Cicatricial Alopecia Secondary to Radiation Therapy: Case Report and Review of the Literature

Gregg A. Severs, DO; Thomas Griffin, MD; Maria Werner-Wasik, MD

Cicatricial or scarring alopecia represents permanent destruction of the hair follicle, histopathologically showing a decreased number of follicular units leaving streamers of fibrosis or hyalinization of surrounding collagen. High-dose radiation therapy (RT) used for treating intracranial malignancy can permanently destroy hair follicles, resulting in permanent alopecia. Typically, there also is clinical scarring of the skin with dermal fibrosis. We report a case of radiation-induced cicatricial alopecia confirmed by histopathology, without obvious clinical scarring or dermal fibrosis. This lack of fibrosis made our patient a good candidate for hair transplantation. The clinicopathologic presentation in this case could be related to the method of RT employed in treating our patient's brain tumor. A literature review of radiation-induced cicatricial alopecia, as well as a brief discussion of the current radiation methods used in the treatment of intracranial malignancy, is presented. We believe that because most anagen follicles are approximately 4 mm deep in the skin, if the dose of radiation superficial to a depth of 5 mm is kept under 16 Gy, which is the approximate lethal dose for hair follicles, the incidence of radiation-induced cicatricial alopecia could be avoided or markedly decreased.

Cutis. 2008;81:147-153.

Accepted for publication March 15, 2007.

Dr. Severs is in private practice, Scranton, Pennsylvania. Dr. Griffin is from the Department of Dermatology, Drexel University, Philadelphia, Pennsylvania. Dr. Werner-Wasik is from the Department of Radiation Oncology, Jefferson Medical College, Philadelphia.

The authors report no conflict of interest.

Correspondence: Gregg A. Severs, DO, 327 N Washington Ave, Suite 200, Scranton, PA 18503 (gsevs@yahoo.com).

Cicatricial or scarring alopecia represents permanent destruction of the hair follicle. Clinically, depending on the cause, there is effacement of follicular orifices in a patchy or diffuse distribution. A biopsy is confirmatory, showing a decreased number of follicular units leaving streamers of fibrosis or hyalinization of surrounding collagen.[1] There are several well-recognized causes of secondary cicatricial alopecia, such as infection, inflammatory processes, and physical sources (eg, radiation, burns).[2] Alopecia and loss of sebaceous and sweat glands in radiated sites is a dose-dependent phenomenon that can be temporary or permanent.[1] Patients usually recover from the hair loss (anagen arrest) associated with radiation therapy (RT), but a sufficiently high dose of radiation used for treating intracranial malignancy can permanently destroy hair follicles.[3]

High-dose RT, resulting in permanent alopecia, typically leads to clinical scarring of the skin with dermal fibrosis. We report a case of radiation-induced cicatricial alopecia confirmed by histopathology, without obvious clinical scarring or dermal fibrosis. This lack of fibrosis made our patient a good candidate for hair transplantation. The clinicopathologic presentation in this case could be related to the method of RT employed in treating our patient's brain tumor. Because of this atypical clinical appearance and the paucity of reports documenting the histopathologic features of radiation-induced cicatricial alopecia, we present the following case and review of the literature.

Case Report

A World Health Organization grade III astrocytoma (anaplastic astrocytoma) was diagnosed in a 25-year-old woman in July 2001. The lesion was surgically removed and the craniotomy was bridged with a titanium plate. She then received 3-dimensional conformal radiation therapy (3D-CRT)

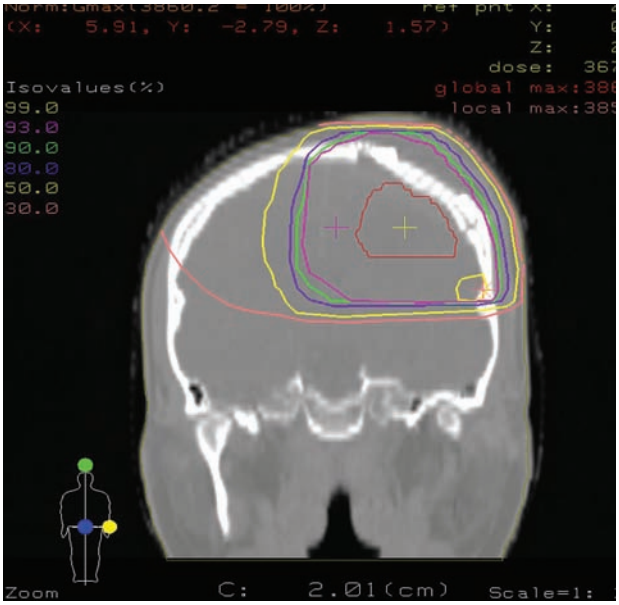

Figure 1. The distribution of radiation therapy doses at depths of particular isodose lines (lines connecting points of equivalent dose) as presented in the Table.

Radiation Isodose Distribution[a]

Radiation Dose, %	Line Color	Tissue Dose, Gy	Tissue Depth
93	Cyclamen	60.0	1.32 cm
90	Green	58.0	1.00 cm
80	Purple	51.6	0.7 cm
50	Yellow	32.2	0.4 cm
30	Pink	19.35[b]	0.1–0.2 cm[b]

[a]The tumor is represented with a red line.
[b]The doses at a depth of 0.1 to 0.2 cm are notoriously difficult to assess precisely, so this is an estimate.

to a total dose of 60.0 Gy in 2.0 Gy fractions administered over 6 weeks with a 4–field beam arrangement (left anterior oblique, left posterior oblique, left lateral, vertex) using 6 MV photons. The distribution of RT doses at depths of particular isodose lines (lines connecting points of equivalent dose) is presented in Figure 1 and the Table.

After RT, she began chemotherapy with temozolomide (October 2001–September 2002). She first noticed hair loss during her second week of radiation, with maximal hair loss at 5 weeks of RT. At its worst, the area of alopecia covered the entire superior aspect of her scalp. The peripheral areas began to regrow during her chemotherapy, approximately 1 to 2 months after discontinuing RT.

On physical examination, the patient had average hair density, except for a residual area of alopecia on the left temporoparietal scalp. Within this area, there was a linear surgical scar and an area of decreased hair density (Figure 2). There was a progressive decreasing density gradient peripherally to centrally, with only miniaturized hairs remaining centrally. The follicular orifices were present and the skin was not bound down, atrophic, or obviously fibrotic, except along the surgical scar.

Punch biopsy specimens (4 mm) were obtained from the area of alopecia on the left parietal scalp (Figure 3) and compared with a control biopsy taken from uninvolved occipital scalp at an area of average hair density. We compared the control biopsy with the alopecia biopsy to demonstrate the depths of typical and destroyed structures and to show the difference in dermal thickness. In the alopecia biopsy site, there were essentially no follicles from 0.1 cm to 0.4 cm, which received between 19.35 and 32.2 Gy of radiation (Figure 1; Table). At a depth superficial to 0.2 cm, which received up to 19.35 Gy of radiation (Figure 1; Table), adnexal structures were damaged. The dermis was thin when compared with the control, measuring 0.2 cm versus 0.4 cm, respectively. The biopsy specimen from the left parietal scalp (Figure 3) showed an intact epidermis. Eccrine ducts and orifices were present. The outer root sheath was present above the sebaceous glands. The dermis showed a decreased number of follicular units. The follicles were either truncated just below the sebaceous glands (Figure 4) or were miniaturized anagen follicles. Truncated follicles showed buds of germinal follicular epithelium below the level of sebaceous glands but no deeper than just below the sebaceous glands. Miniaturized anagen follicles were seen originating in the lower reticular dermis and showed intact internal and external root sheaths. Sebaceous glands and arrector pili muscles were present; however, the sebaceous glands were small, with decreased numbers of lobules when compared with the control. Eccrine glands were present in the lower reticular dermis but

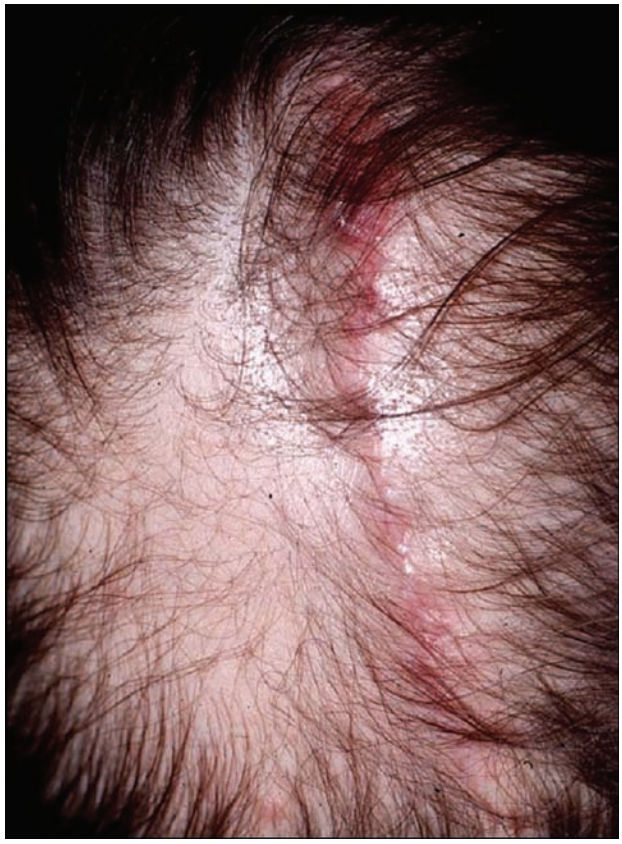

Figure 2. Area of alopecia on the left temporoparietal scalp.

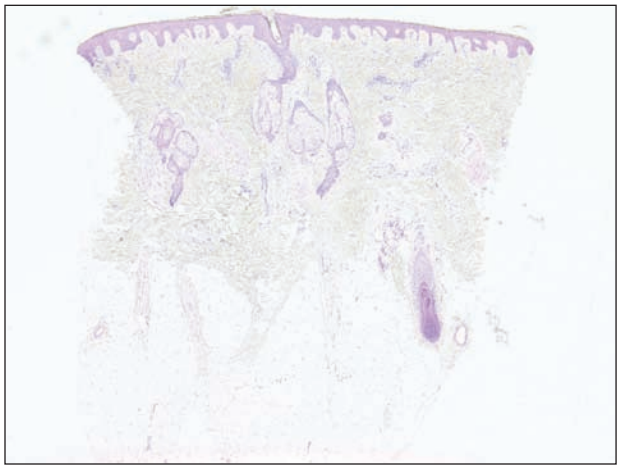

Figure 3. Punch biopsy specimen (4 mm) obtained from the area of alopecia on the left parietal scalp (H&E, original magnification ×2).

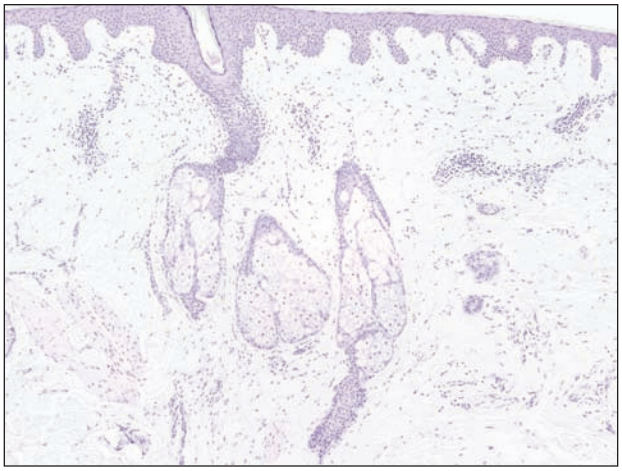

Figure 4. An intact epidermis and hypoplastic sebaceous glands in a punch biopsy specimen from the area of alopecia on the left parietal scalp. A truncated follicle also was present (H&E, original magnification ×10).

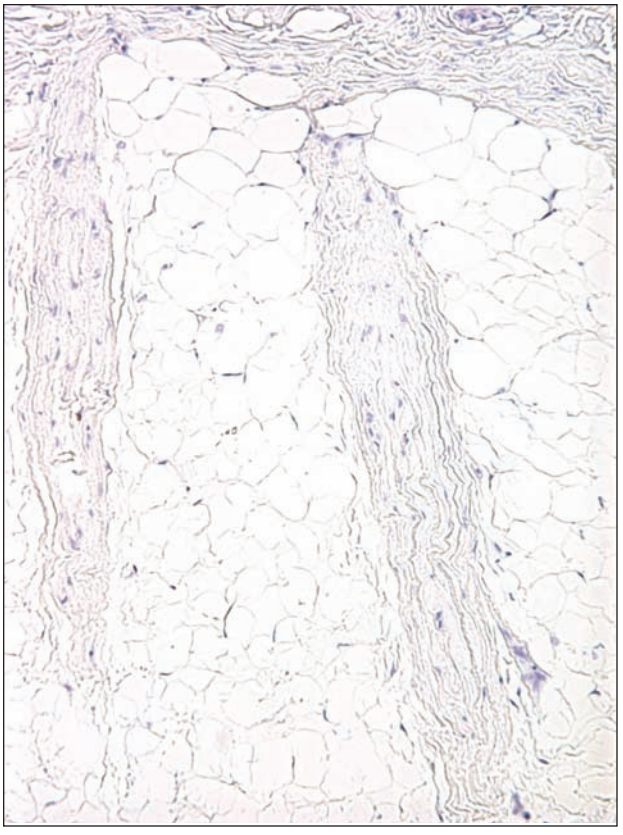

Figure 5. Streamers of scarred follicles were present in the subcutaneous fat (H&E, original magnification ×20).

were decreased in number and size, with fewer acini per gland, and focally showed hyalinization of the basement membrane. Subcutaneous fat was present and was unremarkable. Streamers of scarred follicles were present in the subcutaneous fat (Figure 5).

Comment

In 1896, one year after Roentgen discovered x-rays, Daniel[4] reported that x-radiation caused loss of hair in the human scalp. During the first 2 decades of the 20th century, x-ray epilation of the face for hirsutism was frequently utilized.[5] In 1906, Williams[6] observed that the roots of hair epilated by x-ray were pointed in configuration and hairs that did not fall out spontaneously after exposure to radiation and continued to grow had markedly constricted shafts.

X-ray epilation for the treatment of tinea capitis was standardized by Kienböck[7] in 1907 and Adamson[8] in 1909 and used a suberythema dose. The radiation dose from this technique ranged from 500 rad (5 Gy) to 800 rad (8 Gy).[9] Epilation began in 14 to 21 days and was complete by the end of 4 weeks. The hair began to regrow within 2 to 3 months.[10] Properly implemented, the Kienböck-Adamson technique avoided chronic cutaneous damage and scarring alopecia. However, technical errors were common, with the most frequent mistake being overlapping of the radiation fields.[5,11] Faulty or poorly calibrated equipment often resulted in permanent alopecia.[5,10]

In 1952, Geary[12] histologically studied degeneration of the hair root in the albino rat following epilating doses of x-rays. He found that the matrix of the hair bulb was extremely sensitive to radiation because morphologic changes in this area were detectable as early as one day after exposure. Geary also found that hairs in the anagen phase were much more susceptible to x-radiation than those in the telogen phase.[12]

Van Scott and Reinertson[13] studied the effects of x-radiation on hair roots of the human scalp. They found that changes in the hair root were detected as early as the fourth day after exposure to radiation and were confined to anagen hairs. The earliest radiation effect was reduction of the diameter of the hair bulb. The matrix of the bulb, when present, showed the most marked decrease in diameter. After the fourth postradiation day, the entire hair bulb showed progressive atrophy, leaving only a thin strand of tissue lying below the keratogenous zone. The internal root sheath of the radiated hair persisted and appeared thicker than normal due to the decreased diameter of the bulbar remnant that it encased. At this stage, upon pulling, many hair roots were found to be broken off at a level immediately below the keratogenous zone. At 2 to 3 weeks following exposure, hairs with tapered shafts and small keratinized bulbs were found. In many hairs, the keratogenous zone was absent and evidence of complete cessation of growth was apparent. Other hairs that retained the keratogenous zone continued to produce hair shafts, but the shafts were markedly thinned. The proportion of hairs showing these dysplastic changes were greater in sites receiving the higher doses of radiation.[13]

In 1940, McCarthy[10] described 3 grades of skin reactions to x-rays. A first-grade reaction appears within 16 to 21 days of x-radiation and consists of scarcely perceptible erythema and slight scaliness of the skin with loss of hair. Healing takes place with regrowth of the hair in 2 to 4 months. A second-grade reaction occurs within a week of x-radiation with very marked edema and erythema, often with vesicle formation. The hair is likely to be permanently lost and the involved area becomes dry, scaly, pigmented and atrophic over a period of years. A third-grade reaction occurs a few days after exposure to a single large dose or the last of repeated small doses of x-radiation. Inflammation leading to destruction of the skin and underlying tissue results in ulceration. The ulcers are exceedingly slow to heal and lead to scarring, permanent alopecia, spotty pigmentation, telangiectasia, atrophy of sweat and sebaceous glands, and a tendency to form keratoses and subsequent carcinoma.[10]

Effects of x-radiation on the skin and its appendages are dependent upon both the dose of radiation and the wavelength or energy of the beam. In 1936, Borak[14] studied the doses of orthovoltage radiation that were lethal for epithelium in the epidermis and appendages. He stated that the dose of 1200 R was lethal for sebaceous glands, 1600 R for hair follicles, 2000 R for the epidermis, and 2500 R for sweat glands. These figures are expressed in roentgen (doses in air), not in gray (doses in tissue), and therefore may not be applicable to current radiotherapy, but they suggest differences in the radiosensitivity of these structures.[14] In superficial RT, the difference between 1 R and 1 rad usually is insignificant, though in deep x-ray therapy, these values may be of great variance. Using the International System of Units, 1 Gy is equivalent to 1 J/kg, and because 1 J is equivalent to 10^7 erg/kg or 10^4 erg/g, 1 Gy is equivalent to 100 rad.[15] Thus, the lethal doses above can be approximated in

Gy based on the assumption that 1 R is approximately equivalent to 1 rad and 1 Gy is equivalent to 100 rad. Thus, approximately 12 Gy would be lethal for sebaceous glands, 16 Gy for hair follicles, 20 Gy for the epidermis, and 25 Gy for sweat glands.

The delayed effects of radiation injury progress slowly and often subclinically between 6 months and 1 year.[16] Aside from loss of hair and dryness, there may be little clinical evidence of tissue injury. Histologically, however, many of the features seen in chronic radiodermatitis are already present. In chronic radiodermatitis, hair follicles and sebaceous glands are absent throughout large areas. The only remnant of the pilosebaceous apparatus is the arrector pili muscle, often embedded in a pear-shaped mass of collagen. This pattern of periodically arranged, scarred, atrophic follicles and sebaceous glands often is seen in late radiation damage. Though sweat glands are less radiosensitive than other epithelial elements, some degree of atrophy of both ducts and glands is present and complete destruction is not unusual.[16]

Most skin reactions from radiation treatment of deep-seated tumors have occurred from the use of orthovoltage radiotherapy in the range of 90 to 500 keV.[16] With the advent of megavoltage radiation sources, such as clinical linear accelerators, which use energy ranging from 2 to 40 MeV, the skin is generally spared when targeting deeper tumors. However, even when the optimal conditions of megavoltage irradiation are met, about 25% of patients receiving therapy through parallel opposing fields for deep tumors will have observable skin reactions.[16]

Today, radiation is used in the treatment of many brain neoplasms, either alone or in combination with surgery and chemotherapy.[17] The safe delivery of radiation to malignant or benign intracranial masses is complicated by the sensitivity of healthy surrounding tissue. With advances in the technique and equipment used in the treatment of brain lesions, radiation oncologists are able to use a computed tomographic scan and magnetic resonance imaging to create a 3-dimensional model of the patient's anatomy and tumor; thus, they can more accurately conform the radiation to the shape of the pathologic lesion. This 3-dimensional localization (conformal RT) allows escalation of the dose to the tumor, while neighboring critical tissues receive less radiation.[17]

Technological and computer developments have propelled radiation oncology into the 3D-CRT era.[18] 3D-CRT is increasingly being used to treat primary and metastatic brain tumors. If the tumor is initially treated by surgical removal, 3D-CRT is typically started 2 to 4 weeks after surgery to allow for normal wound healing. Current treatment regimens for primary central nervous system tumors include doses of 50 to 60 Gy in 25 to 30 fractions (1.8−2.0 Gy per fraction) with 3D-CRT. Treatment schedules delivering higher doses or using larger fraction sizes (>2.0 Gy per fraction) are associated with higher risks of central nervous system toxicity. In addition to dose considerations, the volume of brain radiated to high dose must be minimized by using multiple cross-firing treatment beams with careful blocking of uninvolved brain. Multiple coplanar and noncoplanar fields are carefully configured to encompass the tumor and surrounding edema with appropriate margins.[18]

Scalp dose can be controlled with 3-dimensional megavoltage conformal RT, with reduced incidence of permanent alopecia. Megavoltage (deep) radiation has relative skin-sparing properties, which provides a lower dose of radiation to superficial structures when compared with the historically used orthovoltage (superficial) radiation. As seen in our patient's biopsy, the structures in the epidermis and superficial dermis were spared, while many deeper structures were destroyed because of the dose-depth characteristics of megavoltage photon beam RT. With the higher energy used (6 MV), as well as the way the radiation plan includes 4 different beam planes intersecting at the tumor, 3D-CRT provides the tumor with the highest dose of radiation with lower doses to the structures in the paths of the individual beams. While the tumor receives the greatest amount of radiation, the surrounding tissue and structures may receive a high enough dose of radiation to be damaged or destroyed. The area of permanent alopecia seen in our patient was the part of her scalp closest to the tumor and thus received a high enough radiation dose to destroy most of the hair and damage or destroy the adnexal structures in this area. We hypothesize that the follicles that were spared were in telogen phase at the time of treatment and thus less radiosensitive and higher in the dermis than anagen follicles. No hairs were completely spared, with only miniaturized follicles remaining.

As seen in the Table, the dose of radiation received at 0.1 to 0.2 cm was approximately 19.35 Gy, which is above the approximate lethal dose for sebaceous glands (12 Gy) and hair follicles (16 Gy). The dose received at 0.4 cm

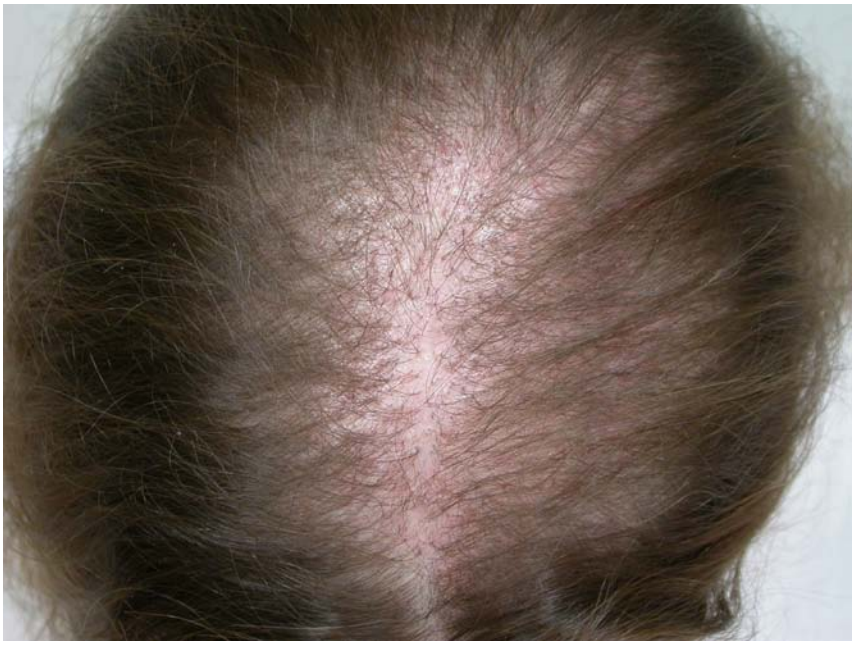

Figure 6. Area of alopecia on the left temporoparietal scalp after 3 sessions of hair transplantation.

was 32.2 Gy, which is lethal to sebaceous glands, hair follicles, the epidermis (20 Gy), and sweat glands (25 Gy). The above-mentioned lethal doses of radiation at these levels in the dermis and subcutaneous tissue correlate well with the histopathologic findings (Figures 3–5) of decreased numbers of sebaceous lobules; truncated, miniaturized, and scarred hair follicles; and decreased numbers and size of eccrine glands when compared with the control biopsy.

Radiation-induced alopecia, a common sequela of radiation treatment of brain tumors, is a major cause of apprehension and loss of self-esteem in patients undergoing RT. Although the reduction of alopecia would not alter the prognosis, it would allay some apprehension and enhance the patient's self-image during and after treatment.

We believe that because most anagen follicles are approximately 4 mm deep in the skin, if the dose of radiation superficial to a depth of 5 mm is kept under 16 Gy, which is the approximate lethal dose for hair follicles, the incidence of radiation-induced alopecia could be avoided or markedly decreased. Furthermore, because the dose used for temporary epilation in the treatment of tinea capitis was between 5 Gy and 8 Gy, if the radiation dose superficial to 5 mm was kept under 5 Gy, even the temporary epilation associated with radiation treatment for intracranial neoplasms could be prevented. It is recognized that the location of the brain tumor will determine the dose in the skin where treatment of a superficial lesion will more likely result in damage to follicles. As radiation techniques continue to improve with even better localization of radiation, we will continue to see fewer radiation effects in surrounding tissue and thus less radiation-induced cicatricial alopecia.

The only reported successful treatment for radiation-induced cicatricial alopecia has been hair transplantation.[19] We performed 3 sessions of hair transplantation on our patient with excellent results (Figure 6). We attribute successful grafting to the fact that substantial dermal and subcutaneous scarring was not present. We plan further transplantation in the future to increase density in this area.

In the future, it would be interesting to conduct a retrospective or prospective study hypothesizing that if the radiation dose at a depth of 4 to 5 mm in the skin (the level of most hair follicles) was kept under 16 Gy (the lethal dose for hair follicles), there may be less incidence of cicatricial alopecia postradiation.

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