Case Report/Case Series

Paradoxical Adipose Hyperplasia After Cryolipolysis

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IMPORTANCE Cryolipolysis is the noninvasive 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 adverse effect following cryolipolysis: paradoxical adipose hyperplasia.

OBSERVATIONS A man in his 40s 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 adverse 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.

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Cryolipolysis is the noninvasive, 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 skin.[1] The treatment device uses a cup-shaped applicator that draws a roll of skin and subcutaneous adipose tissue between 2 cooling plates. Typical treatment time is 1 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 a modest yet appreciable decrease in fat layer thickness.[2]

The US Food and Drug Administration initially approved cryolipolysis for the noninvasive reduction in focal adiposity of the flanks in 2008 and later for the abdomen in 2011. Common adverse effects of the treatment include temporary erythema, edema, and mild pain. Notably, a transient decrease in sensation is seen in two-thirds of patients after treatment, which can persists for up to 8 weeks.[3] Rarely, posttreatment pain may be severe for days after treatment. At present, over 650 000 treatment cycles have been performed worldwide, based on manufacturer data.[4]

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

Report of a Case

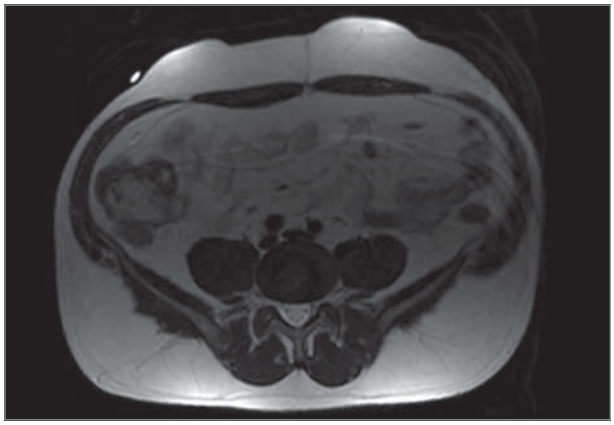
A man in his 40s underwent a single cycle of cryolipolysis to a focal area of adiposity on his periumbilical abdomen. The large applicator (covering a 27.7 × 3.8-cm rectangle) was used for his treatment following manufacturer's recommended vacuum settings (eZ App 8, Zeltiq Aesthetics Inc) and standard preset cooling intensity factor. The initial posttreatment 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 to 2 months after treatment. Approximately 3 months after his treatment, the patient noted gradual, nontender growth of tissue at the site and in the shape of the treatment area. This tissue growth stabilized in size by approximately 5 months after treatment, and remained apparently unchanged thereafter. The patient had not had any notable weight change during his posttreatment 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 periumbilical area corresponding to the treatment site (**Figure 1**). No overlying change to the skin was appreciated. The tissue was

Figure 1. Paradoxical Adipose Hyperplasia Approximately 5 Months Following Cryolipolysis

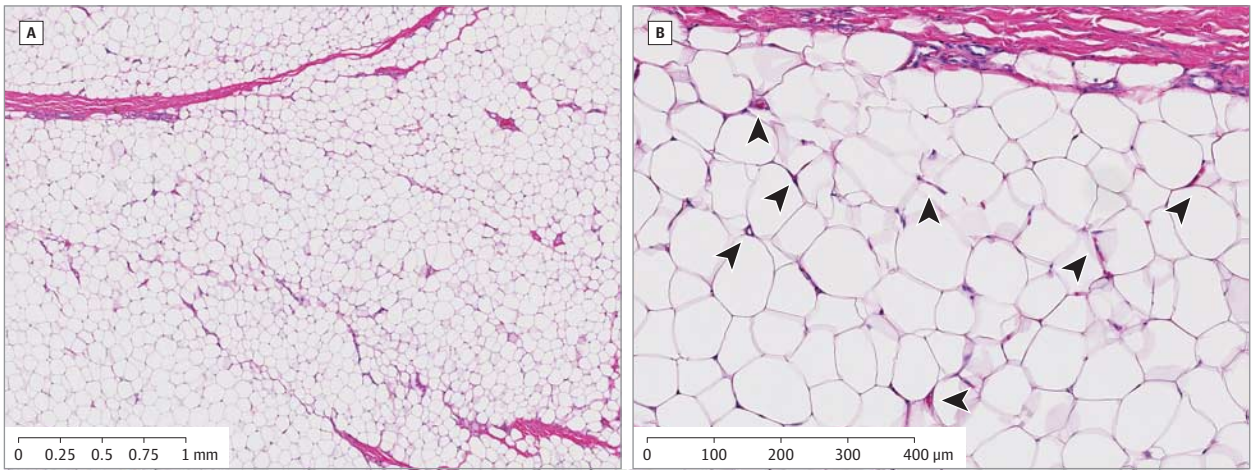
There is a sharply demarcated, rectangular enlargement around the umbilicus corresponding to the treatment zone. This soft-tissue protrusion was soft, mobile, and slightly tender to palpation. The overlying skin was unremarkable.

Figure 2. Soft-Tissue Hyperplasia Composed of Adipose Tissue



Magnetic resonance imaging reveals increased adipose tissue with normal signal intensity. The fat hyperplasia is greatest on the periphery of the treatment zone.

Figure 3. Representative Biopsy Specimens From Abdominoplasty Demonstrates Characteristic Changes to Adipose Tissue



A, Histologic image from an abdominoplasty specimen of paradoxical adipose hyperplasia tissue, demonstrating thickened fibrous septae with increased vascularity (hematoxylin-eosin, original magnification ×2.50). B, Higher magnification revealed an increased vascular network, characterized by capillaries and venules (black arrowheads) (hematoxylin-eosin, original magnification ×10).

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 transverse views showed greater accumulation of tissue at the lateral poles of the applicator (**Figure 2**). This patient did not elect corrective treatment (eg, by liposuction or excision).

In a similar case of PAH, abdominoplasty was performed 9 months after cryolipolysis, and we examined the formalin-fixed tissue specimen by light microscopy. This patient was a woman in her 50s who underwent a single cycle to 3 separate areas of adiposity on her abdomen. Both large and small applicators were used per the manufacturer's recommended vacuum settings. She developed PAH 9 months after treatment. Abdominoplasty was performed, and histopathologic examination 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 3**, A). The most striking finding was an increase in vascularity within the adipose tissue of the affected area (Figure 3, B). The epidermis and dermis appeared normal, suggesting a process limited to the adipose tissue.

Discussion

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 hyperplasia is yet another example of unintended stimulation of tissue growth, following a treatment that injures the target tissue.

To date, 33 confirmed cases of paradoxical hyperplasia have been reported to the device manufacturer as part of postmarketing 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 2 to 3 months after treatment, and, as in the case reported herein, often follows an initial reduction of subcutaneous fat in the treatment area. Of the 33 known cases of PAH at this time, 15 are men and 18 are women. Most patients receiving cryolipolysis are women, although the exact percentage is unknown. Given the relative overrepresentation of male patients with this phenomenon, the incidence of PAH after cryolipolysis seems to be higher in men.[4]

The pathogenesis of this rare phenomenon is unknown. Hypothesized mechanisms include hypertrophy of preexisting adipocytes, recruitment of resident or circulating preadipocyte 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] Septal thickening may be a result of reactive fibrosis owing to damaged adipocytes. It is plausible that the septal thickening could be leading to hypoxia in the adipose tissue. Hypoxic injury is known to increase vascularity by release of hypoxia inducible factor that initiates a cascade of events leading to angiogenesis,[9] increased number of capillaries, and perhaps fat hyperplasia.

In conclusion, paradoxical adipose hyperplasia is a rare delayed adverse effect following cryolipolysis. The risk of PAH is approximately 1 in 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. To date, it is unknown whether other noninvasive treatments that locally injure subcutaneous fat, can produce PAH, or provide a treatment alternative for PAH.

ARTICLE INFORMATION

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Statistical analysis: Avram.
Administrative, technical, or material support: Jalian, Avram, Garibyan, Anderson.
Study supervision: Avram, Mihm.

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