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Uterine intravascular adenomyomatosis: a bizarre hybrid lesion?

Sir,

Uterine adenomyosis is a common pathological entity and very familiar to histopathologists. Less familiar and probably under-recognised is the presence of an intravascular component to the process which occurs in 12−18% of cases, and largely confined to instances of 'deep' adenomyosis. Benign uterine leiomyomas are, if anything, even more frequently encountered than adenomyosis and once again local intrusion ('invasion') into vascular spaces may be seen, usually at or within the margins of the leiomyoma. As with intravenous adenomyosis, this is of no clinical consequence. Rarely, more extensive and often macroscopically visible intravascular invasion is encountered. This quasi-malignant neoplastic process of intravenous or intravascular leiomyomatosis (IVL) with tongues of benign-appearing smooth muscle in large venous and lymphatic spaces within the myometrium shares molecular changes such as der (14)t (12; 14) (q15; q24) with ordinary uterine leiomyomas,[1] and expression profiles that more closely resemble those of leiomyosarcomas.[2]

While seemingly quite separate and pathogenetically unrelated entities, we have encountered an example of a recently described hybrid of intravascular adenomyosis and leiomyomatosis, which displays morphological features of both and which has been termed intravascular adenomyomatosis.[3] These authors reported five cases, four of which had follow up information with no recurrences, as was also the case in a subsequently published case.[4] Only one of the original five cases had extrauterine extension (of intravascular leiomyomatosis). All six cases had histological evidence of uterine adenomyosis and in four examples, the intravascular adenomyomatous component was in close proximity to the adenomyosis, while in two cases it was remote. All six cases also had benign leiomyomas (including one cellular leiomyoma) but the spatial relationship between the leiomyomas and the intravascular component was less clearly described.

Our case was a 48-year-old woman with no significant past medical history, who underwent a subtotal hysterectomy for severe menorrhagia and polymenorrhoea. The uterine body weighed 256 g and measured 110 × 100 × 70 mm. The myometrium was coarsely trabeculated and included three poorly circumscribed mural tan nodules with partly whorled cut surfaces, 12−28 mm in maximum dimensions, and multiple further well defined pale whorled mural nodules 1−2 mm across. Some of the latter displayed central spaces and the overall appearances were typical of florid deep adenomyosis. Occasional circumscribed leiomyomas were also seen.

Histological examination showed normal secretory endometrium and confirmed the presence of several small benign leiomyomas as well as extensive conventional adenomyosis. The 28 mm mural nodule and the smaller ones adjacent to it, by contrast, were complex and haphazard aggregations of discrete islands of entirely unremarkable adenomyosis (mostly with stroma and glands but sometimes stroma only) and tongues of intravascular extension, all within hypertrophied myometrial smooth muscle. About one-third of these intravascular extensions were characterised by typical endometrial stroma only while the remainder exhibited variable mixtures of endometrial type stroma and glands (Fig. 1A), vascular smooth muscle tissue (Fig. 1B) or all three (Fig. 1C). Some intravascular extensions were seen as apparently free-floating, but presumably pedunculated, intravascular islands (Fig. 1D) while others were more obviously attached to the vessel wall by a broad stalk or pedicle and a few were merely sub-endothelial plaques. Numerous transitions between islands of deep adenomyosis and intravascular extensions were present. This phenomenon did not involve the superficial islands of adenomyosis present in the inner third of the myometrium, nor the scattered small benign leiomyomas, even those intravascular extensions that were purely smooth muscle in differentiation. An unusual variation on the general theme was a large solitary intravascular plug composed of an intimate admixture of endometrial type stroma and glands and vascular smooth muscle (Fig. 2A). The endothelial lining had been destroyed but the pattern of smooth muscle stretched around its perimeter was, in our view, diagnostic of a dilated vein and corresponds to one of the more rounded nodules seen in the gross specimen. The basic immunoprofile of the various tissue elements usefully highlighted the variability of the components from area to area (Fig. 2B). Typical adenomyotic foci were present in the lower (endocervical) surgical resection margin. However, intravascular extensions did not compromise the cervical margin or extend to the uterine serosa or the parametrial surgical plane of excision. The patient is presently asymptomatic and has a normal abdominopelvic computed tomography (CT) scan and chest X-ray. The management plan is to repeat these in 6 months time.

Anecdotal descriptions of endometrial tissue in myometrial vascular channels in association with adenomyosis date back almost 70 years[5] while subsequent published series have demonstrated involvement in 14 of 78 cases (17.9%) in one study,[6] 35 of 200 cases (17.5%) in another,[7] and more recently 54 of 434 cases (12.4%).[8] In most cases, as in ours, adenomyotic tissue was attached to the vessel wall and protruded into the vessel lumen beneath the endothelial lining. Contrasting with our case, however, in a significant majority of the examples in each of these studies[6−8] the intravascular component consisted of stroma only, under which circumstances low grade endometrial stromal sarcoma (LGESS) might legitimately enter the differential diagnosis. Typical differentiating features of adenomyosis, however, are the blandness of the stromal and glandular elements, absence of a tumour mass on gross examination,[8] or unequivocal areas of infiltrative neoplasm. Extrauterine extensions, when present, help to confirm LGESS. The presence of endometrial type glands, especially when prominent as in our case, clearly favours adenomyosis, even though these may occasionally be seen in LGESS,[9,10] as may smooth muscle.[11,12] The pattern of vascular involvement suggests to some authors[8] that

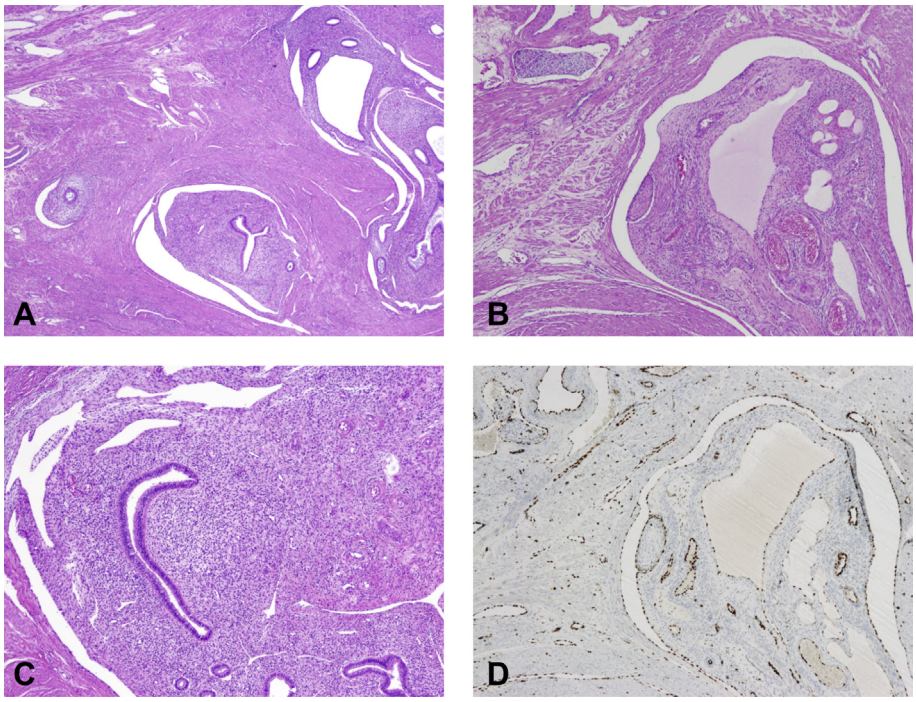

Fig. 1 Intravascular adenomyomatosis. (A) Low power highlighting intravascular intrusion of endometrial and smooth muscle tissue. (B) Small intravascular island of myxoid endometrial stroma (top left) and broader tongue of fibrovascular smooth muscle only (right). (C) Large intravascular tongue of adenomyomatosis with endometrial type glands and stroma to the left, merging with fibrovascular smooth muscle to the right. (D) Free-floating island (same focus as C), with the endothelial lining highlighted by nuclear immunoreactivity to ERG).

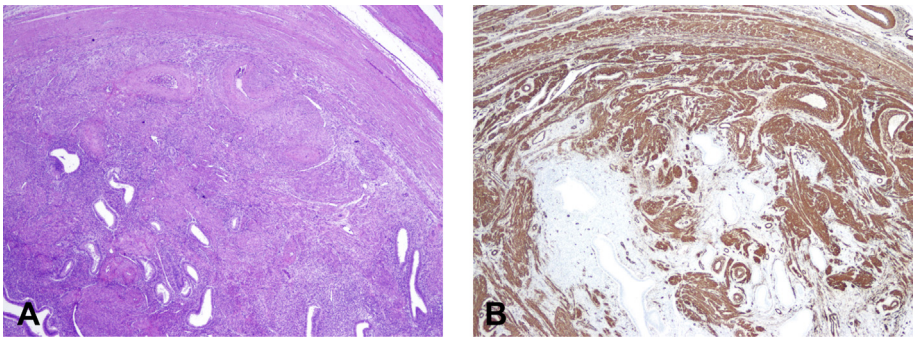

Fig. 2 Large apparently intravascular tongue of adenomyomatosis with smooth muscle wall of dilated vessel stretched around its perimeter (top). (A) Showing disordered admixture of endometrial type glands and stroma and vascular smooth muscle (H&E). (B) Immunostain for smooth muscle actin highlighting laminated muscularis of the dilated vessel wall and smooth muscle component of the intravascular tumour.

adenomyosis develops from multipotential perivascular cells associated with myometrial blood vessels.

IVL most usually (but not always) occurs in conjunction with leiomyomas, and its biological behaviour is considered to be intrinsically benign or, at worst, quasi-malignant.[2] In up to 30% of cases there is extrauterine extension which can occasionally cause death through embolisation or cardiac involvement. The main differential diagnosis of IVL is LGESS with smooth muscle differentiation.[11,12]

The traditional and most popular theory of adenomyosis development is that the basal endometrium invaginates downwards between the myometrial fibres, possibly as a result of weakness in the superficial uterine smooth muscle (the so-called junctional zone) or increased uterine pressure. In our view, the alternative possibility, as introduced above (i.e., from multipotential perivascular cells in the myometrium which develop into endometrial stromal cells with subsequent induction of epithelial structures[8]) supports the notion that uterine adenomyosis is two distinct disorders based on pathogenesis. Superficial adenomyosis might involve down-growths of the basal endometrium through the junctional zone and deep adenomyosis might arise by a process of metaplasia (rather like the still unresolved pathogenetic conundrum of endometriosis: implantation versus metaplasia). Deep adenomyosis is the variant that most frequently demonstrates an intravascular component. While smooth muscle metaplasia is not a feature of uterine adenomyosis (as opposed to the characteristic myometrial hyperplasia induced by the growth of ectopic endometrial tissue in the uterine wall), this is seen in its malignant counterpart from time to time.[11,12]

While the authors of these exceptionally rare lesions have suggested that they are variants of intravenous leiomyomatosis, endometrial tissue differentiation is not a recognised feature of this entity and logic points us away from this notion. Our view is that they share more the features of an endometrial stromal than a smooth muscle neoplasm and carry the burden of an undetermined biological potential. To

date, of the seven cases of intravascular adenomyomatosis (including ours), five show spatial juxtaposition to ordinary adenomyosis and only two do not. Similar molecular changes shared between leiomyomas and intravascular leiomyomatosis might be recapitulated with deep adenomyosis and endometrial stromal sarcoma; for example, the characteristic translocation t (7; 17) (p15; q21) that produces the JAZF1-JJAZ1 gene fusion product and is commonly seen in the latter. In our admittedly single case (FISH analysis performed in the IGENZ laboratory using the ZytoLight SPEC JAZF1 Dual Colour Break apart probe; ZytoVision, Germany), neither deep adenomyosis nor adenomyomatosis showed JAZF1-JJAZ1 gene fusion, implying that such gene rearrangement, frequently required for the multipotential perivascular stromal cells to acquire malignant potential, has not accrued in adenomyosis or adenomyomatosis. Further molecular studies in a well-funded molecular genetics laboratory will undoubtedly shed light on this problem in time.

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Amir Maghsoudi, Jennifer Roberts, Peter Russell

Douglass Hanly Moir Pathology, Macquarie Park, NSW, Australia

Contact Prof Peter Russell.
E-mail: prussell@dhm.com.au

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Ectopic cervical well differentiated thymic carcinoma: report of a diagnostically challenging rare case

Sir,

Ectopic thymic neoplasms are uncommon and are, with very few exceptions, thymomas of various types.[1] Only rare cases of thymic carcinomas have been reported in the literature.[2–8] The theory behind the origins of ectopic thymic neoplasms is based on the assumption of defective migration of embryonic thymus leading to the formation of ectopic thymic tissue.[1] This concept explains the presence of thymic tissue in the submandibular region, lateral neck, thyroid, paratracheal region and pericardial location but it does not easily explain the presence of ectopic thymic rests in the lung and pleural surfaces where ectopic thymic neoplasms also have been reported. The cervical region is the most common site for ectopic thymic neoplasms and these frequently pose diagnostic challenges. Analogous to the thymus proper, a spectrum of non-neoplastic lesions such as ectopic unilocular/multilocular thymic cysts to neoplastic lesions such as ectopic thymomas or thymic carcinomas can arise.

In this paper, we detail the clinicopathological features of an ectopic cervical well-differentiated thymic squamous cell carcinoma.

The patient first presented at 9 years old with a left submandibular well-circumscribed cystic lesion of 3 × 3 cm. It was a painless, cystic and mobile lump, with no overlying skin changes. A computed tomography (CT) scan performed showed a 3 cm lesion at level I. He underwent excision biopsy of the lesion and microscopic examination showed an encapsulated and partly cystic lesion composed of anastomosing trabeculae of mildly atypical squamous cells with whorl-like structures vaguely reminiscent of Hassall's corpuscles (Fig. 1A,B). No increased mitotic activity was seen. The lesion also contained a lymphoid stroma featuring CD3+ T cells and some TdT positive lymphocytes (Fig. 1C). No lymphoid follicles or subcapsular sinus was seen. At that time, the rendered diagnosis was ectopic thymic cyst. Three months later, the patient presented with another 2.5 cm painless, solid and mobile lesion in the same location. This lesion showed very similar histopathological features as the original excision (Fig. 1D). The diagnosis this time was ectopic thymic tissue with hyperplastic changes. No further treatment was given.

Eight years later, at age 17, the patient presented with two well-circumscribed left sided neck lesions: 5 cm over level IV and 3 cm over level II. Thorough clinical examination on