A case report of pudendal arteries angioplasty with sirolimus drug-coated balloon and drug-eluting stent associated with intracavernous autologous peripheral blood mononuclear cells injection for untreatable vasculogenic erectile dysfunction

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Background
Erectile dysfunction (ED) is a prevalent health problem that seriously impacts men’s quality of life. The potential treatment of ED by percutaneous approach has emerged with valid angiographic results and a significant improvement in symptoms and quality of life. In addition, cell-based regenerative therapies aiming at enhancing neovascularization have been successfully performed with peripheral blood mononuclear cells (PBMNCs) in diabetic patients affected by critical limb ischaemia.

Case summary
We report a case of a young insulin dependent (ID) diabetic patients who suffered of severe vasculogenic erectile dysfunction associated with a poor response for more than 1 year to oral phosphodiesterase-5 inhibitors (PDE5i) and intracavernous (IC) phosphodiesterase type 1 (PDE1) therapy. At selective angiography of the pelvic district, a severe atherosclerotic disease of the internal iliac and pudendal artery was evident with absence of distal vascularization of the cavernous bodies. The patient was treated by mechanical revascularization with drug-coated balloon and drug-eluting stent placement associated with IC injection of autologous PBMNCs. Immediate and 1-year clinical and angiographic follow-up are described.

Discussion
Percutaneous revascularization with drug-coated balloon and drug-eluting stent associated with IC injection of autologous PBMNCs cells injection is a safe and effective procedure to restore normal erectile function in diabetic patients affected by severe vasculogenic ED not responding to conventional oral drug therapies.

Keywords
Erectile dysfunction • Sirolimus-eluting balloon • Autologous peripheral blood mononuclear cells • Case report

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Introduction

Erectile dysfunction (ED) is defined as the recurrent inability to achieve and maintain an erection satisfactory for sexual intercourse. Erectile dysfunction is a prevalent health problem that seriously impacts men’s quality of life and their partners.1 Although the majority of ED patients can be satisfactorily treated with phosphodiesterase type-5 inhibitors (PDE5i),2 these drugs can cause a variety of side effects that make them unsuitable for some patients. Moreover, particular patient subsets, such as those affected by diabetes, are poor responders to PDE5i treatment in more than 40% of cases.3

In this setting, diabetic patients are characterized by a multifactorial disease of sexual function characterized by endothelial cells (ECs) dysfunction, and reduction in cavernous nerves and cavernous smooth muscle cells (CVSMCs) content.4 In these patients, utilization of stem cells has been proposed for ED treatment, based on the hypothesis that transplantation of stem cells into the penis might replenish depleted EC or CSMC content.

Peripheral blood mononuclear cells (PBMNCs) constituted by monocyte/macrophage and lymphocyte populations are known to act as a rich source of paracrine mediators and angiogenic factors, able to create trophic support for neo-endothelium. The role and the efficacy of a cellular therapy with PBMNCs have been documented in diabetic patients with chronic limb ischaemia that was not susceptible to revascularization, with decreased ischaemic pain and significative reduction of minor and major amputations.

It has been demonstrated that mechanical revascularization with drug-coated balloons (DCB) and drug-eluting stents (DES) can significantly improve erectile function in patients not responding anymore to oral phosphodiesterase inhibitors or intracavernous injection of prostaglandins. The first combined treatment (balloon angioplasty with DCB and DES together with intracavernous autologous PBMNCs injection by Hematrate® blood filtration system) is illustrated and described.

Timeline

| Day 1          | May 13, 2019         | ED not responding to PDE5i |
|----------------|----------------------|----------------------------|
| Day 2          | May 14, 2019         | Dynamic Doppler confirming vasculogenic ED |
| Day 3          | May 15, 2019         | Peripheral Angiography + PTA + MNCs injection |
| Day 4          | May 16, 2019         | Discharge |
| Day 35         | June 19, 2019        | MNCs injection |
| 12 Month FU    | July 25, 2020        | Stress Angina Positive Stress test |
| Day 70         | July 24, 2019        | MNCs injection |
| Day 367        | July 26, 2020        | PTCA on LAD + Pudendal control angiography |

Recently, the potential treatment of ED by percutaneous approach has emerged with valid angiographic results and a significant improvement in symptoms and quality of life. A Swiss group reported the 1-year outcomes in 50 consecutive patients affected by erectile dysfunction and internal pudendal artery (IPA)stenosis.8 Patients were treated employing standard balloon angioplasty (16%), drug-coated balloon (DCB, 27%), or drug-eluting stent (DES, 55%) implantation. Procedure success was achieved in 49 (98%) of 50 patients. At 12 months, 30 (65%) of 46 patients achieved a minimum of clinically relevant improvement in the International Index of Erectile Function Questionnaire score (IIEF).8

In this case report, we present to the best of our knowledge, the first combined treatment (balloon angioplasty with DCB and intracavernous autologous PBMNCs injection) in a patient affected by insulin-dependent diabetes mellitus and severe erectile dysfunction related to bilateral atherosclerotic disease. Clinical and angiographic long-term follow-up is described.
Case presentation

A 57-year-old gentleman with a history of active smoking, insulin dependent diabetes mellitus (IDDM), hypertension, dyslipidaemia, and chronic coronary artery disease (CAD), presented complaining of severe ED. He underwent percutaneous coronary intervention (PCI) in 2010 with implantation of three DES on left anterior descending artery, OM1, and right coronary artery. He was asymptomatic for chest pain, and echocardiography demonstrated normal cardiac function. He had normal external genitalia and secondary sexual characteristics. Sexual hormones analyses were in the reference range (total testosterone 7.34 ng/dL; free testosterone 17 pg/mL; sex hormone binding globulin 54 nmol/L; DHEA-S 394 g/dL). Ultrasound evaluation revealed normal prostate. Patient was taking 1 tablet of Bisoprolol 1.25 mg in the morning. He showed no response to increasing doses of different oral PDE5i drugs as well as no response to intra-cavernosal injections to prostaglandin E1 (IC-PDE1) over a 1-year period. Libido was normal. Dynamic Doppler Ultrasound with IC injection of PDE1 (Caverject® 10 mcg and after 10 min additional 10 mcg) showed a peak systolic velocity (PSV) of 12 cm/s on the left cavernosal artery and a PSV of 6 cm/s on the right cavernosal artery suggestive of a bilateral severe vasculogenic ED (normal response after Caverject > 25 cm/s). International Index of Erectile Dysfunction-5 questionnaire (IIEF) score was 3 points (normal 26–30; severe ED 6–10; moderate ED 11–16; mild ED 17–25). Selective angiography showed significant and diffuse atherosclerotic disease of the right mid and distal internal pudendal artery (IPA) associated with absence opacification of distal vascularization of the cavernous bodies and critical stenosis of the left internal iliac artery (IIA) (Figure 1A and D). By utilization of a 6 Fr. left internal mammary guiding catheter (Cordis, Milan, Italy), the left IIA was engaged, and a 0.014” BMW wire (Abbott, Milan, Italy) was utilized to cross the stenosis. After non-compliant 5 mm × 40 mm balloon pre-dilatation at 10 atm (Sequent Neo NC, B.Braun), a self-expandable 6 mm × 18 mm bare-metal stent (Vascuflex® – B.Braun) was precisely placed at the ostium of the vessel with no residual stenosis (Figure 1B). Then, the IPA was engaged, and stenosis crossed by a Sion Blu 0.014” wire (Asahi Intecc Co. Japan) followed by semi-compliant balloon 2.0 mm × 20 mm (Sequent Neo, B. Braun) inflation at 10 atm in the proximal, mid, and distal segments and subsequently by sirolimus-eluting balloon 2.5 mm
× 30 mm inflation (Magic Touch ED, Concept Medical) at proximal and middle segments followed by 2.0 mm × 20 mm sirolimus balloon inflation at the distal segment for 2 min at 8 atm, respectively. After waiting for 10 min to rule out elastic recoil, a 2 × 18 drug-eluting stent (DES; Supraflex Cruz, SMT) was implanted in the mid-segment of the IPA due to >30% residual stenosis with an optimal final acute result at control angiography (Figure 1E). Femoral access was closed by a 6 Fr Angioseal VIP closure device (Terumo Europe).

One hundred and twenty millilitre volume of peripheral blood was utilized to concentrate 12 mL of autologous mononuclear cells by point-of-care device (Hematrate® Blood Filtration System, Cook Regentec), designed to obtain an autologous concentration of mononuclear cells (MNCs) utilizing whole-blood selective filtration (Figure 2A). Mononuclear cells were immediately injected into the cavernous bodies under echo-guidance (Figure 2B). This procedure was repeated at 35 and 70 days after the index procedure, following the same protocol used for critical limb ischaemia non-option patients.6

The patient’s hospital course was without complications. He was discharged with aspirin 100 mg lifelong, clopidogrel 75 mg for 1 year (choice related to the presence of multiple risk factors, previous coronary revascularization and multiple stents placement in the pudendal arteries usually considered a low flow district), rosuvastatin 20 mg, and fenofibrate 200 mg, Tadalafil 5 mg/daily, and vitamin E supplementation. After 3-months from the procedure, the patient reported an excellent response to PDE5i. At 6-month, the patient underwent Dynamic Doppler ultrasound with 10 mcg of IC-PDE1, which showed peak systolic velocity of 27 cm/s on the left and 32 cm/s on the right cavernosal arteries. IEF-5 score was 16 (delta IEF 13), suggestive of an excellent mid-term result. No complication was observed at the site of MNCs injection at the time of out-patient visit. At 1-year follow-up, the patient reported stable improvement in sexual function with an IEF-5 score of 18. He underwent control angiography demonstrating complete stent patency of the left IIA (Figure 1C) and excellent result on the right IPA with a marked increase in vascularization of the distal IPA and common penile artery (Figure 1F and ─arrows).
Discussion

Given the high prevalence of erectile dysfunction in the diabetic male population and the significant psychological impact this symptom has on affected patients, different therapeutic approaches have been proposed. Although the mainstay of all therapies is represented by oral PDE5i in this setting, almost half of patients affected by diabetes do not respond to oral PDE5i treatment. Therefore, mechanical revascularization of the internal pudendal and dorsalis penis arteries has been proposed in patients who are not responsive to oral PDE5i treatment.

In addition, the need to develop a curative treatment for ED that could provide spontaneous unassisted intercourse has stimulated interest in utilizing adjunctive therapeutic modalities. The most futuristic treatment option in the vasculogenic ED is represented by autologous mononuclear cell intracavernous injection to increase the release of angiogenic cytokines within the corporal cavernosa and stimulate neovascularization, as outlined in this case report.

Peripheral blood mononuclear cells (PB-MNCs) concentrated by Hematrate releases angiogenic cytokines including fibroblast growth factor, vascular endothelial growth factor, hepatocyte growth factor, and granulocyte-colony stimulating factor and contains CD34+ endothelial progenitor cells and CD34+KDR+ producing therapeutic angiogenesis in ischaemic tissue. Noteworthy, both PB-MNCs and shockwaves therapy, also used in non-responder patients, showed a common mechanism of action which is the ability to polarize...
inflammatory macrophage (M1) into anti-inflammatory and angiogenic macrophages M2. 

**Conclusion**

Revascularization with DCB and DES associated with IC autologous PBMNC injection is a safe and effective procedure to restore normal erectile function in diabetic patients affected by severe vasculogenic ED not responding to PDE5i therapy. The idea of the PBMNC cell therapy used as adjuvant therapy to revascularization (Figure 3), is based on the focus of trying to solve both the macro-vascular problem and the damaged microcirculation, well described in the diabetic patients. Larger series and future RCT are needed to confirm this preliminary experience.

**Lead author biography**

Dr Sangiorgi was born in Florence on October 4th 1965. He graduated at the University of Rome Tor Vergata in 1990. He is Board Certified in Cardiology (1994) and in Surgical Pathology (1999). He served as a Fellow in Cardiovascular Disease at the Mayo Clinic and Foundation, Rochester, USA from 1991 to 1998. He is currently the Chief of Cardiac Cath Lab of the University of Rome Tor Vergata. He is member of the ESC, SICI-GISE and SCAL. He served as board of Directors in the Italian Society of Interventional Cardiology (GISE). He is also a member of the Working Group on Interventional Cardiology and Coronary Circulation of the ESC. Dr Sangiorgi is author of 380 medical papers in major international peer reviewed journals.

**Supplementary material**

Supplementary material is available at European Heart Journal - Case Reports online.

**Slide sets:** A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

**Consent:** The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

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