodeling occur (23-30). Conservative medical therapy is recommended during this first phase. The second phase is the "*stabilization*" stage, wherein the disease stops progressing, the plaque stops growing, and any pain usually subsides. Surgical treatment is recommended during this second phase if there is a severe penile deformity that hinders sexual intercourse or if severe erectile dysfunction is present (23, 24, 26, 27,30-34).
The conservative medical treatment in the first phase of PD includes oral therapies, penile infiltrations, including vitamin E, colchicine, potaba, tamoxifen, *pentoxifylline* (PTX), bioactive food extracts with an antioxidant action (L-arginine, carnitine, propolis, bilberry, coenzyme Q10, etc.), *non-steroidal anti-inflammatory drugs* (NSAIDs), *phosphodiesterase 5* (PDE-5) inhibitors, penile infiltrations (verapamil, corticosteroids, *interferon-α2b* (IFNa2b), *pentoxi-*

fylline (PTX), hyaluronic acid, and *clostridium histolyticum collagenase* (CCH) (26, 33, 35-40).
The physical treatment in the first phase of PD includes *extracorporeal shock wave therapy* (ESWT), iontophoresis, and penile traction and vacuum devices (26, 33, 59, 60).
Surgical treatments for PD are targeted to each patient's specific needs and may include corporoplasty, with or without grafts, and the possible insertion of a penile prosthesis (28, 31, 32, 34, 36, 41).
PD diagnostics involves penile palpations, photographic documentation of the deformation (according to the Kelâmi guidelines), *penile dynamic Doppler ultrasound* (PDDU), and the completion of questionnaires for pain (VAS), erectile function (IIEF), and psychometric evaluations like the *Peyronie's Disease Questionnaire* (PDQ) (10, 42-47).
The scientific literature reports eleven human patients with PD who have recovered following medical treatment with antioxidants (48-51). Cases of PD resolution have been published before, but only in experimental studies in rats (52-54). The scientific literature has always reported the possibility of the spontaneous resolution of PD (31, 55-57). However, some studies do not agree with this possibility (58-59). We believe that treating oxidative stress (a key mechanism of inflammation) with antioxidants is the best therapeutic approach to treat PD (35, 60-62).
Multimodal treatment aims to achieve superior outcomes compared with using a single substance or therapy alone. All the antioxidants we use have anti-inflammatory and antifibrotic properties by blocking the activity of the NF-kB factor. In our multimodal treatment, we have also used NSAID (diclofenac), although administered locally to avoid possible long-term toxic effects due to oral administration (63, 64).
This case report aimed to present four cases of patients with PD who experienced plaque regression following "*multimodal*" antioxidant therapy (with oral antioxidants, topical diclofenac gel, and penile perilesional injections with 60 mg of pentoxifylline).
Our recent four articles have shown that the duration of multimodal treatment needed to regress Peyronie's plaque directly depends on the plaque's size (48-51). Therefore, larger plaques require a relatively longer time to completely regress. In our recent case report, a patient with PD achieved complete plaque regression in just four months of combined antioxidant therapy, as his plaque was small (51).

Methods

This case series includes four cases of patients with PD in the first phase who experienced the plaque's disappearance following "*multimodal*" antioxidant therapy including various oral antioxidants, topical diclofenac gel and propolis cream, and penile perilesional injections with a potent antioxidant and antifibrotic substance, pentoxifylline, specifically for cases involving penile plaques with volumes of > 0.100 cm^3.
The complete list of antioxidant substances used is shown in the following tables 1, 2, 3, and 4. The diagnosis of PD included a detailed medical history; penile palpation; a physical examination of the penis, documenting penile deformity using the Kelâmi method and measuring the angulation; *penile dynamic Doppler ultrasound* (PDDU) + elastography, measuring the plaque in three dimensions and calculating its volume (cm^3) using the ellipsoid formula (volume = 0.524 × length × width × thickness) and the deformation index (strain ratio); and the completion of the following questionnaires: IIEF to assess erectile function, VAS to assess pain, and the Questionnaire (PDQ symptom bother) to evaluate the psychosexual impact of the disease (10, 42-47, 65, 66).
The strain ratio (or deformation index), indicating the plaque's stiffness was detected via echo-elastography. The strain ratio, expressed as a number, represents the ratio between the stiffness of the pathological tissue (plaque) and that of the adjacent normal tissue. The four patients were treated at our andrology clinic between January 2019 and November 2023. All patients signed an informed consent form for the multimodal treatment. During the consent process, patients were informed that the treatment for PD would be lengthy due to the chronic nature of the disease. The patients also agreed to the publication of their clinical data, provided that they be published anonymously. All these patients did not consent to the publication of photos of their penises, even though they would have been published anonymously.
A single andrologist operator performed and assessed PDDU with elastography on all patients in a single session. We used the Philips HD 15 machine (*Washington, United States*) that was later upgraded to a Philips Affinity 70 G (*Washington, United States*). In each of the 4 cases described, we reported the type of ultrasound machine used.
Diagnostic follow-up evaluations were conducted before and approximately every 6-12 months throughout the conservative treatment.

Results

Case series presentation

In each case presented, several treatment cycles combined with antioxidants were necessary before reaching complete plaque reabsorption. We describe the four individual cases in detail, with their personal clinical characteristics present before and at the end of treatment when the therapeutic goal was achieved. A table listing the individual variations obtained after each treatment cycle is included for each clinical case presentation.

Case 1

Case 1 was a 57-year-old Caucasian man, a non-smoker, suffering from chronic prostatitis, with the presence at the origin of a congenital penile curvature (dorsal of 25 degrees, left lateral of 5 degrees, and right lateral of 5 degrees), before the appearance of PD. The patient did not report any traumatic events involving his penis in the previous 6-12 months. He reported that he had started to notice a penile curvature, different from usual, approximately 6-8 months earlier. At the time of our visit, the patient did not report any penile pain (VAS score = 0) nor complained of erectile dysfunction. The IIEF score was 26. The PDQ symptom bother score was 11. In our observations, the penile deformation presented as a multiplanar curve, with a significantly reduced penile diameter in its distal third. The goniometric

Table 1.
Case 1: clinical data collected before, during, and after antioxidant treatment.

Ultrasound measurements	Plaque strain ratio	Dorsal curve of 41 degrees a right lateral curve of 17 degrees, and a left lateral curve of 17 degrees	VAS score	IIEF score	PDQ bother score	
Basal plaque: 12.1 × 10.4 × 4.23 mm (volume = 0.279 cm^3 Distal plaque: 24.0 × 29.3 × 4.35 mm with two internal calcifications measuring 5.2 × 9.3 mm and 5.0 × 8.0 mm (volume = 1.60 cm^3) Total volume of the two plaques = 1.879 cm^3	Basal plaque = 1.8 Distal plaque = 2.53		0	26	11	
First cycle of multimodal treatment with antioxidants (6 months)						Orally: L-carnitine 1000 mg + Propolis 700 mg + Ginkgo biloba 240 mg + Bilberry 180 mg + Coenzyme Q-10 100 mg + Silymarin 400 mg + Boswellia 200 mg + Vitamin C 50 mg + Vitamin E 48 mg + Superoxide dismutase 11000 IU/g 10 mg/daily/for 6 months; + Topically: Propolis cream/2 x daily + Diclofenac gel 4%/daily/for 6 months; + Peri-lesional penile injections: Pentoxifylline 60 mg (with 30 G needle) every 2 weeks for 6 months.
Ultrasound measurements	Plaque strain ratio	Dorsal curve of 33 degrees a right lateral curve of 17 degrees, and a left lateral curve of 17 degrees	VAS score	IIEF score	PDQ bother score	
Basal plaque: 8.72 × 6.85 × 2.80 mm (volume = 0.087 cm^3) Distal plaque: 17.6 × 17.1 × 2.91 mm with internal calcification measuring 3.3 x 2.4 mm (volume = 0.458 cm^3) The other internal calcification was no longer detectable The total volume of the two plaques = 0.545 cm^3 After the first treatment cycle, the total volume of the two plaques decreased by 70.9% compared with the initial situation	Basal plaque = 1.6 Distal plaque = 2.21		0	26	8	
Second cycle of multimodal treatment with antioxidants (12 months)						Orally: L-carnitine 1000 mg + Propolis 700 mg + Ginkgo biloba 240 mg + Bilberry 180 mg + Coenzyme Q-10 100 mg + Silymarin 400 mg + Boswellia 200 mg + Vitamin C 50 mg + Vitamin E 48 mg + Superoxide dismutase 11000 IU/g 10 mg/daily/for 12 months; + Topically: Propolis cream/2 x daily + Diclofenac gel 4%/daily/for 12 months; + Peri-lesional penile injections: Pentoxifylline 60 mg (with 30 G needle) every month for 12 months.
Ultrasound measurements	Plaque strain ratio	Dorsal curve of 33 degrees, a right lateral curve of 7 degrees, and a left lateral curve of 7 degrees	VAS score	IIEF score	PDQ bother score	
Basal plaque: 4.4 × 4.52 × 2.13 mm (volume = 0.022 cm^3) Distal plaque: 9.91 × 8.5 × 2.14 mm with internal calcification measuring 2.8 x 1.6 mm (volume = 0.094 cm^3) Total volume of the two plaques = 0.116 cm^3 After the second treatment cycle, the total volume of the two plaques decreased by 93.8% compared with the initial situation	Basal plaque = 1.2 Distal plaque = 1.53		0	27	4	
Third cycle of multimodal treatment with antioxidants (18 months)						Orally: L-Carnitine 1000 mg + Propolis 700 mg + Ginkgo biloba 240 mg + Bilberry 180 mg + Coenzyme Q-10 100 mg + Silymarin 400 mg + Boswellia 200 mg + Vitamin-C 50 mg + Vitamin-E 48 mg + Superoxide dismutase 11000 IU/g 10 mg/daily/for 6 months; + Topically: Propolis cream/2 x daily + Diclofenac gel 4%/daily/for 18 months; + Peri-lesional penile injections: Pentoxifylline 60 mg (with 30 G needle), 1 penile injection every 2 months for 12 months
Penile plaques were no longer detectable	Absence of non-elastic penile areas	After the regression of the plaques, the same penile congenital condition that preceded PD was present, with a dorsal curve of 10 degrees				Total therapy duration until plaque's disappearance = 30 months

VAS = visual analog scale, a pain measurement questionnaire (score range: 0-10) (45); IIEF = International Index of Erectile Function, a questionnaire for assessing erectile function with a score range of 0-30, indicating different ED severity levels (no ED, score range: 26-30) (46); PDQ symptom bother = PD Questionnaire symptom bother for evaluating the psychosexual impact, with a score range of 0-30 (10, 47, 66). The strain ratio (deformation index), detected via echo-elastography, indicates the plaque's stiffness (65). It is expressed as a number, representing the ratio between the stiffness of the pathological tissue (plaque) and that of the adjacent normal tissue. When elastography does not detect any anelastic area (plaque), the strain ratio index corresponds to 1. In this case, the image displayed on the ultrasound machine screen does not show any index.

measurements showed a dorsal curve of 41 degrees, a right lateral curve of 17 degrees, and a left lateral curve of 17 degrees. Upon palpation, two basal and distal penile plaques of approximately 10 mm and 20 mm in length were detected, respectively, both with a fibrous consistency. Two plaques were present in the penile eco-elastography examination. The first penile plaque was located in the basal third and measured 12.1 × 10.4 × 4.23 mm (volume = 0.279 cm^3), while the second plaque was located in the distal third and measured 24.0 × 29.3 × 4.35 mm (volume = 1.60 cm^3). Two calcifications in the second plaque measured 5.2 × 9.3 mm and 5.0 × 8.0 mm. The total volume of the two plaques was 1.879 cm^3. The ultrasound appearance of the basal plaque was iso-hyperechoic, and that of the distal plaque was iso-hyperechoic-calcific.

The strain ratios of the two basal and distal penile plaques were 1.8 and 2.53, respectively. The cavernous arteries showed a normal arterial flow and end-diastolic velocity in the PDDU examination (with a penile injection of 10 mcg of alprostadil). The patient then underwent multimodal therapy with antioxidants. The complete list of antioxidant substances in the multimodal treatment administered to the patient, alongside the pre-treatment clinical data and those related to each subsequent follow-up after the three treatment cycles, is shown in Table 1.

After completing the third cycle of six perilesional penile injections with 60 mg of pentoxifylline (every 2 months), the patient delayed the scheduled follow-up after 12 months and continued oral and local home therapy for an additional 6 months. The follow-up was then performed 18 months after the last check-up.

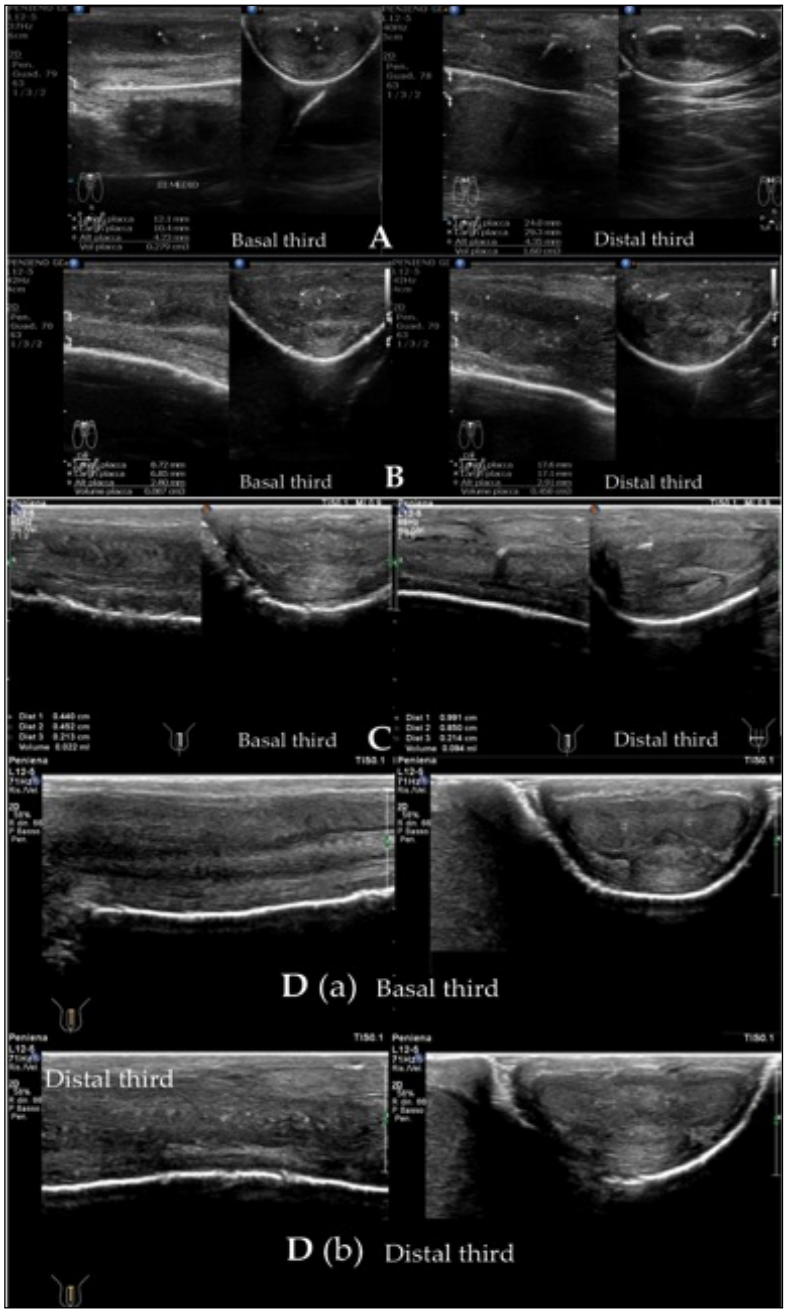
Images of the ultrasound examination before, during, and after treatment are presented in Figure 1.

After three treatment cycles, totaling 36 months of multimodal antioxidant therapy, the patient underwent a complete follow-up, and no penile nodules were palpable. No plaque was detected in the ultrasound examination.

The patient did not report any penile pain (VAS score = 0) nor complained of erectile dysfunction. The IIEF score was 27. The PDQ symptom bother score was four.

The patient had an excellent psychological state, and the penis's appearance was comparable to the condition before PD (congenital curvature of the penis), The patient expressed satisfaction with the excellent results achieved at the end of our treatment.

Figure 1.
Images of the ultrasound exam (longitudinal and transverse scan) are shown before (A), during (B) and (C), and after multimodal treatment (D).



Case 2

A 48-year-old Caucasian man, a non-smoker, reported that he had suffered from prostatitis in the past but had no related symptoms at the time of the visit. The patient reported that he already had a congenital penile curvature before the onset of PD. The congenital penile deformity consisted of a mild dorsal curvature of 10 degrees.

The patient did not report any traumatic events involving his penis in the previous 6-12 months. He reported that he had started to notice a penile curvature, different from usual, approximately 9 months earlier. The patient did not report any penile pain (VAS score = 0) nor complained of erectile dysfunction at the time of our visit. The IIEF score was 27. The PDQ symptom bother score was 10. In our observation, the penile deformation presented with a dorsal curve of 45 degrees. Upon palpation, two plaques were detected at the basal third level and the distal level of the penis, approximately 10

mm and 15 mm in length, respectively. Both plaques had a fibrous consistency. Two plaques were present in the penile eco-elastography examination. The first penile plaque was located at the basal third and measured 9.28 × 10.9 × 3.99 mm (volume = 0.212 cm^3), while the second plaque was located in the distal third and measured 14.3 × 11.7 × 2.86 mm (volume = 0.252 cm^3). The total volume of the two plaques was 0.464 cm^3. The ultrasound appearance of the two plaques was iso-hyperechoic. The strain ratios of the two basal and distal penile plaques were 2.1 and 1.89, respectively. The cavernous arteries exhibited a normal arterial flow and end-diastolic velocity in the PDDU examination (a penile injection of 10 mcg of alprostadil). The patient then underwent multimodal therapy with antioxidants. However, the patient did not consent to the publication of photos of his penis, even if published anonymously.

Table 2 displays the full list of antioxidant substances

Table 2.

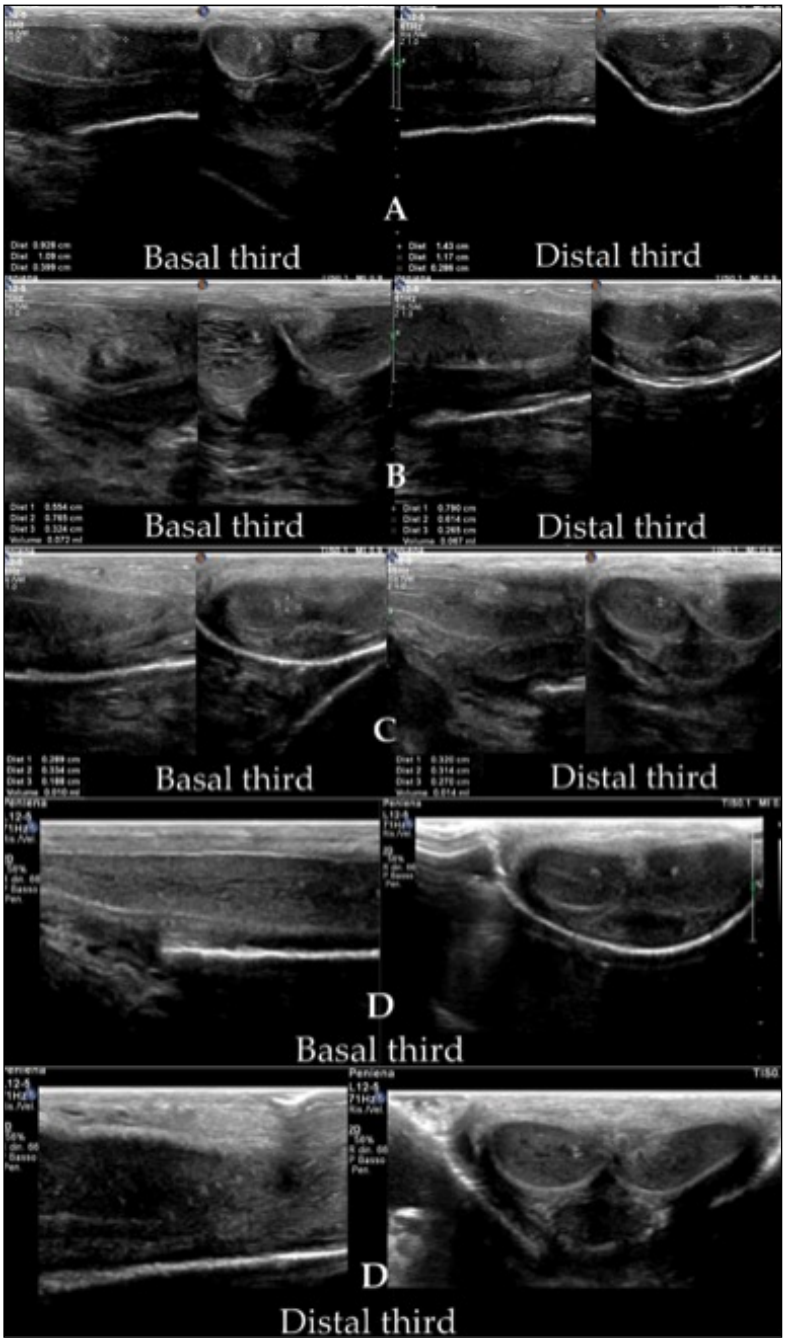
Case 2: clinical data collected before, during, and after antioxidant treatment.

Ultrasound measurements	Plaque strain ratio	Dorsal curve of 45 degrees	VAS score	IIEF score	PDQ bother score	
Basal plaque: 9.28 × 10.9 × 3.99 mm (volume = 0.212 cm^3) Distal plaque: 14.3 × 11.7 × 2.86 mm (volume = 0.252 cm^3) Total volume of the two plaques = 0.464 cm^3	Basal plaque = 2.1 Distal plaque = 1.89		0	27	10	
First cycle of multimodal treatment with antioxidants (6 months)						Orally: L-carnitine 1000 mg + Propolis 700 mg + Ginkgo biloba 240 mg + Bilberry 180 mg + Coenzyme Q-10 100 mg + Silymarin 400 mg + Boswellia 200 mg + Vitamin C 50 mg + Vitamin E 48 mg + Superoxide dismutase 11000 IU/g 10 mg/daily/for 6 months; + Topically: Propolis cream/2 x daily + Diclofenac gel 4%/daily/for 6 months; + Peri-lesional penile injections: Pentoxifylline 60 mg (with 30 G needle) every 2 weeks for 6 months.
Ultrasound measurements	Plaque strain ratio	Dorsal curve of 42 degrees	VAS score	IIEF score	PDQ bother score	
Basal plaque: 5.54 × 7.65 × 3.24 mm (volume = 0.072 cm^3) Distal plaque: 7.9 × 6.14 × 2.65 mm (volume = 0.067cm^3) Total volume of the two plaques = 0.139 cm^3 After the first treatment cycle, the total volume of the two plaques decreased by 70% compared with the initial situation	Basal plaque = 1.87 Distal plaque = 1.69		0	27	6	
Second cycle of multimodal treatment with antioxidants (12 months)						Orally: L-carnitine 1000 mg + Propolis 700 mg + Ginkgo biloba 240 mg + Bilberry 180 mg + Coenzyme Q-10 100 mg + Silymarin 400 mg + Boswellia 200 mg + Vitamin C 50 mg + Vitamin E 48 mg + Superoxide dismutase 11000 IU/g 10 mg/daily/for 12 months; + Topically: Propolis cream/2 x daily + Diclofenac gel 4%/daily/for 12 months; + Peri-lesional penile injections: Pentoxifylline 60 mg (with 30 G needle) every month for 12 months.
Ultrasound measurements	Plaque strain ratio	Dorsal curve of 42 degrees	VAS score	IIEF score	PDQ bother score	
Basal plaque: 2.89 × 3.34 × 1.88 mm (volume = 0.010 cm^3) Distal plaque: 3.2 × 3.14 × 2.7 mm (volume = 0.014 cm^3) Total volume of the two plaques = 0.024 cm^3 After the second treatment cycle, the total volume of the two plaques decreased by 94.8% compared with the initial situation	Basal plaque = 1.62 Distal plaque = 1.26		0	27	4	
Third cycle of multimodal treatment with antioxidants (12 months)						Orally: L-Carnitine 1000 mg + Propolis 700 mg + Ginkgo biloba 240 mg + Bilberry 180 mg + Coenzyme Q-10 100 mg + Silymarin 400 mg + Boswellia 200 mg + Vitamin-C 50 mg + Vitamin-E 48 mg + Superoxide dismutase 11000 IU/g 10 mg/daily/for 6 months; + Topically: Propolis cream/2 x daily + Diclofenac gel 4%/daily/for 12 months.
Penile plaques were no longer detectable	Absence of non-elastic penile areas	After the regression of the plaques, the same penile congenital condition that preceded PD was present, with a dorsal curve of 10 degrees				Total therapy duration until plaque's disappearance = 30 months

VAS = visual analog scale, a pain measurement questionnaire (score range: 0-10) (45); IIEF = International Index of Erectile Function, a questionnaire for assessing erectile function with a score range of 0-30, indicating different ED severity levels (no ED, score range: 26-30) (46); PDQ symptom bother = PD Questionnaire symptom bother for evaluating the psychosexual impact, with a score range of 0-30 (10, 47, 66). The strain ratio (deformation index), detected via echo-elastography, indicates the plaque's stiffness (65). It is expressed as a number, representing the ratio between the stiffness of the pathological tissue (plaque) and that of the adjacent normal tissue. When elastography does not detect any anelastic area (plaque), the strain ratio index corresponds to 1. In this case, the image displayed on the ultrasound machine screen does not show any index.

included in the multimodal treatment given to the patient, alongside the clinical data before treatment and at each follow-up after the treatment cycles.
The images from the ultrasound examination before, during, and after treatment are presented in Figure 2.
After undergoing three cycles of treatment, which lasted a total of 30 months, the patient had a comprehensive follow-up assessment that revealed no palpable penile nodules. The ultrasound examination did not detect any plaque. The patient did not report any penile pain (VAS score = 0) nor complained of erectile dysfunction, the IIEF score was 27. The PDQ symptom bother score was four. The patient's psychological well-being was excellent, and the penis's appearance was similar to its pre-PD state (a congenital dorsal curvature of the penis of 10 degrees). The patient expressed satisfaction with the outstanding results obtained after completing our antioxidant treatment.

Figure 2.
The images from the ultrasound examination (longitudinal and transverse scans) are shown in sequence: before (A), during (B) and (C), and after (D) the multimodal treatment.



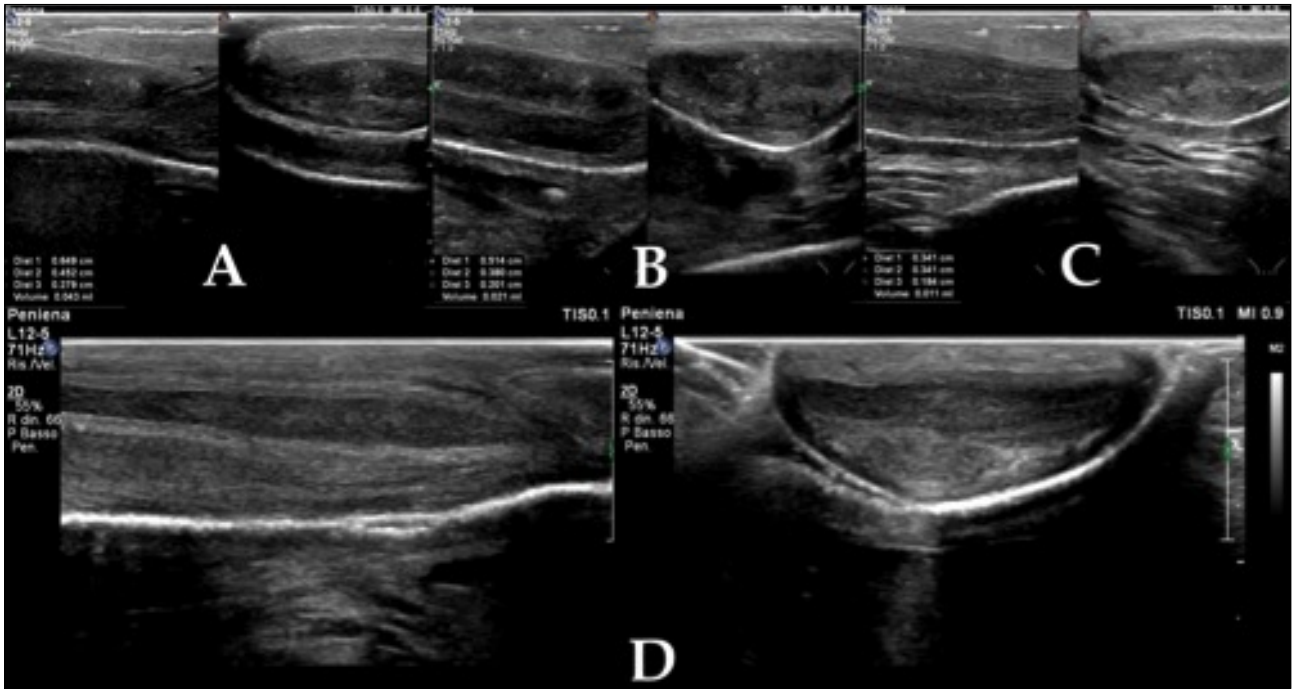
Case 3
A 42-year-old Caucasian man, a non-smoker, reported having fibromyalgia. The patient mentioned experiencing a traumatic event to his penis during sexual intercourse approximately 4 months before. He noticed a slight dorsal curvature of the penis under the glans, at the distal third of the penis, approximately 2 months ago. He also reported feeling pain in the penis during erection and sometimes at rest for the past 2 months. During the visit, the patient reported penile pain during erection (VAS score = 5) but did not mention erectile dysfunction. His IIEF score was 26, and the PDQ symptom bother score was 14. The penile deformity observed was a 20-degree sub-glandular dorsal curve. No penile plaque was detected upon palpation.
A plaque was detected in the penile echoelastography examination. The plaque was located in the distal third of the penis and measured 6.49 × 4.52 × 2.79 mm (volume = 0.043 cm^3). The ultrasound appearance of the plaque was isoechoic with mild hyperechogenicity in its distal portion. The plaque strain ratio was 1.8. The cavernous arteries showed normal arterial flows and end-diastolic velocities during the PDDU examination (a penile injection of 10 mcg of alprostadil). The patient underwent multimodal therapy with antioxidants but without penile injections of pentoxifylline due to the plaque's small size. Table 3 shows the complete list of antioxidant substances included in the multimodal treatment administered to the patient, alongside the clinical data before treatment and at each follow-up after the treatment cycles.
The images from the ultrasound examination before, during, and after treatment are presented in Figure 3.
After undergoing three cycles of treatment, which lasted a total of 18 months, the patient had a comprehensive follow-up assessment that revealed no palpable penile nodules. The ultrasound examination did not detect any plaque, the patient did not complain of penile pain (VAS score = 0), and the IIEF score was 27. The PDQ symptom bother score was four. The patient's psychological state was excellent, and no curvature of the penis was noticeable during the erectile phase. The patient expressed satisfaction with the outstanding results obtained after completing the antioxidant treatment.

Table 3.
Case 3: clinical data collected before, during, and after antioxidant treatment.

Distal plaque ultrasound measurements: 6.49 × 4.52 × 2.79 mm (volume = 0.043 cm^3)	Plaque strain ratio	Dorsal curve	VAS score	IIEF score	PDQ bother score	
	1.8	20 degree	5	26	14	
First cycle of multimodal treatment with antioxidants (6 months)						Orally: L-carnitine 1000 mg + propolis 700 mg + Ginkgo biloba 240 mg + bilberry 180 mg + coenzyme Q-10 100 mg + silymarin 400 mg + Boswellia 200 mg + vitamin C 50 mg + vitamin E 48 mg + superoxide dismutase 11000 IU/g 10 mg/daily/for 6 months; + topically: propolis cream/2 x daily + diclofenac gel 4%/daily/for 6 months;
Distal plaque ultrasound measurements: 5.14 × 3.8 × 2.01 mm (volume = 0.021 cm^3) After the first treatment cycle, the total volume of the two plaques decreased by 51.1% compared with the initial situation	Plaque strain ratio	Dorsal curve	VAS score	IIEF score	PDQ bother score	
	1.62	8 degree	3	27	10	
Second cycle of multimodal treatment with antioxidants (12 months)						Orally: L-carnitine 1000 mg + propolis 700 mg + Ginkgo biloba 240 mg + bilberry 180 mg + coenzyme Q-10 100 mg + silymarin 400 mg + Boswellia 200 mg + vitamin C 50 mg + vitamin E 48 mg + superoxide dismutase 11000 IU/g 10 mg/daily/for 6 months; + topically: propolis cream/2 x daily + diclofenac gel 4%/daily/for 6 months
Distal plaque ultrasound measurements: 3.41 × 3.41 × 1.84 mm (volume = 0.011 cm^3) After the first treatment cycle, the total volume of the two plaques decreased by 74.4% compared with the initial situation	Plaque strain ratio	Dorsal curve	VAS score	IIEF score	PDQ bother score	
	1.2	5 degree	0	27	4	
Third cycle of multimodal treatment with antioxidants (6 months)						orally: L-Carnitine 1000 mg + Propolis 700 mg + Ginkgo biloba 240 mg + Bilberry 180 mg + Coenzyme Q-10 100 mg + Silymarin 400 mg + Boswellia 200 mg + Vitamin-C 50 mg + Vitamin-E 48 mg + superoxide dismutase 11000 IU/g 10 mg/daily/for 6 months; + topically: Propolis cream/2 x daily + Diclofenac gel 4%/daily/for 6 months
Penile plaques was no longer detectable	Absence of non-elastic penile areas	Absence of penile curvature	VAS score 0	IIEF score 27	PDQ bother score 4	Total therapy duration until plaque's disappearance = 18 months

VAS = visual analog scale, a pain measurement questionnaire (score range: 0-10) (45); IIEF = International Index of Erectile Function, a questionnaire for assessing erectile function with a score range of 0-30, indicating different ED severity levels (no ED, score range: 26-30) (46); PDQ symptom bother = PD Questionnaire symptom bother for evaluating the psychosexual impact, with a score range of 0-30 (10, 47, 66). The strain ratio (deformation index), detected via echo-elastography, indicates the plaque's stiffness (65). It is expressed as a number, representing the ratio between the stiffness of the pathological tissue (plaque) and that of the adjacent normal tissue. When elastography does not detect any anelastic area (plaque), the strain ratio index corresponds to 1. In this case, the image displayed on the ultrasound machine screen does not show any index.

Figure 3.
The images from the ultrasound examination (longitudinal and transverse scans) are shown in sequence: before (A), during (B) and (C), and after (D) the multimodal treatment.



Case 4

A 47-year-old Caucasian man, a non-smoker, reported having irritable bowel syndrome. He reported that he had been suffering from erectile dysfunction for approximately 10 years. The patient had been taking a 10 mg tadalafil tablet before sexual intercourse for this disorder for several years.

The patient did not remember any traumatic event involving his penis. He reported noticing the appearance of penile deformity and penile pain during erection for approximately 9 months. Upon penile examination, a 15 mm long nodule with a fibrous consistency was palpable. The VAS score was three. The patient's IIEF score was 20, and the PDQ symptom bother score was 15. The penile deformity observed consisted of a 30-degree dorsal curvature of the penis associated with another curvature to the left of the same degree. The middle third level of the penile shaft had an "hourglass" appearance. A plaque was detected in the penile echo-elastography examination in the middle third of the penis and measured 18.8 × 15.8 × 3.42 mm (volume = 0.532 cm^3). The ultrasound appearance of the plaque was iso-hyperechoic. The plaque strain ratio was 2.3. In the PDDU examination (a penile injection of 10 mcg of alprostadil), the cavernous arteries showed normal arterial flows, while the end-diastolic speeds were high (12.2 cm/s on the right; 10.6 cm/s on the left), indicating veno-occlusive insufficiency. The patient underwent multimodal therapy with antioxidants, including periodic perilesional penile injections with 60 mg of pentoxifylline. However, we allowed the patient to continue taking one 10 mg tadalafil tablet before sexual intercourse.

Table 4 shows the complete list of antioxidant substances included in the multimodal treatment administered to the patient, alongside the clinical data before treatment and at each follow-up after the treatment cycles.

The images from the ultrasound examination before, during, and after treatment are presented in Figure 4.

After completing three treatment cycles over 30 months, the patient underwent a thorough follow-up evaluation that showed no palpable penile nodules. An ultrasound examination also did not find any plaque. During the PDDU examination (a penile injection of 10 mcg of alprostadil), the cavernous arteries showed normal arterial flows, while the end-diastolic velocities remained elevated

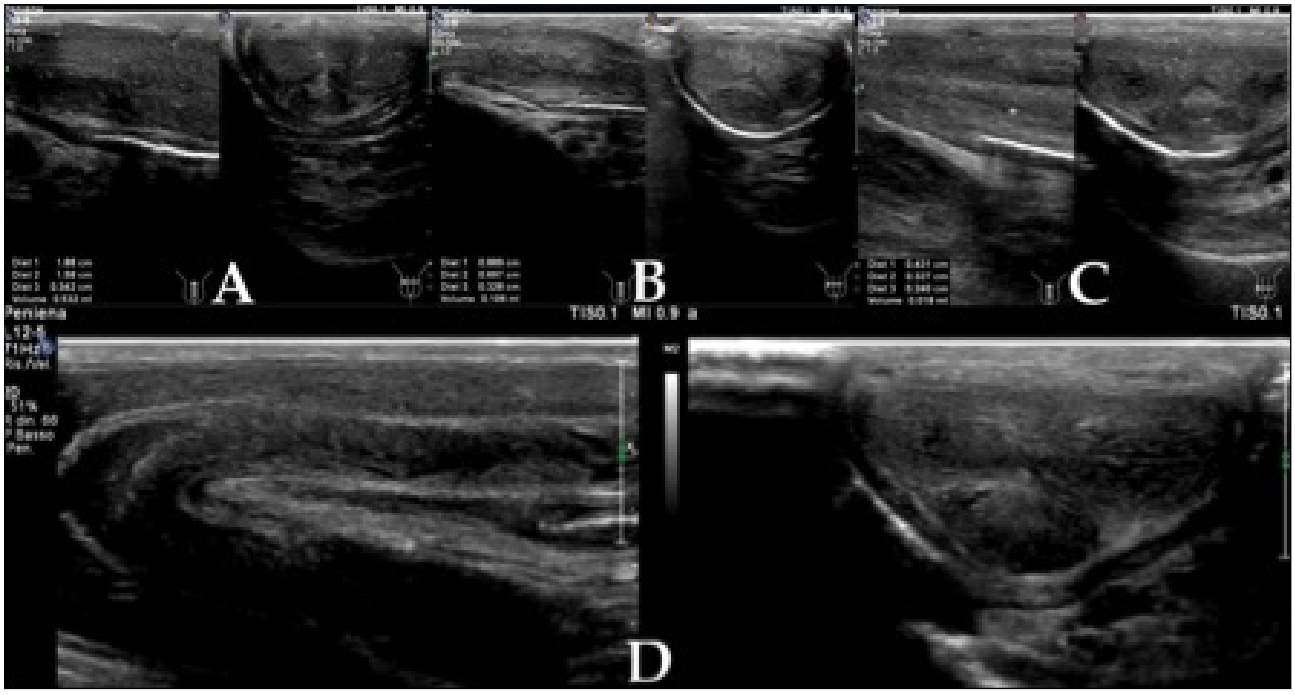
Table 4.

Case 4: clinical data collected before, during, and after antioxidant treatment.

Plaque on the penile mid-shaft Ultrasound measurements: 18.8 × 15.8 × 3.42 mm (volume = 0.532 cm^3)	Plaque strain ratio 2.3	A dorsal curve of 30 degrees and a left lateral curve of 30 degrees	VAS score 3	IIEF score 20	PDQ bother score 15	
First cycle of multimodal treatment with antioxidants (6 months)						Orally: L-carnitine 1000 mg + Propolis 700 mg + Ginkgo biloba 240 mg + Bilberry 180 mg + Coenzyme Q-10 100 mg + Silymarin 400 mg + Boswellia 200 mg + Vitamin C 50 mg + Vitamin E 48 mg + Superoxide dismutase 11000 IU/g 10 mg/daily/for 6 months; + Topically: Propolis cream/2 x daily + Diclofenac gel 4%/daily/for 6 months; + Peri-lesional penile injections: Pentoxifylline 60 mg (with 30 G needle) every 2 weeks for 6 months
Plaque on the penile mid-shaft Ultrasound measurements: 8.89 × 6.97 × 3.28 mm (volume = 0.106 cm^3) After the first treatment cycle, the total volume of the two plaques decreased by 80.0% compared with the initial situation	Plaque strain ratio 1.7	A dorsal curve of 20 degrees and a left lateral curve of 20 degrees	VAS score 1	IIEF score 22	PDQ bother score 12	
Second cycle of multimodal treatment with antioxidants (12 months)						Orally: L-carnitine 1000 mg + Propolis 700 mg + Ginkgo biloba 240 mg + Bilberry 180 mg + Coenzyme Q-10 100 mg + Silymarin 400 mg + Boswellia 200 mg + Vitamin C 50 mg + Vitamin E 48 mg + Superoxide dismutase 11000 IU/g 10 mg/daily/for 12 months; + Topically: Propolis cream/2 x daily + Diclofenac gel 4%/daily/for 12 months + Peri-lesional penile injections: Pentoxifylline 60 mg (with 30 G needle) every 2 weeks for 12 months
Plaque on the penile mid-shaft Ultrasound measurements: 4.31 × 3.27 × 2.42 mm (volume = 0.018 cm^3) After the first treatment cycle, the total volume of the two plaques decreased by 96.6% compared with the initial situation	Plaque strain ratio 1.1	A dorsal curve of 12 degrees and a left lateral curve of 10 degrees	VAS score 0	IIEF score 22	PDQ bother score 8	
Third cycle of multimodal treatment with antioxidants (12 months)						Orally: L-Carnitine 1000 mg + Propolis 700 mg + Ginkgo biloba 240 mg + Bilberry 180 mg + Coenzyme Q-10 100 mg + Silymarin 400 mg + Boswellia 200 mg + Vitamin-C 50 mg + Vitamin-E 48 mg + Superoxide dismutase 11000 IU/g 10 mg/daily/for 6 months; + Topically: Propolis cream/2 x daily + Diclofenac gel 4%/daily/for 18 months
Penile plaques was no longer detectable	Absence of non-elastic penile areas	A dorsal curve of 10 degrees and a left lateral curve of 5 degrees	VAS score 0	IIEF score 22	PDQ bother score 6	Total therapy duration until plaque's disappearance = 30 months

VAS = visual analog scale, a pain measurement questionnaire (score range: 0-10) (45)); IIEF = International Index of Erectile Function, a questionnaire for assessing erectile function with a score range of 0-30, indicating different ED severity levels (no ED, score range: 26-30) (46); PDQ symptom bother = PD Questionnaire symptom bother for evaluating the psychosexual impact, with a score range of 0-30 (10, 47, 66). The strain ratio (deformation index), detected via echo-elastography, indicates the plaque's stiffness (65). It is expressed as a number, representing the ratio between the stiffness of the pathological tissue (plaque) and that of the adjacent normal tissue. When elastography does not detect any anelastic area (plaque), the strain ratio index corresponds to 1. In this case, the image displayed on the ultrasound machine screen does not show any index.

Figure 4.
The images of the ultrasound examination (longitudinal and transverse scans) are shown in sequence: before (A), during (B) and (C), and after (D) the multimodal treatment.



(8.8 cm/s on the right; 8.6 cm/s on the left), indicating persistent occlusive insufficiency, albeit modestly improved after our treatments. The IIEF score was 22, while it was 20 before our treatment. Erectile dysfunction was moderately improved because, initially, the plaque likely deprived the penis of a portion of functioning erectile tissue.
The patient did not report any penile pain (VAS score = 0). After the plaque completely regressed, we observed a residual penile deformity characterized by a dorsal curve of 10 degrees and a left lateral curve of 5 degrees. Before our treatment, the initial penile deformity consisted of a dorsal curve of 30 degrees and a left lateral curve of 30 degrees. The PDQ symptom bother score was four. The patient's psychological state had certainly improved compared with pre-treatment; however, the erectile dysfunction still caused some concern for the patient. The patient reported that the slight residual penile deformation no longer worried him. The patient was pleased with the good results achieved after finishing the antioxidant treatment.
Complete resorption of the PD plaque after treatment occurred in all cases. The disappearance of Peyronie's plaque occurred over a period ranging from 18 to 36 months, in relation to the volume of the plaque.

Discussion

The scientific literature has documented eleven PD human patients who have recovered following medical treatment with bioactive food extracts with antioxidant properties (48-51). All 11 cases already published that had achieved complete plaque reabsorption after antioxidant treatment involved men in the first phase of PD. Before these experiences, cases of PD healing had been published, but these were experimental studies on rats in which PD-like plaques were induced with solutions of human fibrin and thrombin or with transforming growth factor-b1 (52-54).
Before these healing experiences, the scientific literature had always reported the possible spontaneous resolution of the disease in 3.2-13% of cases, as expression of the natural history of PD (31, 55-57). However, some of these studies were not based on instrumental exams but on patient self-reports via questionnaires. Like other authors with extensive experience in this disease, we believe PD cannot resolve spontaneously (58, 59). In a study published in 2013, we demonstrated that penile curvature can improve without the disease regressing. Without treatment, Peyronie's plaque in its progression can extend to the contralateral side of the curve and cause a reduction in the elasticity of the cavernous tissue, resulting in a paradoxical improvement of the penile curvature (29).
Numerous articles in the scientific literature on PD consider surgical treatment the "*gold standard*" and the ideal and definitive therapeutic option. Unfortunately, these considerations have led most uroandrologists to believe that PD is an incurable disease, resulting in a widespread pessimistic attitude and resistance to medical therapy for PD. On the contrary, we have always believed that since PD is related to chronic inflammation, the best treatment would be to treat this disease like any other chronic inflammatory disease.
Long-term treatment of PD patients with NSAIDs, corticosteroids, or other drugs can lead to chronic damage or toxicity in organs such as the liver, kidneys, immune system, and gastrointestinal system. Therefore, we have

always believed that targeting oxidative stress, a key mechanism in inflammation, with antioxidants is the best therapeutic approach for interrupting the inflammatory process of this disease (35, 60-62). Although antioxidants are not included in the current EAU *European Association of Urology* (EAU) and *American Urological Association* (AUA) guidelines for treating PD, three randomized studies in the literature have discussed the use of antioxidant substances in PD patients (31, 32, 68-70). Additionally, several controlled studies have shown positive outcomes when antioxidants have been used in combination (61, 62, 67). The EAU and AUA guidelines strongly recommend infiltrative therapy with *collagenase clostridium histolyticum* (CCH) or interferon alpha-2b (31, 32, 39). However, we did not employ CCH in treatment as it is indicated for PD in the "*stabilization phase*". On the contrary, our PD patients were all in the active phase of the disease. Furthermore, in Italy, the drug Xiapex (CCH) has been withdrawn from the market by the *Italian Medicines Agency* (AIFA) as of January 1, 2020. Additionally, we did not utilize interferon alpha-2b due to its high cost and potential side effects, including fever and flu-like symptoms, fatigue, nausea, diarrhea, vomiting, and dizziness. The positive response to our treatments is attributed to the antioxidant properties of the substances used, which can interrupt inflammation and negatively interfere with oxidative stress, a key factor in fibrogenesis (19, 20).

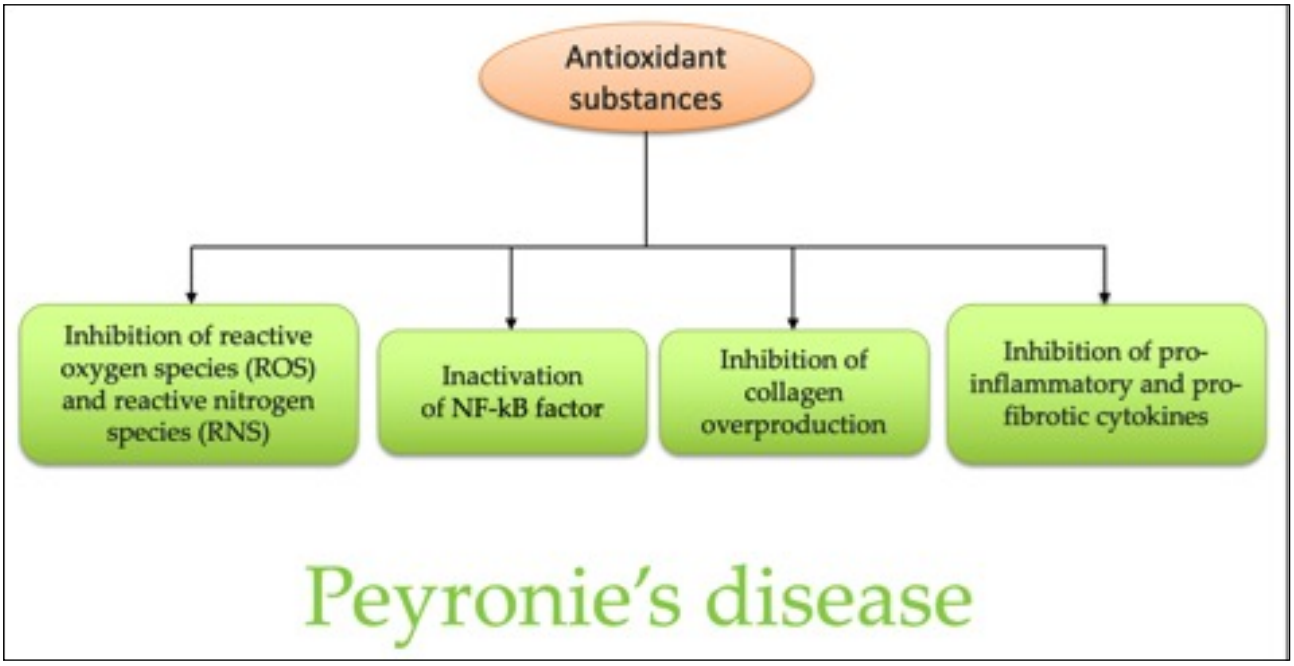
Figure 5 shows the interfering activities of antioxidants on the various pathogenetic mechanisms involved in PD. Propolis, bilberry, silymarin, boswellia, coenzyme Q-10, carnitine, and Ginkgo biloba exhibit antioxidant and antifibrotic activity, inhibit pro-inflammatory cytokines, metalloproteins with anti-elastic properties, the COX-2 enzyme, and NF-kappa-B factor (22). Coenzyme Q-10 also protects cellular membranes from lipid peroxidation caused by reactive species, and regenerates vitamin E to its natural and non-oxidized state after it has oxidized from exerting its antioxidant action (22). Carnitine also reduces the production of *inducible nitric oxide synthase* (iNOS), inhibits fibroblast proliferation and their differentiation into osteoblasts, and induces vasodilation through an endothelial mechanism that utilizes the nitric oxide pathway (22).

Superoxide dismutase (SOD) protects the human body from tissue damage caused by ROS by removing superoxide anion. SOD has anti-inflammatory action and inhibits fibroblast proliferation (22, 71). Vitamin C acts as a scavenger against reactive species and inhibits pro-inflammatory cytokines, and fibroblast proliferation (22). Vitamin E is a ROS scavenger and inhibits NF-kB factor, COX-2, pro-inflammatory cytokines, PDGF, and fibroblast proliferation (22, 35). *Pentoxifylline* (PTX) inhibits ROS, myofibroblastic differentiation, collagen deposition, NF-kB factor, pro-inflammatory cytokines, TGF-beta-1, COX-2, iNOS protein expression, and PAI-1 and stimulates fibroblast apoptosis. In our multimodal treatment, we also used diclofenac (an NSAID) administered locally to avoid potential organ damage associated with long-term oral therapy (29, 30). Diclofenac also has antioxidant properties and has been demonstrated to penetrate tissues deeply (63, 64).

The multimodal antioxidant treatment for PD described in this article is the same as described in our recent articles and differs only in the dose of PTX used for penile injections, which is 60 mg instead of 100 mg. We noticed that by reducing the dose of PTX, we achieved the same results as in the past with higher doses of PTX.

The treatment lasted for an extended period in three of the four cases described here (30-36 months). A pro-

Figure 5.
Inhibitory action of antioxidant agents on the main pathogenetic mechanisms of Peyronie's disease.



longed treatment duration is essential due to the chronic inflammatory nature of PD, which requires time for complete plaque resorption. The treatment duration may also be affected by the size of the PD plaque. The excellent result obtained in the third case, with a shorter treatment time (a year and six months) compared with the other three cases, is likely because of the early diagnosis (four months after the penile trauma). In this case, we were able to provide the patient with a shorter course of treatment without periodic penile injections, as the plaque was small (0.043 cm^3) because the PD was in an early stage. In our treatment plan involving penile injections, we progressively extended the time between each pentoxifylline injection throughout the treatment process. This approach was based on the understanding that even minor peri-lesional injections can cause trauma, which is a known trigger for developing PD. We preferred increasing the intervals between injections (every 2 weeks > every month > every 2 months) whenever regression of the disease was observed during scheduled follow-ups to minimize the risk of new traumas.

It has been reported in the literature that ultrasound evaluation of the penis in PD cannot provide adequate plaque measurements. We believe, however, that an accurate plaque size can be obtained if a highly sensitive and up-to-date ultrasound machine with an elastographic module is used and, above all, if an expert clinician with great experience in this disease performs the evaluation (31, 65, 72, 73).

Therefore, we believe that our findings resulted from both the treatment substances and the specific ultrasound evaluation method we employed. This method enabled us to accurately diagnose the affected area (plaque) and closely monitor its progression during scheduled follow-ups.

Conclusions

Despite the small sample size in this case report, our multimodal antioxidant treatment yielded highly satisfactory outcomes, allowing for the complete disappearance of the penile plaques in the disease area. We believe that the excellent responses to our therapy were due to the appropriate use of antioxidant substances, as well as the use of a very sensitive and up-to-date ultrasound machine capable of recognizing the plaques and providing their locations and precise dimensions. Additionally, having a clinician with great experience in PD conduct the echoelastography examinations contributed to the positive outcomes. Specialists may find this case series of great interest for uroandrological practice, despite the limited number of cases presented. However, randomized controlled trials with a larger number of PD patients are needed to demonstrate the efficacy of the multimodal antioxidant treatment.

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Conflict of interest: The authors declare no potential conflict of interest.