Rheumatology International (2019) 39:387–393
https://doi.org/10.1007/s00296-018-4227-6

Rheumatology
INTERNATIONAL

CASES WITH A MESSAGE

Systemic sclerosis induced by the use of cocaine: is there an association?

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Received: 30 September 2018 / Accepted: 11 December 2018 / Published online: 15 December 2018

Abstract

The association between cocaine abuse and systemic sclerosis (SSc) is rarely described. Two new cases of this association are presented: two young adults, after using inhaled cocaine for a few years, were diagnosed with SSc. While a 24 year-old white female patient presented with diffuse SSc with multiple digital ulcers and scleroderma renal crisis (SRC), a 27 year-old male patient presented limited SSc with skin ulcers and digital gangrene, rapidly evolving to death due to massive intestinal hemorrhage. The authors performed a literature search and found only eight previously published cases. The clinical picture of these patients shows a predominance of vascular involvement, including multiple ulcers and SRC. There is no association with specific SSc autoantibodies. The concomitance of alcohol and other drugs abuse, as well as the presence of drug adulterers, complicates a clear understanding of the role of cocaine in SSc patients.

Keywords Systemic sclerosis · Environmental factors · Cocaine · Drug-induced scleroderma

Introduction

Systemic sclerosis (SSc) is an autoimmune systemic disease that affects connective tissue of skin and internal organs such as lungs, kidneys, heart, and gastrointestinal tract. This multisystem condition is characterized by alterations of the microvasculature, disturbances of the immune system and deposition of collagen [1, 2]. The etiology of SSc remains unknown and genetic, occupational, and environmental factors have been associated with susceptibility to disease [1–4].

Cocaine is an addictive stimulant which blocks presynaptic reuptake of noradrenaline and dopamine and has well-known pharmacologic effects on the cardiovascular and cerebrovascular systems [5]. In the past four decades, cocaine has been implicated in the pathogenesis of several autoimmune syndromes, including connective tissue diseases (CTD), vasculitis and autoantibody production [6–9]. In a few case reports cocaine has been implicated on SSc and scleroderma-like disorders, but the rationale for this association remains not completely understood [10–16].

In this article we aim to present two new cases of SSc probably induced by cocaine and to discuss the association of this drug with the induction of autoimmunity.

Case descriptions

Case 1

A 24-year-old white female patient was referred to our institution in January 2016, in the fifth month of an uncomplicated pregnancy. She complained of Raynaud's phenomenon

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and progressive skin thickening for the last 2 years. She reported regular use of inhaled cocaine over the past **3** years. On physical examination, she presented with modified Rodnan Skin Score (mRSS) = 15, multiple digital pitting scars, tendon friction rubs at the ankles and wrists, facial telangiectasias and pigmentary disturbances. She had the diagnosis of diffuse SSc and was regularly followed up by the High Risk Obstetric Clinic, without intercurrences, until a cesarean delivery at the 38th week of gestation.

After the birth of a healthy newborn, she evolved with worsening of the skin thickening and digital ulcers, with persistently elevated blood pressure levels. The patient did not have arterial hypertension prior or at the time of diagnosis or during pregnancy, and did not use steroids previously. Laboratory tests revealed normocytic normochromic anemia, high C-reactive protein (CRP) of 5.3 mg/L (reference range < 5.0 mg/L) and erythrocyte sedimentation rate (ESR) of 29 mm/h (reference range < 10 mm/h), with normal thyroid and liver function. Serum urea was 93 mg/dL (reference range of 10–50 mg/dL) and serum creatinine 2.1 mg/dL (reference range of 0.50–0.90 mg/dL), with 24-h urine protein of 1.5 g. Antinuclear antibody (ANA) was positive (nucleolar pattern), but anticentromere (ACA), anti-topoisomerase I (anti-Scl-70), anti-dsDNA, anti-RNP, anti-SSA/Ro and anti-SSB/La antibodies, antineutrophil cytoplasmic antibody (ANCA) and rheumatoid factor were negative, also presenting normal results of serum complement C3 and C4. High-resolution computed tomography (HRCT) of the chest revealed diffuse ectasia of the esophagus and no abnormalities in lung parenchyma. Doppler echocardiogram revealed normal systolic and diastolic function and estimated pulmonary artery systolic pressure of 39 mmHg.

Due to the progressive renal dysfunction, the hypothesis of scleroderma renal crisis (SRC) was discussed. Captopril was introduced (225 mg/day), with stabilization of renal function. Renal biopsy was performed and revealed a thrombotic microangiopathic process with intimal proliferation, thrombi, onion skin lesions and fibrointimal sclerosis, compatible with SRC. Monthly intravenous cyclophosphamide (750 mg/m²) was initiated for the diffuse SSc. Patient progressed to improvement in renal function and cutaneous thickening after 12 pulses of cyclophosphamide, and was subsequently prescribed mycophenolate mofetil, currently at the dose of 2.0 g/day. In October 2018, she had stabilized renal function (serum creatinine 1.5 mg/dL) and significant skin improvement (mRSS = 5), but presented digital ulcers (Fig. 1a) and pigmentary disturbances (Fig. 1b). Nailfold capillaroscopy showed scleroderma pattern (Fig. 1c).

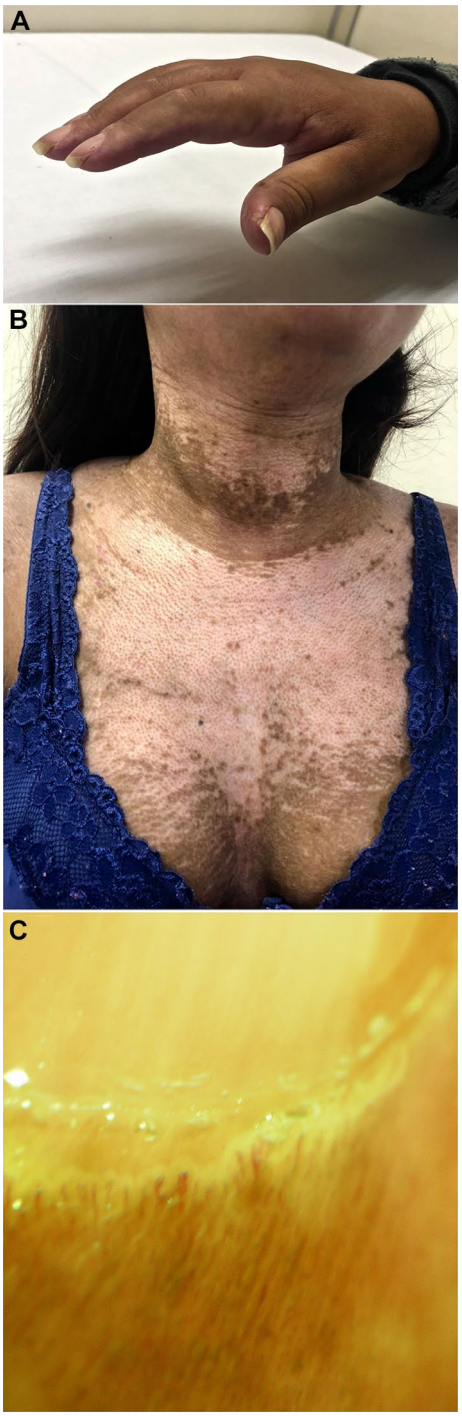

Fig. 1 Patient 1: digital ulcer of the first finger of the right hand (**a**); pigmentary disturbances characterized by hypo- and hyperpigmented skin on neck and chest (**b**); nailfold capillaroscopy showing SD pattern with capillary deletion **(c)**

Case 2

A 27-year-old African-Brazilian man was hospitalized in our service for investigation in August 2018. He complained of a 25 kg loss in the last 9 months, associated with skin thickening of the extremities, Raynaud's phenomenon and multiple digital ulcers, evolving to fixed cyanosis and necrosis of the third right-hand finger 2 weeks before the hospitalization

(Fig. 2a). He also referred alcohol intake of approximately 40 g per day for 5 years and inhaled cocaine use for 2 years, with no prior medical history of rheumatic or autoimmune disease. On physical examination, the patient presented skin thickening affecting face, hands and feet, sparing trunk and proximal limbs. He also had digital ulcers in the right foot (Fig. 2b), shallow ulcers at elbows (Fig. 2c) and back (Fig. 2d), microstomia and pigmentary disturbances at trunk, back, and limbs.

Laboratory investigation showed positive ANA, with nucleolar pattern. Anti-Scl70, anti-dsDNA, anti-Sm and lupus anticoagulant were positive. Serum complement C3 was slightly decreased (53; reference range 67–149 mg/dL), while C4 was normal (13; reference range 10–38 mg/dL). Anti-SSA/Ro, anti-SSB/La, Anti-Jo1, ANCA and rheumatoid factor were negative. Hemogram showed anemia (hemoglobin level 9 g/dl), leukopenia (leukocytes 3810/mm^3) and lymphopenia (lymphocytes 580/mm^3), with elevated CRP (6.2 mg/dL) and hypergammaglobulinemia at the serum protein electrophoresis (3 g/dL). There was normal liver, kidney, and thyroid function. Serology for hepatitis B, C and HIV was negative. Chest HRCT demonstrated esophageal ectasia, without interstitial lung disease. Doppler echocardiogram showed an ejection fraction of 50%, associated with a mild myocardial compromise; vegetations or thrombi were not visualized.

The patient was diagnosed as an overlap of limited SSc with systemic lupus erythematosus (SLE) and started treatment with prednisone 15 mg/day and methotrexate 15 mg/week; tramadol 100 mg/day and morphine were prescribed for the digital gangrene. The patient was not anticoagulated. Because of the drug addiction, he received counseling and follow-up with a psychologist; no signs of drug abstinence were seen during the period of hospitalization. In the second week of hospitalization, he presented with acute abdominal pain, followed by massive lower gastrointestinal (GI) bleeding and hypovolemic shock. There were no upper GI bleeding, fever or purpura. The hypothesis of mesenteric vasculitis was not confirmed, as patient progressed to death in 24 h. Necropsy was not performed due to family refusal.

Review of literature

A literature search through MEDLINE and Scopus database between January 1980 and August 2018 was performed by the junior author, supervised by the senior author, according to published recommendations [17]: ; the terms used were “scleroderma”, “systemic sclerosis”, “drug-induced” and “cocaine”. The reason for choosing 1980 as the starting date of our search was related to the publication of the first preliminary criteria for the classification of SSc [18], by

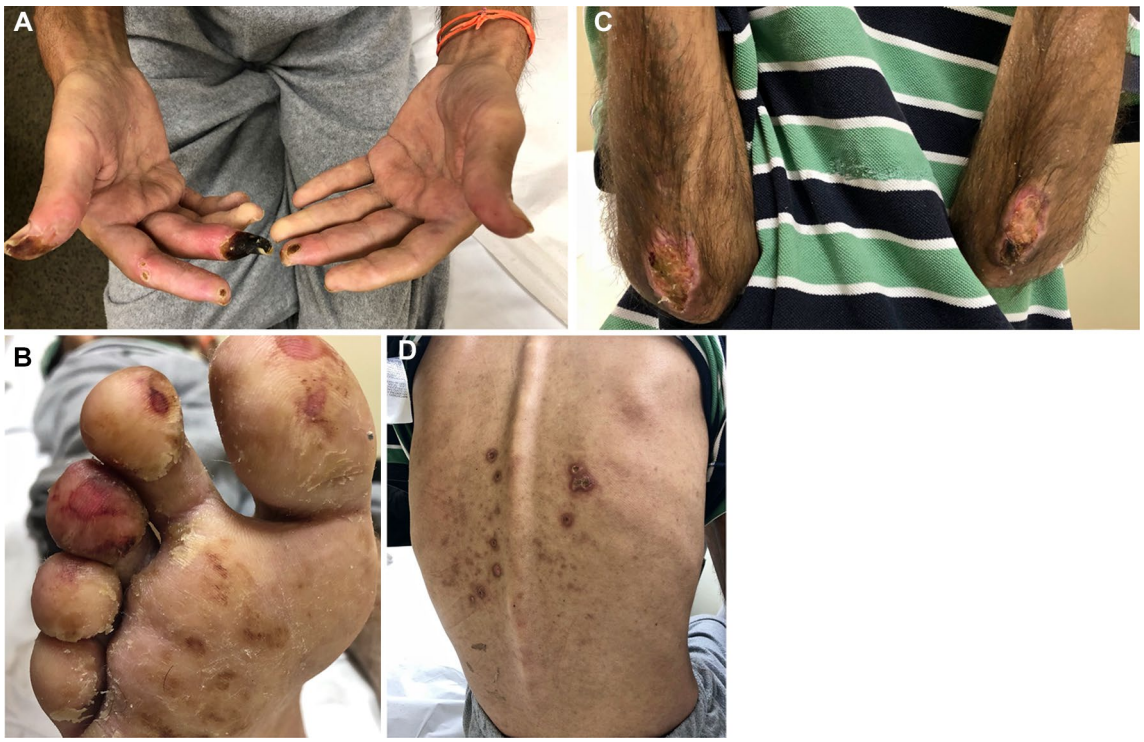

Fig. 2 Patient 2: digital ulcers and fixed cyanosis and necrosis of the third right-hand finger (**a**); multiple digital ulcers in the right foot (**b**); skin ulcers on the elbows **c**; skin ulcers and pigmentary disturbances on the back (**d**)

the American Rheumatism Association (currently American College of Rheumatology). There was no restriction in language for the search.

Discussion

The analysis of these two cases raises the possibility that the previous use of cocaine can act as a trigger for SSc. Nevertheless, many questions are important to discuss regarding this association.

Initially, our revision of literature showed only eight previous cases describing the association of cocaine abuse and SSc. These cases are summarized in Table 1, that also includes the present two cases. The epidemiologic characteristics of these 10 patients showed a predominance of young or middle-aged men without preference for ethnicity or SSc subset. The clinical picture consisted predominantly of vascular involvement (Raynaud's phenomenon, digital ulcers, SRC), without significant esophageal and lung involvement; kidney biopsy confirmed the diagnosis in two of the three cases suggestive of SRC. ANA was positive in seven of nine patients, with a significant predominance of nucleolar pattern (positive in six patients). Specific SSc autoantibodies were rarely positive (one ACA and two anti-Scl70). The time of drug abuse varied; although five patients referred less than 5 years of cocaine abuse, some cases presented long-standing use.

Among the other CTD associated with the use of cocaine, the clinical picture is also characteristically linked to the vascular involvement, similar to that observed in the cocaine-induced SSc. Several case reports described clinical presentations that mimic ANCA-associated vasculitis after cocaine abuse such as idiopathic granulomatosis with polyangiitis (GPA), with cutaneous vasculitis, nasal septal destruction, pauci-immune crescentic glomerulonephritis and detection of cytoplasmic-staining antineutrophil cytoplasmic antibodies (c-ANCA) by immunofluorescence with positive anti-proteinase-3 antibody confirmed by immunoassay [19, 20]. Other patients presented with cerebral angiitis [21], scrotal gangrene [22], urticarial vasculitis [23] and eosinophilic granulomatosis with polyangiitis (EGPA) [24]. In addition, other antibodies such as ANA and antiphospholipid antibodies can be present [25]. The analysis of the cocaine-induced SSc patients corroborated these findings, as the only common clinical characteristic of the whole group was the presence of vascular involvement. Digital ulcers were quite common, including some severe cases, as our second patient.

Among the few patients with SLE associated with the use of cocaine described in the literature, most of them presented nephritis and serositis with positive ANA, and some cases with positive anti-dsDNA [9]. In our second patient, an overlap with SLE was diagnosed, as the patient presented anemia, lymphopenia, positive anti-dsDNA, anti-Sm and lupus anticoagulant, with decreased C3. The possibility of ANCA vasculitis was raised, but ANCA was negative twice. A kidney biopsy was scheduled, but unfortunately the patient died before a complete evaluation was concluded. The death of this patient, although not confirmed by the necroscopic study, is supposed to be associated with intestinal vasculitis leading to a massive GI hemorrhage.

Renal involvement is another presentation of cocaine users. Cocaine has been associated with lesions in several renal compartments, with sporadic reports of cocaine-induced acute interstitial nephritis (AIN) [26–29]. The clinical presentation of AIN can range from asymptomatic oliguria to decline in creatinine clearance, and also fever, rash, malaise, nausea, vomiting, and abdominal pain. The pathophysiology of tubulointerstitial lesion remains unclear, but it is possibly associated with an immunologic disturbance like a delayed hypersensitivity reaction. Due to the heterogeneity of renal involvement induced by cocaine and its histopathologic findings, renal biopsy may be a procedure of great importance for accurate diagnosis, differential diagnosis with other nephropathies and prompt therapy to lower chance for end-stage renal disease [28–31]. In our first patient, it was important to perform a kidney biopsy, which confirmed the diagnosis of SRC. And it is also noteworthy that, although the frequency of SRC is decreasing in the last two decades, it affected three of the ten cocaine-induced SSc patients. Unfortunately, anti-RNA polymerase III, a known marker of SRC, was not performed in any patient.

A very important concern in the cocaine-induced CTD is the fact that it is quite frequent that drug addicts use more than one illicit drug. Other drugs, such as heroin, can be associated with some cases of CTD. And importantly, these illicit drugs are commonly contaminated with other substances, as levamisole. In addition, specific tests for detecting some drug constituents or contaminants are not routinely available or these substances may have short half-life, which makes it difficult to detect, such as the levamisole half-life of 6 h. Levamisole, an immunomodulating compound used as a veterinary antihelminthic and recognized for causing severe side effects, has been used as a cutting agent and to potentiate the psychotropic effect of cocaine by increasing dopamine in the brain [32]. In 2009, almost two-thirds of cocaine samples seized by the US Drug Enforcement Agency were found to be contaminated with levamisole [33]. Recently, many cases where cocaine was contaminated with levamisole were described in the literature and it has been associated with the induction of a wide range of autoimmune syndromes, such as agranulocytosis [34], cutaneous vasculitis [35–38] (commonly leukocytoclastic vasculitis with obliterative small vessel thrombosis), necrotizing ANCA-associated pauci-immune glomerulonephritis [39–41] and positive tests for ANCA, anti-myeloperoxidase antibody,

Table 1 Patients with cocaine-induced scleroderma

	Trozak et al. [10]		Kerr [11]	Kilaru et al. [12]	Lam et al. [13]	Attousi et al. [14]	Axiyan et al. [15]	Bakal et al. [16]	Case 1	Case 2
	1	2	3	4	5	6	7	8	9	10
Sex	M	M	M	M	F	M	M	M	F	M
Ethnicity	W	W	NI	B	NI	B	B	NI	W	B
Current age, years	40	24	27	21	33	46	65	52	24	27
Time of drug abuse, years	3	4–5	9	4	NI	NI	> 20	NI	3	2
SSc clinical variant	lSSc	lSSc	lSSc	lSSc	NI	NI	lSSc	NI	dSSc	lSSc
Modified RSS	NI	NI	NI	NI	NI	NI	NI	NI	15	6
Puffy fingers	+	+	+	+	−	−	−	−	−	−
Sclerodactyly	−	−	+	+	−	+	+	+	+	+
RP	+	+	−	+	+	+	+	+	+	+
Digital tip ulcers	−	−	+	+	−	+	+	+	−	−
Fingertip pitting scars	+	+	+	−	−	−	−	−	−	+
Telangiectasia	+	−	−	−	−	−	−	−	+	
Abnormal NFC	ND	ND	ND	ND	ND	ND	ND	ND	+	ND
Lung involvement										
PAH	−	−	−	−	−	−	−	−	−	−
ILD	−	−	−	−	−	−	+	−	−	−
Esophageal involvement	−	−	−	−	+	+	−	−	+	+
SRC	−	−	−	−	+	+	−	−	+	−
					No renal biopsy	Renal biopsy compatible			Renal biopsy compatible	
ACA	+	−	−	−	−	−	−	NI	−	−
Anti-Scl-70	−	−	+	−	−	−	−	NI	−	+
Anti-RNA polymerase III	ND	ND	ND	ND	ND	ND	ND	NI	ND	ND
ANA	−	1:1280 Nucleolar	1:80 Fine speckled	1:640 Nucleolar	1:160 Nucleolar	1:1280 Nucleolar	−	NI	1:160 Nucleolar	1:1280 Nucleolar

ACA Anticentromere Antibody, *ANA* Antinuclear Antibody, *B* Black, *dSSc* Diffuse Systemic Sclerosis, *F* Female, *ILD* Interstitial Lung Disease, *lSSc* Limited Systemic Sclerosis, *M* Male, *ND* Not Done, *NFC* Nailfold Capillaroscopy, *NI* Not Informed, *PAH* Pulmonary Arterial Hypertension, *RP* Raynaud´s Phenomenon, *RSS* Rodnan Skin Score, *SRC* Scleroderma Renal Crisis, *SSc* Systemic Sclerosis, *W* White

anti-proteinase-3 antibody, antiphospholipid antibodies, including lupus anticoagulant and IgM predominant anti-cardiolipin and anti-beta 2 glycoprotein 1 antibodies, anti-nuclear, and anti-dsDNA antibodies [42, 43].

Positive ANA was a common finding in the cocaine-induced SSc patients, especially with the nucleolar pattern. However, specific SSc autoantibodies were not frequent. Interestingly, a recent revision of 30 patients with vasculitis exposed to cocaine adulterated with levamisole showed a high prevalence of many autoantibodies, as ANCA (85%), lupus anticoagulant (73%), anti-dsDNA (35%), anticardiolipin IgM (24%) and IgG (14%, both with positivity in moderate titers). ANA was also frequent, with titers ranging from 1:40 to 1:1280, although in these cases the most frequent pattern was homogeneous. Other laboratory findings included hypocomplementemia (57%, with isolated low C3 in 47%), anemia (73%), lymphopenia (70%), leukopenia (28%), neutropenia (17%), thrombocytopenia (10%) and hemolytic anemia (10%) [32]. These findings help to explain the clinical and laboratory profile of our second patient, although it was not possible to confirm that the cocaine used by the patient was adulterated.

As there are just a few cases of cocaine-induced CTD, especially SSc, the pathogenesis of this association remains unknown. Nevertheless, recent studies have suggested that the chronic and acute use of cocaine is able to activate specific innate immune response components [44]. There is evidence that the cocaine users have higher serum interleukin-6 (IL-6) levels and lower serum IL-10 levels, when compared to healthy controls [45]. These findings shed light on the critical contribution of IL-6 to the development of tissue fibrosis, inflammation and vasculopathy associated with SSc, being associated with poor prognosis [46]. Other pro-inflammatory cytokines possibly involved in these processes are IL-1β and TNFα, frequently observed in crack abusers; it is important to note that crack is cocaine in its freebase form [47].

Another important aspect of the cocaine-induced SSc is the difficult management of these patients. Important socio-economic concerns, allowed to the severe clinical picture and depression, seem to be associated with this process, as many patients were not adherent to the proposed treatment and were lost to follow-up. We would like to point out our second case, who developed significant and extremely painful skin and digital ulcers and evolved to death due to massive GI hemorrhage in a short period of time.

The hypothesis that SSc can be induced by cocaine has many limitations related to the lack of studies properly conducted evaluating this association beside the complexity of studying autoimmune diseases pathogenesis, in particular SSc. We envision that in patients with a proper genetic background cocaine can be an important trigger for SSc-associated vasculopathy. Regarding the SRC presented by our first patient, there is an uncertainty whether cocaine can lead to vasculopathy itself or even precipitate the SRC in a patient with SSc; in this case, the kidney biopsy findings suggestive of vasculopathy associated with other clinical and laboratory findings of SSc, as the skin thickening (mRSS = 15), digital pitting scars, tendon friction rubs, telangiectasias, pigmentary disturbances, diffuse ectasia of the esophagus, ANA nucleolar pattern, and SD pattern at the nailfold capillaroscopy suggest that the clinical picture of SSc could have been triggered by cocaine. Regarding the severe vasculitis presented by the second patient, ANCA-associated vasculitis was a real suspicion and a common presentation of contamination with levamisole, but ANCA test was negative twice, reinforcing that this clinical picture could be attributable to SSc. We could not do specific anti-MPO and anti-PR3 ELISA for confirmation.

Concluding, although it is not possible to confirm that cocaine abuse is definitely associated with SSc, these two case descriptions and the literature review are important to stress out the fact that cocaine can be an important inducer in a disease with such pathogenesis complexity and multifactorial causes as SSc, as well as shed light to new and potentially important public health consequences of cocaine abuse.

Author contributions RA and LMBS collected the data and provided the photographs, analyzed the results and wrote the manuscript, under the guidance of PDSB; APLA, HCS, and DCOA contributed to the writing and critically reviewed the manuscript; PDSB designed, analyzed the results, critically reviewed the manuscript and wrote the final version. All authors read and approved the final manuscript.

Funding No funding was received for this study.

Compliance with ethical standards

Conflict of interest Dr. Andreussi declares no conflict of interest related to this article. Dr. Bueno Silva declares no conflict of interest related to this article. Dr. Carriço da Silva declares no conflict of interest related to this article. Dr. Luppino-Assad declares no conflict of interest related to this article. Dr. Andrade declares no conflict of interest related to this article. Dr. Sampaio-Barros declares no conflict of interest related to this article.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from the two patients prior to submission of this article for consideration as a case-based review.

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