

Diagnostic dilemmas and potential pitfalls in the evaluation of endometrial adenocarcinoma

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Abstract

Endometrial adenocarcinoma is the most common malignancy of the gynaecologic tract, and therefore one of the most commonly encountered surgical pathology specimens. Accurate diagnosis, grading and staging are necessary to direct therapy for this common disease. Evaluation of these cases is usually straightforward. Some cases, however, may be complicated by a variety of issues such as difficulty assessing depth of invasion; difficulty assessing cervical involvement; possibility of synchronous ovarian primaries; evaluation of lymphovascular space invasion; difficulties with FIGO grade (especially in the company of altered differentiation); and subtle patterns of myoinvasion. The purpose of this review is to emphasize these problematic areas and offer straightforward guidelines to apply when these situations are encountered. Proper recognition of these diagnostic challenges will hopefully improve grading and staging accuracy, and subsequently therapy, for the multitudes of women affected by this disease.

Keywords endometrial carcinoma; neoplasm grading; tumour staging

Introduction

Evaluation of a hysterectomy specimen in the context of endometrial carcinoma is one of the most common tasks facing surgical pathologists. The International Federation of Gynaecology and Obstetrics (FIGO) staging system uses the depth of tumour invasion and spread of tumour to adjacent structures (such as the cervix, serosa or adnexa) to determine the need for further treatment. Therefore, correct evaluation of these important features is critical. Furthermore, determination of a FIGO grade (1 through 3) provides insight into the potential aggressiveness of endometrioid tumours. The majority of cases present little

problem in the determination of FIGO grade and stage; however, complicating factors do arise. The purpose of this review is to emphasize some of the more common challenges that may arise in the evaluation of hysterectomy specimens, and offer guidelines for addressing these problem areas.

Depth of invasion

Assessing depth of invasion in endometrial cancer can be one of the most common problems plaguing practicing pathologists. As depth of invasion is one of the most important factors influencing prognosis, accurate determination is vital in predicting outcome and further therapy. Two important “cutoffs” should be kept in mind when evaluating tumours for myometrial invasion: first, is invasion present (Stage Ia); and second, if it is present, does it extend more than 50% of the way through myometrium (Stage Ib). Although the prognosis for non-invasive and Stage Ia tumours is overwhelmingly favourable, superficial invasion should be sought because lymphovascular invasion is much more likely to be present when invasion is detected.

Diagnosing superficial invasion can be one of the most difficult steps in evaluating uterine cancer. Irregular endomyometrial junctions, tangential sectioning, and exophytic tumours with stromal smooth muscle metaplasia are common confounding factors. In a review of 100 endometrioid endometrial adenocarcinomas, Ali et al.¹ delineated well defined, easy to follow criteria for invasion in the context of an irregular endomyometrial junction. Invasion was defined as the presence of “neoplastic epithelial cells surrounded by myometrium without intervening stroma,” along with the presence of either “jagged infiltrative” contours or desmoplasia. In contrast, an irregular endomyometrial junction consisted of “at least one undulation that measured at least 2–3 mm in magnitude”. Endometrial stroma, which may be difficult to detect, should be present in all foci of the irregular endomyometrial junction, and absent around any glands deemed invasive (Figures 1 and 2). When an irregular endomyometrial junction is seen, care must be taken to assure that tangentially sectioned glands along the endomyometrial junction are not misinterpreted as invasive.

Endometrial stroma has the ability to undergo metaplastic change to a smooth muscle, fibroblastic or myofibroblastic phenotype. The appearance of this metaplastic stroma may be confused for myometrium, leading to a misdiagnosis of invasion. These metaplastic foci are composed of eosinophilic cells (when compared to native endometrial stromal cells) in poorly formed fascicles that merge with adjacent normal endometrial stroma; the lack of well-organized smooth muscle bundles is a clue to the appropriate interpretation (Figure 3). Metaplasia can be a prominent finding within the endometrial stromal component of exophytic tumours, and its existence should be kept in mind when considering a diagnosis of invasion on endometrial biopsy, hence the general rule-of-thumb to (almost) never diagnose invasion in biopsy specimen.

Cancerous involvement of adenomyosis is a relatively frequent finding, and one that can present diagnostic difficulty. The presence of normal endometrial glands or stroma is a helpful feature of non-invasion; however, they may not be present due to tumour overgrowth. A well circumscribed, smooth border surrounding a cluster of glands is more likely to be associated with

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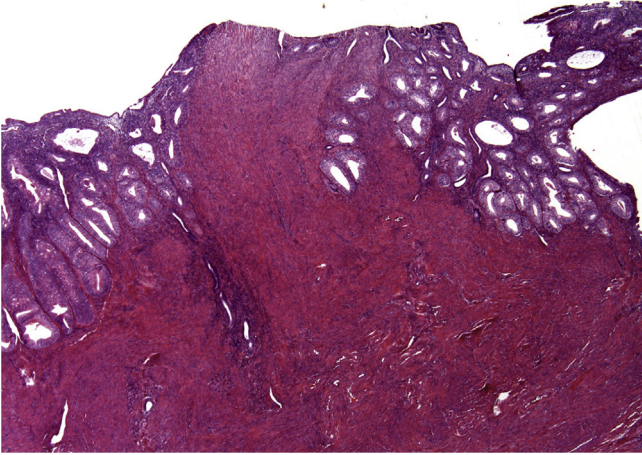


Figure 1 An example of an irregular endomyometrial junction. Note the presence of undulating myometrium and normal endometrial glands extending into the myometrium (left of centre).

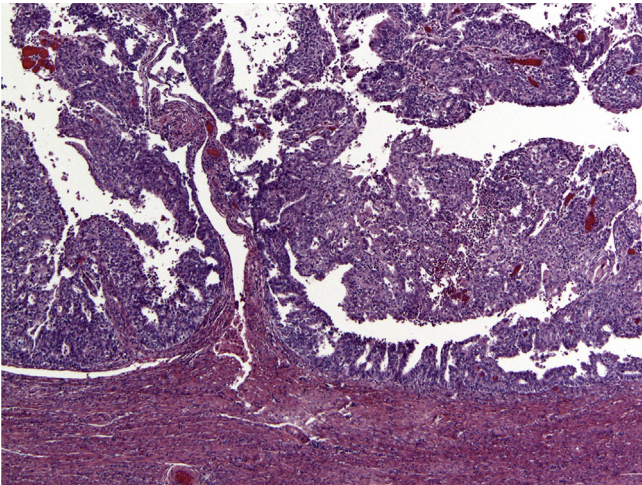


Figure 2 Malignant endometrial glands and myometrium without intervening endometrial stroma. This is an example of broad-front tumour invasion.

adenomyosis involved by carcinoma, whereas irregular glandular protrusions and jagged contours extending from adenomyotic foci are signs of invasion (Figure 4). Desmoplasia is a helpful feature, but this is not always present. Further complicating the issue is the “adenomyosis-like” pattern of invasion.² This pattern of invasion is characterized by nested groups of endometrial glands with or without associated desmoplasia. These nests typically display irregular (albeit well circumscribed) borders, and lack normal endometrial glands and stroma.

Two additional patterns of invasion can also lead to confusion: “broad-front” or pushing borders, and adenoma malignum-like invasion. Broad-front invasion is characterized by a well delineated swath of malignant glands that push into the myometrium without intervening stroma between the malignant glands and the myometrium (Figure 2). Desmoplasia is often absent or subtle. Gross evaluation of the uterus is key in identifying this type of invasion. Sections should be taken to demonstrate areas of pushing invasion adjacent to the perceived

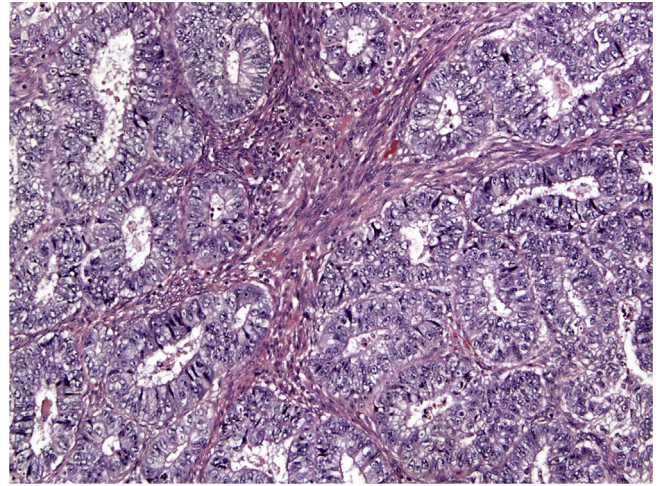


Figure 3 Fibromuscular metaplasia of the endometrial stroma. Spindled, eosinophilic cells can be seen in an arborizing pattern between malignant glands. There is a conspicuous lack of fascicle formation. This appearance is not indicative of invasion.

“normal” endomyometrial junction, i.e. the “shoulder” of the lesion. Presence of tumour adjacent to the arcuate arteries and veins is a helpful feature that suggests invasion into the outer half of the myometrium if present. Adenoma malignum-like invasion is exceedingly rare. This pattern is marked by scattered, well differentiated glands that invade the myometrium with little to no desmoplastic response. Longacre and Hendrickson noted that focal cytologic atypia, epithelial pseudostratification, loose and oedematous stroma around glands, and inflammatory infiltrates surrounding glands and lymphovascular invasion help to identify this pattern of invasion.³

Cervical involvement

Cervical involvement can be seen in up to 20–30% of hysterectomies performed for endometrial carcinoma,^{4–6} and it has long been considered a negative prognostic indicator. The

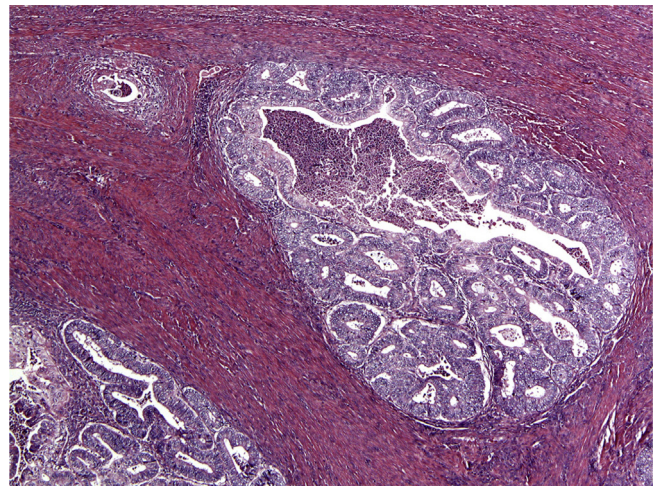


Figure 4 Adenomyosis-like invasion with a small focus of traditional desmoplastic invasion denoted by a single gland (upper left). Irregularly shaped, and/or single glands can be helpful in identifying invasion.

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