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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 hemithyroidectomy; 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 eighth to tenth thoracic dermatomes. A closer view (c) demonstrates the flesh colored soft skin lesions that ranged in size from 3 mm to 10 mm in greatest diameter.](image-url)
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).

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 lesion 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 NFI 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

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

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
Segmental neurofibromatosis, referred to as mosaic neurofibromatosis 1, results from a postzygotic mutation in the NFI 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.

References


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