

# Photodynamic Therapy for Nevus Sebaceus With Topical $\delta$ -Aminolevulinic Acid

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

## REPORT OF A CASE

A 38-year-old woman was examined because of an extensive nevus sebaceus of Jadassohn (NSJ) covering the right side of her scalp and her face. The lesion first became apparent on the crown of her scalp when she was 12 years old and then gradually extended to the occiput. By the age of 20 years, it appeared on the right side of her face. A partial excision was done on the right temple, but the lesion recurred and later extended further down to the right preauricular area (**Figure 1**). Two biopsies were performed (of the right temple and preauricular areas) to rule out malignant transformation in the most recent proliferative parts. Both biopsy specimens showed a marked increase in the number of sebaceous glands in association with striking irregular papillary epidermal hyperplasia consistent with NSJ (**Figure 2**). There was no evidence of malignancy. The tumor in the preauricular area was of mostly cosmetic concern to the patient, but she refused further surgical intervention.

## THERAPEUTIC CHALLENGE

Our goal was to find an effective, relatively noninvasive, and cosmetically acceptable method for the treatment of this extensive NSJ.

## SOLUTION

After giving informed consent, the patient underwent topical  $\delta$ -aminolevulinic acid photodynamic therapy (PDT). Twenty percent  $\delta$ -aminolevulinic acid (DUSA Pharmaceuticals, Tarrytown, NY) was mixed in an oil-in-water emulsion (Eucerin Lotion; Beiersdorf-Jobst, Norwalk, Conn) and applied thickly to the preauricular lesion. Plastic film (Saran Wrap; Dow Brands, Indianapolis, Ind) was placed over the cream to confine the drug to the treatment site as well as to increase penetration. After light shielding with aluminum foil for 4 hours, a Wood lamp examination in a darkened room showed the typical red fluorescence of protoporphyrin IX (PPIX) limited to the tumor. The area was then anesthetized locally with in-

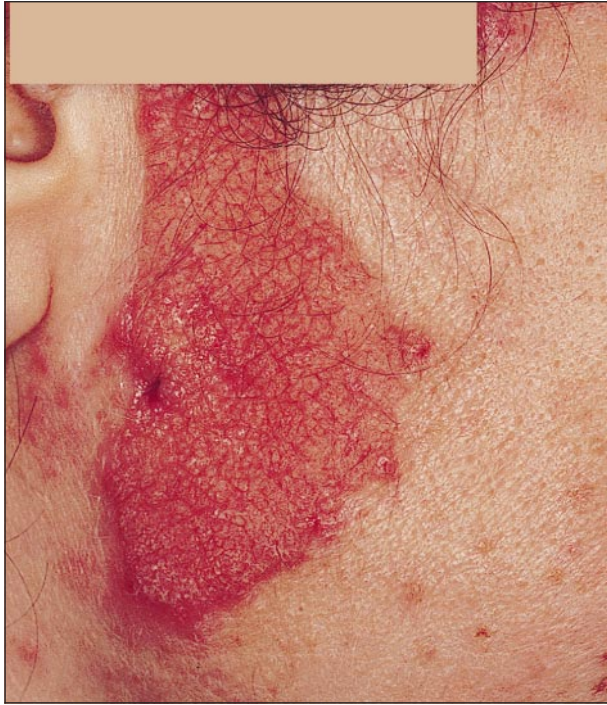
jection of 1% plain lidocaine and exposed to 630-nm laser light from an argon pumped tunable dye laser (CR-599 dye laser; Coherent, Palo Alto, Calif). A total dose of 100 J/cm<sup>2</sup> was given, fractionated in 2 doses of 50 J/cm<sup>2</sup>, at an irradiance of 50 mW/cm<sup>2</sup>, over an exposure field of 5 cm in diameter. To treat the whole preauricular area, 2 adjacent areas of the NSJ were treated consecutively.

Immediately after treatment, the NSJ was edematous and blanched, with erythema surrounding the treatment field. Within 3 to 5 days, superficial crusting developed, with complete healing in 2 to 3 weeks. Similar treatment sessions were repeated every 4 to 8 weeks, with a total of 13 treatment sessions. With each treatment session, the lesion regressed with flattening and decreased in size. Two remaining tumor nodules did not completely resolve and were curetted immediately before  $\delta$ -aminolevulinic acid application at the last 2 treatment sessions.

The final cosmetic result was excellent, with clinical resolution of the NSJ, no textural changes, mild focal hypopigmentation at the sites of the curettage, and focal comedo formation (**Figure 3**). There has been no recurrence of the lesion in the 16 months after discontinuation of therapy. A biopsy specimen taken after the final treatment session, from normal-appearing skin at a site of former NSJ, showed normal epidermis. The superficial parts of the sebaceous glands had been replaced by a widened and fibrotic dermis. Large hyperplastic sebaceous lobules were still present in the reticular dermis, presumably corresponding to sites beyond the depth of effective photodynamic therapy (**Figure 4**). There were no signs of dysplasia in the keratinocytes, melanocytes, fibroblasts, or endothelial cells.

## COMMENT

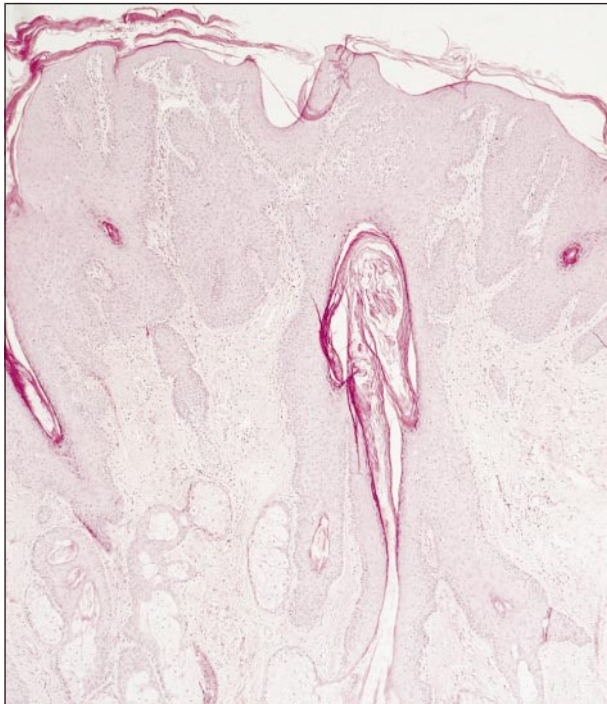
Nevus sebaceus of Jadassohn usually appears at birth or in early childhood, but it may be flat and inconspicuous.<sup>1</sup> The characteristic appearance may not develop until puberty, when it becomes thickened and more elevated.<sup>2</sup> For this reason, many patients are first examined



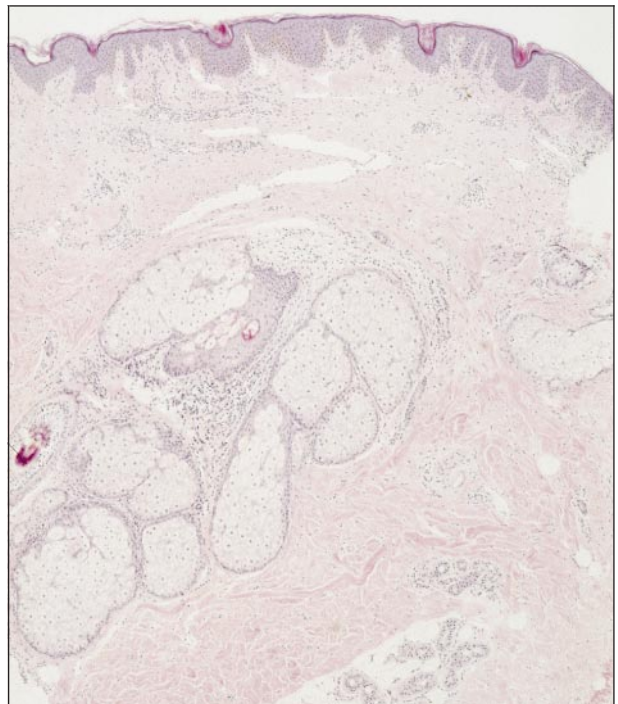
**Figure 1.** Right preauricular area of the patient showing a large tumor lobule of nevus sebaceus immediately before treatment.



**Figure 3.** Clinical resolution of the tumor after 13 treatment sessions, with no textural change, mild focal hypopigmentation, and focal comedo formation.



**Figure 2.** Routine section of untreated nevus sebaceus showing striking papillary epidermal hyperplasia with a marked increase in the number of sebaceous glands (hematoxylin-eosin, original magnification  $\times 50$ ).



**Figure 4.** Routine section of treated nevus sebaceus, showing normal epidermis, destruction of the superficial parts of the sebaceous glands, and replacement by fibrotic dermis. Large hyperplastic sebaceous lobules are still present in the reticular dermis (hematoxylin-eosin, original magnification  $\times 50$ ).

at this stage. Gradually, lesions may extend further or become more nodular. Of particular significance is the development of secondary tumors.<sup>3,4</sup> It is believed that nevus sebaceus arises from pluripotent epithelial germ cells with a capacity to dedifferentiate into various epithelial tumors, both benign and malignant. The most frequent are syringocystadenoma papilliferum and basal cell carcinoma.

Other malignant tumors reported are squamous, sebaceous, and apocrine carcinomas. The risk of malignancy is difficult to establish with precision, and malignant change may occur at any age. Because of this risk, complete surgical excision is recommended, pref-

erably before puberty, because the lesion will thicken and the risk of malignancy increases with age. In this case, the location and extent of the lesion would have made excision possible by means of tissue expansion techniques. However, the patient refused any surgical intervention. We opted for PDT with topical  $\delta$ -aminolevulinic acid because of its successful application for the treatment of other skin tumors.

In PDT, patients are first administered a photosensitizer, followed by exposure of the treatment sites to light. This generates highly reactive toxic oxygen intermediates, which lead to cell killing.<sup>5,6</sup>  $\delta$ -Aminolevulinic acid is the first committed precursor in the biosynthetic pathway of heme. Exogenous administration of  $\delta$ -aminolevulinic acid bypasses the negative feedback control exerted by heme on  $\delta$ -aminolevulinic acid synthetase, leading to the production and accumulation of the intermediate metabolite PPIX in epidermal cells and pilosebaceous units. Protoporphyrin IX is a potent endogenous photosensitizer. Subsequent exposure to light leads to selective destruction of cells containing accumulated PPIX.<sup>7,8</sup>

There is evidence of selective PPIX accumulation in sebaceous glands after  $\delta$ -aminolevulinic acid administration. Divaris et al<sup>9</sup> injected  $\delta$ -aminolevulinic acid intraperitoneally into albino mice. Fluorescence microscopy of frozen sections showed intense red fluorescence in the sebaceous glands and a much weaker fluorescence within the epidermis and the hair follicles. Little or no fluorescence was detected in the dermis and blood vessels. Whole-body exposure to light resulted in destruction of sebaceous glands, damage to the hair follicles, focal epidermal necrosis, and acute inflammatory changes. The epidermis gradually recovered, and the pilosebaceous units returned to their normal morphological characteristics but with a persistent reduction in number. Synthesis of PPIX in epidermal appendages is a unique feature of  $\delta$ -aminolevulinic acid over other photosensitizers, and topical application circumvents the photosensitivity that is induced by systemic agents.

Oxygen is required during PDT to produce the intermediate singlet oxygen,<sup>10</sup> and we therefore used a local anesthetic without epinephrine to avoid vasoconstriction. In situ consumption of tissue oxygen because of light exposure may itself be a rate-determining factor in PDT. Fractionation of the light exposure optimizes tissue oxygen consumption by PDT<sup>11,12</sup> and was used in this case. Wood lamp examination showed no PPIX fluorescence after a delivered fluence of 50 J/cm<sup>2</sup>, but PPIX fluorescence gradually reappeared 15 to 30 minutes later. The reappearance of PPIX fluorescence requires viable tissue and suggests incomplete destruction of the lesion.

Red light near 630 nm is usually used for tumor treatment, corresponding to one of the drug's absorption maxima. This wavelength region also permits deep tissue penetration, because an optical window exists in the skin for 600- to 800-nm light. Either lasers or nonlaser light sources can be used for PDT. The monochromatic output of lasers can provide an exact wavelength corresponding to an absorption maximum of the photosensitizer, maximizing drug activation efficiency. Protoporphyrin IX has several visible-light absorption maxima,

with an optimal wavelength for cell killing of 635 nm.<sup>13</sup> Irradiation of PPIX also generates photoproducts that may be active in vivo at 670 nm.<sup>14,15</sup> Therefore, broad-band light sources, including light-emitting diode (LED), arc, and incandescent lamps, might have some advantage over lasers.

Drug and/or light penetration into skin represents a potential limitation for topical PDT of tumors.<sup>16</sup> It may account for the slow clinical clearing of the lesion and the histological persistence of the deep portion of the lesion. Addition of dimethyl sulfoxide (DMSO) as a "penetration enhancer," ethylenediaminetetraacetic acid (EDTA) as a chelator, or topical desferrioxamine, an iron chelator, to the  $\delta$ -aminolevulinic acid vehicle<sup>17-19</sup> could potentially increase  $\delta$ -aminolevulinic acid penetration and/or PPIX synthesis. Curettage immediately before  $\delta$ -aminolevulinic acid application and PDT seems to hasten the resolution of the bulky and resistant areas.

Comedones occurred focally in the NSJ treated by PDT. The remaining deep sebaceous lobules might account for the comedo formation. Long-term development of cysts might also be a possibility, but these have not occurred in this case. The replacement of the papillary dermis and upper dermis by fibrosis may serve as an anatomical barrier between the epidermis and dermis, which may reduce the likelihood of clinical recurrence. Although this NSJ may recur after PDT, there has been no sign of this for at least 16 months.

The patient experienced no serious adverse effects. The painful burning sensation, typical of PDT during light exposure, was easily controlled with a local anesthetic. Complete healing always occurred within 2 to 3 weeks. An excellent cosmetic result was obtained, with complete clinical resolution and no scarring.

Although PDT with  $\delta$ -aminolevulinic acid causes selective destruction of NSJ with excellent cosmetic results, there are several important limitations. Multiple treatment sessions were required, although this could be limited by curettage before PDT treatment. The superficial necrosis and crusting, although well tolerated in this case, may be unacceptable to some patients. Most importantly, the deep component of the lesion was not eliminated, so that the patient may develop clinically visible NSJ recurrences as well as the associated benign and malignant tumors. Therefore, long-term, periodic follow-up will be important.

This is the first case, to our knowledge, of an extensive NSJ successfully treated with topical  $\delta$ -aminolevulinic acid and PDT. Photodynamic therapy may become a new treatment modality for this lesion, particularly for large lesions in cosmetically sensitive areas, but larger studies with longer follow-up times are needed. This case also underlines the interactions of  $\delta$ -aminolevulinic acid and PDT with sebaceous glands and the potential use for other sebaceous gland disorders, including acne vulgaris, sebaceous hyperplasia, and other tumors of epidermal origin.

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### Editor's Comment

**P**hotodynamic therapy (PDT) for skin lesions has been long on promise but short on clinically practical applications. Topical aminolevulinic acid (ALA) has the potential to make PDT practical by eliminating systemic photosensitivity and the need for intravenous administration.

A single treatment with the ALA-PDT combination has shown very promising results for the treatment of actinic keratoses. Treatment with ALA-PDT has yet to demonstrate efficacy that approaches that of standard therapy for superficial basal cell carcinoma and Bowen disease. With ALA's affinity for sebaceous glands, it may be useful for the treatment of sebaceous hyperplasia and acne. The very good cosmetic results achieved with ALA-PDT for the nevus sebaceous in the above case report could potentially be achieved with less treatments if done before the lesion hypertrophies at puberty.

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Section Editor