Nevoid Basal Cell Carcinoma Syndrome and Non-Hodgkin's Lymphoma

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Nevoid basal cell carcinoma syndrome (NBCCS) is a hereditary disorder with a predilection for numerous basal cell carcinomas in addition to odontogenic keratocysts, palmoplantar pitting, and skeletal malformations. NBCCS has been associated with a number of benign and malignant neoplasms. We report the first case of NBCCS in association with non-Hodgkin's lymphoma.

Nevoid basal cell carcinoma syndrome (NBCCS), also known as basal cell nevus syndrome, Gorlin syndrome, Gorlin-Goltz syndrome, or fifth phacomatosis,[1,2] is an autosomal dominant disease linked to chromosome 9q22.3-q31.[3-5] It is a progressive degenerative multisystem disease characterized by a predisposition to develop basal cell carcinomas (BCCs) of the skin, palmoplantar pitting, odontogenic keratocysts, bifid ribs, kyphoscoliosis, short fourth metacarpals, ocular abnormalities, calcified dural folds, endocrine abnormalities, and various internal neoplasms.[1,2]

Internal neoplasms that have been reported in association with NBCCS include medulloblastoma,[6] craniopharyngioma,[7] meningioma,[2] astrocytoma,[8] oligodendroglioma,[1] ovarian fibroma,[9] ovarian fibrosarcoma,[10] cardiac fibroma,[11] fetal rhabdomyoma,[12] rhabdomyosarcoma,[1] ameloblastoma, squamous cell carcinoma of the jaw cyst, seminoma,[1] melanoma,[13] leiomyoma,[14] thyroid adenoma,[14] adenocarcinoma of the rectum,[14] benign mesenchymoma,[14] adrenal cortical adenoma,[15] and Hodgkin's disease.[14,16,17] There have been three reported cases of Hodgkin's disease, but no previously reported cases of NBCCS and non-Hodgkin's lymphoma to our knowledge. We describe the first known report of non-Hodgkin's lymphoma associated with NBCCS.

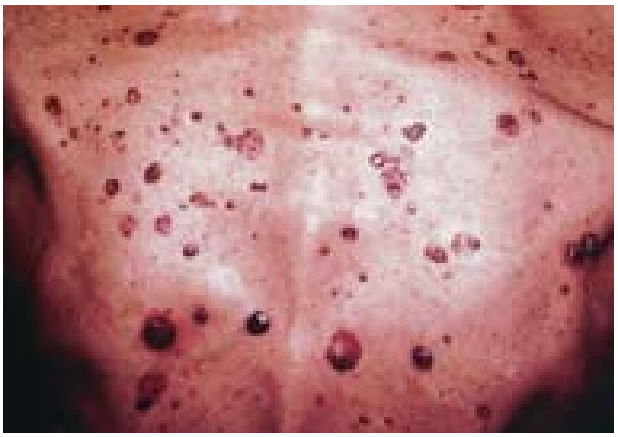

FIGURE 1. The back of a patient shows multiple basal cell carcinomas. (Photograph courtesy of MAJ Thomas Hirota, MC, USA.)

Case Report

A 54-year-old white man presented with numerous basal cell cancers. He was first diagnosed with NBCCS 26 years ago, at the age of 28, when a routine dental film demonstrated multiple mandibular odontogenic keratocysts. Before this, several BCCs had been removed, but no link to NBCCS had been made. Throughout his life, the patient reported more than 150 skin cancers treated. Prior radiologic reports described calcifications in his falx cerebri and bifid ribs. Other confirmatory findings were palmoplantar pitting, cleft palate, and the mandibular odontogenic keratocysts. He had no family history of NBCCS and no children.

Almost 3 years ago, he was evaluated for persistent cough, dyspnea, bilateral lower extremity edema, and left pleural effusion. The patient did not consent to further recommended evaluation and testing until symptoms progressed. One year ago, he was hospital-

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FIGURE 2. Profile of face shows multiple tumors and large mandibular nodule. (Photograph courtesy of MAJ Raymond Schwab, MC, USAF.)

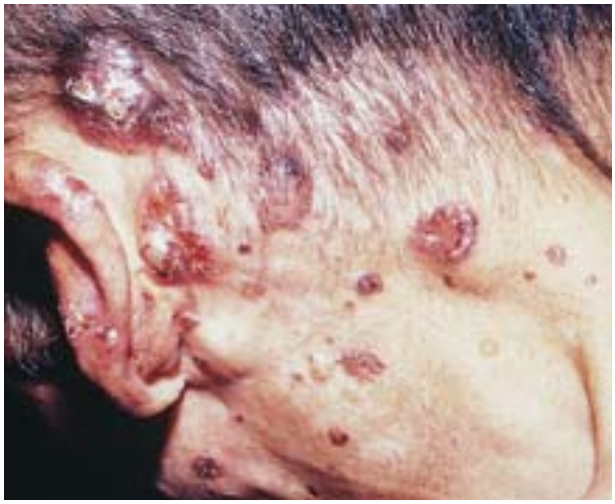

FIGURE 3. Neck with lymphadenopathy.

ized for dyspnea, left pleural effusion, generalized lymphadenopathy, thrombocytopenia, and normocytic anemia. Following in-patient testing and evaluation, including a bone marrow biopsy, follicular mixed large and small cell lymphoma was diagnosed.

Cutaneous examination revealed a cachectic man with multiple waxy papules, plaques, and tumors on his face, neck, upper chest, back (Figure 1), and lower right extremity. The largest tumors were a 4 × 5-cm erythematous, weeping, fungating mass on his right mandible (Figure 2) and a 3 × 4-cm erythematous mass on his right distal tibia. Additionally, the patient had visible lymphadenopathy in the axillae, anterior and posterior cervical triangles (Figure 3), and supraclavicular spaces, and in a linear pattern reminiscent of rosary beads along the mid-thoracic ribs both anteriorly and posteriorly. Musculoskeletal findings included kyphoscoliosis and prominent supraorbital ridges. Hypertelorism was not present. Neither shortened fourth metacarpals (Albright's sign) nor ocular abnormalities were evident. A single palmar pit was seen on the hypothenar eminence of the right hand. Several more pits were noted after highlighting with topical povidone-iodine (Betadine®) on the palmar skin for 10 minutes and removing.

Oral examination demonstrated micrognathia and poor dentition with numerous missing teeth. Laboratory testing was remarkable for a normocytic anemia, thrombocytopenia, and hypoalbuminemia. A Panorex of the jaw revealed a possible cystic area of the right posterior maxillary tuberosity and evidence of healing cysts of the right and left mandibular bodies. There was no evidence of bony involvement by the large cutaneous mandibular tumor on computer tomographic (CT) scan. A CT scan of the head revealed calcification of the falx cerebri and tentorium cerebelli. Rib series noted a relatively hypoplastic left anterior seventh rib. Chest X-ray revealed a large left pleural effusion. An echocardiogram demonstrated normal left ventricular size and wall motion and a mild pericardial effusion. A CT scan of the chest revealed hepatosplenomegaly, generalized lymphadenopathy involving clavicular, axillary, mediastinal, retroperitoneal, and periaortic nodes, as well as a left lower lobe infiltrate and nonloculated pleural effusion. A bone marrow biopsy as well as a lymph node biopsy demonstrated stage IVB non-Hodgkin's lymphoma. Chemotherapy was started with fludarabine, mitoxantrone hydrochloride (Novantron®), and dexamethasone for his lymphoma. The BCCs were treated with either curettage or excision with secondary intention healing. He has responded well to the chemotherapy with reduction in size of the adenopathy and an improved functional status.

Comments

In 1993, Evans *et al*[16] defined the specific criteria for diagnosing NBCCS. Major criteria include the following: more than 10 BCCs at any age or more than two BCCs under the age of 30 years, histologically confirmed odontogenic keratocyst or polyostotic bone cyst, more than three palmar or plantar pits, lamellar calcification of falx cerebri, and family history of NBCCS.[16] Minor criteria include the following: congenital skeletal anomaly (rib or spine), congenital malformation (such as cleft palate/lip, polydactyly, cataract, coloboma, and microphthalmia), macrocephaly with a head circumference over the 97th percentile with frontal bossing, cardiac or ovarian fibroma, medulloblastoma, and lymphomesenteric

cysts. The diagnosis was established by the presence of two major, or one major and two minor criteria. Our patient satisfied four of the five major criteria with odontogenic keratocysts, greater than two BCCs before age 30, more than three palmar pits, and calcification of the falx cerebri. His minor criteria included kyphoscoliosis and micrognathia.

Onset of BCCs in these patients is typically between puberty and 35 years of age.[2] Although it is inherited in an autosomal dominant fashion, 60% of patients have no family history due to a high spontaneous mutation rate.[2] The histologic patterns found in BCCs in this syndrome include nodular, superficial, morpheaform, cystic, adenoid, fibroepithelial, and pigmented.[2] Odontogenic keratocysts may occur in up to 50 to 65% of patients with NBCCS.[1,2] They occur primarily on the mandible, and may begin formation as early as the seventh year of life, peaking in the second to third decade. Cysts can cause tooth displacement as was evident in our patient. Jaw cysts frequently recur despite surgical removal. Palmar pitting, a frequent finding in NBCCS, occurs in approximately 65 to 80% of patients.[1]

The implicated genetic defect in basal cell nevus syndrome has been localized to chromosome 9q22.3-q31, *patched* (PTCH) gene.[18] The prevailing hypothesis is that this gene has a tumor suppressor function and that the loss of PTCH protein function results in BCC tumorigenesis. NBCCS patients inherit a germline mutation of one allele of the PTCH gene and thus require only one further postnatal "hit" to inactivate it.[19] These hits or insults may be caused by ultraviolet or X-ray irradiation, or chemical carcinogens, in addition to simple random genetic alterations. Alterations in the PTCH gene are implicated not only in this syndrome, but also in approximately 50% of sporadic BCCs not associated with the syndrome.[20] Additionally, PTCH gene mutations have been identified in sporadic meduloblastomas,[21] breast cancer, meningioma, and other primitive neuroectodermal tumors of the central nervous system.[18,21,22] There are also increasing data showing similar effects with activating mutations of the proto-oncogenes sonic hedgehog and smoothened protein, which are two components of the hedgehog signaling pathway, which the PTCH protein inhibits.[19] Investigators have used a tissue microdissection technique to study areas of squamous neoplasia within four BCCs (not from patients with NBCCS).[23] They found that the areas of squamous neoplasia had the same genetic defect in the PTCH gene as was found in the rest of the BCC. They suggest that this technique may be useful to study different tumor components in conjunction with genetic analysis to assess whether or not they have similar or diverse genetic changes.

Optimal treatment of a patient with dozens or even hundreds of BCCs presents the clinician with a challenge. Fatal cases of BCC can occur, though rarely. The overall incidence of metastasis for BCCs ranges from 0.0028% in dermatologic practice[24] to 0.1% in surgical centers.[25] Its incidence in NBCCS is not documented,[26] though only a small fraction of the lesions are believed to become invasive.[1] It can occur, however, when a patient has had prolonged untreated lesions, extensive local invasion, large lesions, or multiple local recurrences. Common sites of metastasis for BCC include the lymph nodes, lung, and bone.[25,26] The majority of the primary tumors are located on the head and neck.[25] Life expectancy averages 8 to 10 months for metastatic BCC.[27] Our patient had no evidence of BCC metastasis.

Although surgery is the treatment of choice for BCCs, it may not be practical when the tumors are quite numerous. While some tumors may require standard excision or even Mohs' micrographic surgery, others may be treated with shave excision or a combination of curettage and excision. Other therapeutic options that have been used to treat BCCs in this syndrome include curettage and electrodesiccation, topical 5-fluorouracil, cryosurgery, intralesional interferon alpha-2b, carbon dioxide laser vaporization (with or without curettage), and photodynamic therapy.[28] Intralesional interferon requires a number of sessions and carries a high cost, while photodynamic therapy should be used only for superficial BCCs. Radiotherapy should be avoided in the treatment of this disease since it is well documented that radiation exposure increases the incidence of the BCCs.[14,29] In our patient, we elected simple multiple superficial excisions and curettage.

Three cases of Hodgkin's disease have been cited in the literature.[14,16,17] All three describe the Hodgkin's disease preceding the diagnosis of NBCCS by several years. They hypothesized that the therapy for the Hodgkin's disease may have accelerated the development of the BCCs in these patients. It is postulated that the gene for NBCCS may act as a tumor suppressor gene perhaps for many types of cell lines and may explain the diversity of the tumors.[5] This patient with NBCCS is the first known reported association with non-Hodgkin's lymphoma. While we may postulate some role of the PTCH gene defect, only further study with microdissection of different tumors in conjunction with genetic analysis may elucidate its role in this and other tumors seen in association with the NBCCS syndrome. Non-Hodgkin's lymphoma should now be included among the malignancies associated with NBCCS.

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