Problematic areas and new developments in uterine mesenchymal tumours

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Abstract

Pure mesenchymal tumours of the uterus broadly comprise two major categories, smooth muscle neoplasms and endometrial stromal neoplasms. Of these the most common tumours are smooth muscle tumours of the uterus, the majority of these are benign and are recognised as leiomyomata routinely. Leiomyosarcoma is the commonest malignant mesenchymal tumour of the uterus accounting for >50% of uterine sarcomas and comprising 1–2% of uterine malignancies. Variants of both benign and malignant tumours are recognised and increasingly, through the evolution of more sophisticated immunohistochemistry and molecular techniques we are aware of the many "pitfalls" in their diagnosis which will be discussed in this review. The second major category comprises endometrial stromal tumours which has undergone re-classification in the WHO 2014 classification and has been the subject of a recent review in this journal. Despite it being the second most common uterine sarcoma, it is encountered infrequently in routine diagnostic practice, and its benign counterpart is approximately 8× less frequent. Endometrial stromal tumours will not be comprehensively considered in this review, but only in the context of differential diagnosis.

This review will attempt to update the reader with recently described entities that may lead to diagnostic confusion and provide a diagnostic approach.

Keywords inflammatory myofibroblastic tumour; leiomyoma; leiomyosarcoma; PEComa; solitary fibrous tumour; uterus

Introduction

Problematic areas in uterine smooth muscle tumours may be related to their unusual gross appearance at macroscopic examination when they deviate from that expected of a usual benign smooth muscle tumour i.e. leiomyoma, which is the commonest neoplasm encountered on a routine basis. The lack of a well-defined border with the surrounding myometrium and the lack of a white whorled appearance that bulges on cut-section is concerning. Whilst these deviations from the usually encountered leiomyoma may represent "degenerative" changes within a leiomyoma, they may also be indicative of a leiomyoma variant, or malignancy. On occasion the use of exogenous hormonal preparations may contribute to the alteration of the extracellular matrix and consequently to the gross appearances of a leiomyoma. The myxoid and epithelioid variants of leiomyosarcoma can be challenging to diagnose. These have different criteria for the diagnosis of malignancy to the usual spindle cell smooth muscle tumour. In rare situations, the tumours may not be smooth muscle in origin and may represent other lesions, two of the recently described lesions being PEComa and inflammatory myofibroblastic tumour. A solitary fibrous tumour (SFT) may on rare occasions be confused with a leiomyosarcoma, particularly on imaging, where it may present as a large uterine mass.

Endometrial stromal tumours[1] are soft, cream or yellow lesions with variable cystic change, typically presenting as intrauterine polypoid lesions in continuity with an intramyometrial component. If low grade sarcoma they may be associated with "worm-like" plugs of tumour within vascular spaces.

Endometrial stromal tumours and their distinction from uterine smooth muscle tumours can also be problematic histologically particularly when stromal neoplasms feature overlapping morphologic features with smooth muscle tumours. This problem is compounded in curettage material by the paucity of tissue available for histological assessment, together with the fragmented nature of the biopsy material and the lack of adjacent myometrium to enable assessment of the tumour/myometrial interface. Thorough, generous and judicious sampling in hysterectomy specimens taken from the tumour/myometrial interface in diagnostically problematic cases can be most rewarding, as this is where both tumour invasion and lymphovascular space permeation are most likely to be identified.

Immunohistochemistry must be used judiciously in the diagnosis of uterine mesenchymal tumours and many of the problems encountered by pathologists are due to the lack of appreciation of the specificity of certain markers, particularly when used in isolation and not as part of a panel. This issue will be addressed in the review.

Finally, there have been several developments in the use of molecular studies that have led to a better understanding and classification of the uterine stromal neoplasms, acknowledged in the 2014 WHO[2] classification of uterine mesenchymal tumours.

Gross examination

The macroscopic examination of mesenchymal tumours cannot be overemphasised. Much information is obtained from seeing the gross specimen. A single large solitary mass with a heterogenous cut surface and a fleshy texture is likely to be a leiomyosarcoma (Figure 1). Haemorrhagic and necrotic areas are recognised. In others, deviations from the usual gross appearance may not be so obvious but loss of the uniform, whorled appearance characteristic of leiomyomata (Figure 2) should prompt diligent sampling. Sections of the tumour/myometrial interface are most rewarding, particularly in diagnostically challenging tumours. It is at the interface where the irregular, infiltrative border will be appreciated or vascular invasion identified. Multiple appropriately sampled sections frequently are all that is required in problematic cases to enable a definitive diagnosis to be made. Where the neoplasm is well defined but

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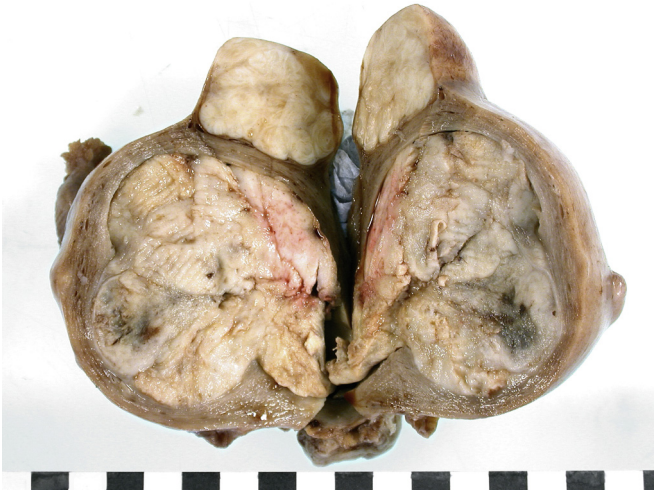

Figure 1 Heterogenous cut surface of large mass, a leiomyosarcoma adjacent small leiomyoma for comparison.

Figure 3 Cellular leiomyoma note yellow cut surface.

Figure 2 Leiomyoma, note whorled cut surface.

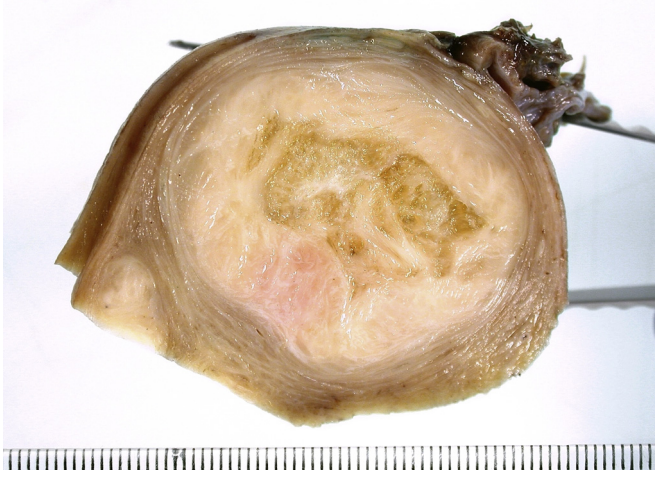

Figure 4 Hydropic features centrally with microcyst formation, characteristic of a patient on Ulipristal acetate.

lacks the typical whorled appearance, a tan/yellow cut surface when related to the endometrium may be suggestive of an endometrial stromal nodule or when intramural of a cellular leiomyoma (Figure 3). Streaks of yellow areas may be suggestive of a lipoleiomyoma. Hydropic degeneration in leiomyomata with the formation of microcysts, may be seen in patients who have been treated with Ulipristal acetate (Figure 4).

Endometrial stromal tumours are typically seen as polypoid lesions within the uterine cavity and may be associated with an intramyometrial component exhibiting a "worm-like" invasive pattern within the myometrium. Both leiomyosarcoma and endometrial stromal sarcoma can on occasion be deceptively well-defined lesions macroscopically. In these situations, it is imperative to return to the specimen to sample further blocks.

Problematic areas in smooth muscle tumours

The usual spindle cell leiomyoma is composed of fascicles of spindle cells with elongated, blunt ended "cigar" shaped nuclei with eosinophilic cytoplasm. There are typically no mitoses and there is no evidence of cytologic atypia or of coagulative tumour cell necrosis. Variable amounts of collagenous tissue may be seen initially occupying the stroma in between smooth muscle cells and later replacing smooth muscle cells. At times, extensive hyalinisation may make it difficult to recognise the neoplasm as a smooth muscle neoplasm. This is usually a feature of post-menopausal leiomyomata where both dystrophic calcification and ossification may be encountered.

Variants of usual spindle leiomyomata may cause diagnostic problems as they have some features which overlap with those of leiomyosarcoma. It is therefore important to sample these lesions thoroughly so that the other features required to make a diagnosis of leiomyosarcoma are excluded with confidence.

Mitotically active leiomyoma

These are tumours which grossly appear no different to the usual leiomyoma. They may be submucosal in location and are typically small in size, although they are known to vary in size from 6 mm to 200 mm (median 60 mm). They are a lesion of the reproductive age group.[3, 4] Most of the cases described in the literature appear to be associated with the secretory phase of the menstrual cycle suggesting that the increased mitotic activity may be a progesterone related effect.[5] The use of exogenous

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