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Single Case

Treatment of Cutaneous Neurofibromas in Patients with Neurofibromatosis Type 1

Bartosz Wozniak[a, b] Torsten Bove[c] Tomasz Zawada[c] Jacek Calik[b, d]

[a]Department of Dermatology and Venereology, Regional Specialist Hospital, Wroclaw, Poland; [b]Old Town Clinic, Wroclaw, Poland; [c]TOOsonix A/S, Hoersholm, Denmark; [d]Department of Oncology, Academic Hospital Wroclaw, Wroclaw, Poland

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Cutaneous neurofibroma · Neurofibromatosis · Neurofibromatosis type 1 · Dermatology · High-intensity focused ultrasound · Focused ultrasound

Abstract
Neurofibromatosis type 1 is a genetic disorder impacting approximately 2.5 million people worldwide, often leading to development of numerous benign yet disfiguring cutaneous neurofibromas (cNF). Removal of cNF is limited to excision or laser ablation with common post-operation complications and scarring. The current case explores a new approach to removal or reduction of cNF by a minimally invasive and pain-reduced treatment modality. A 40-year-old female patient with numerous cNF across her body underwent a single treatment using a 20 MHz dermatologically focused ultrasound device on seven selected cNF on the upper back. Each cNF was treated in a single session of 20–60 s without anesthesia due to manageable pain. Only one minimal adverse reaction in the form of dyspigmentation in a single treated tumor was noted from treatment or during the healing of a thin scab that formed on each cNF a few days after treatment. At the 12-month follow-up, four out of seven treated cNF showed full remission, two showed partial or significant reduction in tumor volume, while two did not respond to treatment. The reason for the variability is not fully understood, but speculations include difference in tissue content, e.g., due to tumor age. The method is concluded to be a promising candidate for a new safe and minimally invasive treatment that can potentially be used for single-session removal/reduction of a large number of cNF. Further research should focus on refining treatment parameters and strategies to enhance response predictability.

Correspondence to:
Torsten Bove, torsten.bove@toosonix.com

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Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder that is caused by a mutation in, or a deletion of, the tumor suppressor neurofibromin gene NF1. The condition affects 1 in 1,900–3,500, and it is estimated that about 2.5 million people worldwide are affected relatively evenly distributed among gender and ethnicity [1, 2]. Serious clinical manifestations of NF1 include optic pathway glioma, bone dysplasia, and significantly increased risks of certain cancers, including female breast cancer, malignant peripheral nerve sheath tumors, and brain tumors [1, 3]. The disorder is therefore associated with an overall 8–15-year reduction in average life expectancy in both men and women [1].

A further feature that affects the majority of NF1 patients is the development of cutaneous neurofibromas (cNF). cNF occur along the peripheral nerves beneath the skin surface. The tumors are benign and composed of multiple cell types including Schwann cells, fibroblasts, immune cells (such as mast cells and macrophages) and other elements of the nerve [2, 4]. Clinically they present as cutaneous lesions ranging from small nascent and sessile bumps barely visible or palpable on the surface of the skin to large, well-defined globular and pedunculated soft tumors up to a few cm in diameter [2, 4]. cNF start appearing from childhood, and often continue with development of hundreds, or even thousands, of tumors covering all parts of the body in late adulthood [3, 5]. Although these tumors do not have a known potential for malignant transformation, and thus are not life-threatening, they are the main NF1-associated health problem for most adult patients. Minor local clinical complications, such as pain, itching, and ulceration (e.g., from tumors entangled in clothing) are common, but the conspicuous nature and a perception of being aesthetically disfigured are the overwhelming problems reported by patients. This issue often leads to social isolation and a significantly decreased quality of life [4, 5].

Despite the obvious clinical relevance, there are no medical treatments available for removal or prevention of cNF today. In practice, options for removal are therefore limited to surgical or electrosurgical excision, or various ablative laser treatments. In particular, ablative CO_2 lasers and Nd:YAG lasers have proven to yield good results with reasonable patient satisfaction. Limiting factors for all existing methods are however that they rely on local anesthesia and creation of an open wound. Post-operation complications from sutures (surgical excision), infections, and general pain during healing are therefore common, and post-operation scarring is inevitable [5, 6]. The current case study aims to investigate a new modality for removal or reduction of cNF that has a more favorable overall balance between safety, efficacy, cost, and esthetic outcome.

The proposed treatment uses a high-intensity focused ultrasound (HIFU) device (System ONE-M®, TOOsonix A/S, Hoersholm, Denmark). The device targets features in the dermis and epidermis, and reproducibly delivers a clinically efficient thermal and mechanical insult. Each dose induces a localized heating to approximately 60–65°C that will induce cell necrosis and denaturate fibrous tissue. By choosing a handpiece for the device, where the insult is applied in the same depth as the bulk of the cNF, a noninvasive or minimally invasive treatment for removal or reduction of cNF is therefore hypothesized. The device is shown in Figure 1.

During HFU treatment and during the subsequent healing period, some local reaction at treated sites is inherent to the mechanical and thermal insult dosed directly to the skin. Efficient cNF destruction or reduction by HIFU is related to various inflammatory responses, whereby weal-and-flare, edema, and erythema are considered as expected treatment-associated side effects. Long-term effects, such as infection, scarring, and chronic dyspigmentation are in contrast non-intended and must therefore be characterized as adverse events.

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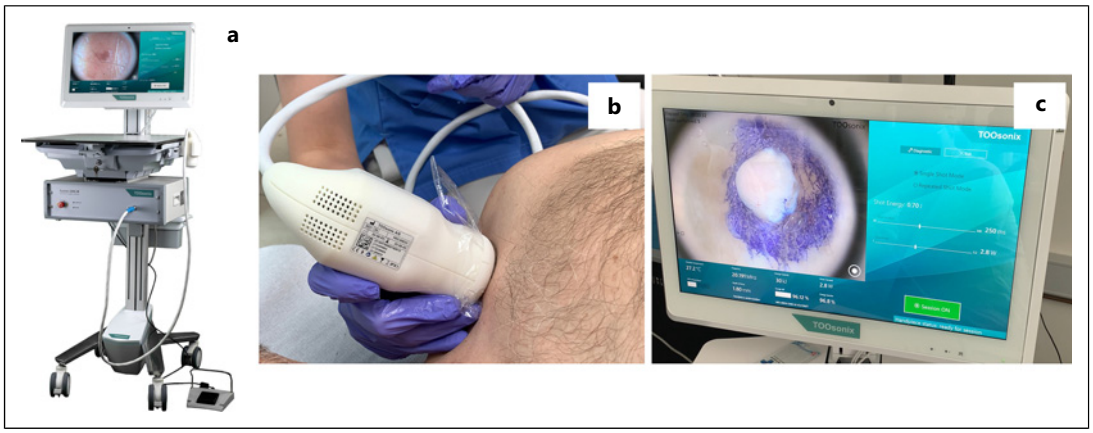

Fig. 1. Device used for treatment of cNF. **a** TOOsonix System ONE-M focused ultrasound device operating at 20 MHz. Handpieces with different focal depths can be connected to system, providing focused acoustic energy delivery to a selected maximum depth ranging from the epidermis to mid-dermis. **b** Handpiece applied perpendicular to the skin surface under treatment. **c** Example of user interface when handpiece is placed on a globular cNF outlined with a pen marker. Live video-feed provides visual guidance during treatment. A red crosshair on the screen indicates the accurate target location for the acoustic energy delivery below the skin surface.

The device has earlier been demonstrated to provide safe and efficient treatment of other dermatological conditions, including basal cell carcinoma and Kaposi's sarcoma [7], actinic keratosis [7, 8], seborrheic keratosis [9], superficial vascular tumors [10], and various papillomavirus [11, 12]. Pain levels have been reported to be tolerable without anesthetics, typically with a pain score around 3–6 on a 0–10 numerical rating scale. Likewise, side effects during post-operation healing have generally been very mild, without need for special precautions or wound care outside normal hygienic practices. After treatment, patients are therefore advised to clean the treated area(s) regularly as a part of their normal bathing routine and potentially apply moisturizing cream to soften scabs and thereby prevent early unwanted removal/release.

No adverse events have been reported during any of the above treatments. The method therefore offers a potential to perform a relatively simple treatment to a large number of cNF distributed over an entire body in a single session without pre- or post-operation complications. The CARE Checklist was completed by the authors for this case report and attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534270).

Case Presentation

The patient, a 40-year-old female, was admitted to the clinic due to hundreds of cutaneous tumors covering her entire body. Positive germline testing for NF1 was conducted at the age of 12 years, with gradual development of the large number of cNF and other characteristic clinical symptoms of the condition, such as freckling in skin folds and café-au-lait macules [13]. Over several years, removal of problematic cNF on the arms, legs, and torso has been performed by surgical excision, ablative laser therapy, and electrocautery. These procedures were generally not satisfactory for the patient due to pain, scarring, and prolonged healing time.

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Since the aesthetic outcome and post-operational function/limitations were considered important aspects for the patient, and due to the relative benign nature of cNF, the patient was actively requesting possible alternative treatment options. Based on the small size of each individual cNF combined with the expectation for low pain during the procedure and no downtime following treatment, it was agreed to test the 20 MHz dermatologically focused ultrasound device described above.

Seven cNF on the upper back were chosen for an initial test treatment. The selected cNF were 5–15 mm in diameter with clearly visible vertical growth, thus classifying them as globular and/or pedunculated according to [4, 5]. These kinds of lesions were reported by the patient as the most disturbing in her everyday life. All the included cNF were evaluated clinically and with dermoscopy using a digital dermoscope (FotoFinder Medicam 1000®, FotoFinder Systems GmbH, Bad Birnbach, Germany). Macroscopic and dermoscopy pictures were taken before the procedure.

Due to the typical location of cNF in the mid-dermis, a handpiece with a nominal focal depth of 2.3 mm was used for all treated cNFs, thus selecting the deepest available standard focal depth delivered with the system. A single treatment was performed on the selected tumors by initially outlining each cNF with a permanent pen. Standard ultrasound gel (Aquasonic 100®, Parker Laboratories Inc., NJ, USA) was applied on the target area to provide acoustic coupling between the handpiece and skin. "Shoulder-by-shoulder" HIFU doses of 1.2 J/dose at durations of 150 ms/dose were administered by systematically moving the handpiece in steps of approximately 1 mm (e.g., in a spiral from the center of the cNF) before activation of each dose via a footswitch. The treatment was considered complete when the full cNF including a small margin of approximately 1 mm had been covered by HIFU doses. The manual positioning of each dose could be monitored accurately in real-time via an integrated dermoscope in the handpiece, providing a high-resolution video-feed to the screen of the system, and individual doses could typically be observed as small contractions of the skin surface. Doses were repeated at an interval of approximately 1 s. No pre-treatment topical or intralesional anesthesia was used. The highest reported pain during the procedure was 5 on a 0–10 numerical rating scale. Follow-up visits were conducted after 3 and 12 months.

During the visits, the patient reported very mild side effects from treatment with development of thin scabs in all treated areas that resolved after approximately 2 weeks. The treated areas were however not painful, and no liquid discharge, ulcerations, bruising, infections, or other side effects were noted. During the period after the scabs were discharged, some inflammatory redness could be observed, which gradually faded over the following months, and presented similar to the surrounding skin at the 12-month follow-up. One treated tumor (T7) exhibited hyperpigmentation in the periphery of the treatment area, while the central area had tendency for hypopigmentation. No other adverse events were reported.

Figure 2 shows the area of the upper back of the patient before treatment and after 12 months. The numerous cNF and post-operation scarring from previous surgical and laser treatments are clearly observed.

Figure 3 shows examples of dermoscopic pictures of treated tumors before treatment and after 12 months. Each tumor was assessed by the clinician and rated by its clinical size and appearance compared to baseline. Assessment of tumor reduction was done on a descriptive scale (increased size, no response, partial reduction, significant reduction, complete remission). Of the seven treated tumors, three had complete remission. Two had significant or partial reduction, and thereby still visible tumor volume above the normal skin surface. Two treated tumors showed no response to treatment. Further clinical notes were made based on either clinical assessment or dermoscopic characterization. The clinical evaluation of the cNF before and 12 months after the single treatment is summarized in Table 1.

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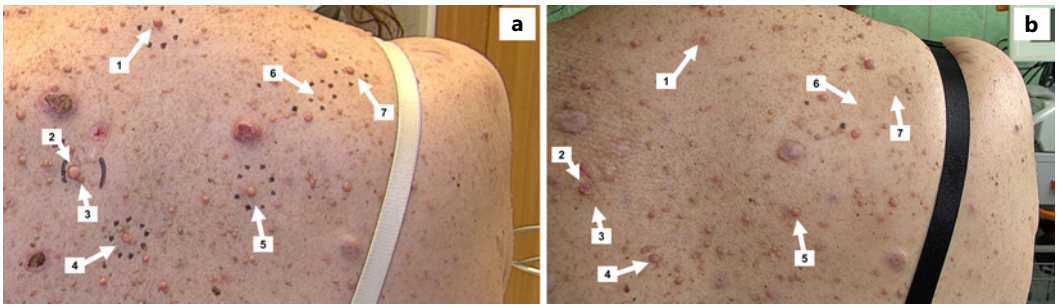

Fig. 2. Upper back of the patient before treatment (**a**) and 12 months after treatment (**b**). The photos illustrate the several hundred cNFs varying in size from barely visible (but palpable) sessile tumors to large globular and pedunculated tumors above 1 cm in diameter. Wounds, scabs, and scars from earlier surgical removal and laser treatments are clearly visible. The six tumors selected for HIFU treatment are indicated by white-numbered squares.

Discussion

The current case illustrates a new focused ultrasound method for treatment of cNF in patients with NF1. The treatment is performed in a clinically simple procedure, where each individual cNF is covered by HIFU doses, in a session taking approximately 1 min per tumor. The treatment is thus performed with very similar methodology, dosing, and duration compared to previously reported cases on a range of other common dermatological lesions treated by HIFU [7–12].

The efficacy of a single treatment performed on seven cNF was generally high, with improvements observed in five of seven treated targets (71%). These five tumors were clinically observed to have reduced volume and healed with no or very minor adverse response.

Some dyspigmentation in the form of hyperpigmentation in the periphery combined with hypopigmentation in the central region of the treated area was observed for one tumor (T7). Hyperpigmentation is however a part of cNF presentation [13], and therefore not a surprising treatment response. The reaction was furthermore categorized as mild (grade 1) without need for intervention [14] and therefore well below the threshold for reportable adverse events. With the observed reduction of overall tumor volume without other significant adverse reactions, the overall result was seen as a clear aesthetic improvement over baseline by both doctor and patient.

Surprisingly, two of the seven (29%) cNF did not show any visible reduction in volume or change in structure at all. The two nonresponsive tumors (T4 and T5) were neither the smallest nor largest among the treated tumors, and the direct volumetric reduction from treatment therefore does not necessarily seem to correlate with original size or thickness. The original clinical evaluation of pre-treatment appearance and texture did not indicate any difference from the overall group. With all treated tumors located within a small area of the upper back, the variance also does not seem to correlate with anatomical location. Some variances may be due to the manual treatment modality, but normal treatment status, skin response, and patient-experienced pain were observed during treatment of all seven tumors. The unexpected variation was further exemplified in a treatment of a “double” tumor (T2 and T3), where T2 had only partial reduction while its immediate neighbor, T3, had full remission.

The reason for the observed variability in response is therefore not immediately clear. It can be speculated that the cellular and fibrotic contents of cNF are not the same among

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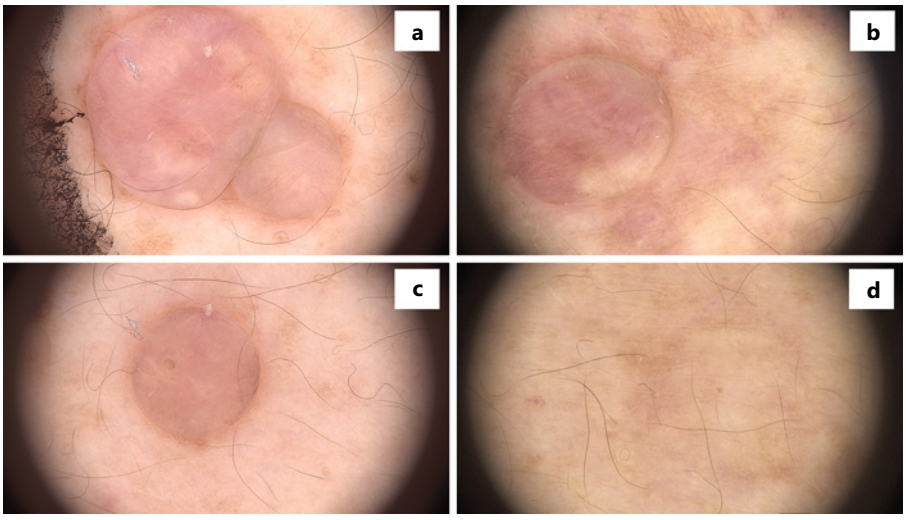

Fig. 3. Dermoscope pictures of HIFU-treated tumors. **a**, **b** A "double-tumor," T2/T3, before treatment and after 12 months, respectively. The larger section (T2) had a partial reduction in volume only, while the smaller (T3) had full remission. **c**, **d** Tumor T6 before treatment and after 12 months. The tumor is fully reduced, and the skin structure is almost fully normalized in the treated area.

Table 1. Overview of cNF tumors with clinically observed characteristics before and 12 months after HIFU treatment

Number	Type	Diameter, mm	Thickness, mm	12-month result. Clinician's descriptive assessment
T1	Pedunculated	10	5	Significant reduction; thickness reduced to 1 mm
T2	Globular (double w T3)	15	4	Partial reduction; thickness reduced to 1 mm
T3	Globular (double w T2)	5	2	Complete remission
T4	Globular (irregular)	11	3	No effect
T5	Globular (regular)	10	3	No effect
T6	Globular (regular)	7	2	Complete remission of normalized skin
T7	Globular (regular)	10	3	Complete remission of hyperpigmentation

The dimensions of the tumors are based on measurements of the protruding tumor boundary in relation to the surrounding normal flat skin plane.

tumors, even if they appear clinically similar. Ultrasound propagation and attenuation functions would therefore not be similar, and the actual energy absorption in the target could consequently be very different. Correspondingly, a difference in tumor content could also involve cells or fibrotic tissue that are more resistant to the thermal and mechanical effects of the focused acoustic energy than other.

Pain during treatment was relatively low and described to be momentary only. While even lower pain level is always preferred, this reported moderate level would potentially allow for treatment of several tens of cNF in one single coherent session. To decrease

treatment pain further, premedication in the form of topical analgesic cream or oral pain relief tablets has been successfully reported earlier [7, 12], and this approach could therefore also be applied to pain-sensitive patients in this case.

In the days following the treatment, the patient had very mild side effects, with development of a thin scab that released spontaneously after some 10–14 days. The period following immediately after treatment to full healing of the skin structure was therefore reported to be generally problem-free, and the patient had not been restricted in any daily activities during this period. No signs of recurrence or regrowth of tumors were noted from clinical or dermoscope examinations at the 3- and 12-month visits.

With the extremely limited statistical data generated from this single case, larger studies to optimize dosing and treatment strategies are naturally needed. This work should first of all include a larger population with treated cNF located on all relevant anatomical locations. It could, e.g., also include studies on the efficacy and patients' acceptance of repeating treatment on low-responding tumors after a few weeks. Work could finally be done to fully explain the varied response between clinically similar cNF. Such work could, e.g., involve histopathology, elastography, or systematic selection/grouping of tumors with known history (age).

In conclusion, the current early results are encouraging, and demonstrate the potential for a safe, minimally invasive, and easily accessible new treatment modality. The method can potentially be used to remove or decrease tumor volume in a large fraction of a patient's cNF. Small and developing cNF may be of particular interest, as the method allows more controlled and manageable treatment in both horizontal and vertical direction. This could in turn decrease the need for more severe surgical procedures to nonresponsive cNF only, and thus ultimately decrease the overall physical and psychological burden for the NF1 patient group.

Statement of Ethics

This study was conducted ethically and in accordance with the World Medical Association Declaration of Helsinki. The patient signed a written informed consent regarding participation in treatment and publication of the case including anonymized photographs. Ethical approval was not required for this study in accordance with local/national guidelines.

Conflict of Interest Statement

Torsten Bove and Tomasz Zawada are shareholders of TOOsonix A/S. The authors have no other conflicts of interest to declare.

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Author Contributions

All named authors meet the International Committee of Medical Journal Editors criteria for authorship. Bartosz Wozniak contributed to obtaining informed consent, diagnosis, treatment, clinical and dermoscopic images, patient follow-up, figure/table review, literature review, and writing/revision of the manuscript. Torsten Bove and Tomasz Zawada

contributed with figure/table review, literature review, and writing/revision of the manuscript. Dr. Jacek Calik contributed to diagnosis, patient follow-up, figure/table review, literature review, and writing/revision of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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