POST-SURGERY NECROSIS
of the nipple-areola complex treated with intensive oxygen-ozone therapy. A case report.

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ABSTRACT
The partial or total necrosis of the nipple-areola complex (NAC) is a not rare complication of nipple-sparing mastectomy (NSM) after breast cancer surgical treatment. In order to repair the defects dressing changes, debridement, skin grafting or implants have been proposed. On this background “biologically active oxygen” administrated either locally or systemically as hyperbaric oxygen or oxygen-ozone therapy appears an attractive, safe and potentially useful approach to improve the results of conventional treatments. Indeed “biologically active oxygen” was shown to favour healing processes due to its ability to control infections and to stimulate regenerative processes. Based on our personal experience in the field as well as on the available scientific literature we describe herein a successful case report of NAC necrosis that occurred in a 50-years old women three days after NSM. We treated the patient with a combined, local and systemic, approach of oxygen-ozone therapy. The healing was completed after 16 weeks. The procedure was safe and well tolerated. Although some evident limitations the study supports the potentially usefulness of oxygen-ozone therapy in NAC necrosis treatment.

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Background

The nipple is one of the key defining visual features of a breast: the surgical removal of the nipple-areola complex (NAC) in a woman due to radical mastectomy for cancer treatment causes the loss of the point in the profile at which the most natural convexity of breast occurs thus rising psychological and relationship problems (1). In order to prevent such unwanted side effect without compromising the surgical intervention efficacy more than 30 years ago nipple-sparing mastectomy (NSM) with immediate breast reconstruction allowed replace conventional radical surgery for the treatment of selected patients suffering from breast cancer (2) thus improving their satisfaction (3). Indeed preserving the NAC not only helps to prevent the above reported problems but also eliminates the need for staged nipple reconstruction and areola tattooing, after which there can be loss of projection and fading over time, respectively (4). However NSM still remains a difficult technique because after dissection, the remaining breast skin and nipple-areola complex (NAC) must be thin enough to be free of neoplastic tissue and thick enough to preserve tissue perfusion (5). Therefore one of the most common complications of NSM – accounting for 0 to 20% of all cases (6) – is the partial or total NAC necrosis, a condition that negatively affects cosmetic results (7, 8). Superficial skin loss can recover spontaneously but full-thickness skin loss can result in infection and eventual prosthesis loss (6). Obesity, cigarette smoking, incision type, flap thickness, and preoperative irradiation are the most common risk factors for loss of breast skin (9) while pre-operative vascular assessment by nuclear magnetic imaging can be helpful in the risk assessment (10).

Once NAC necrosis occurs after NSM, surgical procedures are often performed to repair the defects that can be resolved with dressing changes, debridement, skin grafting or implants (7, 11, 12).

In such context it is reasonable that – despite the absence of clear clinical evidence – an additional and safe procedure aimed to favour the regeneration of soft tissues can be of support to the conventional treatment of NAC necrosis as optimisation of cosmetic result and/or fastness of recovery.

Among such procedures are hyperbaric oxygen therapy and oxygen-ozone therapy. This latter (as such or in the form of ozonised oil/water or other devices) due to its general safety, tolerability and efficacy in tissue repair and regeneration has been applied – although its exact biochemical mechanism is not completely clear (13) – either locally or systemically (intravenously e.g. as major ozonated autohemotherapy or by rectal insufflation) in breast diseases with different purposes (14, 15) thus mimicking some favourable previously demonstrated effects of hyperbaric oxygen therapy on NSM (16-18). On this basis we applied a specific protocol of oxygen-ozone therapy in a case of NAC necrosis.

Case presentation

In December 2014, a 50-year-old woman was admitted to our medical centre with a diagnosis of NAC necrosis following breast surgery. Three days before the patient had undergone surgery for breast augmentation. During the intervention, aimed by aesthetic purposes, the surgeon had found in the context of breast tissues a lipoma showing the size of a tangerine located into the inferior-medial quadrant of the left breast. He had decided right away to remove the mass. Following the appearance of NAC necrosis the surgeon decided to send the patient to our observation just three days after the surgical intervention. Our team confirmed the diagnosis of NAC necrosis. Indeed the interested area showed a blackish appearance and resulted insensitive to the needle pricking (Figure 1). The woman had not significant history for diseases but was on overweight and smoker. After collecting clinical history data we visited the patients who undergo to conventional chest radiography, electrocardiography, and common blood/urine laboratory analyses in order to exclude any possible contra-indication to the planned treatment. According to the pooled data the patient was considered as good candidate to our protocol of oxygen-ozone therapy.

Figure 1.
Nipple-areola complex necrosis. The lesion occurred in a 50-years old woman, after three days after nipple-sparing mastectomy. The interested area showed a blackish appearance and resulted insensitive to the needle pricking.
**Therapeutic approach**

After obtaining the informed consent we performed on the patient to an original protocol based on the combination of local and systemic oxygen-ozone treatment (Medozon Compact, Herrmann Apparatebau, Elsenfeld, Germany). Local oxygen-ozone administration was done as mesotherapy by injecting 20 mL of a 10% oxygen-ozone mixture in saline solution in the nipple’s area. Then the wound was medicated daily with 10% iodopovidone (Betadine™, Meda Pharma S.p.A, Milan, Italy) and sterile gauze. Systemic oxygen-ozone was performed injecting intravenously 250 mL of a 30% oxygen-ozone mixture in saline solution (8 mL per minute). At the end of therapeutic seat an association of amoxicillin with clavulanic acid was prescribed daily (1 g three times a day) for 5 days in order to prevent any eventual bacterial complication. The protocol was repeated two times for week in the first six weeks and then once weekly in the next four weeks.

**Results**

In the period of treatment the healing process was slow but constant: the fourth therapeutic seat (i.e. at the end of second week) the nipple started to bleed and the patient experienced a partial recovery of the sensitivity to needle pricking (Figure 2). After 12 weeks the necrotic nipple was transformed to eschar and then released from breast tissues spontaneously thus exposing an apparently health skin showing a normal sensitivity (Figure 3). During the whole period of treatment the patient was cooperative, adhered to the protocol and did not experience any significant disturb or compliant.

**Discussion and conclusions**

The NAC necrosis is a frequent complication NSM often causing complains due to its impact on aesthetic and breast functions as well as on psychological/social domains of women (4–6). Often described after cancer therapy in our case the necrosis followed the excision of a lipoma that was surprisingly not detected during the preliminary ultrasound examination before the breast augmentation procedure. May be that a preliminary accurate assessment (NMR?) (10) as well as a ultrasound analysis could have revealed the lipoma before surgery thus allowing the surgeon to plan better the intervention and prevent such unwanted side effect. On the other hand the patient was at risk for NAC necrosis being either in overweight and smoker (6).

In order to avoid the undesired pathophysiological, psychological and social burden of NAC necrosis the surgeon must follow firstly the guidelines if available or the good practice in order to warrant a health, fast and safe anatomical and/or functional recovery of injured breast tissues. In our case we followed the conventional protocol of treatment but recognising that the substance leakage did not require a skin graft we applied to the simple cleaning and disinfection of the wound under antibiotic systemic covering an additional, local and systemic, protocol of oxygen-ozone therapy. Indeed ozone therapy showed great usefulness especially in the management of pain or infections, due to its immune-stimulating, antimicrobial and analgesic effects (19–22). Moreover either in animal models (23–25) or in human diseases, like diabetic foot (26, 27), including skin disorders (28) ozone was able to activate regenerative processes may be by modulating cell structure and functions (29) through reactive oxidising species (13) thus favouring wound healing processes (30).

In our hand this protocol allowed to reach a satisfying result without any additional surgical intervention or drug

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**Figure 2.**
Nipple-areola complex necrosis after local and systemic oxygen-ozone therapy. Appearance of the lesion at the end of second week (A) and at the end of third week (B).

**Figure 3.**
Nipple-areola complex necrosis after local and systemic oxygen-ozone therapy. Appearance of the lesion at the end of twelfth week (A) and at the end of sixteenth week (B).
treatment thus suggesting the ability of herein used gaseous mixture to work “physiologically”. This was evidenced by the absence of any unwanted side effect.

This case report suggest that a locally and systemic combined oxygen–ozone therapy can be of support to the wound healing after NAC necrosis, a condition that complicates 4.8% of all NSM interventions in Italy (31).

However some limitations affecting our work and in particular the impossibility to make a comparison of such treatment with other treatments; moreover the lack of both histological examination and oxidative stress biomarkers assessment (32) made almost impossible to establish the eventual mechanism underlying the observed effect; furthermore the patient did not report any eventual changes on lifestyle occurring during the treatment thus impeding us to evaluate the possible impact of other variables on the results.

Despite such evident limitations this case report can be a possible base for future research aimed to find more physiological safe and fast treatment of NAC necrosis.

References