Case Report/Case Series

Dystrophic Calcification and Accentuated Localized Argyria After Fractionated Carbon Dioxide Laser Therapy of Hypertrophic Scars

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Lasers are powerful tools for the treatment of scars. The ablative laser, more widely used in the 1980s and 1990s, is known to be effective but involves a significant risk of adverse effects. Although reduced with proper technique and postoperative management, erythema, dyspigmentation, acneiform eruptions (milia and acne), eczematous dermatitis, infections, and scarring are not uncommon. The subsequent development of nonablative lasers yielded a substantial reduction in adverse effects but at the expense of decreased efficacy. Thus, fractional photothermolysis has gained significant popularity because of its increased efficacy and decreased adverse effect profile when compared with nonablative and ablative laser therapy, respectively. The concept involves the formation of multiple, evenly spaced microscopic treatment zones, which generate columns of thermal damage without spread to adjacent tissue. The surrounding, undamaged tissue acts as a reservoir of viable cells to promote rapid healing. Fractional photothermolysis has been combined with many nonablative and ablative devices, including carbon dioxide (CO₂).

Although significantly reduced compared with traditional ablative laser therapy, adverse effects, including infection, acneiform eruptions, prolonged erythema, pigmented alteration, scarring, ectropion formation, eruptive keratoacanthomas, recall phenomenon, anesthesia toxic effects, delayed purpura, superficial erosions, and dermatitis, have been reported. Until recently, most of the literature on the adverse events associated with fractionated CO₂ laser therapy has focused on patients receiving cosmetic resurfacing and rejuvenation rather than treatment for hypertrophic scars. However, Clayton and colleagues conducted a descriptive, retrospective, 6-month study in which they analyzed the adverse events in patients with hypertrophic burn scars after treatment with pulsed dye laser, CO₂ laser, and others. They found that all adverse events were exceedingly rare, with postoperative pain the most common event associated with the CO₂ laser.
ser. In 42 treatments with the CO₂ laser, no cases of hyperpigmentation were observed.

### Report of a Case

We describe 2 previously unreported but potentially interrelated adverse effects of fractionated, ultrapulsed CO₂ laser treatment of hypertrophic scars. Our patient is a teenage girl who survived an episode of toxic epidermal necrolysis with nearly 100% body surface area involvement 8 years earlier. She initially presented to our clinic 4 years ago for consideration of fractional laser resurfacing because her hypertrophic scars had not improved with previous pulsed dye laser treatments. At that time she was noted to have diffuse, faint, blue-gray discoloration, which was initially believed to represent postinflammatory hyperpigmentation after her remote full-thickness epidermal injury. However, a subsequent biopsy specimen revealed scattered black granules intermixed throughout the dermal scar and surrounding basement membranes, suggesting this pigmentation instead represented localized argyria, likely arising in areas where the silver-impregnated dressing (Acticoat; Smith & Nephew Inc) was used 4 years earlier (Figure 1A).²

The patient was subsequently treated with test spots of fractionated 1550-nm, 2940-nm, and 10 600-nm lasers to her legs. Clinical results and patient preference determined that fractionated CO₂ was the best modality to improve scar pliability and texture. Three years ago, she received her first fractionated CO₂ laser treatment (Lumenis UltraPulse; Lumenis Ltd) to the entirety of her bilateral anterior thighs. During the next 3 years, she underwent several fractionated CO₂ treatments to her face, chest, back, abdomen, and legs, with settings as aggressive as 25 to 40 mJ and 10% density using the Deep FX setting and intermittently using the Active FX settings of 90 mJ and density 3 to her back and face to help improve superficial textural changes. The patient continued to adhere to strict UV light avoidance throughout the treatment period given her extensive scarring and risk of malignant tumors. After each session throughout her treatment course, the patient experienced worsening hyperpigmentation in areas treated with the CO₂ laser (Figure 1B). This was originally believed to represent postinflammatory hyperpigmentation secondary to CO₂ laser resurfacing, but the patient elected to pursue further treatment given the improvements in pliability and texture. Eventually, the worsening hyperpigmentation began to create emotional distress for the patient, and 2 subsequent skin biopsies of the right thigh and left abdomen were performed.

The biopsy specimen from a sun-protected area of worsening hyperpigmentation after CO₂ laser therapy on her left abdomen (Figure 2A) revealed zones of superficial calcification spaced at regular intervals and at approximately the same dermal depth suggestive of dystrophic calcification in the wake of fractionated ablative laser, which has not been previously reported. The superficial calcifications were surrounded by so-called pseudo-ochronotic fibers (Figure 2B), which have been previously described,²,⁶ superimposed on granular deposits similar to her initial (pre-laser) argyria biopsy specimens. Although granular silver deposits were appreciated in her pretreatment biopsy specimens, pseudo-ochronotic fibers were not. The calcifications and rare black grains contained silver by scanning electron microscopy with energy dispersive x-ray analysis (SEM/EDXA) (Figure 3A and B). Silver granules were also noted along the basement membrane of the eccrine glands, typical of argyria (Figure 3C and D). The pseudo-ochronotic fibers were accentuated with darkfield microscopy (Figure 4A and B) in a fashion similar to the preexisting granular silver deposits noted previously. With SEM/EDXA, short linear deposits of silver compatible with the distribution of pseudo-ochronotic fibers were detected focally in the biopsy specimen from the thigh (Figure 4C), as previously described by Hris-
However, SEM/EDXA of the abdominal biopsy specimen was unable to confirm micronized silver particles coating collagen or elastin fibers as the cause of their pseudo-ochronotic appearance, which was likely due to detection limitations of the SEM/EDXA method, because the amount of silver deposited in the case described by Hristov et al was significantly greater than in our current case.

**Discussion**

To our knowledge, neither dystrophic calcification nor worsening of cutaneous pigmentation in conjunction with the appearance of pseudo-ochronotic fibers has been reported after ablative fractional resurfacing. Serum silver and urinary organic acid levels were normal in our patient, ruling out systemic argyria and alkaptonuria as alternative explanations for the worsening hyperpigmentation, respectively. Findings typical of drug-induced hyperpigmentation or drug complex deposition were not identified. In addition, the patient demonstrated no signs or symptoms of connective tissue disease or other conditions associated with dystrophic calcification, and the calcium-phosphorus product was normal.

It is possible that the coating of dermal fibrils with silver (creating a pseudo-ochronotic appearance) after ultrapulsed CO2 therapy may represent a physicochemical change in previously deposited dermal silver granules, similar to the hyperpigmentation seen as crystalline gold deposits are converted to colloidal gold in patients with chrysiasis treated with nanosecond ruby laser. Indeed, mere exposure to incident light has previously been reported to induce changes in the physical properties of dermally deposited silver and thus influence the degree of hyperpigmentation. However, we do not believe that exposure to incident UV light was responsible for worsening of localized argyria in our patient because pseudo-ochronotic fibers were observed in sun-exposed and sun-covered areas. In addition, we hypothesize that photothermal changes in the laser-skin interaction mediated by deposited silver may have created the pattern of dystrophic calcification seen on the biopsy specimen, but this is purely speculative and based on the lack of a better explanation for this distinct histologic finding.

**Conclusions**

We believe a history of systemic or localized argyria, or perhaps any prior exposure to silver-impregnated dressings, covered areas. In addition, we hypothesize that photothermal changes in the laser-skin interaction mediated by deposited silver may have created the pattern of dystrophic calcification seen on the biopsy specimen, but this is purely speculative and based on the lack of a better explanation for this distinct histologic finding.

Laser tattoo removal with the Q-switched ruby, Q-switched Nd:YAG, and pulsed green dye lasers cause irreversible ink darkening in some cases. The exact mechanism is not fully understood, although a reduction of ferric oxide (red) to ferrous oxide (black) has been proposed. Tattoo ink that contains titanium has also been implicated in tattoo darkening after attempted removal with the Q-switched ruby and Nd:YAG lasers. A similar mechanism has been suggested because laser irradiation has been proven to cause a reduction of Ti4+ to Ti3+, resulting in a white to blue color change. Although never reported in the literature, conversion of nanocrystalline silver, which is present in Acticoat dressings, to silver oxide may explain the worsening hyperpigmentation after CO2 laser therapy in our patient. However, because of histologic differences, this theoretical pathomechanism has limitations. Argyria is characterized by deposits of silver granules and pseudo-ochronotic fibers (after treatment), whereas iron and titanium tattoos have dispersal and increased prominence of tattoo ink with scattered vacuoles in the upper and midreticular dermis.

We have subsequently treated selected areas of dyschromia with a Q-switched Nd:YAG laser and have found clinical improvement in the discoloration. However, subsequent biopsies have not been performed.

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Figure 2. Biopsy Specimen From a Sun-Protected Site That Received at Least 2 Ultrapulsed Carbon Dioxide Laser Treatments

A, Note the regular pattern of calcification corresponding with tissue ablated using the deep fractional setting on the laser (arrows) (hematoxylin-eosin, original magnification ×20). B, Pseudo-ochronotic fibers can be seen (arrows) surrounding the calcifications (hematoxylin-eosin, original magnification ×100).
Figure 3. Biopsy Specimen From a Sun-Protected Site That Received at Least 2 Ultrapulsed Carbon Dioxide Laser Treatments.

A, Scanning electron micrograph (SEM) of an unstained section mounted on a carbon disk showing white silver-containing calcifications in the superficial dermis (white circle) (original magnification ×270). B, Energy dispersive x-ray analysis (EDXA) from the particle circled in white in panel A, showing the presence of silver (Ag), sulfur (S), calcium (Ca), phosphorus (P), oxygen (O), sodium (Na), and carbon (C). C, An SEM showing white silver-containing granules (white square) associated with the basement membrane of a sweat gland (original magnification ×1000). D, An EDXA from the particle within the white square in panel C, showing the presence of silver (Ag), selenium (Se), and oxygen (O).

Figure 4. Biopsy Specimen From a Sun-Protected Site That Received at Least 2 Ultrapulsed Carbon Dioxide Laser Treatments

A, Specimen of sun-protected site (hematoxylin-eosin, original magnification ×40). Arrows indicate pseudo-ochronotic fibers, which are highlighted by darkfield illumination. B, Same field viewed under darkfield illumination, showing accentuation of pseudo-ochronotic fibers (arrows). C, An energy dispersive x-ray analysis map for silver showing short linear deposits compatible with the distribution of pseudo-ochronotic fibers seen in the biopsy specimen from the thigh (original magnification ×3500).
should be considered in the decision to treat burn patients with ultrapulsed CO₂ laser therapy based on the clinical and histologic features presented above. Continual surveillance for traumatic calcification should also be considered because fractionated treatments for burn scars continue to gain popularity.

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