Adenofibromas are common in the ovary, may be seen in association with endometriosis or ovarian inclusion cysts, and can coexist with a variety of epithelial tumors including endometrioid, serous, clear cell, transitional (Brenner tumors), and mucinous (1). Moreover, adenofibromas may precede and/or accompany epithelial malignancies (2). In contrast to ovarian adenofibromas (OAs), adenofibromas arising in the fallopian tube are rarely reported, with the majority discovered as incidental findings at the time of histological examination for other disorders (3–8). However, because the fallopian tube is not routinely completely sampled and examined histologically, the incidence of tubal adenofibroma is not known. Recently, while conducting a study of women with BRCA mutations, we developed a protocol for complete examination of the fallopian tube that...
concentrated on the fimbria (sectioning and extensively examining the fimbria [SEE-FIM] protocol) (9,10). When applying this protocol, we discovered that many fallopian tubes contained small stromal-epithelial proliferations that resembled OAs. To evaluate further the nature of this entity, we designed a study to determine the frequency of fallopian tube adenofibroma (FTA) and compare its stromal and epithelial phenotype to OA.

MATERIALS AND METHODS

Case Selection
This study was approved by the human investigation committee at Brigham and Women’s Hospital. Three groups of cases were analyzed. The first consisted of a consecutive series of 88 fallopian tubes that were not associated with tubo-ovarian malignancy or inflammatory disorders that were entirely examined histologically using the SEE-FIM protocol, as described previously (11). The second consisted of 30 consecutively accessioned fallopian tubes from women undergoing risk reduction salpingo-oophorectomies for inherited BRCA1 or BRCA2 mutations. The third consisted of 12 consecutive cases of completely examined fallopian tubes in patients with OA. The purpose of this approach was to determine the frequency of FTA in cases of OA and to compare the immunohistochemical profiles of OA with those of FTA.

Classification of FTAs
The diagnosis of adenofibroma was based on the presence of stromal-epithelial proliferations that closely resembled those previously described in the ovary, which included the following features: (1) dense interlacing bundles of collagen, which contrasted with the more delicately arranged subepithelial collagen of the plica with its underlying smooth muscle in the muscularis and round ligament, (2) small epithelial clefts and/or glandular spaces in the stroma, and (3) distortion of the normal plical architecture. Lesions measuring at least 3 mm in 1 dimension were arbitrarily classified as FTAs; smaller lesions were classified as early lesions and termed incipient FTAs (iFTAs), and the presence or absence of epithelial clefts and/or glandular spaces was considered optional (not necessary to be present because of their small size) but was documented.

Immunohistochemistry
Immunostaining was performed with attention to either focal (present in discrete loci) or diffuse (present throughout most of the lesion) distribution, with the following primary antibodies to:
1. CD10 (clone 56C6, Novocastra, Newcastle Upon Tyne, UK), WT-1 (clone 6F-H2, Dako, Carpenteria, CA), which has been identified in endometrial stromal differentiation and in ovarian cortex in association with inclusion cysts and various stages of endometriosis development (12);
2. Calretinin (polyclonal rabbit, Zymed, San Francisco, CA), a marker distinguishing mesothelium from müllerian tubal epithelium (13);
3. Inhibin (clone R1, Serotec, Oxford, UK), which has been reported in unusual variants of OA (14);
4. Desmin (clone D33, Dako), a marker for smooth muscle differentiation (15);
5. WT-1 (clone 6F-H2, Dako), a marker for mesothelium and for serous differentiation in müllerian epithelium; and
6. Estrogen receptor (clone 1D5, Dako).

In addition, selected cases were immunostained with:
7. Ki67, a broad-spectrum marker for cell DNA proliferation (clone MIB-1, Dako) (16);
8. bcl-2 (clone 124, Dako), which selectively stains tubal secretory cells (Ronny Drapkin, Department of Pathology, Brigham and Women’s Hospital, Boston, MA, unpublished data); and
9. LhS28 (clone LhS28, Abcam, Cambridge, UK), which targets the ciliary body of ciliated cells (17).

| TABLE 1. Pathological findings in adenofibromas discovered upon complete examination of bilateral fallopian tubes in 88 consecutive cases not associated with tubo-Ovarian malignancy or inflammatory disorders and not associated with ovarian neoplasia |
|----------------|----------------|----------------|----------------|----------------|
|                | No. cases | No. cases with bilateral adenofibroma | No. cases with multiple lesions | Comments |
| > 3 mm but < 1 cm | 9 | 1 | None | 0.3-2.3 cm (mean, 0.7 cm) |
| > 1 cm < 3 mm | 3 | None | 7 | 3 associated with adenofibroma > 3 mm |
The above were analyzed using Heat Induced Epitope Retrieval by pressure cooker (30 s at 125°C [18–24 PSI] with citrate buffer pH 6.0). The Envision Horseradish Peroxidase Method with 3,3'-diaminobenzidine as chromogen (DakoCytomation, Carpinteria, CA) was used for antibody detection. Appropriate negative and positive controls were applied.

RESULTS

Frequency of FTAs and Associated Clinicopathologic Findings

Table 1 summarizes the pathological findings in 88 consecutively examined bilateral salpingectomies using the SEE-FIM protocol. A wide spectrum of clinical findings was seen in the 88 cases (data not shown), and there was no significant association with any condition including endometriosis. Overall, 26 of 88 (30% overall frequency) consecutively examined bilateral fallopian tube specimens contained adenofibromas (FTAs and/or iFTAs). Twelve FTAs were identified (11 cases; 14% overall frequency), 3 of which exceeded 1 cm in dimension (Fig. 1). Twenty-nine iFTAs were identified (18 cases; 20% overall frequency) (Fig. 2). The iFTAs were bilateral in 4 cases, multiple in 10, and were associated with an FTA in 3 (Table 1). In a single fallopian tube, the greatest number of adenofibromas identified was 3 (1 FTA and 2 iFTAs). Fourteen (70%) of 20 cases of iFTA had an epithelial component; all 6 of the iFTAs without an epithelial component measured less than 0.1 cm. All of the FTAs and iFTAs were located in the fimbria. Of the 30 women undergoing surgery for BRCA mutations, 7 (23%) contained adenofibromas, all iFTAs. The iFTAs were bilateral in 1 case. Two in 1 tube contained an epithelial component and measured 0.2 cm.

Table 2 summarizes the pathological findings of 12 consecutive cases of OA, in which the bilateral salpingectomies were examined using the SEE-FIM protocol. Of 12 consecutive OAs with complete...
examination of the fallopian tubes, 3 (25%) contained coexisting FTAs. Two of these also contained an iFTA. All of the coexisting FTAs and iFTAs were located in the fimbria.

The mean age of patients with FTAs and iFTAs in the 88 consecutively examined bilateral salpingectomies using the SEE-FIM protocol was 55 years (range, 41–80 y). The mean age of patients with FTAs and iFTAs in the 12 consecutive cases of OA in which the bilateral salpingectomies were examined using the SEE-FIM protocol was 56 years (range, 49–67). All FTAs and iFTAs were incidental findings at the time of pathological examination.

**Histopathology**

The stromal component of the FTAs ranged from hypercellular to more densely collagenous or hyalinized. The latter was most prominent in the larger lesions (Fig. 1). The relative proportion of lesion containing an epithelial component and the extent of cystic change were variable (Fig. 1). The iFTAs typically exhibited a distinct but architecturally subtle change in the tubal mucosa, characterized by mild irregularity in the mucosal surface contour, with blunting of the plica and few if any glands in the subepithelial stroma. The latter was typically arranged in small patches of uniformly oriented spindle cells that usually merged gradually with the

**TABLE 2. Pathological findings in adenofibromas discovered upon complete examination of bilateral fallopian tubes in 12 consecutive cases associated with an OA**

<table>
<thead>
<tr>
<th>No. cases</th>
<th>No. cases with bilateral adenofibroma</th>
<th>No. cases with multiple lesions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 mm but &lt;1 cm</td>
<td>3</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>&gt;1 cm</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 mm</td>
<td>2</td>
<td>1</td>
<td>None</td>
</tr>
</tbody>
</table>

OA indicates ovarian adenofibroma.
surrounding mesenchymal tissue (Fig. 2). The epithelial lining of iFTAs and the intralesional glands varied from cuboidal to pseudostratified and contained variable percentages of secretory and ciliated cells.

Immunohistochemical Findings

Immunohistochemistry for WT-1, calretinin, inhibin, estrogen receptor, and desmin was performed on 6 cases (2 FTAs and 4 iFTAs). Where identified, the stroma and epithelium were diffusely WT-1 and ER positive, in all cases examined, and in both epithelium and stroma. The stroma also showed variable (focal or diffuse) immunopositivity for calretinin and inhibin in 5 of 5 (4 focal) and 4 of 5 (2 focal), respectively. Rare scattered stromal cells were positive for desmin in 4 of 4 cases. Two of 4 cases showed focal positivity for calretinin in the epithelial component. The epithelial component was negative for inhibin and desmin.

CD10 immunohistochemistry was performed on 16 cases (12 FTAs and 4 iFTAs). Fifteen (93%) of 16 cases stained with CD10 (11 FTAs and 4 iFTAs). CD10 staining marked the spindled stroma in iFTAs.
In contrast, in larger lesions (FTAs), the staining was not uniformly distributed, being most prominent at the epithelial-stromal interface (Fig. 3). The epithelial component was negative for CD10.

Immunohistochemistry for Ki-67, LhS28, and bcl-2 was performed on 11 FTAs and 3 iFTAs to determine the relative contribution of ciliated and secretory cells. In all cases, a mixed population of both cell phenotypes was identified, similar to that seen in the adjacent normal tube (Fig. 4). There was no appreciable difference in index of Ki-67 staining in the epithelium lining of the iFTAs or FTAs relative to the adjacent salpingeal epithelium (not shown).

CD10, inhibin, bcl-2, and LhS28 immunostaining was also performed on 6 OAs. Like the FTAs, inhibin was diffusely distributed in the stroma in variable intensity, contrasting with discrete focal intense staining in luteinized cells of the adjacent normal ovarian stroma. CD10 staining was also most intense in stroma beneath the epithelium lining the surface (Fig. 3E, F) and glands within the tumor. The lining epithelium, composed of both secretory and ciliated cells, was identical to that in the FTAs (not shown).

**DISCUSSION**

This is the first study to systematically examine the fallopian tubes with attention to the frequency of tubal adenofibroma. Although adenofibromas have been reported in the fallopian tube, they have been presumed uncommon, a conclusion that has at least 3 explanations. The first is the fact that fallopian tubes are not extensively sampled, and sections of the fimbria are not routinely submitted for histological examination. The second is that unless grossly apparent, a tubal adenofibroma is not likely to result in selected sampling and a detailed pathological analysis. As a result, smaller lesions would go unnoticed. Third, as shown in this study, criteria for adenofibroma that are restricted to those with stromal proliferation and a well-developed epithelium would not recognize some of the more subtle examples (iFTAs < 1 mm without a glandular component) that were included in this report. Although large clinically significant tubal adenofibromas are indeed uncommon, the overall frequency (30%) of tubal adenofibroma (iFTAs and FTAs) as shown in this study is greater than previously appreciated and similar to that seen in women undergoing...
risk-reducing salpingo-oophorectomy for BRCA mutations (23%).

It might be argued that the iFTAs do not merit classification as adenofibromas, but as variants of tubal stromal differentiation, or fibromas. We classified these smaller lesions as iFTAs for the following reasons: (1) similar to adenofibromas, they were associated with alterations, albeit sometimes subtle, in the overlying epithelium, even when not accompanied by an intrastromal glandular proliferation; (2) iFTAs and FTAs seemed to be part of a continuous spectrum of size, and it is not surprising that smaller lesions were less likely to exhibit intrastromal glands; and (3) the immunohistochemical findings, with frequent CD10 and inhibin positivity, were identical in both groups. Despite the prior reports linking CD10 immunostaining to endometriosis, we found it in larger FTAs and OAs. Thus, although CD10 immunostaining is intriguing from a pathogenetic point of view, we did not consider its presence sufficient to implicate endometriosis as the source of the lesions described in this report (12,18). Inhibin staining, although assigned to areas of sex cord differentiation in OAs, can be seen sporadically in endometrial and ovarian stroma and is not necessarily considered indicative of sex cord differentiation [[19] and personal observations Marisa R. Nucci and Christopher P. Crum, unpublished data]. Nevertheless, the presence of both CD10 and inhibin staining in iFTAs readily distinguished these lesions from the surrounding normal tubal stroma, further evidence of the specialized stromal differentiation of iFTAs.

Two properties of iFTAs raise important questions about their histogenesis and their relationship to OAs. The first is their exclusive location in the fimbria. This is particularly interesting in view of the close proximity of the fimbria to the ovarian cortex and the access of the fimbrial mucosa to the latter via exfoliation of epithelial cells or direct transfer via tubo-ovarian adhesions. The coexistence of OAs with FTAs in 25% of cases is not conclusive evidence of fimbrial-ovarian transfer, but leaves open this possibility in view of the exclusive location of FTAs to the fimbria. Second, recent studies have provided support for the tube as a source of both serous and endometrioid neoplasms, both of which traditionally have been assigned to the ovarian cortex or, in the case of endometrioid differentiation, the endometrium (10,11,20,21). Significantly, tubal, serous, and endometrioid neoplasms are most common in the distal fallopian tube (3,10,11,20,21–24). Similar to the ovary, the distal tube plays host to not only malignant serous and endometrioid neoplasms, but also benign conditions such as adenofibromas. The virtually identical epithelial composition of these tumors, irrespective of location in the ovary or tube, supports the concept of a common fimbrial-ovarian epithelial phenotypic spectrum, also supported by expression array studies (25). Whether the presence of adenofibromas in both sites is explained by transport or a shared susceptibility (“field effect”) remains to be determined. However, this and other studies indicate that the distal fallopian tube is a credible source of a range of epithelial proliferations previously assigned to the ovary.

REFERENCES


