Case Report:
Morphological Characterization of the Breast in Proteus Syndrome Complicated by Ductal Carcinoma In Situ

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Abstract. Proteus syndrome (PS) is a severe, variable, and rare disorder with asymmetric and disproportionate overgrowth of body parts, cerebriform connective tissue nevi, epidermal nevi, dysregulated adipose tissue, and vascular malformations. It is associated with benign and occasionally malignant tumors. We report the first case of ductal carcinoma in situ (DCIS) in a 28-yr-old woman with PS who underwent a mastectomy for asymmetric overgrowth. The cut surface of the tissue showed a discrete, white, lobulated, solid mass with multiple cysts with occasional small polypoid nodules. Microscopically, the tissue was characterized by neoplastic and non-neoplastic changes. The former consisted of multiple intraductal papillomas and low-grade intraductal papillary, solid, and cribriform carcinoma. The non-neoplastic changes were characterized by cysts of various sizes, lined by cuboidal or apocrine cells, focally with epithelial papillary proliferation; the lumens contained eosinophilic, mucicarmine-positive, and PAS-positive material. Variable ductal proliferation and periductal, peri- and intra-lobular fibrosis with loose fibrous connective tissue was present. The carcinoma was positive for ER, PR, CK7, and MIB-1 (40%), and negative for p53 and CK20 staining. We conclude that DCIS may be one of the tumors associated with PS and that the proliferative phenotype serves as an initiator for carcinogenesis. This case highlights the difficulty of recognizing small foci of carcinoma in an asymmetrical overgrowth of the breast in a young woman with PS.

Keywords: Proteus syndrome, intraductal carcinoma, intraductal papilloma, breast proliferative changes

Introduction

Proteus syndrome (PS) is a variable, rare, and sporadic disorder characterized by asymmetric and disproportionate overgrowth of subcutaneous connective tissue, bone, skeletal muscles, central nervous system, ocular tissue, and viscera with vascular malformations [1-3]. In Greek mythology, Proteus was a sea god who could change his shape. The syndrome, PS, is associated with multiple benign tumors, such as invasive lipomas, gigantic epidermal nevi, ovarian cystadenomas, mono-

morphic adenomas of the parotid gland, and occasionally, by malignant tumors such as mesotheliomas (peritoneum, tunica vaginalis of testis) and testicular yolk sac tumors [2,4-6]. Only 2 reports describe breast abnormalities in PS, ie, intraductal papillomas, hyperplastic fibrocystic changes, and asymmetric overgrowth [2,7].

We describe a patient with PS and intraductal carcinoma of the breast, a complication that has not been previously described to our knowledge. This report includes a microscopic description of associated findings and discusses the implications of the findings for understanding the pathophysiology of this disease and the management of individual patients.
Case History
A 28-yr-old Caucasian female presented to the NIH for evaluation of overgrowth. She was the product of an uncomplicated pregnancy, labor, and delivery. Birth parameters were normal and no overgrowth was noted until overgrowth of the soles of her feet commenced at a few mo of age. At about 6 mo of age she had the onset of asymmetric overgrowth of soft tissue of several fingers. At about 9 yr of age she was noted to have scoliosis. Numerous surgical operations were performed to reduce and limit the overgrowth of the limbs, with varying success. Spinal fusion was performed at 13 yr of age. At 21 yr of age the patient was noted to have severe asymmetry and macromastia of the right breast associated with pain of the back, neck, and shoulder. She underwent a right breast biopsy for a palpable mass as well as right-sided reduction mammoplasty. At the age of 22 yr, she developed excessive vaginal bleeding and was diagnosed as having endometrial polyps. Microscopic examination of these polyps revealed an endometrioid adenocarcinoma. She was treated only with megestrol acetate because she wanted to preserve the uterus.

When the patient was examined at the age of 23 yr, her height, body wt, and head circumference were normal. A small hyperostosis of the right mastoid was present. The palate was narrow and the dentition was crowded. Several of her fingers (right thumb, third finger, and palm, and left third finger) had distorting, irregular overgrowth and surgical scars. Significant breast asymmetry was present but no discrete mass could be identified on palpation. The soles of the feet had the remnants of cerebriform connective tissue nevi and post-surgical scars with several open, draining wounds, presumably decubiti. The left leg had dilated veins and several irregular, diffuse soft tissue masses (compatible with lipomas or lymphatic vascular malformations). A linear verrucous epidermal nevus of the right shoulder was present.

On follow-up evaluation at 28 yr of age, the patient’s physical examination was essentially unchanged except for healing of the foot decubiti. Pelvic examination revealed an enlarged cervix. Fine needle aspiration of the breast revealed findings suggestive of a papillary lesion. The patient decided to undergo a right mastectomy with reconstruction, which was performed at North Shore University Hospital, in Manhasset, NY.

The patient’s family history was negative for any signs of tissue overgrowth, breast cancer, or gynecologic cancer.

Materials and Methods
The surgical specimen was formalin-fixed, embedded in paraffin, and stained with hematoxylin-eosin, periodic acid Schiff (PAS), and mucicarmine. Histochemical stains were performed, such as CK7, CK20, P53, and MIB (Dako Co., Carpinteria, CA), as well as receptor studies for estrogen receptor (ER) and progesterone (PR) (Ventana Medical Systems, Inc., Tucson, AZ). Samples were also sent for cytogenetic analysis by karyotyping.

Results
The mastectomy specimen measured 18 cm x 13 cm x 4 cm, and showed on its cut surface a lobulated appearance with solid and cystic areas (Fig. 1). The solid areas were tan, white, and rubbery; the cysts varied from 0.5 to 2 cm in diameter and they were filled with dark, thick, jelly-like material. The smooth inner surface of some cysts contained sessile polypoid nodules, ranging from 0.5 to 1.0 cm in diameter.
Fig. 2. Intraductal papilloma: A. note delicate arborizations of papillary structures lined by cuboidal epithelium and focally associated with cystic dilatation (H&E stain, 125x magnification); B. atypical epithelial hyperplasia is evident in some areas (H&E stain, 250x magnification).

Fig. 3. Intraductal carcinoma; A. papillary; B. solid with necrosis; C. cribriform; (H&E stain, 250x magnification).
Fig. 4. Non-neoplastic changes: A. cysts, ductal hyperplasia, and apocrine metaplasia; B. interstitial fibrosis with ductal distortion; (H&E stain, 125x magnification).

Fig. 5. Hormone receptor immunostains: A. most of the tumor cells stain positive for ER receptors; B. more than half of the tumor cells stain positive for PR receptors (250x magnification).

Table 1. Results of histological staining procedures.

<table>
<thead>
<tr>
<th>Stain</th>
<th>Neoplastic tissue</th>
<th>Non-neoplastic tissue</th>
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<tbody>
<tr>
<td>ER</td>
<td>+ 95%</td>
<td>+ 60%</td>
</tr>
<tr>
<td>PR</td>
<td>+ 65%</td>
<td>+ 100%</td>
</tr>
<tr>
<td>Mucicarmine</td>
<td>+ (lumen)</td>
<td>+ (lumen)</td>
</tr>
<tr>
<td>PAS</td>
<td>+ (lumen)</td>
<td>+ (lumen)</td>
</tr>
<tr>
<td>CK7</td>
<td>+ 60%</td>
<td>+ 100%</td>
</tr>
<tr>
<td>CK20</td>
<td>- 0%</td>
<td>- 0%</td>
</tr>
<tr>
<td>p53</td>
<td>- 0%</td>
<td>- 0%</td>
</tr>
<tr>
<td>MIB-1</td>
<td>+ 40%</td>
<td>+ &lt; 5%</td>
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Table 2. Diagnostic criteria for Proteus syndrome

General Criteria: mosaic distribution, progressive course, and sporadic occurrence

Specific Criteria:
Category A: Cerebriform connective tissue nevus
Category B:
1. Epidermal nevus
2. Disproportionate overgrowth of 2 of the following: limbs, skull, auditory canal, vertebrae, or viscera
3. Specific tumors before age 30 yr: parotid monomorphic adenoma, or bilateral ovarian cystadenomas
Category C:
1. Dysregulated adipose tissue
2. Vascular malformations
3. Characteristic facial phenotype

Diagnosis requires all 3 general criteria, plus either 1 from category A, 2 from category B, or 3 from category C.

[Adapted from reference 1]
Neoplastic and non-neoplastic changes were evident on microscopic examination of the mastectomy specimen. The former consisted of multiple intraductal papillomas, at times associated with solid atypical epithelial hyperplasia (Fig. 2). Other areas had features of intraductal carcinoma, including papillary, solid, and cribriform components (Fig. 3). The non-neoplastic changes consisted of irregular ductal proliferation with cystic dilatation, some places associated with apocrine metaplasia, and interstitial fibrosis with distortion of the ducts and lobules (Fig. 4). These changes were admixed with histologically normal but overgrown breast tissue.

Table 1 summarizes the histologic staining characteristics of the neoplastic and non-neoplastic changes. The carcinoma was ER and PR positive (Fig. 5), with 40% proliferative activity in the MIB-1 stain, and negative staining for p53. Mucicarmine-positive and PAS-positive staining of material in the lumen of ducts and cystic spaces was present in both the neoplastic and the non-neoplastic areas. Cytogenetic studies of cultured cells showed a 46,XX karyotype.

Histologic sections of breast tissue from the patient's prior lumpectomy was reviewed by two of the authors (PR and EK). Non-neoplastic and benign neoplastic changes were present that were similar to those of the mastectomy specimen.

Discussion

Our patient fulfilled the diagnostic criteria of PS (see Table 2) [1,8]. She met the 3 general criteria of sporadic occurrence, progressive course, and patchy or mosaic distribution. She also had a cerebriform connective tissue nevus (specific criterion A) (by history—not confirmed), linear verrucous epidermal nevus (criterion B1), and progressive and distorting bony overgrowth (criterion B2). Overgrowth of the breast with inhomogeneity led to the mastectomy.

Proteus syndrome is very rare, affecting about 100 patients in the developed world, and few patients with PS have had documented breast lesions. One report of a patient with PS described enlarged breasts with bilateral fibrocystic changes, mild to marked epithelial hyperplasia, and an intraductal papilloma in one breast [7]. In another report, hyperplasia of the breast is mentioned [2],

The patient who is reported here had non-neoplastic and neoplastic changes of the breast, the former consisting of cysts, and proliferation of the connective tissue and epithelial structures. Admixed with the non-neoplastic changes were intraductal papillomas, and intraductal papillary, solid, and cribriform carcinoma, a finding that, to the best of our knowledge, has not previously been reported in PS. The carcinoma was ER, PR, and CK7 positive, CK 20 and p53 negative, with a proliferation index in the MIB-1 stain of 40%.

This case demonstrates that the breast like other organs (eg, parotid gland, ovary, uterus, kidney, testis) may be affected by dysregulated overgrowth with the subsequent development of neoplasia [4]. The tumor of our patient had a normal karyotype. There are no reports of cytogenetic aberrations in patients confirmed to have PS by the current clinical diagnostic criteria.

The difficulty of diagnosing and treating overgrowth in PS is apparent in our patient. Asymmetric overgrowth may be comprised of a combination of hyperplasia and benign and malignant tumors. It is challenging to determine whether to biopsy a mass in a patient with PS. This is because of two conflicting factors: benign masses are very frequent (essentially universal) in PS, but it is likely that PS predisposes to malignancies [2]. If all such masses were biopsied or removed, patients with PS would be subjected to an unreasonable number of surgical operations. For these reasons, the decision to undertake surgery is difficult.

When a biopsy is performed, it can be difficult to interpret the results since (as in the present report) the overgrown tissue is heterogeneous and may contain small foci of malignancy, and the biopsy may therefore not necessarily include the carcinoma. Biopsies of overgrown tissue in PS must be interpreted with great care, as they may not represent the range of pathology within these complex lesions. Cancer should be considered early in the differential diagnosis of any breast mass in a patient with PS.

Was the development of a breast carcinoma in our patient with PS due to her genetic background (endometrioid carcinoma at 23 yr of age) or related to the PS? We favor the second hypothesis based on the patient's lack of a familial history of breast or gynecologic malignancy. Endometrial carcinoma
has been described in a 25-yr-old woman with PS [2]. In addition different tumors can coexist in a patient with PS [2].

This case illustrates the concept that overgrowth of PS may provide a cellular milieu that is favorable for carcinogenesis. Consistent with current models of tumor progression [9], the histologically normal overgrowth of PS may provide the first step of the multistep somatic genetic pathway from normal to malignant tissue.

In summary, the overgrowth of PS can involve any tissue and the affected patients are predisposed to malignancies. The patient described here shows that the breast may be affected by the dysregulated overgrowth, resulting in deformity with non-neoplastic and neoplastic changes, such as intraductal papillomas and intraductal carcinoma.

Acknowledgements

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References