Uterine tumour resembling ovarian sex cord tumour is an immunohistochemically polyphenotypic neoplasm which exhibits coexpression of epithelial, myoid and sex cord markers

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Aims: To describe the clinicopathological and immunohistochemical findings in four cases of uterine tumour resembling ovarian sex cord tumour (UTROSCT).

Methods: Four UTROSCTs were stained with a wide range of antibodies, including epithelial (AE1/3, epithelial membrane antigen), myoid (desmin, α smooth muscle actin, h-caldesmon), sex cord (α inhibin, calretinin, melan A, CD99) and neuroendocrine (chromogranin, CD56) markers as well as hormone receptors (oestrogen receptor, progesterone receptor, androgen receptor), vimentin, CD10, WT1 and HMB45.

Results: The tumours ranged from 0.8 to 19.5 cm. Three were relatively well circumscribed intramural myometrial lesions; the other was a pedunculated mass attached to the uterine serosa. The tumours were variably composed of solid, corded, trabecular, nested, glandular and retiform arrangements of tumour cells. In three cases, cells with eccentric nuclei and abundant eosinophilic cytoplasm, resulting in a rhabdoid appearance, were a prominent feature. Three cases were diffusely positive with AE1/3 and all with epithelial membrane antigen. Positivity with myoid markers was common with 3, 4 and 1 case respectively staining with desmin, α smooth muscle actin and h-caldesmon; 2, 4, 1 and 2 cases respectively were positive with α inhibin, calretinin, melan A and CD99. All were chromogranin negative and exhibited diffuse strong staining with CD56. All were diffusely positive with oestrogen receptor, progesterone receptor, vimentin and WT1. Three cases were androgen receptor positive and all were CD10 and HMB45 negative.

Conclusions: UTROSCT exhibits a polyphenotypic immunophenotype with coexpression of markers of epithelial, myoid and sex cord lineage as well as hormone receptors.

Uterine tumours resembling ovarian sex cord tumours (UTROSCTs) are rare primary uterine neoplasms which morphologically resemble ovarian sex cord stromal tumours. They were originally described by Clement and Scully in 1976.¹ In this seminal publication, these neoplasms were classified into two groups: type I were typical endometrial stromal neoplasms with focal areas with a sex cord-like pattern; in type II tumours, the sex cord-like elements were exclusive or predominated. Type I neoplasms are now generally referred to as endometrial stromal tumours with sex cord-like elements while type II tumours are designated UTROSCT.² In the latest World Health Organization classification of tumours of the female genital organs, UTROSCT is classified separately to endometrial stromal neoplasms.² However, there is ongoing debate as to the exact histogenesis, ie whether they represent variants of endometrial stromal neoplasm or are separate unrelated tumours.

There have been several studies which have examined the immunophenotype of UTROSCT.^{3–15} In general, these neoplasms have a variable immunophenotype, sometimes with coexpression of epithelial, myoid and sex cord markers as well as hormone receptors. In this study, we describe the clinicopathological features of four uterine neoplasms composed entirely of sex cord-like elements ie UTROSCTs. We have especially focused on the immunophenotype of these neoplasms and have undertaken an extensive immunohistochemical analysis, using markers of epithelial, myoid, sex cord and neuroendocrine lineage as well as hormone receptors. We have included markers which have not been investigated previously, or only

rarely, in UTROSCT. We discuss the histogenetic implications of the immunophenotype and its value in differential diagnosis.

MATERIALS AND METHODS

Cases

The four cases were derived from the archives of the Department of Pathology, Royal Group of Hospitals Trust, Belfast and from the referral practice of one of the authors (WGM).

Immunohistochemistry

A single block from each case was selected for immunohistochemistry. Sections of 4 μ m thickness were cut from the paraffin wax-embedded blocks, floated onto sialinised slides, and dried overnight at 37°C, before deparaffinisation in xylene and rehydration through graded ethanols. Staining was performed using an automated staining machine (Ventana Nexes, Strasbourg, France). Table 1 lists the markers used in the study together with their sources, dilutions and methods of pretreatment. Pretreatment for all antibodies, except where stated in table 1, consisted of heating in a pressure cooker for 2 min in pH 7.8 buffer. Diaminobenzidine was used as the chromogen and sections were counterstained using haematoxylin (Ventana). For negative controls, the primary antibody was omitted and replaced with immunoglobulin (IgG1, Dako, Ely,

Abbreviations: EMA, epithelial membrane antigen; SMA, smooth muscle actin; UTROSCT, uterine tumour resembling ovarian sex cord tumour

Table 1 Antibodies used in study with sources, dilutions and methods of pretreatment

Antibody	Source	Dilution	Pretreatment
AE1/3	Dako (Ely, UK)	1:100	Protease 1 (4 min)
Epithelial membrane antigen	Dako	1:10	See materials and methods
Desmin	Dako	1:100	See materials and methods
α smooth muscle actin	Dako	1:500	See materials and methods
h-caldesmon	Dako	1:50	Pressure cooker 2 min, pH 7.8 buffer; protease 3 (2 min)
α inhibin	Dako	1:200	See materials and methods
Calretinin	Zymed (San Francisco, CA, USA)	1:50	See materials and methods
Melan A	Dako	1:10	See materials and methods
CD99	Dako	1:10	None
Oestrogen receptor (clone sp1)	Labvision (Fremont, CA, USA)	1:200	See materials and methods
Progesterone receptor	Dako	1:50	See materials and methods
Androgen receptor	Novocastra (Newcastle, UK)	1:100	See materials and methods
Vimentin	Dako	1:400	See materials and methods
WT1	Dako	1:50	See materials and methods
CD10	Novocastra	1:5	See materials and methods
CD56	Novocastra	1:50	See materials and methods
Chromogranin	Dako	1:600	See materials and methods
HMB45	Dako	1:100	See materials and methods

UK) at an equivalent concentration. Appropriate positive controls were used.

Cases were scored as negative, focally positive (<50% cells staining) or diffusely positive (>50% cells staining).

RESULTS

Clinical details

The four patients were aged 43, 51, 73 and 84 years, respectively. Two underwent hysterectomy and bilateral salpingo-oophorectomy, one underwent hysterectomy and left salpingo-oophorectomy, and one underwent hysterectomy. Indications for the operative procedure were a fibroid uterus, an ovarian cyst, menorrhagia and a radiologically diagnosed mass in the left adnexal region.

Pathological findings

Grossly three lesions were located in the myometrium and measured 0.8, 2.0 and 3.0 cm, respectively. The other measured 19.5 cm and was a pedunculated mass attached to the serosa of the left side of the uterus by a pedicle. All were well circumscribed. Two of the tumours were yellow, one was described as off-white, and the colour of the other was not mentioned in the pathology report.

Histologically all four tumours were situated in the myometrium without involvement of the endometrium. They were predominantly well circumscribed but exhibited minor irregularity of the edge with infiltration and entrapment of the surrounding myometrial smooth muscle. There was no evidence of the widely infiltrative myometrial invasion characteristic of most endometrial stromal sarcomas. Three of the tumours exhibited similar features and were mainly composed of epithelioid cells with round nuclei, sometimes with small nucleoli. There were no nuclear grooves. A proportion of the tumour cells had a rhabdoid appearance with eccentric nuclei and abundant eosinophilic cytoplasm, sometimes with a glassy appearance. In one case, a minor proportion of the tumour cells had foamy cytoplasm. There was little in the way of nuclear pleomorphism, and the mitotic count was low with <1 mitotic figure per 10 high power fields (HPFs). The tumour cells assumed a variety of architectural patterns with nests, cords and trabeculae predominating, sometimes with an Indian file pattern. Other architectural patterns, including solid, glandular and retiform, made up a minor proportion of the neoplasms. In the other case (the largest neoplasm), the cells were ovoid to

spindle shaped with scanty cytoplasm. There was little in the way of nuclear pleomorphism and there were 2 mitoses per 10 HPFs. There were no nuclear grooves. The predominant architectural patterns in this neoplasm were solid and retiform. No Leydig cells were present in any of the neoplasms. There was no necrosis or vascular invasion. There were no areas of conventional endometrial stromal neoplasm. Figure 1 illustrates examples of the histology of the neoplasms.

Incidental pathological findings included complex hyperplasia of the endometrium in one case, benign leiomyomata in two, and an ovarian serous cystadenoma in one.

Immunohistochemistry

Table 2 presents the immunohistochemistry results. Figures 2–4 illustrate examples of positive staining with various markers.

Three of the four cases exhibited diffuse strong cytoplasmic positivity with AE1/3. The fourth was negative. All four cases were positive with epithelial membrane antigen (EMA); three cases exhibited diffuse membranous and cytoplasmic positivity of weak to moderate intensity, and one exhibited focal weak staining.

Three cases exhibited focal or diffuse strong cytoplasmic positivity with desmin and the fourth was negative. All cases were α smooth muscle actin (SMA) positive; two cases exhibited diffuse strong and two exhibited focal strong cytoplasmic staining; h-caldesmon exhibited diffuse weak cytoplasmic positivity in one case.

Two cases exhibited focal weak to moderate cytoplasmic positivity with α inhibin and two were negative. Three cases showed focal and one diffuse strong nuclear and cytoplasmic positivity with calretinin. One case exhibited diffuse weak cytoplasmic positivity with melan-A and three were negative. Two cases exhibited focal membranous positivity of weak to moderate intensity with CD99 and two were negative.

All four cases exhibited diffuse nuclear positivity of moderate to strong intensity with oestrogen receptor and progesterone receptor. Three cases exhibited nuclear androgen receptor positivity of moderate intensity, one focal and two diffuse.

All four cases exhibited diffuse strong cytoplasmic positivity with vimentin and diffuse nuclear staining of moderate intensity with WT1. There was diffuse strong membranous and weaker cytoplasmic positivity with CD56 in all cases and all were chromogranin, CD10 and HMB45 negative.

Figure 1 Uterine tumour resembling ovarian sex cord tumour composed of solid and nested arrangements of cells (A). In some cases, the tumour cells have a rhabdoid appearance with an Indian file growth pattern (B). Case exhibiting focal glandular differentiation (C). In one case, there was a prominent retiform growth pattern (D).

DISCUSSION

Similar to other studies, the neoplasms we report occurred in women in the reproductive and postmenopausal age groups. Three were relatively well circumscribed intramural myometrial masses, in common with most previous reports. The other was a pedunculated mass attached to the serosa of the uterus; occasional previously reported UTROSCTs have had a similar location.³ Rarely tumours have been described within the cervix.^{10–12} Two of our neoplasms had a yellow cut surface, a characteristic, but not specific, feature of UTROSCT, and a point of similarity to ovarian sex cord-stromal tumours. The histological appearances were similar in three cases, the presence of cells with a rhabdoid phenotype being a notable feature. This has only briefly been mentioned in other reports of UTROSCT.¹⁰ However, the morphology of UTROSCT appears variable, judging by the previously reported cases. In one of our

cases, an 84 year old woman, the endometrium exhibited complex hyperplasia. While this may be a coincidental finding, it raises the possibility of hormone production by this particular neoplasm; ovarian sex cord-stromal tumours, of course, commonly elaborate hormones.

Since the original description of UTROSCT,¹ several studies, mostly of individual cases (the largest reported seven tumours), have examined the immunophenotype of these neoplasms.^{3–15} These have revealed variable expression of epithelial, myoid and sex cord markers as well as hormone receptors. The results of the present study confirm the polyphenotypic immunophenotype of UTROSCT. We included an extended panel of markers, some of which have not been investigated at all, or only occasionally, in UTROSCT. We included markers of ovarian sex cord and endometrial stromal tumours, epithelial, myoid and neuroendocrine markers and hormone receptors. We now discuss the results of the immunohistochemical staining, and compare these with those of previous studies. At this point, we will note that all four of our neoplasms were composed entirely of sex cord-like elements. We reserve the diagnosis of UTROSCT for neoplasms entirely composed of such elements. Others use this term for tumours composed of >50% of sex cord-like elements, the remainder comprising a typical endometrial stromal neoplasm. As discussed later, we believe that the latter type I tumours of Clement and Scully¹ may have a different histogenesis to those composed entirely of sex cord-like elements. For this reason, in reviewing the previous immunohistochemical studies, we have attempted to include only type II tumours of Clement and Scully,¹ ie those composed entirely of sex cord-like elements.^{3–15} However, given that type I and II tumours have often been lumped together and the exact percentage of the neoplasm composed of sex cord-like elements not always detailed, on occasions this has been problematic.

Three of our four neoplasms were diffusely positive with the broad spectrum cytokeratin AE1/3. Of the previously reported UTROSCTs, 22 of 26 have been positive with anti-cytokeratins, illustrating that these neoplasms commonly express epithelial markers. An interesting observation in our study, and one which has not been focused on previously, was that all four

Table 2 Summary of the immunohistochemical findings in four cases

Antibody	Case 1	Case 2	Case 3	Case 4
AE1/3	D+	–	D+	D+
Epithelial membrane antigen	D+	D+	D+	F+
Desmin	D+	–	D+	F+
α smooth muscle actin	D+	F+	D+	F+
H-caldesmon	–	–	D+	–
α inhibin	F+	–	F+	–
Calretinin	F+	F+	D+	F+
Melan-A	–	–	D+	–
CD99	–	F+	F+	–
Oestrogen receptor	D+	D+	D+	D+
Progesterone receptor	D+	D+	D+	D+
Androgen receptor	D+	F+	–	D+
Vimentin	D+	D+	D+	D+
WT1	D+	D+	D+	D+
CD10	–	–	–	–
CD56	D+	D+	D+	D+
Chromogranin	–	–	–	–
HMB45	–	–	–	–

Figure 2 Uterine tumour resembling ovarian sex cord tumour exhibiting positivity with AE1/3 (A), epithelial membrane antigen (B), desmin (C) and α smooth muscle actin (D).

tumours expressed EMA, albeit of weak or moderate intensity. This is perhaps slightly surprising since UTROSCT is thought by some to represent the uterine counterpart of an ovarian sex cord-stromal tumour and possibly to be derived from misplaced gonadal tissue. Cytokeratin immunoreactivity is not uncommon in ovarian sex cord-stromal tumours,^{16–18} but EMA positivity is unusual,¹⁸ although focal staining has been described in 50% of a small series of juvenile granulosa cell tumours,¹⁹ and one of us (WGM) has occasionally observed positivity in other types of ovarian sex cord-stromal tumour. EMA positivity argues against a true sex cord-stromal neoplasm, similar to those which arise in the ovary, although immunoreactivity with sex cord markers (discussed below) suggests that UTROSCT exhibits sex cord differentiation to some extent. EMA staining has only occasionally been undertaken previously in UTROSCT and 2 of 13 cases have been positive.

In one of the largest and most detailed immunohistochemical studies of UTROSCT, desmin was positive in 3 of 5 cases and immunoreactivity was confined to small foci morphologically resembling smooth muscle.⁷ The authors were uncertain whether these foci represented an integral component of the tumour or entrapped smooth muscle. They did not use other smooth muscle markers. In contrast, other studies have revealed smooth muscle marker positivity in UTROSCT with altogether 8 of 25 and 13 of 18 cases respectively being positive with desmin and α SMA.^{3–15} Our neoplasms were typically positive with desmin and α SMA, with 3 and 4 cases respectively exhibiting immunoreactivity. This positivity involved the tumour cells and was not confined to foci resembling smooth muscle. In all of our cases, we consider any smooth muscle component to be entrapped and not an integral component of the tumour since such foci were only found at the periphery of the neoplasms. However, others consider cells with a myoid appearance to be an integral component of UTROSCT since in some cases these cells have expressed sex cord, in addition to myoid markers.¹⁵ It has been suggested that diffuse desmin immunoreactivity is against a UTROSCT⁷ and suggestive of a smooth muscle neoplasm but,

given our immunohistochemical results, we do not agree with this statement. In contrast to desmin and α SMA, h-caldesmon, another smooth muscle marker, was negative in three cases and weakly positive in one. Only two UTROSCTs have previously been stained with h-caldesmon and one was positive.

We stained our cases with a variety of markers which are commonly expressed in ovarian sex cord-stromal tumours. Calretinin and α inhibin are the two best known and most widely utilised markers of an ovarian sex cord-stromal tumour, the former being slightly more sensitive and the latter a more specific marker of this group of neoplasms.^{20–34} Two of the cases were positive with α inhibin and all four were positive with calretinin. Melan A and CD99 may also be positive in ovarian sex cord-stromal tumours,^{35–38} and 1 and 2 of our neoplasms respectively were immunoreactive. Positivity with these markers has been shown previously in UTROSCT.^{3–7} Fourteen of 26, 10 of 11, 7 of 15 and 22 of 24 cases examined have been positive with α inhibin, calretinin, melan A and CD99 respectively, suggesting that UTROSCT may exhibit sex cord differentiation although, as discussed, EMA positivity is unusual in ovarian sex cord-stromal tumours and argues against a true sex cord-stromal neoplasm. Furthermore, although the overall morphological appearances are suggestive of a sex cord-stromal neoplasm, the histological picture in most cases, including those we report, is not characteristic of any particular type of ovarian sex cord-stromal tumour. For example, although the various patterns, such as solid, nested, trabecular, corded and glandular, would be compatible with an adult granulosa cell tumour, the nuclear features are not typical of this neoplasm. However, occasional cases have been considered to be indistinguishable from a Sertoli or Sertoli-Leydig cell tumour.⁶ Nuclear WT1 positivity was present in all four neoplasms. Only one UTROSCT has been stained previously with WT1 and this was positive.⁸ WT1 immunoreactivity does not shed any particular light with regard to the histogenesis of UTROSCT since this may be positive in ovarian sex cord-stromal, endometrial stromal and uterine smooth muscle tumours as well as ovarian epithelial neoplasms of serous type.^{39–42} Of interest is that all four neoplasms in our study were diffusely

Figure 3 Uterine tumour resembling ovarian sex cord tumour exhibiting positivity with sex cord markers α inhibin (A), calretinin (B), CD99 (C) and CD56 (D).

and strongly positive with CD56, a widely used neuroendocrine marker. It has been shown recently that ovarian sex cord-stromal tumours are almost invariably positive with CD56⁴³; therefore CD56 positivity in UTROSCT may be a manifestation of sex cord differentiation. These tumours are unlikely to exhibit neuroendocrine differentiation, as chromogranin, a highly specific neuroendocrine marker, was negative, as it was in the two other cases previously examined. CD56 has not hitherto been investigated in UTROSCT.

CD10 was negative in all four tumours. This is a widely used marker of endometrial stromal neoplasms, most of which are

diffusely positive.^{44 45} As discussed, an endometrial stromal origin is one theory of the histogenesis of UTROSCT. CD10 is a relatively non-specific marker; for example, in the uterus immunoreactivity is common in smooth muscle tumours and some epithelial neoplasms may also stain.^{45 46} Our results differ somewhat from prior studies in that 9 of 12 cases stained previously have been CD10 positive.

All of our cases exhibited nuclear immunoreactivity with oestrogen receptor and progesterone receptor, which has been shown in other studies of UTROSCT, with 13 of 15 and 15 of 16 cases respectively being positive. Three cases were positive with

Figure 4 Uterine tumour resembling ovarian sex cord tumour exhibiting nuclear positivity with oestrogen receptor (A), progesterone receptor (B), androgen receptor (C) and WT1 (D).

androgen receptor, which has not been studied previously. Androgen receptor expression has not been widely investigated in gynaecological mesenchymal neoplasms but endometrial stromal and uterine smooth muscle tumours are not uncommonly positive.^{47, 48} Not surprisingly, all four tumours were diffusely positive with vimentin, which has been the case in all 17 UTROSCTs examined previously. HMB45 was negative in all cases. This has only been investigated previously in two cases of UTROSCT, which were negative.¹⁵

The differential diagnosis of UTROSCT is potentially wide and may include an endometrial stromal and an epithelioid smooth muscle neoplasm, a metastatic ovarian sex cord-stromal tumour, a carcinosarcoma and primary and metastatic epithelial neoplasms, especially endometrioid adenocarcinoma with sex cord-like features and lobular breast carcinoma. A perivascular epithelioid cell tumour (PEComa)⁴⁹ might also be considered. This would be positive with HMB45. Interpreted in isolation, positivity with any of the markers discussed may result in an erroneous diagnosis. A polyphenotypic immunophenotype is, we believe, characteristic of UTROSCT and may be useful in differential diagnosis. For example, an epithelioid smooth muscle neoplasm would be expected to be positive with smooth muscle antibodies, hormone receptors and sometimes cytokeratin markers. However, this would be negative with sex cord markers. Similarly, an endometrioid adenocarcinoma or metastatic breast lobular carcinoma, while positive with anti-cytokeratins, EMA and sometimes hormone receptors, would be negative with smooth muscle and sex cord markers.

Given the polyphenotypic immunophenotype, we believe that UTROSCT is most likely derived from an uncommitted cell with the capacity to differentiate along several lines and express epithelial, myoid and sex cord markers. Some neoplasms express markers of all these lineages and others of one or two. An origin from displaced gonadal sex cord cells is also a possibility but EMA positivity is against this theory. As discussed, another major theory of histogenesis is that UTROSCTs represent a variant of endometrial stromal neoplasm. Focal sex cord-like elements may be present in otherwise typical endometrial stromal neoplasms and it is possible that UTROSCT represents an endometrial stromal tumour in which these elements are exclusive or predominate. However, it is our opinion that the sex cord-like elements in endometrial stromal neoplasms differ morphologically in most cases from UTROSCT, the former being composed of typical endometrial stromal cells which form tubular, trabecular and other arrangements, the latter typically having larger rounder nuclei and more abundant cytoplasm. Most UTROSCTs are relatively well circumscribed, while most endometrial stromal neoplasms (endometrial stromal sarcomas) exhibit a widely infiltrative growth pattern; this is a further argument against an endometrial stromal origin. Moreover, judging by previous studies the sex cord-like elements in endometrial stromal neoplasms exhibit less of a polyphenotypic immunophenotype,^{3, 4, 7} and it is our belief that these are not related to UTROSCT. However, the theory that UTROSCTs are a variant of endometrial stromal neoplasm is difficult to disprove. Endometrial stromal neoplasms not uncommonly contain rearrangements involving chromosomes 6, 7 and 17, most commonly a t(7;17) translocation.⁵⁰ One possible means of investigating a relationship between UTROSCT and endometrial stromal neoplasms is to use molecular techniques, such as fluorescence in situ hybridisation, to examine whether similar translocations to those found in endometrial stromal neoplasms are present in UTROSCT. We are only aware of cytogenetic analysis being performed on a single case of UTROSCT.⁹ This revealed two balanced chromosomal translocations, namely t(X;6) and t(4;18). These translocations have

Take-home messages

- Uterine tumour resembling ovarian sex cord tumour (UTROSCT) exhibits a polyphenotypic immunophenotype with coexpression of markers of epithelial, myoid and sex cord lineage, as well as hormone receptors.
- CD56 positivity is further evidence of true sex cord differentiation.
- The polyphenotypic immunophenotype may be useful in diagnosis and in the exclusion of other neoplasms.
- UTROSCT is likely to be derived from an uncommitted cell with the capacity for multidirectional differentiation.

not been shown previously in endometrial stromal neoplasms and, although based on only a single case, this is further supportive evidence that UTROSCT is histogenetically distinct from endometrial stromal neoplasms.

Given the relatively well circumscribed nature and bland morphological features in our cases, a benign behaviour might be expected. However, we have no follow-up. Since some of these neoplasms may exhibit a more infiltrative growth pattern and even vascular invasion, rare tumours have metastasised⁵¹ and only a few cases have been reported with long term follow-up, we feel UTROSCTs should be regarded as of uncertain but low malignant potential.⁵² We consider that the uncertain behaviour is an additional argument for not classifying these as variants of endometrial stromal tumour since the behaviour of the latter group of neoplasms is well established based on the circumscription of the lesions. Endometrial stromal nodules are well circumscribed and exhibit a benign behaviour, while endometrial stromal sarcomas exhibit infiltrative myometrial or vascular invasion and have a potential malignant behaviour. Since many UTROSCTs have a slightly infiltrative edge, they are not readily classified as benign or malignant using the accepted criteria for endometrial stromal neoplasms.

In summary, we report four cases of UTROSCT and in doing so have undertaken a detailed immunohistochemical analysis. Characteristically these neoplasms coexpress epithelial, myoid and sex cord markers, as well as hormone receptors. However, judging by this and previous studies, the immunophenotype is variable. A polyphenotypic immunophenotype is a characteristic feature of UTROSCT and may be helpful in diagnosis and in the exclusion of other lesions. Furthermore the polyphenotypic immunophenotype suggests an origin from an uncommitted cell with the capacity for multidirectional differentiation.

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