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Case Report

Segmental neurofibromatosis and cancer: report of triple malignancy in a woman with mosaic Neurofibromatosis 1 and review of neoplasms in segmental neurofibromatosis

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Abstract

Background
Segmental neurofibromatosis, referred to as mosaic neurofibromatosis 1, patients present with neurofibromas or café au lait macules or both in a unilateral segment of the body.

Purpose
A woman with segmental neurofibromatosis and triple cancer (renal cell carcinoma, mixed thyroid carcinoma, and lentigo maligna) is described and cancers observed in patients with segmental neurofibromatosis are reviewed.

Methods
PubMed was used to search the following terms, separately and in combination: cancer, malignancy, mosaic, neoplasm, neurofibroma, neurofibromatosis, segment, segmental, tumor.

Results
Malignancy (13 cancers) has been observed in 11 segmental neurofibromatosis patients; one patient had three different cancers. The most common neoplasms were of neural crest origin {malignant peripheral nerve sheath tumor (3 patients) and melanoma (3 patients)] and gastrointestinal tract origin [colon (1 patient) and gastric (1 patient)]. Breast cancer, Hodgkin lymphoma, lung cancer, kidney cancer, and thyroid cancer each occurred in one patient.

Conclusions
Similar to patients with von Recklinghausen neurofibromatosis 1, individuals with segmental neurofibromatosis also have a genodermatosis-associated increased risk of developing cancer.

Key Words: cancer, malignancy, mosaic, neoplasm, neurofibroma, neurofibromatosis, segment, segmental, tumor

Introduction

Segmental neurofibromatosis is a variant of neurofibromatosis 1 [1-4]. Patients with neurofibromatosis 1 have an increased risk for developing malignancy [5-8]. A woman with segmental neurofibromatosis who developed triple cancer—renal cell carcinoma, thyroid cancer, and lentigo maligna—is described and malignancies in patients with mosaic neurofibromatosis 1 are reviewed.

Case report

A 72-year-old woman presented for an evaluation of her skin. She was previously managed by other dermatologists and had a history of non-melanoma skin cancers that had been diagnosed and treated 21 months earlier: a squamous cell carcinoma in situ on the right side of her nose and basal cell carcinoma on the left side of her lower lip. She also had a lentigo maligna (melanoma in situ) on her right shoulder that had been excised 27 months prior.

Her past medical history was significant for two visceral malignancies; following treatment, neither tumor has recurred. A renal cell carcinoma of the right kidney was diagnosed in 2011, 4 years ago. There has been no recurrence following a nephrectomy that removed the tumor. In November 2012, nearly 2 years ago, thyroid carcinoma was diagnosed. She underwent a right hemi-thyroidectomy; pathology revealed an encapsulated, minimally invasive mixed carcinoma: follicular and papillary carcinoma. Following initial treatment with radioactive iodine, she underwent a total thyroidectomy and postoperative radioactive iodine thyroid ablation.

Her cutaneous examination was remarkable for multiple asymptomatic flesh colored papules and soft pedunculated nodules, ranging in greatest diameter from 3 mm to 1.0 cm, on her right lower back (Figure 1). The 10 skin lesions were localized to a segment of her body that corresponded to her right eighth to tenth thoracic dermatomes. Neither brown patches (café au lait macules) nor freckles in the axilla or groin were present. Iris hamartomas (Lisch nodules) were also absent.

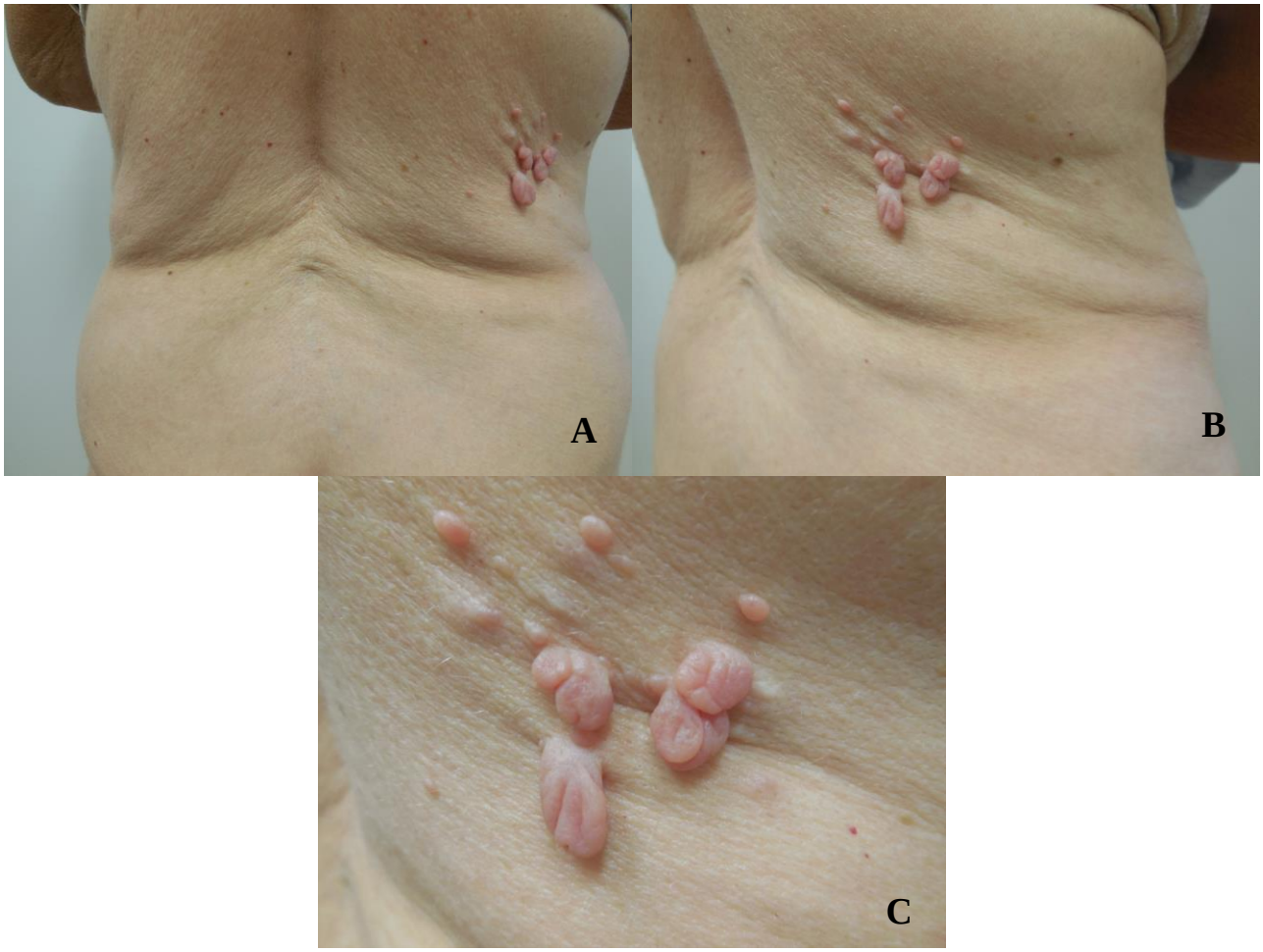

Figure 1 (a,b and c). Clinical presentation of segmental neurofibromatosis. Posterior (a) and lateral (b) distant views of papules and pedunculated nodules within a unilateral segmental distribution corresponding to the patient's right eight to tenth thoracic dermatomes. A closer view (c) demonstrates the flesh colored soft skin lesions hat ranged in size from 3 mm to 10 mm in greatest diameter.

Three of the nodules were biopsied for pathologic examination. All showed similar changes. There was a circumscribed nodule composed of delicate wavy fibrils of neural origin with elongated fibroblasts and surrounding mucinous stroma in the dermis, diagnostic of a neurofibroma (Figure 2).

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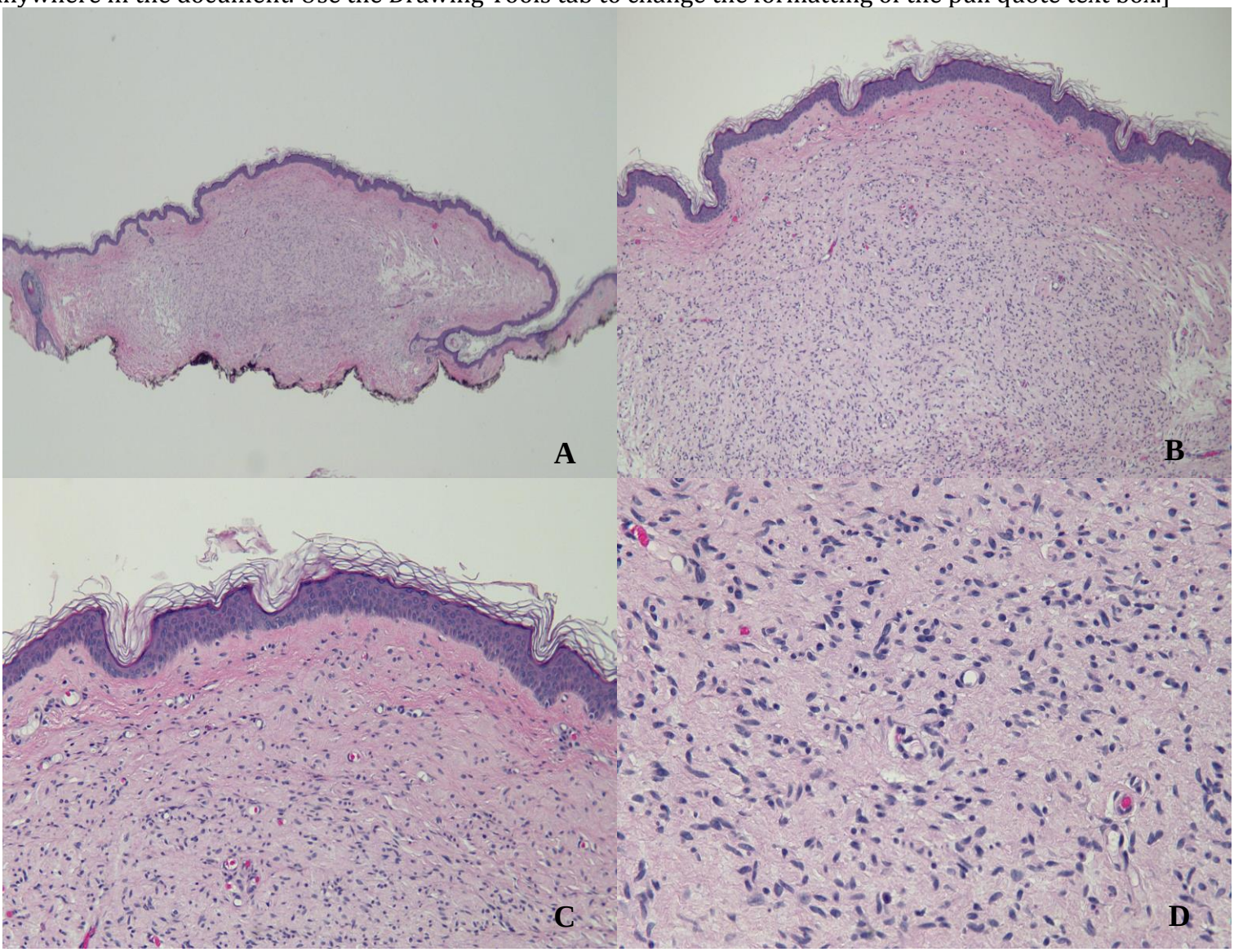

Figure 2 (a, b, c and d). Microscopic features of a segmental neurofibroma. Distant (a) and closer (b, c, and d) views of a biopsied nodule shows a circumscribed nodule in the dermis. It is composed of wavy fibrils of neural origin and elongated fibroblasts. The surrounding stroma is mucinous [Hematoxylin and eosin; a, X4; b, X10; c, X20; d, X40]

The skin lesions had been present since her 30s. There was no family history of neurofibromatosis 1 in her parents or three daughters. Correlation of her medical history, clinical presentation, and pathology evaluation established a diagnosis of segmental neurofibromatosis.

Discussion

Neurofibromatosis 1 is an autosomal dominant genodermatosis with malignant potential that has an incidence of about 1 in 2500 live births. Heterozygous germ-line mutations of the *NF1* gene, a tumor suppressor gene that codes for neurofibromin, causes neurofibromatosis 1. In addition to neurofibromas, other cutaneous features may include café au lait macules, axillary and groin freckling, glomus tumors, and xanthogranulomas [7-11].

Benign and malignant tumors have been observed in patients with neurofibromatosis 1. Somatic loss of the *NF1* gene expression leads to RAS (and its downstream signaling pathways) activation and cell growth deregulation resulting in tumorigenesis in these individuals. Commonly associated neurofibromatosis 1 tumors include optic glioma, glioblastoma, malignant peripheral nerve

sheath tumor, gastrointestinal stromal tumor, breast cancer, leukemia, non-Hodgkin lymphoma, pheochromocytoma, duodenal carcinoid tumor, and rhabdomyosarcoma [5,6,9-12].

Segmental neurofibromatosis, also referred to as mosaic neurofibromatosis 1, is an uncommon subtype of neurofibromatosis 1. Patients typically have neurofibromas and/or café au lait macules in a single unilateral segment of the body. It occurs as the result of a postzygotic mutation in the *NF1* gene, causing somatic mosaicism [1-4,13-16].

The current patient had neurofibromas since her 30s. The diagnosis of segmental neurofibromatosis was only established, at age 72 years, when three of the lesions were biopsied. There was no family history of neurofibromatosis 1; neither her parents nor any of her daughters had cutaneous features of neurofibromatosis 1.

Similar to neurofibromatosis 1 patients, who have a 7% lifetime risk for cancer, individuals with the segmental subtype also demonstrate an increased incidence (5%) of cancer [17]. Including the current patient, 13 cancers have been reported in 11 patients with segmental neurofibromatosis (Table 1) [18-26]; none of the patients had a family history of neurofibromatosis 1 and only one patient (case 2) had other systemic involvement. The most commonly observed malignancies (46%, 6/13 cancers) were of neural crest origin: malignant peripheral nerve sheath tumor (3 patients) and melanoma (3 patients). Other cancers included 2 patients with gastrointestinal neoplasms (colon and gastric carcinoma) and 1 patient with one of the following: renal and thyroid cancer, breast cancer, lung cancer, or Hodgkin lymphoma.

Table 1. Characteristics of segmental neurofibromatosis patients with cancer

C	A S	Cancer	SN site	AF	CALM	NF Dermatome	Ref
1	32 M	Hodgkin Lymphoma	L: Upper extremity	No	Yes	Yes Cervical: 6	18
2 [a]	48 M	Malignant Melanoma (Upper trunk)	L: Neck	No	No	Yes [b] Cervical: 3-5	19
3	61 M	Colon (Adenocarcinoma)	L: Back	Yes	Yes	Yes [c] Lumbar: 1-4	20
4	61 M	Gastric (Adenocarcinoma)	R: Abdomen, Back L: Back	No	Yes	Yes; [d] Thoracic: 10-11 (R and L)	21
5	41 W	Melanoma In Situ (R breast)	L: Lower extremity	No	Yes [e]	No	22
6	43 W	MPNST (R thigh/ groin)	R: Lower extremity	No	No	Yes Lumbar: 1-3	23c1
7	45 W	Breast (L, infiltrating ductal carcinoma)	L: Upper extremity	No	No	Yes Cervical: 6-8	24
8	48 W	MPNST (Pelvis)	L: Buttock	No	No	Yes [f] Lumbar: 5 Sacral: 1-2	23c2
9	64 W	MPNST (L thigh)	L: Pubis	No	No	No	25
10	68 70 72 W	Renal Cell Ca (R) Thyroid Lentigo Maligna (R shoulder)	L: Back	No	No	Yes Thoracic: 8-10	CR
11	72 W	Lung (L lower lobe, Bronchoalveolar carcinoma)	L: Axilla, Back, Lower extremity	No	Yes [g]	Yes Cervical: 7-8 Thoracic: 1-2 Lumbar: 4-5	26

Abbreviations: A, age (years) at tumor diagnosis; AF, axillary freckling; C, case; Ca, carcinoma; CALM, café au lait macule; CR, current report; L, left; M, man; MIS, melanoma in situ; MPNST, malignant peripheral nerve sheath tumor; NF, neurofibroma; R, right; Ref, reference; S, sex; SN, segmental neurofibromatosis; W, woman

[a] The patient had additional cutaneous features (large congenital nevus, plexiform neurofibroma and schwannoma) and systemic manifestations (multiple osseous abnormalities including fusion of the cervical spine, marked kyphosis, and scoliosis.
[b] A small subcutaneous neurofibroma was excised during a left posterolateral neck dissection. The patient also had a bilateral congenital nevus occupying the cervical 3-5 dermatomes.
[c] The café au lait macule contained neurofibromas that occupied the left back lumbar 1-4 dermatomes.
[d] The café au lait macules were located on the left abdomen and the left back occupying the thoracic 8-11 dermatomes.
[e] The patient presented with a huge café au lait macule with numerous nevocellular nevi (nevus spilus).
[f] There was a solitary neurofibroma on the left buttock. The peripheral malignant nerve sheath tumor arose out of a neurofibroma in the pelvis near the left sciatic notch.
[g] There were 2 café au lait macules present since birth and early childhood. In addition, there were multiple lentiginous macules that were also on the left thigh and patella area.

Non-melanoma skin cancer also occured in patients with segmental neurofibromatosis. Lupton et al described a 50-year-old man with segmental neurofibromatosis with neurofibromas, a plexiform neurofibroma of the right external auditory canal, a nevus sebaceous (with an associated syringocystadenoma papilliferum), a keratoacanthoma of the right scalp, and a basal cell carcinoma of the left cheek [27]. In addition, the patient in this report also had two non-melanoma skin cancers.

The current patient had three primary malignancies: renal cell carcinoma, thyroid cancer, and lentigo maligna. All of the other patients with malignancy-associated segmental neurofibromatosis had only one cancer. The development of segmental neurofibromatosis followed the diagnosis of cancer in three of the patients (cases 7, 9, and 11).

Renal cell carcinoma has rarely been described in neurofibromatosis 1 patients. Renal cell carcinoma was described in a woman who had a family history of neurofibromatosis 1 and von Hipple-Lindau disease [which is characterized by hemangioblastomas of the brain, spinal cord and eye (retinal angiomas), clear cell renal cell carcinoma, pancreatic neuroendocrine tumor, pheochromocytoma, endolymphatic sac tumor (of the inner ear) and cysts (of the genital tract, kidney, and pancreas)]; she had both neurocutaneous syndromes [28]. At 38 years of age, she developed shock and died following the surgical exploration of her posterior fossa to evaluate a tumor of the left cerebellum; postmortem examination showed disseminated neurofibromas of the skin and small intestine, numerous café au lait macules, a cerebellar hemangioblastoma, a renal cell carcinoma of the left kidney, bilateral pheochromocytomas, and multiple cysts of the pancreas [28].

Thyroid cancer has infrequently been observed in neurofibromatosis 1 [29]. Although patients with multiple endocrine neoplasia type 2 (MEN2) have medullary thyroid carcinoma and pheochromocytoma associated with either parathyroid adenoma (type 2a) or mucosal neuromas (type 2b), medullary thyroid cancer is uncommon in patients with neurofibromatosis [30,31]. However, albeit seldom, nonmedullary thyroid cancer (follicular [32,33], papillary [34-36] or mixed [37] carcinoma) has been reported in neurofibromatosis 1 patients.

Conclusion

Segmental neurofibromatosis, referred to as mosaic neurofibromatosis 1, results from a postzygotic mutation in the *NF1* gene and presents as neurofibromas—with or without café au lait macules—in a single unilateral segment of the body. Malignancies have been described in 11 individuals (4 men and 7 women) with segmental neurofibromatosis. Neoplasms of neural crest origin were the most common: malignant peripheral nerve sheath tumor (3 patients) and melanoma (3 patients). A gastrointestinal tract tumor was noted in 2 patients: colon cancer and gastric carcinoma. Other malignancies included breast cancer, Hodgkin lymphoma, lung cancer, renal cancer, and thyroid cancer. In summary, similar to individuals with von Recklinghausen neurofibromatosis 1, patients with segmental neurofibromatosis also have a genodermatosis-associated increased risk of developing cancer.

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