Pathologic Quiz Case

A 70-Year-Old Woman With Postmenopausal Bleeding

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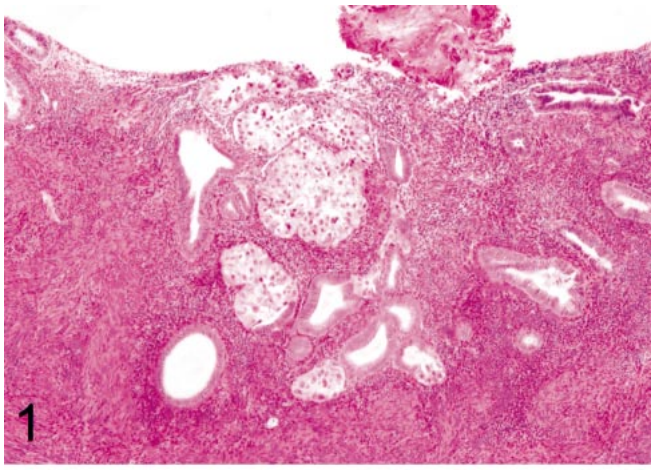
A 70-year-old woman presented with a history of lower abdominal pain that had been present for 6 months, during which time she had an episode of vaginal bleeding. Her gynecological examination was unremarkable and showed a smooth cervix, small uterus, and nonpalpable adnexa. A preoperative endometrial biopsy performed at an outside institution was reported as carcinoma. Subsequently, the patient underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and staging pelvic and para-aortic lymphadenectomy.

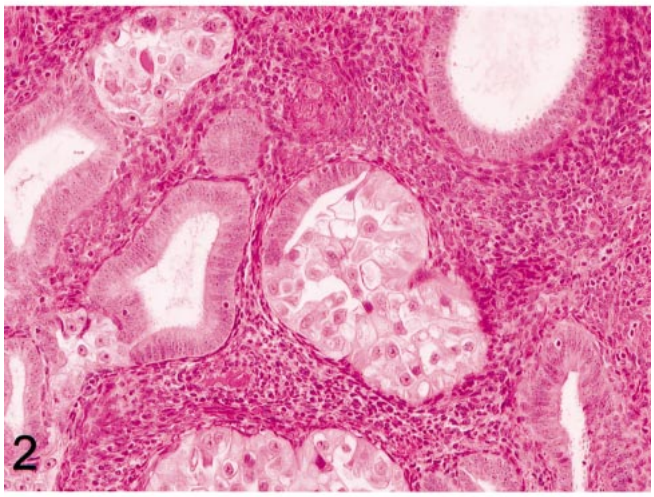
On gross examination, the uterus with attached cervix, bilateral fallopian tubes, and ovaries weighed 105 g. The serosa was pink and smooth. The opened uterus revealed a pink, flat endometrial cavity, with no masses identified. Serial sectioning of the uterine wall demonstrated subserosal and intramural leiomyomata. Bilateral ovaries, fallopian tubes, and parametria were unremarkable. The specimen was exhaustively sampled.

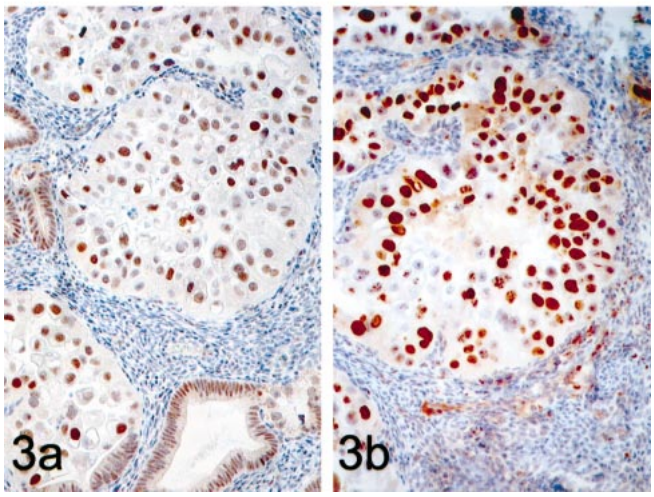
On microscopic examination, the endometrial surface epithelium and some of the endometrial glands were partially lined or completely replaced by highly atypical cells overlying a basement membrane. The uninvolved endometrium showed atrophic changes. The atypical cells had clear cytoplasm, marked nuclear pleomorphism, coarse chromatin, irregular nuclear membranes, and prominent eosinophilic nucleoli. Some of these cells had scant cytoplasm and enlarged pleomorphic nuclei protruding into the lumen of glands in a hobnail appearance. Mitotic figures were not identified. These cytologic changes were focally limited to the surface epithelium and some endometrial glands. No evidence of invasion into the endometrial stroma or into the myometrium was identified (Figure 1, hematoxylin-eosin, original magnification ×100; Figure 2, hematoxylin-eosin, original magnification ×200). The endocervix was not involved. Three pelvic and 3 para-aortic lymph nodes were negative for metastatic carcinoma. Bilateral fallopian tubes, ovaries, and parametria were unremarkable microscopically.

Immunohistochemical staining for p53 showed focal nuclear staining (Figure 3, a; original magnification ×200), and immunohistochemical staining for Ki-67 showed the atypical glands to have a moderate to high proliferative index (Figure 3, b; original magnification ×200).

What is your diagnosis?







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Pathologic Diagnosis: Endometrial Intraepithelial Carcinoma, Clear Cell Type

Endometrial intraepithelial carcinoma (EIC) is a recently described lesion characterized by the replacement of atrophic endometrial surface epithelium and glands by malignant cells resembling high-grade invasive endometrial carcinoma.[1–3] Although this lesion has been referred to as carcinoma in situ or uterine surface carcinoma, the term *EIC* is preferred because of its association with metastatic disease.

Endometrial intraepithelial carcinoma is mostly found in postmenopausal women,[2,4] and it usually presents as uterine bleeding. Endometrial intraepithelial carcinoma has no association with hyperestrogenism.

Endometrial intraepithelial carcinoma can be found in uteri without invasive serous carcinoma, frequently in a polyp arising in an atrophic endometrium. It also has been described in association with invasive, extrauterine serous carcinomatosis in the absence of an invasive endometrial serous carcinoma.[2]

On careful examination, EIC is found in nearly all uteri containing serous carcinoma and is considered to be its precursor. Rarely, it has also been identified in uteri containing clear cell carcinoma and endometrioid carcinoma.[1,3,5]

Molecular genetic studies have demonstrated immunohistochemical overexpression of p53 protein, loss of heterozygosity of chromosome 17p, and corresponding p53 mutations in most serous carcinomas and EICs.

Microscopically, markedly atypical cells with enlarged nuclei, granular or vesicular chromatin, and prominent eosinophilic nucleoli line the surface epithelium and involve glands of atrophic endometrium, either partially or completely. In many instances, the malignant epithelium involving glands is contiguous with that on the surface.[3] Mitotic figures are usually numerous, and the proliferation marker Ki-67 shows a very high proliferation index. Immunohistochemical staining shows diffuse, strong staining for p53 in most cases of EIC; however, it can also be absent.

Endometrial intraepithelial carcinoma must be distinguished from benign metaplastic or degenerative changes, such as clear cell metaplasia, eosinophilic cell change, hobnail change, and tubal metaplasia, which can mimic the cytologic changes seen in EIC. The most useful features in making the distinction include nuclear atypia and immunohistochemical staining for p53 and Ki-67. The endometrial epithelial metaplasias usually present minimal atypia. The cells in glands or on the surface of the endometrium have bland nuclei with smudged chromatin, lack nucleoli, and may have a degenerative appearance.[3,6] In tubal metaplasia, ciliated cells and intercalated cells are also present. Moreover, reactivity for Ki-67 shows a low proliferation index in metaplasias, whereas it is very high in EIC,[3] and staining for p53 is typically negative or shows weak nuclear staining in metaplasias, while in EIC it is usually strongly and diffusely positive.

Although the data on the behavior and prognosis of EIC are limited, recent studies have shown that patients with EIC and no evidence of invasive serous carcinoma, vascular or myometrial invasion, and no extrauterine disease have a survival rate of 100% after a mean follow-up of 27 months.[7]

In conclusion, EIC is a distinctive malignant entity that should be carefully distinguished from benign metaplastic changes in the postmenopausal woman. Because of its association with both uterine and extrauterine invasive serous carcinoma, the patient with EIC should undergo careful staging at the time of hysterectomy.

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