

LETTER TO EDITOR

Intratesticular infiltration of platelet-rich plasma, polynucleotides, dermal and adipose cell in secretory azoospermia

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To the Editor,

Regenerative medicine represents an innovative approach to treating chronic-degenerative pathologies. *Mesenchymal stem cells* (MSCs), particularly those derived from adipose tissue, are widely studied for their self-renewal, differentiation, and paracrine activities (1, 2).

Adipose tissue is currently considered a true endocrine organ capable of modulating numerous physiological processes, including male reproductive function (3-11). Recent studies demonstrate that *adipose-derived stem cells* (ADSCs) efficacy is primarily mediated by their secretome – comprising growth factors, cytokines, and exosomes – which promotes angiogenesis and tissue regeneration (4, 7). Furthermore, adipocytes and preadipocytes play a key role in regulating the tissue microenvironment, including specific contexts such as testicular tissue (12). The use of ADSCs has shown emerging applications in treating male infertility due to their regenerative and immunomodulatory properties (13, 14).

The combined use of platelet-rich plasma (PRP) and biomimetic scaffolds, such as polynucleotides, represents an advanced strategy to enhance cell survival and clinical efficacy (3, 5). *Non-obstructive azoospermia* (NOA) is characterized by the absence of spermatozoa in the ejaculate due to impaired production within the testes. Unlike obstructive azoospermia, which results from physical blockages, NOA stems from intrinsic testicular dysfunction (e.g., genetic anomalies like Klinefelter syndrome, hormonal imbalances, or damage from chemotherapy). NOA is a significant cause of male infertility, often presenting with reduced testicular volume and elevated FSH levels. Diagnosis typically involves hormonal profiling, genetic testing, and occasionally testicular biopsy (15).

We treated with autologous regenerative treatment a 34-year-old male patient who presented with a history of recurrent Ewing's sarcoma of the right femur at age 17, after four surgeries and four cycles of adjuvant polychemotherapy (Prot. AIEPISG/SSG III). He had been oncologically clear for a 7-year follow-up. He sought consultation after two years of unsuccessful attempts at conception. Physical examination revealed bilateral testicular hypotrophy, confirmed by ultrasound and color Doppler ("*bilaterally inhomogeneous and hypoechoic testes*"). Two semen analyses confirmed "*Azoospermia*". A subsequent bilateral testicular biopsy confirmed "*Non-obstructive secretory azoospermia*". After informed consent, the patient underwent blood and cell sampling for autologous regenerative treatment (Table 1).

Postoperatively, the patient was asymptomatic (no pain or fever). Testicular ultrasound at 7 days and 1 month post-infiltration showed increased testicular size with bilateral hyperechoic areas of approximately 18 x 22 mm for each testicle (Figures 1, 2).

Semen analysis at 3 months revealed the presence of spermatozoa, classified as cryptozoospermia (extremely rare mature spermatozoa). At 6 months, semen analysis showed alternating results between cryptozoospermia and azoospermia; the patient is currently awaiting potential cryopreservation.

The proposed protocol integrates three fundamental elements:

1. *Mesenchymal Cells*: ADSCs provide regenerative and immunomodulatory effects via their secretome (4, 7).
2. *Platelet-Rich Plasma* (PRP): A concentrated source of growth factors (VEGF, PDGF, EGF) essential for angiogenesis (6).
3. *Polynucleotide Biological Scaffold*: Enhances cell stability, survival, and differentiation.

Table 1.
Study protocol summary.

Category	Protocol Details
Clinical Findings & Diagnosis	Bilateral testicular hypotrophy (confirmed by ultrasound and color Doppler) Two semen analyses confirming "Azoospermia" Bilateral testicular biopsy confirming "Non-obstructive secretory azoospermia"
Materials Used	• Platelet-Rich Plasma (PRP) (Regen Lab) • Polynucleotides (Plinest, Mastelli) • Medigraft System • Liposmart Pure Flow Kit
PRP Preparation	Centrifugation of 20 ml of venous blood for 5 minutes to isolate the platelet concentrate
Dermal Processing	4 mm punch biopsy with mechanical deconstruction and filtration down to 50 microns. • Cell viability: ~85% • Total cells: $\sim 1.5 \times 10^6$ • Stem cells (ASCs): ~5% • Presence of pericytes, endothelial cells, and progenitor cells
Adipose Tissue Processing	Lipoaspiration (50–80 ml) followed by progressive filtration (1200 and 700 microns) to obtain the stromal vascular fraction (SVF)
Injection Procedure	Bilateral injection into the testicular parenchyma in a single "one-step" session. Sequential infiltration using 27-gauge needles: PRP → Polynucleotides (scaffold) → Dermal cell suspension → Pre-adipocytes
Post-Procedure Therapy	Discharge with antibiotic therapy (Ciprofloxacin 500 mg every 12 hours for 7 days) and Paracetamol as needed

Figure 1.
Left testicle.

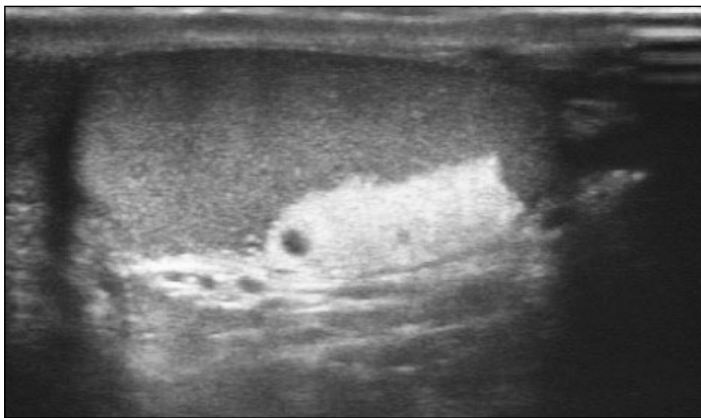


Figure 2.
Right testicle.



Recent literature supports the combined approach (cells + PRP + scaffold) as a cutting-edge strategy in regenerative medicine (3, 5). Furthermore, mechanical processing techniques comply with European regulations regarding "minimal manipulation" (10). Following stem cell injection, a three-month observation period is necessary as spermatogenesis requires approximately 65-70 days. The success rate of this method is inversely proportional to the degree of spermatogenic impairment. While many studies exist in vitro and in animal models (rats, rams, etc.), its application in humans for NOA is a developing frontier (15-23). PRP has been shown to improve sperm quality and facilitate tissue regeneration by reducing oxidative stress and maintaining hormonal balance (23).

This is an "off-label" procedure that is justifiable given the absence of valid, authorized therapeutic alternatives.

The "off-label" treatment is supported by robust evidence documented in national and international scientific literature; it does not constitute unauthorized "experimentation", but rather use in exceptional cases.

Detailed informed consent from the patient and privacy were obtained.

So ethical approval is important but not mandatory, according to current laws and the applications carried out by others, we do not consider the intervention of the ethics committee mandatory because all the procedures performed are permitted and consolidated. In some cases, such as the use of PRP, a communication to the relevant transfusion service is sufficient. The processing of preadipocytes is carried out with "minimum permitted manipulation of filtration".

CONCLUSIONS

The "one-step" sequential intratesticular infiltration of PRP, polynucleotides, and autologous dermal/adipose cells is an innovative, safe, and minimally invasive strategy for tissue regeneration and the reactivation of spermatogenesis in NOA patients. While current evidence shows a high safety profile and promising results, further controlled clinical trials are necessary to confirm long-term efficacy and safety in a larger patient cohort.

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DECLARATIONS

Ethical approval and consent for participate: The use of PRP, polynucleotides, and dermal/adipose-derived cells for tissue regeneration in the EU is regulated according to origin, manipulation, and intended use. Autologous PRP, governed by Directive 2002/98/EC and Italian Legislative Decree 191/2007, is considered a non-transfusional blood component and may be used clinically when obtained through minimal manipulation with CE marked devices; substantial manipulation falls under the Advanced Therapy Medicinal Product (ATMP) framework of Regulation (EC) 1394/2007. Polynucleotides are regulated by the Medical Device Regulation (EU) 2017/745 and classified as Class III medical devices. Dermal and adipose-derived cells are regulated by Directive 2004/23/EC when minimally manipulated, whereas procedures involving enzymatic isolation or cell expansion constitute ATMPs, requiring GMP manufacturing and AIFA authorization or Hospital Exemption.

This is an "off-label" procedure that is justifiable given the absence of valid, authorized therapeutic alternatives. The "off-label" treatment is supported by robust evidence documented in national and international scientific literature; it does not constitute unauthorized "experimentation," but rather use in exceptional cases. So ethical approval is important but not mandatory. According to current laws and the applications carried out by others, we do not consider the intervention of the ethic committee mandatory because all the procedures performed are permitted and consolidated. In some cases, such as the use of PRP, communication to the relevant transfusion service is sufficient. The processing of preadipocytes is carried out with minimum permitted manipulation of filtration. Detailed informed consent from the patient and privacy were obtained.

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