

Congenital and acquired pigmented lesions: to treat or not to treat with lasers?

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Because laser treatment of benign pigmented lesions has such a low potential for scarring, this modality has been widely used to treat a wide variety of pigmented lesions. Some of these pigmented lesions contain an increased number of melanocytes, some do not. A variety of laser systems can be used to remove pigmented lesions. The most widely accepted are the Q-switched lasers. These lasers exert their biological effect by selectively targeting melanosomes in both melanocytes and keratinocytes. Organellespecific damage occurs as a result of the selective absorption of high-energy, nanosecond laser pulses (1). Selective photothermolysis of melanosomes occurs because of high local temperature changes with subsequent melanosome fracture (2). Melanocyte death may follow melanosome fracture. Cultured melanocyte death is also associated with highpressure acoustic waves (3). Thus a combination of microthermal and thermally initiated mechanical injury appears to underlie the biological effects of these lasers. Laser treatment of nonmelanocytic pigmented lesions is now a well-accepted modality of treatment. Laser treatment of melanocytic pigmented lesions remains more controversial. This chapter will review our current understanding the laser-induced effect on pigmented lesions, the currently available pigmented lesion lasers and the effect of these lasers on a variety of congenital and acquired pigmented lesions.

Dr. Leon Goldman, the father of laser medicine, was among the first to use a Q-switched ruby laser at a 50- μ sec pulse duration to evaluate the laser-induced damage threshold of pigmented lesions. His studies suggested a selective effect, perhaps at the level of the melanosome. It was 20 years later when Polla et al. (4) and Dover et al.

(5), in separate studies, demonstrated that the Q-switched ruby laser targeted individual melanosomes. Electron microscopic analysis of these thermally damaged targeted melanosomes revealed membrane disruption and disorganization of the internal contents of these organelles. The destruction of melanosomes appeared to be pulsewidth dependent. Both pulse durations of 40 nsec and 750 nsec disrupted melanosomes; longer pulse durations such as 400 μ sec did not cause specific melanosomal damage. This is consistent with the theory of selective photothermolysis, which states that the pulse duration of an emitted laser wavelength must be less than the thermal relaxation time of the targeted object. A typical 1.0- μ m melanosome has a thermal relaxation time somewhere between 0.5-1.0 μ sec.

The specific cause of melanosomal destruction is unknown. Plasma formation probably does not occur. The peak powers produced, with lasers used to interact with melanosomes, are quite low for such an occurrence. Shock wave and/or cavitation damage, the photomechanical physical effects produced from thermal expansion, and/or the extreme temperature gradients created within the melanosomes are the more likely explanations. Studies of acoustic waves generated by pulsed irradiation of melanosomes and pigmented cells support these possibilities. Melanin absorbs and localizes the high-intensity irradiation from Q-switched lasers, thereby creating a sharp temperature gradient between the melanosome and its surrounding other structures. This gradient leads to thermal expansion and the generation and propagation of acoustic waves, which can mechanically damage the melanosome-laden cells (1).

Tissue repair following laser-induced melanosomal disruption demonstrates a two-stage initial transient cutaneous depigmentation followed by subsequent repigmentation weeks later (6). Black guinea pig skin irradiated with 40-nsec Q-switched ruby pulses at radiant exposures of 0.4 J/cm² or greater whitens immediately, fades in 20 minutes, depigments 7-10 days later, and then repigments 4-8 weeks after treatment. Of note is that repigmented guinea pig skin displays a persistent leukotrichia that can last up to 4 months after laser irradiation. Guinea pig skin exposed to radiant exposures less than that of threshold exposure (less than 0.3 J/cm²) undergoes paradoxical melanogenesis. This may be due to either a sublethal change in the melanosome (interfering with the normal feedback inhibition of melanogenesis) or simply postinflammatory hyperpigmentation. Further studies are required to evaluate the therapeutic implications of this paradoxical reaction.

Laser irradiation leads to histologic melanosomal disruption and vacuolization of pigmentladen cells in the basal layer. Both keratinocytes and melanocytes exhibit pigment and nuclear material condensation at the periphery of laser-irradiated cells. This leads to a characteristic "ring-cell" appearance. Epidermal necrosis and regeneration of a pigmented epidermis follow over the next 7 days.

Human skin observations have been similar to those seen in guinea pigs. The Q-switched ruby laser targets human melanosomes. After treatment there is subsequent sloughing of the killed pigmented cells. Transient hypopigmentation is followed by gradual repigmentation to the normal constitutive color. Other short-pulsed, highfluence, pigment-specific lasers produce similar clinical and histologic findings in human skin (7-9).

Three action spectrum studies have analyzed the ability of different wavelength pulsed lasers to disrupt cutaneous pigment. Anderson et al. (2) evaluated the effects of a Q-switched Nd:YAG laser with a pulse duration of 10-12 nsec at three distinct wavelengths (355, 532, and 1064 nm) on guinea pig skin. The threshold exposures for immediate skin whitening—the sign of laser-induced melanosomal changes—required energy fluences of 0.11, 0.20, and 1.0 J/cm² at 355, 532, and 1064 nm, respectively. These findings show that the threshold exposure dose is wavelength dependent. Furthermore, longer wavelengths (which are less well absorbed by melanin) require higher energy fluences to induce these changes. At all

evaluated wavelengths, electron microscopic examination revealed disrupted melanosomes within keratinocytes and melanocytes. Histologically, irradiated basal cells showed a characteristic "ring cell" appearance, presumed secondary to vacuolization and peripheral condensation of the cellular pigment. As expected, the transient immediate whitening of the laser-treated area exhibited delayed epidermal depigmentation followed by repigmentation back to constitutive skin color.

Flashlamp pulsed tunable lasers (6) with pulse duration of 750 nsec demonstrate the relationship between wavelength and whitening threshold. Threshold fluences were found to be 0.44, 0.62, 0.76, and 0.86 J/cm² at 435, 488, 532, and 560 nm, respectively.

Finally, Sherwood et al. (10) performed an action spectrum study of guinea pig skin using a flashlamp pulsed tunable laser with pulse duration of 300 nsec at four different wavelengths (504, 590, 720, and 750 nm). The 504 nm wavelength was found to produce the most pigment-specific injury, with the longer wavelengths causing more disruption of the basement membrane, leading to subsequent pigmentary incontinence.

Today there are numerous lasers that can specifically target pigmented lesions, including green light lasers (510 nm pulsed dye, 532 nm frequency-doubled Nd:YAG), red light lasers (694 nm ruby and 755 nm alexandrite), and near-infrared lasers (1064 nm Nd:YAG). The wide range of lasers that can be used to treat pigment is a result of the broad absorption spectrum of melanin. Even so, other less pigment-specific lasers have been used to treat pigmented lesions, including the argon, krypton, KTP, copper vapor, CO₂, and most recently the Er:YAG lasers. The CO₂ laser exerts its effect on tissue by simple vaporization of water-containing cells. Textural skin changes and scarring may result from this nonselective destruction. A very low wattage CO₂ laser appears to reduce the risk of scarring and has been used effectively to treat superficial epidermal pigmented lesions, such as solar lentigines. The Er:YAG laser also vaporizes water-containing cells and may more precisely ablate superficial layers of skin than does the CO₂ laser.

It should be noted that wavelengths not selectively absorbed by melanin indiscriminately destroy nonpigmented as well as pigmented structures in the skin. Alternatively, those lasers with wavelengths which (1) preferentially absorbed by melanin over other cutaneous chromophores (such as hemoglobin) and (2) penetrate to the

depth of the targeted pigment can be utilized to more selectively target cutaneous pigment. Lasers emitting wavelengths between 630 and 1100 nm may provide selective melanosome absorption and good skin penetration because of the longer wavelengths as well as higher selection of melanin over hemoglobin.

Pulsed lasers with appropriate wavelengths have a distinct theoretical advantage over non-pulsed continuous wave devices in the selective destruction of cutaneous pigment. The green and blue light (488 and 514 nm, respectively) of the argon laser is specifically absorbed by melanin. However, because of its long pulse duration, this system effectively functions as a continuous wave laser. Thus although the laser selectively targets the melanin chromophore, the heat is conducted from the absorbing melanosomes to surrounding tissue, causing excessive thermal damage with resultant hypopigmentation and increased scarring potential. Similar findings can ensue after use of the krypton (520-530 nm), KTP (532 nm), and copper vapor (511 nm) lasers, all of which are nonpulsed, "quasi-continuous wave" devices.

Pigment-specific lasers can be divided into three categories: green, red, and near-infrared. Green light lasers are further subdivided into both pulsed and nonpulsed systems. Red light lasers are subdivided into short-pulsed (Q-switched) and long-pulsed (normal-mode) systems. The currently available near-infrared laser is short pulsed (Q-switched). Green light lasers do not penetrate as deeply into the skin as do the red and near-infrared lasers owing to their shorter wavelengths. Green light lasers are therefore most effective in the treatment of epidermal pigmented lesions.

Green light pulsed lasers

These lasers produce energy with pulses shorter than the thermal relaxation time of melanosomes. Examples of these lasers include the flashlamp-pumped pulsed dye and frequency-doubled Q-switched Nd:YAG systems. The flashlamp-pumped pulsed dye laser produces a 510 nm wavelength and 300-nsec pulse of energy, whereas the frequency-doubled Q-switched Nd:YAG laser produces a 532 nm wavelength and a 5- to 10-nsec pulse of energy. Both lasers produce excellent results when used to treat epidermal pigmented lesions such as solar lentigines and ephelides (Figs. 1 and 2). Because the green wave

length of these lasers is also well absorbed by oxy-hemoglobin, purpura formation may occur following laser irradiation. The purpura resolves in 1-2 weeks after treatment, with resolution or lightening of the clinical lesion(s) 4-8 weeks after treatment. Occasionally purpura leads to postinflammatory hyperpigmentation.

Flashlamp-pumped pulsed dye laser

Flashlamp-pumped pulsed dye laser treatment results in excellent clearing of epidermal pigmented lesions such as lentigines, ephelides, flat seborrheic keratoses, and cafe-au-lait macules (11-15). In a study of 492 benign epidermal pigmented lesions in 65 patients, 50% of the treated lesions cleared completely after one treatment when treated at fluences of 2-3.5 J/cm² (6). Another 33% of the treated lesions were lightened considerably. Ninety percent of treated epidermal pigmented lesions can be cleared after three treatments. Treatment results can be affected by anatomic location. Although up to 90% of hand and facial lentigines may be cleared, less favorable results are usually seen following treatment of trunk or leg epidermal pigmented lesions. A typical treatment response includes purpura lasting 5-7 days, followed by subsequent sloughing of the treated lesion at 7-14 days. The underlying new skin may remain pink for several days, but fades to normal skin color with rare textural changes or scarring. In another study, 25 patients with solar lentigines showed excellent laser-induced clearing after one to two treatments (13). Fourteen patients with cafe-au-lait macules showed complete clearing after three to six treatments. Two patients with nevus spilus and two patients with Becker's nevi showed clearing with up to six treatments. As a general rule, this laser produces a variable response in some epidermal pigmented lesions such as cafe-au-lait macules, Becker's nevi, and epidermal melasma. Epidermal postinflammatory hyperpigmentation may also respond. Predominantly dermal pigmented lesions show little to no response. Because some pigmented lesions show a variable clinical response, testing representative areas of the lesion may be prudent prior to conducting a full treatment. Even when cafe-au-lait macules and Becker's nevi show resolution after treatment, recurrences have been reported. Recurrences may occur because of the impact of these lasers on melanosomes, with little effect on the pigment-producing



Fig. 1. Lentigines prior to treatment with a pulsed green light laser.



Fig. 2. Clearance of lentigines 6 weeks after laser treatment.

melanocytes. Careful sun protection may retard but will not always prevent recurrence. Because melasma occurs secondary to a combination of genetic, sun-induced, and hormonal factors, successful laser treatment is the exception rather than the rule with the use of this laser.

Frequency-doubled Q-switched Nd:YAG laser

The Q-switched Nd:YAG laser is a solid-state, high-fluence, short-pulsed (10-20 nsec) laser that emits at a wavelength of 1064 nm. By placing doubling crystals in the laser beam's path, frequency doubling halves the wavelength to 532 nm. Epidermal lesions such as lentigines and cafe-au-lait macules can be lightened considerably by the frequency-doubled Q-switched Nd:YAG laser (16-18). In one study, 84% of 17 lentigines lightened by at least 50% after several treatments at 2-5 J/cm² (16). Postoperative purpura developed in all patients and 25% of treated individuals showed transient hyperpigmentation. The degree of response to the laser at this wavelength is proportional to the amount of pigment chromophore present at the treatment site. When high fluences are delivered through small spot sizes, whitening of the skin is noted. This is then followed by pinpoint bleeding, leading to a hemorrhagic crust that falls off in 7-10 days.

Green light nonpulsed (quasi-continuous wave) lasers

Nonpulsed, quasi-continuous wave green light lasers such as the copper vapor (511 nm), krypton

(520-530 nm), and KTP (532 nm) lasers share some characteristics with the aforementioned pulsed green light lasers. However, because the thermal relaxation time of the melanosome is exceeded using these lasers, they do not produce the same consistent clinical results. Although small epidermal pigmented lesions may be successfully cleared, more treatment sessions are usually necessary to achieve similar results to those seen with pulsed green lasers. Robotized scanning devices may allow occasional effective treatment of larger lesions such as cafe-au-lait macules. These green light lasers are not useful in the treatment of dermal pigmented lesions such as nevus of Ota. It should be noted that the epidermal pigmented lesion response following treatment with a noncoherent flashlamp intense pulsed light source is somewhere in between that of the pulsed lasers and nonpulsed systems.

Red light pulsed lasers

The two currently available red light pulsed pigmented lesion lasers are the Q-switched ruby and Q-switched alexandrite lasers. The Q-switched ruby laser emits a 694 nm beam with a 20- to 50nsec pulse duration. The Q-switched alexandrite laser emits a 755 nm wavelength with pulse duration of 50-100 nsec. The longer wavelengths of these lasers allow deeper penetration into the dermis. Their mechanism of action on melanin-containing melanosomes and melanocytes involves selective photothermolysis, photoacoustic mechanical disruption, and chemical alteration of the target tissue. Photoacoustic mechanical

disruption is caused by rapid thermal tissue expansion, creating pressure waves that fragment pigment particles in the dermis. Within the dermis, absorption of the laser energy by melanin-rich stage III and IV melanosomes causes selective pigment destruction.

Q-switched ruby laser

The Q-switched ruby laser is made with a ruby (aluminum oxide) crystal that has been grown in the presence of chromium. This combined crystal is surrounded by a helical flashlamp. The laser, in its natural state, produces a train of nonuniform pulses. In the Q-switched mode, very high peak powers can be attained with each pulse (over 1×10^8 W/cm² per pulse).

Ruby laser light penetrates about 1 mm into the skin, is well-absorbed by melanin, and is minimally absorbed by hemoglobin. Thus this laser can be used for dermal pigmented lesions while avoiding vascular dermal structures. Epidermal pigmented lesions, such as lentigines and ephelides, usually clear after one to four treatments with the Q-switched ruby laser (19-22) (Figs. 3 and 4). Taylor and Anderson (23) reported 29 lentigines that totally cleared after only one treatment. Cafe-au-lait macules, nevus spilus, and Becker's nevi may also respond to treatment with this laser. Ashinoff and Geronemus (19) treated 15 cafe-au-lait macules and found significant lightening after an average of six treatments. Frequent recurrences are the general rule after treatment of cafe-au-lait macules, nevus spilus, and Becker's nevi.

The Q-switched ruby laser is highly effective in treating dermal pigmented lesions such as nevus of Ito and Ota (24). The long wavelength successfully targets the deep spindle cell-shaped dermal melanocytes. Histologically they appear to be destroyed. Geronemus (25) successfully treated 15 patients with nevus of Ota with as many as seven treatment sessions with the Q-switched ruby laser.

Lower eyelid hyperpigmentation secondary to dermal pigmentation may also respond to treatment with the Q-switched ruby laser. Several treatments are usually required (26). Mixed epidermal and dermal lesions such as postinflammatory hyperpigmentation and melasma respond better to this laser than to the green pulsed lasers; however, the results remain somewhat variable (27).

The Q-switched ruby laser may also be used in the treatment of congenital nevi (28). Although occasional significant clinical lightening may oc-

cur, recurrence of pigmentation is the general rule (Figs. 5 and 6). Histologically, residual nevomelanocytes were seen in the deeper dermis. In a recent study, small and medium-size congenital nevi (less than 5 cm in diameter) in 18 children were treated with the Q-switched ruby laser (29). Photographic evaluation revealed an average of 57% clearance of pigmentation in all treated nevi by the fourth treatment session. This improvement increased to a maximum clearance of 76% after approximately eight sessions. Greater than 90% clearance of pigment was noted in five patients. Partial repigmentation was seen in all patients who were followed after discontinuation of therapy. Biopsy findings in one patient revealed a reduction of nevus cells in the papillary and upper reticular dermis. This appeared to be correlated with clinical lightening. There was no such reduction in the lower reticular dermis. The authors suggested that the Q-switched ruby laser be considered as a viable alternative for providing cosmetic improvement in unresectable lesions.

Q-switched alexandrite laser

The Q-switched alexandrite laser is a solid-state laser that emits light at 755 nm with pulse durations of 50-100 nsec. There is less published data about this laser as compared to the Q-switched ruby laser. However, because the wavelength and pulse durations are similar to those of the Q-switched ruby laser, results have been similar. Good clinical responses have been observed after Q-switched alexandrite laser treatment of nevus of Ota (30,31), lentigines and cafe-au-lait macules (32), and benign melanocytic nevi (33,34).

Normal-mode alexandrite and ruby lasers

Recently, long-pulsed ruby (300-3000 μ sec) and alexandrite (2-20 msec) lasers have been shown to be effective in the treatment of Q-switched ruby laser-resistant congenital nevi and other pigmented lesions. These lasers may also be of use in laser-assisted hair removal. The normal-mode alexandrite laser emits light at a wavelength of 755 nm with 2- to 20-msec pulse durations. In a Japanese study a high fluence (10-30 J/cm²) normal-mode ruby laser was used to treat three patients with congenital nevi at intervals of 1-4 months. In all three cases the pigmented lesions were significantly reduced almost to the level of the surrounding normal skin after four laser treatments. Unightly hair growth

Fig. 3. Lentiginos prior to treatment with a pulsed red light laser.

was also reduced. There were no noted recurrences during the 18- to 39-month study period (35). In another report, Nanni and Alster (36) successfully treated a Becker's nevus with a long-pulsed ruby laser.

Near-infrared pulsed lasers

The Q-switched Nd:YAG laser produces a 1064 nm wavelength beam with a pulse duration of 10 nsec. Melanin does not absorb the 1064 nm wavelength well, thus the 1064 nm wavelength is not ideal for the treatment of benign pigmented lesions. Despite less absorption of this wavelength by melanin compared with the green and red light lasers, its advantage lies in its ability to penetrate more deeply in the skin (up to 4-6 mm). Thus this laser may be more useful in the



Fig. 5. Biopsy-proven congenital nevus before laser treatment.

Fig. 4. Clearance of lentiginos 6 weeks after laser treatment.

treatment of lesions in individuals with darker skin tones. Like the Q-switched ruby and alexandrite lasers, the Q-switched Nd:YAG laser is highly effective in clearing nevus of Ota. Histologically the findings at 1064 nm are identical to those of the Q-switched ruby laser. "Ring cells" representing vacuolated pigmented cells with peripheral condensation of pigment are detected in the epidermal basal cell layer.

Rosenbach et al. (33) recently evaluated and compared the response of flat acquired benign melanocytic nevi with both the Q-switched alexandrite and Q-switched Nd:YAG lasers at 6.0 J/cm² (3 mm spot size). With only one treatment, there was improvement. However, after three laser treatments, dramatic clinical lightening was noted in both groups of laser-treated nevi. The Q-switched alexandrite laser, after a third laser session, produced better results than those seen with the Q-switched



Fig. 6. Recurrence of pigmentation 6 months after final laser treatment.

Nd:YAG laser. Twelve-month follow-up of 12 of the 18 treated patients showed no evidence of recurrence or pigment darkening. It should be noted that histologic evaluation showed similar changes in nevi following irradiation by either Q-switched laser. Decreased numbers of epidermal and dermal melanocytes, as well as an overall reduction in epidermal pigment, were the histologic counterparts to the clinical lightening observed.

Grevelink et al. (34) compared the effects of a Q-switched ruby and Nd:YAG laser on congenital nevi. Laser irradiation of congenital melanocytic nevi continues to be a controversial treatment because recurrence of lesions after laser treatment appears to be the general rule. In addition, the effects of laser irradiation on cellular biological behavior and the possible mutagenic responses of nevus cells remains unclear.

In contrast to ultraviolet irradiation, which is known for its ability to induce/inflct specific DNA damage, laser irradiation in the visible and near-infrared wavelengths, as noted previously, appears to exert its effect through thermal and mechanical mechanisms. Ultrarapid heating by the Q-switched laser pulse results in melanosome fracture as well as in rapid heating of the cellular cytoplasm. At present, no malignant transformation following Q-switched laser treatment has been reported. Methods to assess potential malignant transformation in laser-irradiated congenital nevi are currently unavailable. However, the examination of modulation of cell adhesion molecules may detect early molecular changes that could reflect functional behavioral changes of nevus melanocytes. Studies of Q-switched la

ser treatment of melanoma cells *in vitro* showed changes in cell surface receptor expression, with subsequent alteration of such cellular behavior as migration, but this also has been noted in benign nevus cells. Nevertheless, a possible increase in the laser-irradiated migration of benign nevus cells must be of concern. In Grevelink et al.'s (34) study, a number of nevus cells in the superficial and deep portions of congenital nevi were destroyed, thus decreasing the number of cells potentially capable of malignant transformation. However, the deeper melanocytes were often unaffected. It has also been noted that, after initial laser destruction of congenital nevi, repopulation of the initially depleted layers usually occurs within 3-6 months. Such findings may indicate specific growth characteristics of congenital nevi melanocytes, or conditions in the extracellular matrix of these lesions, that support this regenerative behavior.

In the study, both Q-switched lasers affected both the superficial and the deep portions of the congenital melanocytic nevi. Improvement was noted both on macroscopic inspection and microscopic evaluation. The Q-switched ruby laser appeared to be more successful in clearing melanocytes than did the Q-switched Nd:YAG laser. However, with neither laser were all melanocytes destroyed. The authors also noted that repetitive Q-switched laser treatments might not result in the complete eradication of most congenital nevi. Although total resolution is not always possible and regrowth is to be expected, there are exceptions. Ueda and Imayama (35) recently published a case of long-term clearance of a congenital nevus following Q-switched ruby laser



Fig. 7. Congenital nevus prior to treatment with a Q-switched ruby laser. (Photo courtesy of S. Nelson, MD, PhD.)



Fig. 8. No evidence of congenital nevus recurrence years after laser treatment. (Photo courtesy of S. Nelson, MD, PhD.)

treatment (Figs. 7 and 8). Congenital nevi with atypical features and/or of large size should be excised. However, some congenital nevi occur in cosmetically sensitive areas. In such areas where a surgical scar may be unacceptable, lasers should be considered in the cosmetic improvement of these lesions.

Nonselective laser techniques: CO₂/Er:YAG lasers

The CO₂ laser (10,600 nm) and the Er:YAG laser (2940 nm) emit infrared laser energy that is not selectively absorbed by melanin. The Er:YAG laser produces much less thermal damage than is seen with the CO₂ laser and can be used to ablate superficial epidermal pigmented lesions. These lasers are commonly used to secondarily treat epidermal pigmented lesions while being used primarily for skin resurfacing (37-39).

The future

Because melanin absorbs light throughout the visible light spectrum, pigment-specific lasers have become a common tool in the laser surgeon's treatment of a wide variety of benign cosmetic pigmented lesions. Although the use of such systems remains somewhat controversial in the treatment of congenital nevi, it is clear that situations may arise where these lasers can be helpful. When these lasers are used to treat congenital nevi located in surgically compromised anatomic locations, the psychosocial stigma that arises from such a lesion can be lessened. The future will provide us with even more powerful and effective lesion-specific systems that may lead to improved clinical outcomes.

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