Case 3-2008: An 80-Year-Old Woman with Cutaneous Basal-Cell Carcinomas and Cysts of the Jaws

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**Presentation of Case**

*Dr. Gabriela Rolz-Cruz (Dermatology):* An 80-year-old woman was seen in the outpatient clinic of this hospital for management of recurrent ulcerated skin lesions on the scalp.

When the patient was approximately 34 years old, 40 to 50 lesions, which were red and slightly elevated, developed on her back. The lesions were fulgurated at another hospital and resolved. Two years later, lesions on her back recurred and increased in number during the next several years, and similar lesions developed on her scalp. At the age of 40 years, the patient was admitted to this hospital. There were multiple lesions on the scalp: one in the right frontoparietal region (3 by 2 cm), another in the right temporal area, and others in both preauricular areas. There were four lesions over the sternum, one of which was pigmented and 1.0 cm in diameter, and there were approximately 40 lesions on the back, which were red and slightly raised. A full-thickness excision of the largest scalp lesion and split-thickness skin grafting and electrodessication and curettage of the other lesions were performed. Pathological examination of the excised tissue revealed basal-cell carcinoma; the resection margins were close at one edge.

During the next 40 years, the patient was followed in the dermatology tumor clinic of this hospital. Basal-cell carcinoma recurred in the periphery of the previous graft, and additional lesions developed on the scalp, face, neck, chest, and central portion of the back (Fig. 1). She was treated with 5% fluorouracil in propylene-glycol solution applied to the face and torso two or three times a day and sunblock applied to exposed skin. Persistent lesions were treated with electrodessication and curettage or cryosurgery, and other lesions were excised.

When the patient was 50 years of age, the lesions included multiple red and pearly telangiectatic papules on the middle and lateral portions of the back (Fig. 2A), a papule (3 by 2 mm) behind the right ear with telangiectasia, and multiple superficial erythematous papular lesions on the lower portion of the back and scalp. Pseudopits with keratotic lesions and slight depressions in the center, 1 to 2 mm in diameter, were present on both palms (Fig. 2B).

When the patient was 54 years old, biparietal frontal bossing with flattening...
over the frontal area was noted. A radiograph of the skull revealed thickening over the left calvaria, rarefaction of bone over the right calvaria, and extensive calcification of the falx cerebri. Lesions on the temporal–occipital and parietal scalp, ranging from 0.5 to 11.0 cm in diameter, some of which were ulcerated, grew to cover 30 to 40% of the scalp (Fig. 2C).

When the patient was 55 years of age, several of the scalp lesions were excised and covered with a partial-thickness skin graft harvested from the left thigh. Pathological examination of the excised

Figure 1. Distribution of Basal-Cell Carcinoma Lesions.
Lesions are represented by circles, with the size of the circle increasing with the number of lesions.
tissue revealed sclerosing and superficial basal-cell carcinomas. The tumor was present at multiple lateral-resection margins of a lesion from the right temporal area and the vertex; fluorouracil was administered to these areas. A trial of retinoic acid (1.5 mg per kilogram of body weight) was discontinued after 3 months because of hypertriglyceridemia; type III hyperlipidemia was diagnosed. The scalp lesions recurred, and an ulcer developed in the skin graft within 6 months after the excision. A trial of isotretinoin (1.5 mg per kilogram [80 mg per day]) was discontinued after 3 months because of fatigue, headaches, arthralgias, hypertriglyceridemia, and urinary incontinence.

When the patient was 56 years of age, an occipital basal-cell carcinoma was resected, and a partial-thickness skin graft was applied. Lesions continued to develop in the scalp, face, axilla, and groin, and during a 2-year period, the patient required additional split-thickness skin grafts to the scalp, harvested from the left thigh and adjacent scalp. At 60 years of age, Mohs’ micrographic surgery was performed intermittently on selected lesions on the ear, scalp, face, and vulva. A chest radiograph obtained when the patient was 66 years old revealed a deformity of a rib on the left side, thought to be congenital.

At 80 years of age, the patient consulted a dermatologist at another institution because the lesions on the scalp had enlarged and become painful (Fig. 2D); radiation therapy was recommended. She returned to the dermatologic surgery clinic for further treatment.

At 10 years of age, most of her molars had been extracted because of horizontal growth. Between the ages of 22 and 36 years, 10 maxillary

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**Figure 2. Clinical Photographs.**

At 50 years of age, the patient had multiple red and pearly telangiectatic papules on the middle and lateral areas of the back (Panel A). Pseudopits and keratotic lesions with slight depressions in the center were present on both palms (Panel B). At 54 years of age, the patient had lesions on the temporal–occipital and parietal scalp, ranging from 0.5 to 11.0 cm in diameter, some of which were ulcerated, covering 30 to 40% of the scalp (Panel C). When the patient was 80 years of age, scalp lesions enlarged and became painful (Panel D). These included an ulcerated lesion on the right frontal scalp (5.9 cm by 1.9 cm), an ulcerated lesion on the right vertex (5.5 cm by 2.0 cm), and a lesion on the left parietal scalp (2.0 cm by 2.0 cm). Photographs courtesy of Dr. Howard Baden.
and mandibular cysts were excised; pathological examination of an excised maxillary cyst revealed an epidermoid cyst with chronic inflammation. At 64 years of age, the maxillary and mandibular cysts were enucleated, and pathological examination revealed odontogenic keratocysts; recurrent odontogenic keratocysts were removed when she was 72 years old and again when she was 75 years old.

Hysterectomy and bilateral salpingo-oophorectomy had been performed at 55 years of age because of leiomyomas, as was a modified left radical mastectomy for infiltrating lobular carcinoma at 66 and a modified right radical mastectomy for high-grade ductal carcinoma in situ at 70. The patient also had hyperlipidemia; cerebrovascular disease, with a stroke at the age of 74 resulting in aphasia and decreased mental acuity; coronary artery disease with myocardial infarction and coronary-artery bypass grafting at the age of 70 years; and adult-onset, insulin-requiring diabetes. Her medications included ranitidine, sertraline, insulin glargine, and multiple vitamins.

The patient was married and lived with her husband; she had worked as a nurse. She drank alcohol socially and did not smoke cigarettes. Her parents and several siblings had had cardiovascular disease, a sister had brain cancer, and brothers had had colon cancer, lung cancer, and bladder cancer. Her father and a brother had subcutaneous nodules. There was no family history of maxillary cysts or basal-cell carcinomas. On examination of the skin, there was dermatoheliosis of sun-exposed skin. There were multiple benign nevi, seborrheic keratoses, hemangiomas, and basal-cell carcinomas. An ulcerated lesion, 5.9 by 1.9 cm, was present on the right frontal scalp; another ulcerated lesion, 5.5 by 2 cm, was present on the right vertex; and a lesion on the left parietal scalp was 2 by 2 cm.

A management decision was made.

**Figure 3. Radiologic Images of the Skull.**

A skull radiograph obtained when the patient was 54 years of age shows dense calcification within the falx cerebri (Panel A, arrows). A Panorex view of the mandible performed at 63 years of age reveals a well-defined, lucent cyst within the left side of the mandible (Panel B, oval). A chest radiograph performed at the age of 72 years reveals multiple rib anomalies (Panel C): abnormal spacing between the posterior ribs, which are too close together, as well as tapering and expansile cystic changes in two left anterior ribs (oval).
there is extensive calcification within the falx cerebri (Fig. 3A). A Panorex view of the mandible obtained at 63 years of age reveals that the patient is partially edentulous. There is a well-circumscribed, lucent cyst within the left side of the mandible (Fig. 3B). Multiple chest radiographs over the years revealed rib abnormalities, including abnormal spacing between ribs, with two ribs being too close together and expansile cystic changes in two adjacent ribs in the left lower hemithorax (Fig. 3C).

Dr. Ervin H. Epstein: This patient has multiple basal-cell carcinomas, odontogenic cysts of the jaw, and pits of the palms and soles, as well as calcification of the falx cerebri, rib abnormalities with cysts, frontal bossing, and skull abnormalities including rarefaction and thickening. This constellation of findings is diagnostic of the basal-cell nevus syndrome, also known as nevoid basal-cell carcinoma syndrome or Gorlin's syndrome.1,2

Our patient has three major criteria for the basal-cell nevus syndrome: multiple basal-cell carcinomas, odontogenic cysts of the jaw, and pits of the palms and soles. She also has calcification of the falx cerebri, which in someone younger than 20 years is pathognomonic for the basal-cell nevus syndrome but in our patient would be considered suggestive but not diagnostic, since she is over 50. Any two of these criteria are deemed sufficient to establish the diagnosis of the basal-cell nevus syndrome (Table 1).3

Dozens of other abnormalities have been described in patients with the basal-cell nevus syndrome, including developmental anomalies and tumors. This woman's case is a bit unusual in that most patients come to medical attention earlier in life than she did, because of the diagnosis of jaw cysts. The basal-cell nevus syndrome is well known to oral surgeons as a cause of multiple aggressive, frequently recurrent cysts. It is possible that jaw cysts caused this patient's abnormally positioned molars. Similarly, basal-cell carcinomas are usually found in adolescence or even childhood. However, the basal-cell carcinomas may resemble small nevocellular nevi (“moles”) or banal skin “tags,” often at the upper chest and neck, and may elude diagnosis for some years. When a clinician sees a young patient with multiple basal-cell carcinomas, the most straightforward diagnostic procedures for the basal-cell nevus syndrome are an examination of the palms and soles to identify pits and radiography of the skull, ribs, and jaws.

One of the most striking clinical abnormalities in the basal-cell nevus syndrome is a high sensitivity to radiation-induced basal-cell carcinomas. Since perhaps 4% of patients with medulloblastoma have the basal-cell nevus syndrome, and the standard treatment for medulloblastoma is radiotherapy, the possibility of this diagnosis should be considered when planning treatment of any patient with this cancer.

Mutations in the tumor-suppressor gene patched homologue 1 (PTCH1) at chromosome 9q22.3 cause the basal-cell nevus syndrome,4,5 and sporadic basal-cell carcinomas also frequently have mutations in this gene. Mutations in PTCH1 abrogate the ability of the PTCH1 protein to inhibit the hedgehog signaling pathway, which is critical in embryogenesis and development. The resulting abnormal activation of this pathway may help explain the multiple phenotypic abnormalities described in the basal-cell nevus syndrome.2 Approximately 10% of sporadic basal-cell carcinomas have mutations in the smoothened gene (SMO), the proximal target of PTCH1 inhibition, providing additional evidence that the activation of hedgehog signaling is pivotal in carcinogenesis of basal-cell carcinomas, and indeed essentially all basal-cell carcinomas have activation of this pathway.6,7 Several common sporadic cancers — pancreatic, small-cell lung, prostate, and oth-

Table 1. Diagnostic Criteria for the Basal-Cell Nevus Syndrome.*

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<th>Major Criteria</th>
<th>Minor Criteria</th>
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<td>More than two basal-cell carcinomas, or one before 20 yr</td>
<td>Macrocephaly determined after adjustment for height</td>
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<td>Odontogenic keratocysts of the jaw, proved by histologic analysis</td>
<td>Congenital malformations: cleft lip or palate, frontal bossing, “coarse face,” or moderate or severe hypertelorism</td>
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<td>Three or more palmar or plantar pits</td>
<td>Skeletal abnormalities: Sprengel's deformity, marked pectus deformity, or marked syndactyly of the digits</td>
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<td>Bilamellar calcification of the falx cerebri (if younger than 20 yr)</td>
<td>Radiologic abnormalities: bridging of the sella turcica, vertebral anomalies such as hemivertebrae, fusion or elongation of the vertebral bodies, modeling defects of the hands and feet, flame-shaped lucencies of the hands or feet, or translucencies in the skull</td>
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<tr>
<td>Fused, bifid, or markedly splayed ribs</td>
<td>Ovarian fibroma</td>
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<tr>
<td>First-degree relative with the basal-cell nevus syndrome</td>
<td>Medulloblastoma</td>
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<tr>
<td>PTCH1 gene mutation in normal tissue</td>
<td>* These criteria are adapted from Kimonis et al.3</td>
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* These criteria are adapted from Kimonis et al.3
ers — frequently have activation of hedgehog signaling due to increased production of hedgehog ligand rather than mutations in the pathway components. One estimate suggests that hedgehog signaling is implicated in the induction, maintenance, and metastasis of up to 25% of human tumors. Furthermore, since hedgehog signaling may play a role in the maintenance, function, and survival of neoplastic stem cells, hedgehog antagonists now under development may be important in our battle against many human cancers.

The only other gene known to be mutated frequently in basal-cell carcinomas is TP53, which harbors point mutations in approximately 50% of sporadic human basal-cell carcinomas and which is frequently mutated in skin damaged by long-term sun exposure.

The basal-cell nevus syndrome is inherited as an autosomal dominant condition. The severity of phenotypic manifestations varies widely among patients, and no patient has all the abnormalities listed in Table 1. The exact nature of the mutation is not related to the severity of the disease, and the severity varies within a kindred as much as among kindreds. Dark-skinned patients have fewer basal-cell carcinomas than do light-skinned patients, and more cancers develop in patients in Australia than in those living in less sunny climates. These observations suggest that

Figure 4. Basal-Cell Carcinomas (Hematoxylin and Eosin).
The most common pattern was nodular (Panel A), showing large nests of uniform, small, blue cells with peripheral palisading and surrounding mucinous stroma. The second most common pattern was superficial (Panel B), in which a small number of cells similar to those of nodular basal-cell carcinomas are present at, and subjacent to, the basal layer of the epidermis. Also present were basal-cell carcinomas of the infiltrating type, in which cords of tumor cells (two or three cells in thickness) infiltrate soft tissues (Panel C), and fibroepithelioma of the Pinkus type, in which anastomosing cords of tumor cells (two or three cells in thickness) arise from multiple locations in the epidermis, with a proliferative stroma (Panel D).
the severity of manifestations is controlled both by other genes and by environmental insults.

Our patient has aggressive basal-cell carcinomas as well as a family history particularly rich in cancers. Her siblings had cancers of the colon, brain, bladder, and lung, and she had bilateral breast cancers. It may be that her PTCH1 mutation was functioning in the context of a relatively high number of alleles that predispose to cancer. A patient with mutations in both PTCH1 and BRCA1 has been reported.12

**CLINICAL DIAGNOSIS**

The basal-cell nevus syndrome.

**DR. ERVIN H. EPSTEIN’S DIAGNOSIS**

The basal-cell nevus syndrome.

**PATHOLOGICAL DISCUSSION**

*Dr. Thomas J. Flotte:* Several hundred slides of basal-cell carcinomas of the skin that were biopsied or excised from this patient over a 40-year period were reviewed. The most common pattern was nodular, showing large nests of uniform, small, blue cells with peripheral palisading and surrounding mucinous stroma2,11 (Fig. 4A). The second most common pattern was superficial, in which a small number of cells similar to those of nodular basal-cell carcinomas are present at and subjacent to the basal layer of the epidermis (Fig. 4B). In addition to these two patterns, the following patterns were also seen: infiltrating (cords of tumor cells, two or three cells in thickness, infiltrating soft tissues) (Fig. 4C), fibroepithelioma of the Pinkus type (anastomosing cords of tumor cells, two or three cells in thickness, arising from multiple locations in the epidermis, with a proliferative stroma) (Fig. 4D), pigmented (presence of melanin in the tumor), micronodular (many small nodules of tumor separated by stroma), and metatypical (involving keratinization of tumor cells). In this patient, the prevalence of the nodular and superficial patterns was typical of basal-cell carcinomas in the general population, whereas the infiltrating, micronodular, and metatypical patterns were underrepresented as compared with sporadic cases, and the Pinkus pattern was overrepresented.

In addition to the skin samples, excision specimens from three maxillary cysts were available for review. They showed cysts filled with cornified cells (Panel A) and lined with stratified squamous epithelium with a corrugated surface and columnar basal cells (Panel B), diagnostic of an odontogenic keratocyst.2,11

**DISCUSSION OF MANAGEMENT**

*Dr. Epstein:* Dermatologists treat individual basal-cell carcinomas very successfully, routinely achieving cure rates of 95 to 100%. Our success is largely due to the fact that basal-cell carcinomas
essentially never metastasize. Little is available to prevent continued development of basal-cell carcinomas in patients such as ours. Celecoxib, once thought to be a promising agent for the chemoprevention of basal-cell carcinomas, was not found to be effective in clinical trials.\textsuperscript{13} Oral retinoids at high doses inhibit the development of basal-cell carcinoma in patients predisposed by the basal-cell nevus syndrome or xeroderma pigmentosum\textsuperscript{14} or by organ transplantation.\textsuperscript{15} However, oral retinoids generally do not prevent sporadic basal-cell carcinomas in patients at increased risk for nonmelanoma skin cancer. In this woman, side effects of retinoids precluded their use. Prolonged topical application of the retinoid tazarotene, which is used clinically for acne, psoriasis, and photodamage, appears to be an effective treatment for approximately one third of sporadic basal-cell carcinomas.\textsuperscript{16,17}

What can we do for this patient? On the basis of evidence that signaling by platelet-derived growth factor, downstream of the hedgehog signaling pathway, is important to the development of basal-cell carcinoma,\textsuperscript{18} it is tempting to speculate that the growth of basal-cell carcinomas could be affected by inhibition of this kinase with the use of imatinib. However, the efficacy of this treatment has never been tested. Tazarotene or imiquimod, an enhancer of the innate immune system, could be tried; imiquimod is approved by the Food and Drug Administration for the treatment of superficial basal-cell carcinomas, but tazarotene is not. There are several reports of benefits from systemic use of paclitaxel plus carboplatin in cases of locally uncontrollable basal-cell carcinomas.\textsuperscript{19} The scalp could be treated with ionizing radiation, which is of great value in treating sporadic basal-cell carcinomas. The problem is that patients with the basal-cell nevus syndrome are hypersensitive to the carcinogenic effects of ionizing radiation. However, in this elderly patient with uncontrolled basal-cell carcinomas and other debilitating conditions, radiation remains an option for short-term control of the disease. Finally, photodynamic therapy takes advantage of the selective accumulation by tumors of systemically administered photosensitizers or of their increased conversion of 6-aminolevulinic acid to the photosensitizing protoporphyrin IX, followed by treatment with high-intensity light.\textsuperscript{20-22} Unfortunately, photodynamic therapy is most effective against thin, superficial basal-cell carcinomas, and this patient’s scalp tumors may be too deep for this approach without prior surgical debulking.

In summary, there are several management options, but the choice among them should be dictated by the overall assessment of this woman’s general health and preferences. Local ionizing radiation would likely be the best choice for palliation, despite its propensity to exacerbate the development of basal-cell carcinomas several years later.

Dr. Eric S. Rosenberg (Medicine and Pathology): Dr. Baden, how did you treat this patient?

Dr. Howard Baden (Dermatology): An unusual feature of this patient’s illness was that the involvement of the scalp in the basal-cell carcinomas was greater than that of any other part of the body, by a factor of 10. Since the scalp is usually well protected from ultraviolet radiation, this puzzled us. Unfortunately, grafts of skin from other parts of her body to the head promptly developed new cancers. At the time of the most recent consultation, her decline in cognitive status made aggressive surgical or medical treatment difficult. The large lesion on the vertex of the scalp was excised by Dr. Victor Neel (Dermatology), using curettage. The lesion healed remarkably well without a graft, but small erosions persist on the scalp 15 months later; these are managed by her husband, using wound-care techniques.

Dr. Epstein: Dr. Anderson, do you have experience with photodynamic therapy for the basal-cell nevus syndrome?

Dr. Rox Anderson (Dermatology): We have treated several patients with the basal-cell nevus syndrome by using photodynamic therapy, involving both topical and systemic agents. The topical use of aminolevulinic acid is quite promising in these patients. Photodynamic therapy causes the tumor to regress because of oxidative damage, and in contrast to ionizing radiation, does not produce DNA damage; thus, it is less likely than ionizing radiation to cause the development of additional cancers.

**ANATOMICAL DIAGNOSIS**

The basal-cell nevus (Gorlin’s) syndrome with multiple basal-cell carcinomas and odontogenic keratocysts.
REFERENCES


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