Malignant Nodular Hidradenoma in a Patient With Neurofibromatosis Type 1: A Case Report and Review of the Literature

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GOAL

To discuss the clinical manifestations of malignant nodular hidradenoma (MNH)

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the various skin lesions associated with neurofibromatosis type 1 (NF1).
2. Explain the possible complications of NF1.
3. Discuss the clinical presentation of MNH.

CME Test on page 270.

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Neurofibromatosis type 1 (NF1), also known as von Recklinghausen's disease, is one of the most common autosomal dominant inherited disorders. In addition to multiple skin manifestations, patients with NF1 also have an increased risk for developing malignancies. We present a case of malignant nodular hidradenoma (MNH) that occurred in a patient with NF1 who had repeated local recurrences and regional lymph node metastasis and who died with metastatic disease despite multiple reexcisions, chemotherapy, and radiation. Our research of the literature showed no similar report of an MNH in NF1 patients. We also reviewed several skin disorders that have

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been repeatedly documented in patients with NF1, including juvenile xanthogranulomas (JXG); a triple association of JXG, NF1, and juvenile chronic myelogenous leukemia (JCML); multiple granular cell tumors at early ages; and multiple glomus tumors. The incidence of cutaneous malignant melanoma in NF1 patients has not been consistent among various reports. The relative risk of developing epithelial tumors in patients with NF1 remains largely unknown. Because of the rarity of MNH, it is currently difficult to assess whether the tumor represents a concurrent lesion or is associated with neurofibromatosis (NF).

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen's disease, is one of the most common autosomal dominant inherited disorders. The frequency of NF1 is estimated to be 1:3500 in Western populations.[1,2] Skin manifestations of the disease, including the presence of 6 or more café au lait macules, multiple freckles in the axillary or inguinal regions, and multiple neurofibromas, constitute a major part of the National Institutes of Health (NIH) consensus diagnostic criteria for NF1.[1] Infants and children with neurofibromatosis (NF) are often brought to medical attention for their skin lesions. Hence, dermatologists are important components in recognizing and counseling these patients and their family members. Patients with NF1 also have an increased risk for developing malignancies. The tumors that have been well recognized as being associated with NF1 are malignant peripheral nerve sheath tumors (MPNST), optic nerve glioma, astrocytoma, meningioma, rhabdomyosarcoma, pheochromocytoma, carcinoid tumor, and childhood leukemia (Table).[2,3] On the other hand, despite individual case reports, the relative risk for patients with NF1 to develop malignant melanomas or carcinomas is not well-established.[4,5]

Malignant nodular hidradenoma (MNH) is a rare type of malignant skin adnexal tumor that usually occurs in the older adult population. The tumor generally has an aggressive clinical behavior with a high frequency of local recurrence and distant metastasis.[6-8] We report a rare case of MNH occurring in a patient with NF1. The current literature on skin tumors associated with or reported in patients with NF also is reviewed.

Case Report

An 80-year-old white man with a family and personal history of NF1 presented with an area of induration and ulceration on the mid back. Results of a physical examination revealed numerous soft papules and nodules diffusely distributed over the trunk (neurofibromas) and a red, indurated, and ulcerated plaque measuring 5.5×4 cm on the mid back. There was no axillary or inguinal lymphadenopathy. The patient did not have any history or evidence of systemic malignancies. A biopsy of the lesion on the back showed an MNH. The patient underwent a wide surgical excision of the lesion.

The excisional specimen grossly showed multiple polyps protruding from the skin surface, consistent with multiple cutaneous neurofibromas. Histologic sections showed a large, poorly circumscribed, malignant epithelial tumor in the superficial and deep dermis, with focal extension into the subcutis (Figure, A). Focal connection with the epidermis was seen. In a fibrotic stroma with thick hyaline bands of collagen, islands of atypical epithelial cells were present that were basaloid at the periphery and polygonal with abundant clear cytoplasm in the center. The clear cells stained positive with periodic acid-Schiff stain. The tumor showed skin adnexal differentiation forming numerous small ductular spaces with eosinophilic cuticles and some larger cystlike ducts (Figure, B). Foci of squamous differentiation also were present. Zonal necrosis, invasion as single cells (Figure, C) and focal lymphatic invasion also were noted. Mitotic figures, some atypical, were seen throughout the lesion. With immunohistochemical stains, the tumor cells were positive for cytokeratin, and the small ductules were highlighted by a stain for epithelial membrane antigen. Results of a S-100 protein stain were negative within the lesional cells. The tumor nodules were present in the background of characteristic changes of neurofibroma (Figure, D). These findings confirmed the biopsy diagnosis of MNH.

Several months after the initial surgery, the patient had repeated local and regional recurrences of the tumor. In less than a year, he also developed metastatic disease in regional lymph nodes and on the skin of the chest. The patient died with metastatic disease and upper gastrointestinal bleeding approximately one year after the initial presentation.

Comment

To the best of our knowledge, this is the first report of an MNH occurring in a patient with NF1. There have been no specific reports of the occurrence of hidradenomas in NF1 patients, except in an earlier study of neoplastic complications of NF in which one patient, who was reported as having a sweat gland carcinoma on the dorsum of the hand, died of

Neoplasms Associated or Reported in Patients With Neurofibromatosis Type 1

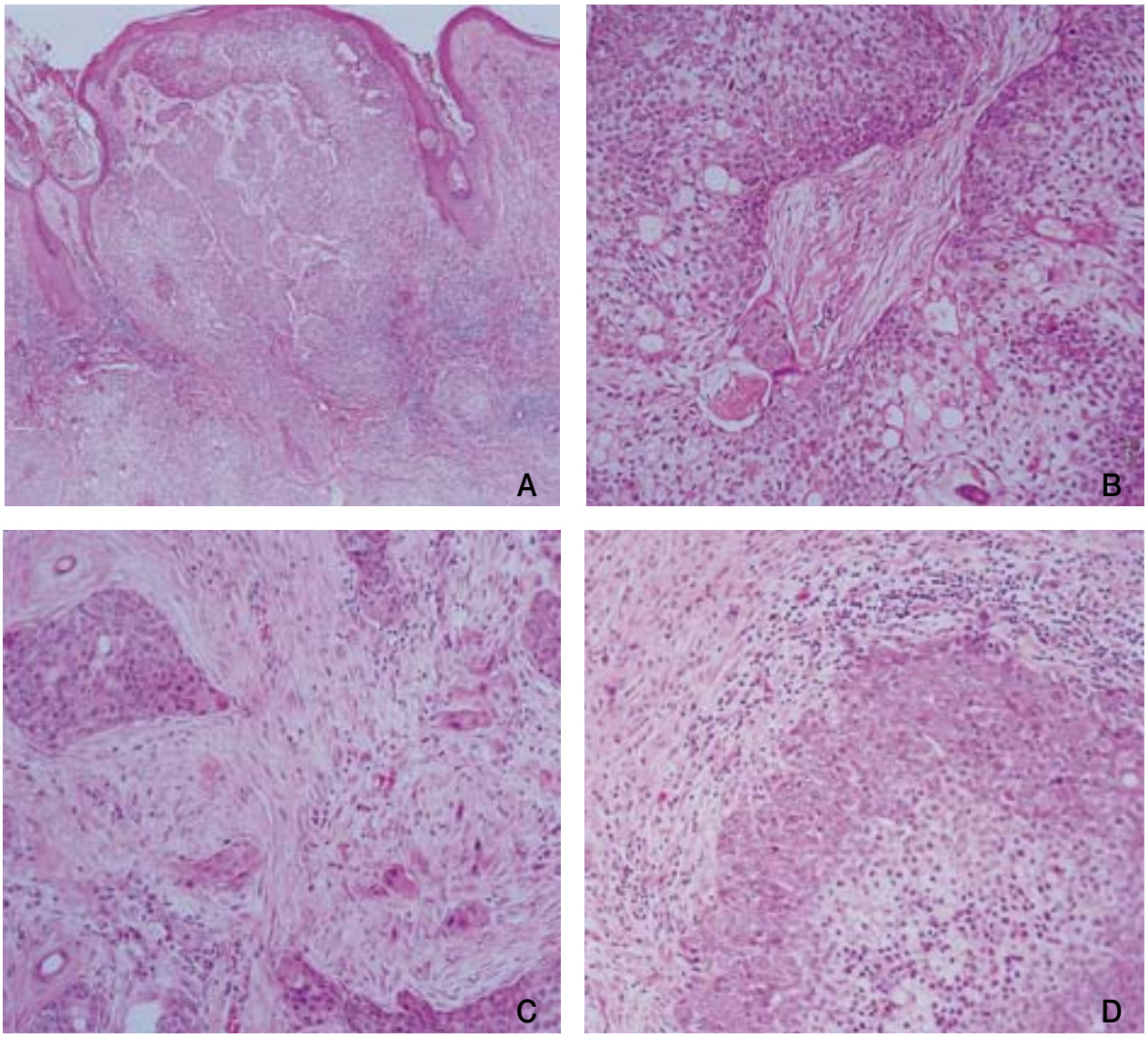
	Cutaneous Neoplasms	Noncutaneous Neoplasms
Tumors with definite or possible association with NF1	Malignant peripheral nerve sheath tumors	Malignant peripheral nerve sheath tumors
	Xanthogranuloma with or without juvenile chronic myelogenous leukemia	Optic nerve glioma
	Multiple granular cell tumors	Astrocytoma
	Multiple glomus tumors	Meningioma
		Rhabdomyosarcoma
		Pheochromocytoma
		Carcinoid tumors
		Myelogenous leukemia in children
Tumors reported in patients with NF1	Malignant melanoma	Neuroblastoma
	Basal cell carcinomas	Medulloblastoma
		Glioblastoma multiforme
		Ganglioneuroma
		Acute lymphocytic leukemia
		Malignant teratoma
		Wilms tumor
		Leiomyosarcoma
		Angiosarcoma
		Synovial sarcoma
		Fibrosarcoma
		Breast carcinoma
		Adenocarcinomas (colon, rectum)

NF1 indicates neurofibromatosis type 1.

lung metastases. The histologic type of this reported sweat gland tumor was not specified.[9] Because of the rarity of this type of tumor, it is currently difficult to assess whether the MNH in the current case represents a merely concurrent lesion or is associated with NF1.

During the follow-up of patients with NF1, dermatologists should look for the malignant transformation of neurofibromas to MPNSTs, which is often signified by a rapidly growing firm tumor, redness of the overlying skin, and pain. In this setting, pain or sudden enlargement of a preexisting mass should lead to biopsy.[10] Although malignant transformation of localized neurofibromas may occur, most MPNSTs arise in association with major nerve trunks and may cause sensory and motor symptoms including projected pain, paresthesia, and weakness. The most common sites include trunk and proximal extremities. Besides MPNSTs, many other skin tumors have either been associated with or reported in NF1 patients (Table). The following discussion focuses on several associated skin lesions.

Juvenile xanthogranulomas (JXG) has been repeatedly documented in NF1 patients. In 1971, Jensen et al[11] reported the occurrence of multiple nevoxanthoendothelioma (JXG) in 2 young boys, one of which had an established diagnosis and



Pathology of the malignant nodular hidradenoma. Low-power view shows a large, poorly circumscribed, malignant epithelial tumor in the superficial and deep dermis (A)(H&E, original magnification ×20). Clear cells, small ductular formation, and larger ducts were present (B)(H&E, original magnification ×200). Tumor islands show an infiltrative growth pattern within a fibrotic stroma (C)(H&E, original magnification ×100). The tumor nodules are present in the background of characteristic changes of neurofibroma (D)(H&E, original magnification ×100).

family history of NF1, and the other patient had numerous café au lait spots. The authors also discussed several earlier reports of children who developed JXG and had either multiple café au lait spots or diagnosed NF.[11] Niimura[10] studied 1200 Japanese patients with NF1 and found JXG in 30% of the patients younger than 3 years. The lesions usually regress spontaneously within 1 to 2 years.[10] Zvulunov et al[12] reviewed 17 well-documented cases of JXG with NF1. The mean age of onset of JXG in these patients is 10 months, with a nearly equal male-female ratio (9:7). Forty-seven percent of the patients have a family history of NF1, similar to the expected 50% rate of spontaneous cases in NF1.[12] Several reports documented a triple association of JXG, NF, and juvenile chronic myelogenous leukemia (JCML).[12,13] A study has shown that the observed frequency of the triple association in the studied population was 30- to 40-fold higher than the expected frequency.[12] Because there is a much higher frequency of JCML in children with NF1 and JXG in comparison with children with NF1 alone, it

has been recommended that a finding of JXG in a young patient with NF1 should alert the clinician of the possibility of the development of leukemia.[1]

Although 5.4% to 25% of cutaneous granular cell tumors may be multiple, this condition is uncommon in childhood or adolescence. In 1990, Martin et al[14] reported the first case of multiple cutaneous granular cell tumors in a child with NF1. In 1997, Sahn et al[15] reported another case of a 4-year-old black girl with multiple cutaneous granular cell tumors, 4 café au lait spots, and bilateral axillary freckling. Although that particular patient did not meet the NIH consensus criteria for NF1, it was postulated that the patient probably had the condition.[15] The usage of the NIH consensus criteria for NF1 in young children may be complicated because the clinical manifestations of NF do not occur at the same time. Café au lait spots are usually present at birth or at infancy, whereas neurofibromas develop in adolescence.[10,15] Several other reports also described multiple cutaneous granular cell tumors in association with certain elements of NF1, albeit the patients did not fully meet the NIH consensus criteria for diagnosing NF1 (reviewed in Sahn et al).[15] Because granular cell tumors are believed to be derived from Schwann cells, an etiopathologic association with NF is considered plausible.[14] The clinical course of the granular cell tumors is usually benign, although rare cases show malignant transformation. In the cases reported in NF1 patients, there is no mention of a malignant transformation.[14,15]

A group in Japan that examined more than 1200 patients with NF1 in the past 25 years reported 3 cases of subungual glomus tumors.[16] Two of the patients had the tumor on multiple nail beds, which is an extremely rare condition. Based on their review of the literature, 4 other reports have described multiple glomus tumors in NF1 patients. Generalized multiple glomus tumors are an autosomal dominant inherited condition. Further investigation is needed on whether glomus tumors are an additional complication of NF1.[16]

There are several reports of cutaneous malignant melanoma in patients with NF1. Because NF and malignant melanoma are both diseases of neural crest origin, people have theorized for many years about an association between the 2 disorders. However, the data on cutaneous melanomas in NF1 have not been consistent among various reports. In a series of 110 NF1 patients, 6 patients (5.4%) had cutaneous melanomas, which indicates an increased incidence.[17] However, Mastrangelo et al[5] found only one case of NF1 in a series of 900 melanoma patients. Others also have believed that the paucity of reports of NF1 patients with associated cutaneous malignant melanoma suggests a lack of increased concurrence.[18] On the other hand, there have been several reports of uveal malignant melanomas, an uncommon condition occurring in patients with NF1 (reviewed in To et al).[19] Because leptomeningeal and ocular melanomas are usually rare, the occurrence in a few patients with NF1 might suggest a possible association.[3]

The relative risk of developing epithelial tumors in patients with NF1 remains largely unknown. In one report of NF1 and childhood cancers, epithelial carcinomas were not observed.[20] However, a review of the NF1 patients seen at the St. Jude Children's Research Hospital revealed 2 cases of multiple colon cancers developed at very young ages.[4] A study of NF1 patients in northern Finland found 2 cases of basal cell carcinomas, one of which developed at a young age (15 years).[2] Without a comparison of the actual frequencies of these cancers developing in NF1 patients with the expected frequencies based on the incidence rates and person-year–at risk, it is very difficult to assess whether these tumors are occurring in NF1 patients in excess.

MNH is a rare form of malignant skin adnexal tumor. The incidence has been reported to be 6% of the eccrine gland carcinomas.[8] The tumor usually presents as a solitary nodule on the head, trunk, or distal extremities. The usual age of occurrence is older than 50 years, although there have been reports of cases in newborns and children.[7,21,22] A recent review by Ashley et al[23] summarized certain clinical features of 14 published cases, all occurring in the head and upper extremities. Most cases (11/14) had lymph node or visceral metastasis.[23] Upon diagnosis, a complete evaluation for local and distant metastasis should be performed, including chest x-ray, bone scan, evaluation of the regional lymph nodes, and other routine laboratory tests. The most accepted treatment is a wide local excision. Radiation therapy is generally not effective, and it may even accelerate the tumor growth. Chemotherapy has been used, and the result is currently undefined.[6,22,24] In general, the clinical course is aggressive with a high frequency of local recurrence and metastasis.[7,21,22,25] Because this is a relatively rare tumor, reporting bias may be responsible for the reported high rate of recurrence or metastatic disease.

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