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Persistent PORT-A-CATH®-Related Fistula and Fibrosis in a Breast Cancer Patient Successfully Treated With Local Ozone Application

To the Editor:

Persistent and delayed healing of fistulae and local infection in previously irradiated areas can increase the risk of systemic complications and complicated clinical management. Cancer patients have impaired immune systems secondary to the tumor or oncology treatments; this impairment decreases spontaneous healing. Surgical options are often associated with adverse side effects together with an increased risk of further delay in wound healing. Hyperbaric chambers have been used to treat delayed wound healing and several radiation-induced side effects.¹ However, this technique is cumbersome and with limited accessibility. Additionally, treatment and assessment of radiation-induced subcutaneous fibrosis has had limited success. We describe a case of a persistent fistula in a previously irradiated area, which was refractory to treatment but which was successfully treated with local ozone applications. The potential role of spectroscopy analysis imaging for objective assessment of subcutaneous fibrosis was demonstrated.

Case

A 46-year-old woman was admitted to our hospital for evaluation of a persistent fistula and leakage secondary to a PORT-A-CATH® (Smiths Medical, St. Paul, MN) inserted in a previously irradiated area. She had been diagnosed three years earlier with right-sided, locally advanced, breast carcinoma (infiltrating ductal carcinoma, T4bN1M0 Stage). She was treated with systemic chemotherapy (fluorouracil, epirubicin, cyclophosphamide, and docetaxel). The tumor decrease was >50% (partial response). She underwent a modified radical mastectomy followed by radiotherapy:

Preliminary data from this study have been presented as invited lectures at the International Meeting of Ozone Therapy Schools, Royal Academy of Medicine, Madrid, Spain in June 2010 and the III Meeting of the World Federation of Oxygen-Ozone Therapy, Brescia, Italy in April 2011.

54 Gy at 2 Gy/day on chest wall, axillar, supra- and infraclavicular areas. Radiotherapy was well tolerated, with some areas of dermatitis Grade II. She proceeded on to hormonal therapy with tamoxifen. Local recurrence in the chest wall occurred two years after the initial diagnosis. A PORT-A-CATH® for chemotherapy administration was inserted in the right infraclavicular area, which had received the radiotherapy. Since insertion, the patient presented with a persistent subcutaneous peri-catheter fistula with continuous leakage, intermittently purulent. The catheter was removed five months later when second-line chemotherapy was concluded (13 cycles of paclitaxel, gemcitabine, and bevacizumab). Fistula and leakage continued uninterrupted during this period and persisted even after the PORT-A-CATH® was removed and several specific antibiotics were administered. The patient reported progressive subcutaneous fibrosis and a decrease in her quality of life secondary to these ongoing symptoms and moderate persistent local pain. She was admitted to our hospital for evaluation of specific treatment four months after the catheter removal (nine months after the fistula was noticeable with its accompanying leakage).

Pretreatment physical examination revealed a hyperpigmented fibrosis plaque in the right infraclavicular area, in the catheter bed. Palpable subcutaneous induration measured 20 × 15 mm, with a fistulous cavity of 2 mm diameter and 25 mm depth. Leakage persisted and needed to be swabbed several times per day, every day (Fig. 1, upper left).

Informed consent was obtained before the commencement of treatment. Ozone therapy was done by insufflations of an O₃/O₂ gas mixture (100 µg/ml) through the fistulous cavity and multiple (four to six) infiltrations distributed around the fibrous induration (6–10 ml of O₃/O₂ gas mixture at 14 µg/ml in each infiltration point). Ozone sessions included 15 minutes of soft vacuum on the fibrosis area.

Spectroscopy analysis was performed using a tissue viability imaging system (TiVi) (TiVi600, Wheels Bridge AB, Linköping, Sweden). It is based on linearly polarized white light, which is partly reflected by the upper layer of the skin and partly diffusely scattered in the deeper dermal layers. This technique generates an image that depends on red blood cell content in the dermal microvascular bed (depth of sampling is about 400–500 µm).² The TiVi device takes a standard photograph and automatically

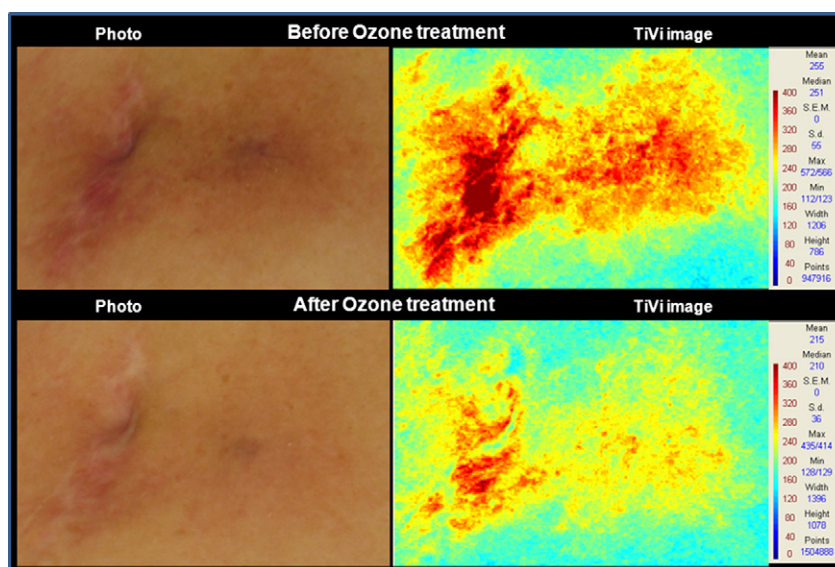


Fig. 1. Details of photograph (left) and objective quantification simultaneously obtained by spectroscopy analysis using linearly polarized light (right). Black areas are with higher red cell content in the dermal micro-vascular bed; in this case related to blood-flow stasis in the fibrosis area. Upper panel: before ozone therapy. Lower panel: after ozone therapy.

performs a reproducible assessment according to the signal properties analyzed. TiVi imaging was performed pre- and post-treatment with ozone.

After two ozone insufflation treatments over two weeks, the fistulous cavity partially closed and the leakage became intermittent. Follow-up treatment was subcutaneous infiltration in the area of fibrosis alone. After the fifth session at the end of five weeks, the leakage disappeared and the fistulous cavity closed completely. The six initial sessions were one per week. The patient was living on another of the Canary Islands and to save traveling time and costs, and because there was clear objective improvement, the seventh session was two weeks later and the eighth session was one month later. Hence, after eight ozone sessions over 12 weeks, the treatment was concluded. Local pain and symptoms had noticeably decreased by the end of ozone therapy, and subcutaneous induration was lower (10×15 mm) and more superficial than initially (Fig. 1, lower left).

Objective quantification using TiVi imaging pre- and post-treatment showed a measurable decrease in blood flow stasis in the fibrosis area (from 255 ± 5 to 215 ± 36 TiVi units, 19%; $P < 0.001$), that is, blood flow in the skin in the fibrosis area was more similar to blood flow in skin areas without fibrosis. There was a similar decrease in the area of the fistulous cavity (from 335 ± 56 to 273 ± 37 TiVi units; $P < 0.001$) (Fig. 1, upper and lower right).

Comment

Subcutaneous PORT-A-CATH®s are widely used to facilitate chemotherapy administration. Anatomically, the placement is technically easier and with lower risk in the right rather than left infraclavicular area. However, irradiated areas have an increased risk of delayed healing and morbidity after local invasive procedures. Often, it is not necessary to administer special pharmacotherapeutic agents but, occasionally, delayed healing can be persistent and debilitating. As with other refractory radiation-related side effects, the most used nonsurgical approach is treatment with hyperbaric chambers.¹ However, the accessibility of the equipment is limited and was unavailable in our center. The surgical approach for

this problem should include block resection of the fibrotic area within the widely irradiated area. Often the consequence is increased morbidity and potential risk of further delay in wound healing.

Our patient was referred to our hospital for ozone therapy because of our previous experience in treating side effects of oncology therapy.^{3,4} We have described the effect of this technique in improving blood flow^{4,5} and tissue oxygenation,⁶ both of which are decreased in radiation-induced fibrosis. Additionally, the antimicrobial properties of ozone augur well for complementary management of the documented infection associated with drained fluid.^{7,8} Based on the mechanism of action of different treatments proposed for radiation-related fistula/fibrosis,⁹ other properties ascribed to ozone therapy can be of additional clinical value, such as immunomodulation,⁸ anti-inflammatory effects through phospholipase A2 decrease,¹⁰ and an enhanced antioxidant system.^{8,10}

In our patient, physical examination (palpation) showed a decrease in the surface dimension of fibrosis and the level of induration. However, these assessments often seem imprecise and subjective. TiVi (Fig. 1, upper and lower right) is noninvasive and highly reproducible. In our patient, changes measured with this technique pre- and post-ozone treatment provided more objective assessment of the changes than palpation, that is, decrease in thickness and dimensions of the induration/fibrosis area.

In conclusion, management of refractory fistulae and fibrosis in previously irradiated areas can be difficult. Local treatment with ozone can be easy and effective especially when more standard treatments are unsuccessful or are not available. Tissue viability imaging using linearly polarized light can be a very useful tool for objective assessment and follow-up of fibrosis.

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Persistent Hiccups: An Unusual Presentation and Treatment

To the Editor:

Hiccups are defined as sudden, involuntary, spasmodic contractions of the diaphragm and external intercostal muscles that result in inspiration that ends abruptly with the closure of the glottis. The innervation of the hiccup reflex includes an afferent pathway via the vagus, phrenic, and sympathetic branches of T6–T12 and the efferent pathway via the phrenic nerve to the diaphragm, glottis, and external intercostal muscles.^{1,2} Hiccups can result from direct injury to the reflex arc or any underlying disease, including injury, irritation, or inflammation affecting one of the nerves involved in the reflex arc.³ The sudden closure of the glottis results in the “hic” sound,⁴ and the upward-jerking motion probably makes up the second part of the word.

Although hiccups do not seem to play a positive physiologic role, there are thousands of etiologies for hiccups reported in the literature and thousands of home and medical remedies to cure to them. The most commonly accepted causes for hiccups include distension of the esophagus