Paradoxical Adipose Hyperplasia After Cryolipolysis

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Abstract

Importance—Cryolipolysis is the non-invasive reduction of fat with localized cutaneous cooling. Since initial introduction, over 650,000 cryolipolysis treatment cycles have been performed worldwide. We present a previously unreported, rare side effect following cryolipolysis, paradoxical adipose hyperplasia.

Observations—A 41-year-old man underwent a single cycle of cryolipolysis to his abdomen. Three months following his treatment, a gradual enlargement of the treatment area was noted. This enlargement was a large, well-demarcated subcutaneous mass, slightly tender to palpation. Imaging studies revealed accumulation of adipose tissue with normal signal intensity within the treatment area.

Conclusions and Relevance—Paradoxical adipose hyperplasia is a rare, previously unreported side effect of cryolipolysis with an incidence of 0.0051%. No single unifying risk factor has been identified. The phenomenon seems to be more common in male patients undergoing cryolipolysis. At this time there is no evidence of spontaneous resolution. Further studies are needed to characterize the pathogenesis and histologic findings of this rare adverse event.

Introduction

Cryolipolysis is the non-invasive, selective destruction of adipose tissue by controlled cooling. The methodology takes advantage of the observation that lipid rich cells are more susceptible to cryoinjury than the surrounding water rich counterparts, such as in the overlying skin1. The treatment device utilizes a cup shaped applicator that draws a roll of
skin and subcutaneous adipose tissue between two cooling plates. Typical treatment time is one hour, during which the temperature of the tissue roll decreases to about 0 °C. Crystallization of cytoplasmic lipids within the adipocytes initiates a cascade of events, characterized by adipocyte apoptosis, panniculitis, and eventual loss of adipocytes. Clinically, this translates into an effective decrease in fat layer thickness.

The Food and Drug Administration initially approved Cryolipolysis for the non-invasive reduction in focal adiposity of the flanks in 2008 and later for the abdomen in 2011. Common side effects of the treatment include temporary erythema, edema, and mild pain. Notably, a transient decrease in sensation is seen in 2/3 of patients post treatment, which can persist for up to 8 weeks. Rarely, post-treatment pain may be severe for days after treatment. At present, over 650,000 treatment cycles have been performed worldwide, based on manufacturer data.

Very rarely, a delayed increase in adipose tissue at the treatment site can occur, which has not yet been reported in the medical literature. We suggest the term “paradoxical adipose hyperplasia” (PAH) for this phenomenon. We present here a case of PAH, along with estimation of the incidence and discussion of potential underlying mechanisms.

**Report of a Case**

A 41-year-old Caucasian man with a past medical history significant for lower back pain underwent a single cycle of cryolipolysis to a focal area of adiposity on his peri-umbilical abdomen. The large applicator (covering an 10.9 × 1.5 inch rectangle) was used for his treatment using manufacturer’s recommended vacuum settings (eZ App 8, Zeltiq Aesthetics, Inc., Pleasanton, CA) and standard pre-set cooling intensity factor (CIF). Treatment was without incident. The initial post-treatment course was typical, including mild erythema, mild discomfort not requiring analgesics, and according to the patient an apparent decrease in fat volume within the treatment zone appearing 1–2 months after treatment. Approximately three months after his treatment, the patient noted gradual, non-tender growth of tissue at the site and in the shape of the treatment area. This tissue growth stabilized in size by approximately 5 months post treatment, and remained apparently unchanged thereafter. The patient had not had any significant weight change during his post treatment course. He was referred to our practice for further evaluation.

On physical examination, there was a rectangular, sharply marginated subcutaneous soft tissue mass in the peri-umbilical area of the cryolipolysis treatment application (Figure 1A). No overlying change to the skin was appreciated. The tissue was mobile, noticeably firmer than surrounding tissue, but not hard. There was slight tenderness to palpation. Magnetic resonance imaging (MRI) was performed, which revealed a local increase in subcutaneous adipose tissue with normal signal intensity, corresponding to the area of the protrusion. Sagittal and cross-sectional views showed greater accumulation of tissue at the lateral poles of the applicator (Figure 1B). This patient did not elect corrective treatment, e.g., by liposuction or excision.

In a similar patient with PAH, abdominoplasty was performed nine months after cryolipolysis, and we examined the formalin-fixed tissue specimen by light microscopy.
This patient was a 56 year-old female with no significant past medical history who underwent a single cycle of cryolipolysis to three separate of adiposity on her abdomen. For her treatments both the large and small applicators were used and treatments were done per manufacturer’s recommended vacuum settings. She developed PAH nine months post treatment in all the treated areas of the abdomen. Abdominoplasty was performed and histopathology of the subcutaneous tissue mass demonstrated areas with disorganized adipocytes that varied in shape and size. There was increased septal thickening around the fat lobules (Figure 2). The most striking finding was an increase in vascularity within the adipose tissue of the affected area. The epidermis and dermis appeared normal, suggesting a process limited to the adipose tissue.

Comment

Paradoxical tissue growth is a phenomenon observed occasionally with device-based therapies. For example, paradoxical hypertrichosis can occur after laser or intense pulsed light treatment for hair removal\(^5\). Paradoxical adipose hypertrophy (PAH) is yet another example of unintended stimulation of tissue growth, following a treatment that injures the target tissue.

At time of authorship of this manuscript, 33 confirmed cases of paradoxical hyperplasia have been reported to the device manufacturer, as part of post-marketing surveillance data. We estimate that the incidence of PAH is about 0.0051%, or about 1 in 20,000 treated patients. No single, common characteristic has been identified among affected individuals at this time. Various anatomic locations have been reported including flanks, abdomen, and upper back. The onset of PAH in all cases is delayed two to three months after treatment and as in the case reported here, often follows an initial reduction of subcutaneous fat in the treatment area. The majority of patients receiving cryolipolysis are women, although the exact percentage is unknown. Of the 33 known cases of PAH at this time, 15 are men and 18 are women. Given the relative over-representation of male patients with this phenomenon, the incidence of PAH after cryolipolysis appears to be higher in men.\(^4\)

The pathogenesis of this rare phenomenon is unknown. Hypothesized mechanisms include hypertrophy of pre-existing adipocytes, recruitment of resident or circulating pre-adipocyte and/or stem cell populations, changes in the expression of receptors or soluble factors associated with adipocyte metabolism, reduction in sympathetic innervation, and hypoxic injury\(^6–8\). Given the increased septal thickening and the presence of increased vascularity on histology it is plausible to suspect that the septal thickening could be leading to hypoxia in the adipose tissue. Hypoxic injury is known to increase number of capillaries and to cause fat hypertrophy.

In summary, paradoxical adipose hyperplasia is a rare delayed side effect following cryolipolysis. The risk of PAH is approximately 1/20,000 and apparently higher in males. At this time, there is no evidence of spontaneous resolution of PAH. When necessary, treatment of PAH has relied on liposuction or abdominoplasty. At this time, it is unknown whether other non-invasive treatments that locally injure subcutaneous fat, can produce PAH or provide a treatment alternative for PAH.

\(^5\) Paradoxical hypertrichosis
\(^6\) Hypoxic injury
\(^7\) Septal thickening
\(^8\) Hypoxic injury
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Figure 1. Paradoxical Adipose Hyperplasia approximately 5 months following cryolipolysis

There is a sharply demarcated, rectangular enlargement around the umbilicus corresponding to the treatment zone. This soft tissue protrusion was soft, mobile, and slightly tender to palpation. The overlying skin was unremarkable.
Figure 2. Soft tissue hypertrophy composed of adipose tissue
Magnetic Resonance Imaging (MRI) reveals increased adipose tissue with normal signal intensity. The fat hypertrophy is greatest on the periphery of the treatment zone.
Figure 3. Representative biopsy specimens from abdominoplasty demonstrates characteristic changes to adipose tissue

(A) Histology from an abdominoplasty specimen of PAH tissue, demonstrating thickened fibrous septae with increased vascularity. (Magnification 2.50x) (B) Higher magnification revealed an increased vascular network, characterized by capillaries and venules (black arrowheads, Magnification 10x).