

Letter

Persistent *portacath*-related fistula and fibrosis in a breast cancer patient successfully treated with local ozone application

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Running head: Fistula, fibrosis and ozone therapy

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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 an impaired immune system secondary to the tumour or to the oncology treatments which decrease 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 as well as 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, here, 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 *portacath* inserted in a previously-irradiated area. She was diagnosed 3 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 tumour decrease was >50% (partial response). She underwent modified radical mastectomy followed by radiotherapy: 54 Gy at 2Gy/day on chest wall, axilar, supra- and infra-clavicular areas. Radiotherapy was well tolerated, with some areas of dermatitis G-II.

She proceeded on to hormonal therapy with tamoxifen. Local recurrence occurred in chest wall 2 years after the initial diagnosis. A *portacath* for chemotherapy administration was inserted in the right infra-clavicular area, which had received the radiotherapy. Since then, the patient presented persistent subcutaneous peri-catheter fistulae with continuous leakage, intermittently purulent. The catheter was removed 5 months later when second-line chemotherapy was concluded (13 cycles of paclitaxel, gemcitabine and bevacizumab). Fistula and leakage continued uninterrupted over all of this period and persisted even after the *portacath* had been removed and several specific antibiotics administered. The patient reported progressive subcutaneous-fibrosis and decrease in her quality-of-life secondary to these persistent symptoms, as well as moderate persistent local pain. She was admitted to our hospital for evaluation of specific treatment four months after the catheter removal (9 months after the fistula was noticeable with its accompanying leakage).

Pre-treatment physical examination revealed a hyperpigmented fibrosis-plaque in the right infra-clavicular area, in the catheter-bed. Palpable subcutaneous-induration measured 20 x 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 *Left, Upper*).

Informed consent was obtained before the commencement of treatment. Ozone therapy was by insufflations of O₃/O₂ gas mixture (100 µg/ml) through the fistulous cavity and multiple, 4-6 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 polarised 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 which depends on red blood cell content in the dermal micro-vascular bed (depth of sampling is about 400-500 µm) (2). The TiVi device takes a standard photograph and automatically performs a reproducible assessment according the signal-properties analysed. TiVi imaging was performed pre- and post-treatment with ozone.

After 2 ozone-insufflation treatments over 2 weeks the fistulous cavity closed partially and leakage became intermittent. Follow-up treatment was subcutaneous infiltration in the area of fibrosis alone. After the 5th session at the end of 5 weeks, the leakage disappeared and the fistulous cavity closed completely. The 6 initial sessions were 1/week. The patient was living in another of the Canary Islands and to save travelling and since there was clear objective improvement, the 7th session was 2 weeks later, and the 8th session was 1 month later. Hence, after 8 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 x 15 mm) and more superficial than initially (Fig. 1 *Left, Lower*).

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) i.e. 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 *Right, Upper and Lower*).

Comment

Subcutaneous *portacath* is widely used to facilitate chemotherapy administration. Anatomically, the placement is technically easier and with lower risk in the right rather than left infra-clavicular area. However, irradiated areas have an increased risk of delayed healing and morbidity following 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 non-surgical approach is treatment with hyperbaric chambers (1). However the accessibility of the equipment is limited, and unavailable in our centre. 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 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 as: immunomodulation (8), anti-inflammatory effects through phospholipase A2 decrease (10) and enhanced antioxidant system (8,10).

In our patient, physical examination (palpation) showed a decrease in the surface-dimension of fibrosis and level of induration. However, these assessments often seem imprecise and subjective. TiVi (Fig. 1 *Right, Upper and Lower*) is non-invasive 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 i.e. 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 polarised light can be a very useful tool for objective assessment and follow-up of fibrosis.

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Figure 1

Details of photograph (*Left*) and objective quantification simultaneously obtained by spectroscopy analysis using linearly polarised light (*Right*). Red colour shows areas with higher red cell content in the dermal micro-vascular bed, in this case related with blood-flow stasis in the fibrosis-area. *Upper*: Before ozone therapy. *Lower*: After Ozone therapy.

