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Convenor: Dr Lyndal Anderson
ICPMR, Westmead Hospital, Sydney, NSW

Lecture :

“A review and update of morphologically bland vulvovaginal mesenchymal lesions”
Professor W. Glenn McCluggage
Royal Group of Hospitals Trust, Belfast, Northern Ireland.

Case Presentations:

Case 1. Presented by Dr Susan Bigby, Middlemore Hospital, Auckland, New Zealand.

Case 2. Presented by Dr Anita Achan, ICPMR, Westmead Hospital, Sydney, NSW.

Case 3. Presented by Dr Jane Nankervis, Southern IML Pathology, Wollongong, NSW.

Case 4. Presented by Dr Raghwa Sharma and Dr Hema Mahajan, ICPMR, Westmead Hospital, Sydney, NSW.

Case 5. Presented by Dr Lyndal Anderson, ICPMR, Westmead Hospital, Sydney, NSW.
A REVIEW AND UPDATE OF MORPHOLOGICALLY
BLAND VULVOVAGINAL MESENCHYMAL LESIONS

W Glenn McCluggage
Department of Pathology
Royal Group of Hospitals Trust
Grosvenor Road
BELFAST
BT12 6BL
Northern Ireland

Tel No:- 00 44 28 9063 2563
Fax No:- 00 44 28 9023 3643
Email:- glenn.mccluggage@bll.n-i.nhs.uk
SUMMARY

Vulvovaginal mesenchymal lesions composed of morphologically bland spindle-shaped cells often pose a particular diagnostic problem for the surgical pathologist not only because of the rarity of these lesions but also because of the wide array of entities with overlapping morphological features. Included in this group of lesions are soft tissue neoplasms that may arise at any site and those which are characteristic of, or relatively specific to, the vulvovaginal region. Lesions that are relatively specific to the vulvovaginal region include well-known neoplasms such as aggressive angiomyxoma and angiomyofibroblastoma as well as more recently described lesions such as cellular angiofibroma and superficial cervicovaginal myofibroblastoma. Fibroepithelial stromal polyp, superficial angiomyxoma, and smooth muscle neoplasms can also occur in, but are not specific to, this site. In this review the clinicopathological features of these lesions are described with an emphasis on recent developments. The value of ancillary studies, especially immunohistochemistry, is discussed although it is stressed that in general these are of limited value and routine morphology remains the mainstay in diagnosis. Morphologically bland spindle cell lesions that are not characteristic of the vulvovaginal region, but which may also occur here, are briefly discussed as are a variety of extremely rare mesenchymal lesions that have recently been described at this site.

Key words: vulva – vagina -- mesenchymal lesions -- differential diagnosis -- immunohistochemistry -- aggressive angiomyxoma – angiomyofibroblastoma – cellular angiofibroma – superficial cervicovaginal myofibroblastoma.
The wide variety of mesenchymal lesions that involve the vulvovaginal region can result in diagnostic difficulties for pathologists due to the relative rarity and their overlapping morphological features. Many of these lesions are relatively specific to or are characteristic of the vulvovaginal region while others may occur at any site with no predilection for this area. Morphologically bland mesenchymal lesions are a particular problem for pathologists and have been the subject of several recent reviews\textsuperscript{1,2}. This review presents an update on these lesions with an emphasis on recent developments. It is important to distinguish between the various entities since the behavior may vary markedly. For example, aggressive angiomyxoma is a locally aggressive infiltrative neoplasm with a marked tendency to local recurrence whereas other lesions such as angiomyofibroblastoma and cellular angiofibroma are well circumscribed with little tendency to local recurrence. Many of these lesions arise from the subepithelial myxoid stroma of the lower female genital tract that extends from the cervix to the vulva and that contains stromal cells that are immunoreactive for hormone receptors. Consequently, many of these lesions exhibit positive immunohistochemical staining for estrogen receptor (ER) and progesterone receptor (PR). In this review, morphologically malignant spindle cell lesions which rarely involve the vulvovaginal region but that are more common in other locations are not discussed, since the histological features of these tumors in the vulvovaginal regions are identical to those in other sites.

**AGGRESSIVE ANGIOMYXOMA**

Aggressive angiomyxoma was first described by Steeper and Rosai in 1983 under the designation aggressive angiomyxoma of the female pelvis and perineum\textsuperscript{3}. This neoplasm usually involves the deep soft tissues of the vulvovaginal region, pelvis, and perineum of females in the reproductive age group\textsuperscript{4,6}. Similar lesions have been described in the
inguinoscrotal region of males and also in the retroperitoneum. When discovered these are usually large lesions which clinically are often thought to represent a cystic lesion, such as a Bartholin’s cyst or a hernia. They often fill the entire pelvis, displacing rather than invading the pelvic structures.

Pathological Features

On gross examination, these tumors are typically poorly circumscribed with a rubbery, fibrous, gelatinous, or myxoid consistency (figure 1). Small cystic foci may be present. Histological examination shows a sparsely cellularity tumor with small ovoid, spindled, or stellate cells that exhibit minimal, if any, nuclear atypia (figure 2). Mitotic figures are not generally seen. The cells are embedded in an abundant stroma that usually is distinctively myxoid (figure 3), although fibrous areas are also common. Occasionally, the fibrous areas predominate, especially in recurrent tumors. In such instances, it may be difficult to distinguish residual or recurrent tumour from non-neoplastic connective tissue. Stromal mast cells and extravasated erythrocytes are common. Numerous stromal blood vessels are present and vary from thin-walled capillary-like vessels to large vessels with thick muscular walls (figure 4). Perivascular collagen and smooth muscle fibers are sometimes a prominent feature and bundles of smooth muscle may also be seen away from blood vessels. Aggressive angiomyxomas are non-encapsulated tumors with an infiltrative edge that often results in the entrapment of adipose tissue and skeletal muscle at the periphery of the tumor. In some lesions, foci resembling angiomyofibroblastoma are found, as discussed later.

Immunohistochemical Findings

There is, as yet, no specific immunohistochemical marker of aggressive angiomyxomas. Tumor cells are typically immunoreactive for vimentin and in some cases α smooth muscle actin (α SMA), desmin, and CD34. Tumor cell nuclei are typically positive for
ER (figure 5) and PR\textsuperscript{8,9}. Androgen receptor positivity has been described in cases in males. Recently, it has been shown that the DNA architectural factor HMGA2 (formerly known as HMGIC), located on chromosome 12, is rearranged in aggressive angiomyxomas, resulting in aberrant HMGA2 protein expression\textsuperscript{10-12}. Nuclear HMGA2 expression is present in aggressive angiomyxoma but generally not in its histological mimics, although HMGA2 transcripts have been demonstrated using molecular techniques in a single angiomyofibroblastoma, as discussed later. Normal tissues adjacent to aggressive angiomyxomas are negative with HMGA2. It has been suggested that HMGA2 may be useful in the diagnosis of aggressive angiomyxomas, its distinction from its mimics, the evaluation of surgical margins, and the determination of the presence or absence of residual disease. Clearly this requires confirmation by further studies.

**Behavior**

Aggressive angiomyxomas are infiltrative neoplasms with a marked tendency to local recurrence, especially in those lesions that extend to the resection margins. Often there is deeper extension than is appreciated on clinical examination and adequate excision with a rim of surrounding normal tissue may be difficult. Tumor recurrence may be delayed and there are often multiple local recurrences. Recently, a seemingly bona fide example of an aggressive angiomyxoma that metastasised to the lung has been described but this is an extremely rare phenomenon\textsuperscript{13}.

The positive immunohistochemical staining of aggressive angiomyxomas for hormone receptors and the observation that occasional cases exhibit rapid growth during pregnancy suggests that they may be hormone-responsive lesions that might be treatable with agents such as gonadotrophin releasing hormone agonists (GnRH agonists)\textsuperscript{14}. Adjuvant therapy using such agents could be considered following excision, especially if the lesion extends to or close
to the resection margins and further excision is not feasible. Treatment of aggressive angiomyxomas with GnRH agonists has a similar rationale to the use of anti-estrogens, such as tamoxifen, in the management of fibromatosis. Fibromatosis has much in common with aggressive angiomyxoma, both being morphologically bland infiltrative mesenchymal lesions with a marked tendency to local recurrence but with little or no metastatic potential. Both neoplasms are commonly positive for ER and PR.

**Differential Diagnosis**

The differential diagnosis can be wide and includes many of the other morphologically bland spindle cell lesions discussed in this review as well as a wide variety of other mesenchymal lesions, both benign and malignant, which show no predilection for the vulvovaginal region. Features of value in distinguishing many of these lesions from aggressive angiomyxoma will be discussed with each tumor type.

**ANGIOMYOFIBROBLASTOMA**

Angiomyofibroblastoma was first described in 1992 as a benign vulvar mesenchymal neoplasm distinct from aggressive angiomyxoma. These tumors usually occur on the vulva of women in the reproductive and early postmenopausal years. Occasional cases have been described in the vagina, as well as a purported case involving the fallopian tube. Rare examples of angiomyofibroblastoma-like tumor have been reported in males. Clinically the vulvar lesions are often thought to represent a cystic lesion, such as a Bartholin’s cyst.

**Pathological Features**

These are usually well-circumscribed lesions that are usually less than 5 cm in diameter, although larger lesions have been described. Histological examination shows a
well-circumscribed but unencapsulated lesion. Characteristically there are alternating hypocellular and hypercellular areas. Numerous, usually thin-walled, capillary-like vascular channels are present. Tumor cell nuclei may be ovoid to spindle shaped but there is often a minor or major component where nuclei have an epithelioid or plasmacytoid appearance (figure 6). These cells often have an appreciable amount of eosinophilic cytoplasm and occasionally multinucleated cells are present. Tumor cells tend to form aggregates, especially around blood vessels, although this feature is not always present. Mitotic figures are rare or absent. The stroma is usually fibrous but may be edematous and small foci of myxoid change can be present. Scattered mast cells and lymphocytes are commonly seen within the stroma. Adipose tissue may be present, especially around the periphery, and a lipomatous variant has been described which contains abundant adipose tissue\textsuperscript{25}. Rare vulvovaginal mesenchymal lesions contain areas resembling both angiomyofibroblastoma and aggressive angiomyxoma and it has been suggested that these are related neoplasms in a spectrum of tumors exhibiting myofibroblastic differentiation. It is recommended that these “hybrid” neoplasms should be regarded as having potential for locally aggressive behavior\textsuperscript{26}.

**Immunohistochemical Findings**

Tumor cells are typically immunoreactive for vimentin, and are more likely to be desmin positive and \(\alpha\) SMA negative than aggressive angiomyxomas. However, there is much immunophenotypic overlap between the two tumors and, in an individual case, immunohistochemistry is unlikely to be of value. There is typically nuclear staining for ER and PR and some cases are positive for CD34. In a single case HMGA2 transcripts were identified using molecular techniques\textsuperscript{27}, although immunohistochemical staining was not performed.
Behavior

Angiomyofibroblastomas generally behave in a benign fashion. Although occasional cases recur locally, especially those that have been “shelled-out” without a surrounding rim of uninvolved tissue, there is no marked tendency for local recurrence. In contrast to aggressive angiomyxomas, in the angiomyofibroblastomas that recur, the recurrence is non-destructive. However, in one recurrent case, the original neoplasm contained areas of typical angiomyofibroblastoma and sarcomatous areas resembling malignant fibrous histiocytoma. The recurrent neoplasm (2 years later) was purely sarcomatous. A series of angiomyofibroblastomas containing sarcomatous areas has been reported in abstract form. The sarcomatous elements were of two types, one that morphologically resembling angiomyofibroblastoma and the other consisting of being poorly differentiated sarcoma resembling leiomyosarcoma or undifferentiated sarcoma. The two types were termed malignant angiomyofibroblastoma and dedifferentiated angiomyofibroblastoma respectively. Based on these studies it is probable that angiomyofibroblastoma has a small risk of sarcomatous transformation, although further studies of well studied cases are required to confirm this.

Differential Diagnosis

In contrast to aggressive angiomyxoma, angiomyofibroblastoma is well circumscribed, has a less myxoid and more fibrous stroma, is more cellular, and often contains a population of plump epithelioid or plasmacytoid tumor cells. Blood vessels are usually thin-walled in contrast to aggressive angiomyxomas which generally have a component of thick-walled vessels. As discussed, immunohistochemistry is of limited value in distinguishing the two tumors. Two cases of an angiofibroblastoma-like stromal response have been found in a fallopian tube that prolapsed into the vaginal vault following hysterectomy.
CELLULAR ANGIOFIBROMA

The cellular angiofibroma, initially described in a series of four cases by Nucci and colleagues in 1997, is a rare benign mesenchymal lesion that usually involves the vulva of middle-aged females. Similar tumors occurring in the vagina have not been reported. Since the original description there have been occasional reports of one or two cases and recently we have described seven additional examples. An identical lesion has been described on the chest wall and similar cases rarely occur in the inguinoscrotal region of males. The preoperative diagnosis, in common with many other vulvovaginal mesenchymal lesions, is usually of a cystic lesion such as a Bartholin’s cyst.

Pathological Features

On gross examination, these are well-circumscribed, firm, white to grey lesions that are usually less than 5 cm in maximal dimension. On microscopic examination, cellular angiofibromas are well circumscribed but unencapsulated. Entrapped adipose tissue is common at the periphery of the tumor (figure 7). The lesions are moderately cellular and are composed of a uniform population of morphologically bland intersecting spindle-shaped cells set in a fibrous stroma (figure 8). Occasionally there is vague nuclear palisading. Mitotic figures, although generally sparse, may be easily identified in some cases and up to 11 mitotic figures per 10 high-power fields (MFs/HPFs) have been described. Numerous blood vessels are present and usually these are small to medium sized with thick hyalinized walls, this being one of the characteristic histological features of this neoplasm. Stromal mast cells and other inflammatory cells are often present.

In the recent series we reported, other morphological features in some cases were vessels without thick hyalinized walls, a hemangiopericytomatous vascular pattern, stromal lymphoid aggregates, scattered multinucleate cells, hypocellular hyalinized areas, myxoid
areas, and focal nuclear pleomorphism reminiscent of symplastic change within a uterine leiomyoma\textsuperscript{37}. These features expand the morphological spectrum of cellular angiofibroma and indicate that some of these tumors do not exhibit the typical morphology originally described or do so only focally.

**Immunohistochemical Findings**

The tumor cells are positive for vimentin but negative for the smooth muscle markers $\alpha$SMA, desmin, and h-caldesmon\textsuperscript{31,37}. Negative staining with smooth muscle markers may be useful in diagnosis since most of the other vulvovaginal mesenchymal lesions are at least focally positive with some of these antibodies. S100 is consistently negative and CD34 is positive in a minority of cases. Epithelial membrane antigen (EMA) positivity has been described in a single case and some examples are CD10 positive. Most tumors exhibit positive nuclear staining for ER and PR\textsuperscript{35-37}.

**Behavior**

Cellular angiofibromas appear to be benign lesions with no metastatic potential. A single case has exhibited local recurrence\textsuperscript{32} but there appears to be limited potential for this, based on the small number of cases reported.

**Differential Diagnosis**

Distinction from aggressive angiomyxoma is based on the circumscription of cellular angiofibroma and its higher cellularity, a more fibrous and less myxoid stroma, and a greater tendency for hyalinization of vessel walls. In comparison to angiomyofibroblastoma, cellular angiofibroma is more monomorphic without epithelioid or plasmacytoid tumor cells and without perivascular cellular aggregates. The vessels in angiomyofibroblastoma are generally thin-walled in contrast to the thick hyalinized vessels found, at least focally, in most cases of
cellular angiofibromas. The presence of adipose tissue within cellular angiofibromas and the character of the cells may result in consideration of a spindle cell lipoma. However, vessels with hyalinized walls are not a feature of spindle cell lipomas, which usually contain a greater amount of adipose tissue and are more consistently positive for CD34 than cellular angiofibromas.

Immunohistochemistry may be useful in the diagnosis of cellular angiofibroma in that there generally is no staining with smooth muscle markers, whereas the latter are at least focally positive in most of the other neoplasms in the differential diagnosis. On the basis of this observation and ultrastructural examination of a single case, it is suggested that cellular angiofibromas exhibit fibroblastic rather than myofibroblastic differentiation, the latter being a feature of many of the other vulvovaginal mesenchymal lesions discussed.

**FIBROEPITHELIAL STROMAL POLYP**

Fibroepithelial stromal polyps are relatively common lesions of the vulvovaginal region, usually occurring on the vagina in women of reproductive age. There appears to be a hormonal association since patients may be pregnant at the time of diagnosis or there may be a history of hormonal usage or tamoxifen therapy. However, the propensity for detection in pregnancy may simply be due to these lesions being discovered at antenatal examination. In pregnant patients, the polyps may regress in the puerperium. The lesions may be multiple.

**Pathological Features**

On gross examination, these are usually polypoid lesions which may be round or villiform. On histologic examination, the polyps are covered by squamous epithelium that is usually unremarkable or hyperplastic. Deep to the surface, within the core of the polyp, are...
spindle and stellate cells, often with tapering cytoplasmic processes. Multinucleated cells or cells with multilobed nuclei are sometimes present, often with a wreath-like appearance (figures 9 and 10). These stromal cells usually extend up to the dermal-epidermal junction without an uninvolved Grenz zone. The stroma may be fibrous, edematous, or myxoid, with edematous and myxoid changes being especially common in larger lesions that have undergone torsion (figure 11). There is usually a component of thick- or thin-walled blood vessels that are most prominent towards the center of the lesion.

Occasionally, especially but not exclusively in pregnancy, a variety of features can be present that result in consideration of a sarcoma46. These features, which may be present singly or in combination, include marked stromal hypercellularity, bizarre nuclear features, numerous mitotic figures (>10 MFs/10 HPFs), and atypical mitoses. The terms cellular pseudosarcomatous fibroepithelial stromal polyp46 and pseudosarcoma botryoides42 have both been used for lesions that exhibit these histological features.

**Immunohistochemical Findings**

The lesional cells are typically immunoreactive for vimentin, desmin, ER, and PR and less commonly for α SMA,47-49 and are typically negative for S100-protein and cytokeratins.

**Behavior**

These are benign lesions and local excision is usually curative. They may recur during subsequent pregnancies and some lesions regress during the puerperium. In those cases that recur locally, recurrence is non-destructive and re-excision can be undertaken. Metastasis has not been reported. The aforementioned histological features that may result in consideration of a sarcoma do not denote malignant behavior, appreciation of which is crucial to avoid overtreatment.
Differential Diagnosis

The diagnosis is usually straightforward in small lesions. Difficulties may occur with large lesions, especially those that exhibit stromal myxoid change resulting in consideration of aggressive angiomyxoma. Appreciation of the polypoid shape may assist in establishing a diagnosis and the presence of multinucleated cells is more typical of stromal polyp than aggressive angiomyxoma. A useful diagnostic feature in fibroepithelial stromal polyps is that the lesional cells extend up to the dermal-epidermal junction without an uninvolved Grenz zone. This finding may be useful in the distinction from angiomyofibroblastoma, cellular angiofibroma, and superficial cervicovaginal myofibroblastoma (discussed later) that are usually separated from the overlying epithelium by a zone of uninvolved tissue.

A variety of sarcomas may enter the differential diagnosis of those cases with atypical histological features. Again appreciation of the polypoid nature of the lesion may be helpful. Sarcoma botyroides usually occurs in a younger age group, a cambium layer is often present, and cells with cross striations may be seen. Positive immunohistochemical staining for skeletal muscle markers, such as myoglobin and myoD1, assists in the diagnosis of sarcoma botyroides.

It should be noted that multinucleated stromal cells, similar to those commonly seen in fibroepithelial stromal polyps, are a not uncommon normal incidental finding in the subepithelial stroma of the lower female genital tract. These cells are especially common in association with uterine prolapse. They are most common in the vulva and vagina but occasionally are seen in the cervix.
SMOOTH MUSCLE NEOPLASMS

Smooth muscle neoplasms are uncommon in the vulvovaginal region\textsuperscript{50-52}, compared to their frequency within the uterus. Most are of vulvar origin. They occur over a wide age range and clinically are often felt to be a cystic lesion, such as a Bartholin’s cyst. Vulvar leiomyomatosis is a rare condition characterized by a multinodular proliferation of smooth muscle. Rarely patients with vulvar leiomyomatosis develop smooth muscle tumors in the esophagus\textsuperscript{53-56} and there may be an association with Alport’s syndrome.

Pathological Features

On gross examination, these are typically well-circumscribed lesions, usually less than 5 cm in maximal dimension, although larger lesions with an infiltrative margin occur rarely. They are generally white and similar in consistency to uterine leiomyomas.

Histologic examination shows three principal histological patterns, namely spindled, myxohyaline, and epithelioid, which may be pure or mixed. The epithelioid and, especially, the myxohyaline patterns are more common in vulvovaginal smooth muscle tumors than they are in their uterine counterparts. The spindle cell pattern consists of cells with elongated blunt-ended nuclei and eosinophilic cytoplasm (figure 12), similar to the cells in the usual uterine leiomyoma. In the myxohyaline variant, the spindle-shaped or epithelioid cells are set in a myxohyaline stroma (figure 13), sometimes resulting in a nested, lacy, or plexiform appearance. Mucin pools may be present. The myxohyaline pattern may result in diagnostic problems but a clue to diagnosis is that there is often merging of these foci with areas of more usual smooth muscle differentiation.
**Immunohistochemical Findings**

The tumor cells are typically positive for the smooth muscle markers α SMA, desmin, and h-caldesmon. ER and PR are also generally positive.

**Behavior**

It is important to appreciate that the criteria that predict malignant behavior in uterine smooth muscle neoplasms cannot be extrapolated to vulvovaginal smooth muscle tumors. There are difficulties in predicting the likelihood of recurrence or metastasis in vulvovaginal smooth muscle neoplasms, since there are few studies with long-term follow-up. Some tumors recur many years after excision and recurrences often show more worrisome histological features than were present in the primary tumors. Features which predict recurrent potential in vulvovaginal smooth muscle neoplasms include any mitotic activity or nuclear pleomorphism or an infiltrative edge. In the presence of any of these features, the possibility of local recurrence (which may be late) should be stated in the pathology report and even neoplasms without these features may occasionally recur. The term “atypical smooth muscle tumour” has been proposed for lesions which do not fulfil the criteria for a diagnosis of leiomyosarcoma (see below) but which have any of the following features: infiltrative margin, nuclear atypia, or any mitotic activity. In such cases, a 1.0 cm margin of excision is recommended whenever possible.

The most commonly used criteria to predict metastatic potential in vulvovaginal smooth muscle neoplasms are those proposed by Tavassoli and Norris. Tumors exhibiting three or more of the following features are classified as leiomyosarcomas: >5 cm in size, infiltrative margin, >5 MFs/10 HPFs, and moderate to severe cytological atypia. Coagulative tumor cell necrosis is also a worrying feature.
Differential Diagnosis

The differential diagnosis can be wide and include many of the other lesions discussed in this review. The characteristic histological findings and immunoreactivity with smooth muscle antibodies (especially h-caldesmon) assist in establishing a diagnosis. It is stressed that many other vulvovaginal mesenchymal lesions may be positive with smooth muscle markers, especially desmin, although it is helpful that cellular angiofibroma, one of the main lesions in the differential diagnosis, is almost always negative for these markers. The distinction between the two tumors is important as mitotic figures may be seen in cellular angiofibromas without clinical significance, whereas any mitotic activity in vulvovaginal smooth muscle tumors indicates a potential for recurrence.
SUPERFICIAL CERVICOVAGINAL MYOFIBROBLASTOMA
(SUPERFICIAL MYOFIBROBLASTOMA OF THE LOWER FEMALE GENITAL TRACT)

In 2001, Larkin et al described 14 cases of a distinctive mesenchymal tumor arising in the superficial lamina propria of the cervix and vagina. The lesions presented as polypoid or nodular masses, most commonly involving the vagina, or in two cases, the uterine cervix. The term superficial cervicovaginal myofibroblastoma (SCVM) was proposed to encompass the superficial location in the cervix or vagina and presumed myofibroblastic differentiation. Recently we have described a series of similar cases that involved the vagina and the vulva. We propose the term “superficial myofibroblastoma of the lower female genital tract” rather than SCVM since some neoplasms have a vulvar location. In both series, several patients had been taking tamoxifen, raising the possibility of a hormone responsive neoplasm.

Pathological Features

Grossly these are well circumscribed lesions with a polypoid or nodular shape. Histologic examination shows a well-circumscribed but unencapsulated lesion covered by unremarkable or hyperplastic squamous epithelium. Deep to the surface epithelium there is usually an uninvolved Grenz zone. The lesions are moderately cellular and are composed of bland ovoid, spindle or stellate cells, often with a wavy appearance (figure 14), embedded in a finely collagenous stroma, sometimes with thicker collagen bundles. Multiple patterns, including lacelike, sieve-like, and fascicular, are a characteristic feature, as are myxoid or edematous foci (figure 15). There are few mitotic figures. The lesions are usually more vascular towards their centers.
**Immunohistochemical Findings**

Tumor cells are positive for vimentin and usually, but not always, desmin\textsuperscript{57,58}. CD34 and $\alpha$ SMA are positive in smaller numbers of cases and most tumors stain for ER and PR. The tumors are negative for S100, EMA, and cytokeratins. Desmin staining often highlights the interconnecting dendritic processes in many of the tumor cells (figure 16). The immunophenotype is nonspecific and is identical to many of the other vulvovaginal mesenchymal lesions discussed in this review.

**Behavior**

Based on the only two series, this is a benign lesion with little potential for local recurrence\textsuperscript{57,58}. Recurrence or metastasis has not been reported to date.

**Differential Diagnosis**

The differential diagnosis includes many of the other mesenchymal lesions discussed in this review. Perhaps the two lesions most likely to be confused with SCVM are the fibroepithelial stromal polyp and the angiomyofibroblastoma. Both fibroepithelial stromal polyps and SCVMs characteristically have a polypoid appearance, although in the former the lesional cells generally extend up to the dermal-epidermal junction whereas in SCVMs there is usually, although not always, an uninvolved Grenz zone. The characteristic multipatterned architecture of SCVM is not a feature of the fibroepithelial stromal polyp that more often contains multinucleated giant cells and is generally of lower cellularity. The immunoprofile of the two lesions is identical. It is probable that SCVMs have been interpreted as fibroepithelial stromal polyps in the past.
The other lesion most likely to be confused with SCVM is the angiomyofibroblastoma. Perivascular aggregates of epithelioid or plasmacytoid cells, a common feature in angiomyofibroblastoma, is not found in SCVM, which characteristically assumes a variety of architectural patterns, the lesional cells being ovoid to spindle shaped. Immunohistochemistry plays no part in distinguishing the two lesions.

The presence of wavy nuclei in SCVM may raise the possibility of a perineurioma or another neural lesion. However, negative staining for EMA and S100 protein helps exclude a perineurioma and other neural lesions.

**SUPERFICIAL ANGIOMYXOMA**

Although more commonly located on extragenital sites, especially the head and neck, superficial angiomyxoma not infrequently involves the vulvovaginal region, almost always the vulva. A synonym is cutaneous myxoma. Occasionally multiple cutaneous myxomas or angiomyxomas are a manifestation of the autosomal dominant Carney’s complex, although this has not been a feature of the reported cases of superficial angiomyxoma occurring in the vulvovaginal region. However, if multiple superficial angiomyxomas are present, the possibility of Carney’s complex should be raised since these patients are at risk for the development of cardiac myxomas.

**Pathological Features**

On gross examination, these are nodular or multinodular lesions involving the skin and or subcutaneous tissue. The cut surface is myxoid or gelatinous. Histological examination shows a multinodular lesion usually located within the dermis and subcutaneous tissue (figure 17). The lesion is composed of morphologically bland spindle and stellate cells set in an
abundant myxoid stroma. Occasional multinucleated cells may be present. There are few or no mitotic figures. Thin-walled capillary-like blood vessels are present, often with a curvilinear pattern, and a characteristic histological feature is the almost invariable presence of neutrophils, which are a useful diagnostic aid. There are often entrapped epithelial elements derived from the overlying skin or skin appendages at the periphery of the lesion.

**Immunohistochemical Findings**

The lesional cells are typically positive for vimentin, CD34, and α SMA but are generally negative for desmin, ER, and PR. S100 positivity has been reported in some, but not all, studies. There is no specific immunophenotype.

**Behavior**

SA is a benign lesion with no metastatic potential. However, local non-destructive recurrence is not uncommon and the lesions should be excised with a rim of normal tissue where possible.

**Differential Diagnosis**

The differential diagnosis includes many of the other site-specific vulvovaginal mesenchymal lesions discussed in this review, especially those with a myxoid appearance, and a variety of other non-site-specific myxoid mesenchymal lesions. One of the main lesions in the differential diagnosis is aggressive angiomyxoma. In general, this is a larger deeper-seated lesion than superficial angiomyxoma and has an infiltrative margin that contrasts with the multinodular growth pattern of the superficial angiomyxoma. The blood vessels are more variable in appearance in aggressive angiomyxoma, usually with a component of thick-walled vessels, whereas the presence of stromal neutrophils favors superficial angiomyxoma. An
absence of ER and PR staining also favors superficial angiomyxoma since most aggressive angiomyxomas are positive with one or both of these antibodies. Positive desmin staining is more in keeping with aggressive angiomyxoma than superficial angiomyxoma.

MISCELLANEOUS LESIONS

A variety of other morphologically bland mesenchymal lesions may involve the vulvovaginal region, most having no specific predilection for this site. The pathological features of these will not be described since they are identical to when these lesions occur at more common sites. It is stressed that when dealing with a vulvovaginal mesenchymal lesion, as well as considering the relatively site specific neoplasms discussed, the pathologist should also consider other mesenchymal lesions. Morphologically bland spindle cell lesions that have been reported in the vulvovaginal region include nodular fasciitis, fibromatosis, spindle cell lipoma, neural tumors (including myxoid variants), hemangiopericytoma, solitary fibrous tumor, mammary-type myofibroblastoma, and dermatofibrosarcoma protuberans. In the following sections a variety of lesions will be briefly discussed which, while rare, are characteristic of the vulvovaginal region and may enter into the differential diagnosis of some of the lesions already described.

Vulvovaginal Mesenchymal Lesions Associated with Paraplegia

Two cases of pseudosarcomatous vulvovaginal mesenchymal lesions in paraplegic or quadriplegic patients have been reported. In one case there was bilateral vulval enlargement, the clinical impression being of labial hypertrophy. On histologic examination, this lesion mimicked aggressive angiomyxoma with a markedly edematous and myxoid stroma. In the other case, the gross appearance was suspicious of a malignant neoplasm and histologically the lesion was interpreted as resembling ischemic fasciitis (atypical decubital fibroplasia) (figure 18). It is possible that both lesions are similar pathogenetically and
represent morphologic variations of the same entity. It is likely that the underlying pathogenesis is pressure-induced ischemic injury followed by aberrant wound healing secondary to immobility and lack of sensation.

**Prolapsed Fallopian Tube Associated with Angiomyofibroblastoma-like Stromal Reaction**

Prolapse of the fallopian tube into the vaginal vault rarely occurs following hysterectomy, especially vaginal hysterectomy. Two cases of fallopian tube prolapse associated with an exuberant angiomyofibroblastoma-like stromal reaction have been described. If the tubal epithelium is overlooked or not sampled, a diagnosis of angiomyofibroblastoma may be made in such cases.

**Postoperative Spindle Cell Nodule**

Postoperative spindle cell nodules (PSCNs), similar to that described elsewhere within the genitourinary tract, may occur in the vulvovaginal region, especially the vagina. This is a reactive, proliferative, pseudosarcomatous lesion that develops after an operative procedure, usually after a period of 1 to 12 weeks but sometimes later. PSCN is a benign lesion that rarely recurs. The history of a recent operative procedure is crucial in establishing the diagnosis. PSCNs are composed of a fascicular arrangement of spindle-shaped cells, often with prominent vascularity (figure 19). These lesions may be densely cellular. There is no significant nuclear atypia but mitotic figures may be numerous and the lesion can have an infiltrative appearance. The discrepancy between the degree of nuclear atypia and the mitotic rate may be a clue to diagnosis. Sometimes there is overlying ulceration. There is immunoreactivity for vimentin and variably for α SMA, desmin, and cytokeratins.
Vulvar Squamous Cell Carcinoma with Prominent Fibromyxoid Stromal Reaction

Occasional vulvar squamous carcinomas, especially in elderly women, are associated with a florid fibromyxoid stromal reaction\textsuperscript{82}. These tumors often involve the clitoris. This is a non-neoplastic stromal reaction to the tumor and different from a spindle cell squamous carcinoma or a carcinosarcoma. It has been suggested that this type of stromal reaction is associated with a worse outcome and a greater likelihood of nodal metastasis\textsuperscript{82}. When the stromal reaction is particularly prominent, the epithelial neoplasm may be overlooked, particularly if the lesion has not been sampled well or if only a small biopsy was taken.

CONCLUSIONS

A wide variety of morphologically bland mesenchymal lesions may involve the vulvovaginal region, some relatively specific to this site and others with a more widespread distribution. When faced with such a lesion, the pathologist should consider a wide range of diagnoses and not just those lesions specific to the vulvovaginal region. It is important to establish a correct diagnosis since the behavior and management of these lesions may differ markedly. Distinguishing the various entities may be difficult because of overlapping morphological features. Histological examination is the mainstay in diagnosis since immunohistochemistry is of limited value because of considerable immunophenotypic overlap, although the distinction between certain lesions may be facilitated by a judiciously chosen immunohistochemical panel.

The full range of site-specific vulvovaginal mesenchymal lesions is probably under-recognized at present and in recent years there has been refinement and expansion of the
morphological appearances of some lesions and description of new entities, such as cellular angiofibroma and superficial cervicovaginal myofibroblastoma. It is likely in the future that molecular techniques will contribute to more precise classification of some of these lesions, as in soft tissue tumors in general, by revealing characteristic chromosomal translocations and other genetic abnormalities.
REFERENCES


Case 1

Presenter: Dr Susan Bigby
Histopathology Laboratory Services, Middlemore Hospital, Auckland, NZ.

**Spindle cell (sarcomatous) carcinoma of the vulva with heterologous elements.**

**Clinical History:**

A 93 year old woman presented with an ulcerated nodule, 40 x 30mm located on the vulva. The patient had a background of biopsy proven genital lichen sclerosus. The lesion was treated with wide local excision without groin node dissection. The patient died one month following surgery of other causes.

**Pathological Findings:**

Histology showed an ulcerated tumour forming an elevated nodule. The tumour was centered on the dermis and extended into the subcutaneous tissue with a depth of 3mm and a thickness of 11mm. There was a monophasic spindle cell population with marked pleomorphism and abundant mitoses. Conventional squamous cell carcinoma was not seen. There was extensive ulceration of the overlying epithelium, but where residual surface squamous epithelium was present, this appeared to merge imperceptibly with the tumour. The spindle cell population merged with areas of malignant osteoid and chondroid, some of which showed mineralization. Scattered multinucleated giant cells were present. There was no perineural or lymphovascular space invasion. The tumour margin was pushing and there was a very sparse peritumoural lymphocytic response.

Adjacent intact epithelium showed squamous hyperplasia with focal basal atypia. Unequivocal features of differentiated VIN were not seen. There was no evidence of lichen sclerosus in the resection specimen, although only a small amount of intact adjacent skin was available for assessment.

The tumour showed focal positivity for CK8/18 and P63. Osteosarcomatous foci were positive for osteocalcin. The tumour was diffusely positive for P53 and small strips of adjacent surface epithelium showed strong basal and parabasal positivity for P53. P16 was negative. Immunohistochemistry for CK5/6, CK-MNF116, AE1/3, CK-HMW, 34BE12, EMA, sma, desmin, caldesmon, CD99, CD34, melan A, S100 and S100 was negative.

**Final Diagnosis:**

**Spindle cell (sarcomatous) carcinoma of the vulva with heterologous elements**
Discussion

Spindle cell (sarcomatoid) carcinoma is a rare subtype of squamous cell carcinoma of the vulva (SCCV). This case is one of a series of four spindle cell carcinomas of the vulva (unpublished) retrieved from the Auckland Regional Gynaecological Oncology database in a study of 213 cases of SCCV over a 17 year period, and from referral material. The incidence of this tumour in our region is 1% of all SCCV. The seminal case presented here shows the characteristic features of this tumour, and illustrates the diagnostic problems that may arise.

Spindle cell carcinoma has been reported at many anatomical sites. Nomenclature has varied, with similar tumours reported as spindle cell carcinoma, sarcomatoid carcinoma, and carcinosarcoma. Spindle cell carcinoma is rare in the vulva with only nine cases reported in detail to date1-9 A further 2 cases were included in a large study of squamous cell carcinoma of the vulva (SCCV) by Gosling and Abell.10 This is the second case with malignant heterologous elements.

Spindle cell carcinoma is reportedly more common in older patients and typically presents as ulcerated polypoid lesion following a short history. Of the 13 cases of vulval spindle cell carcinoma or carcinosarcoma available for analysis (nine published and four in our series), the median age of presentation was 74 years (range 43-93). The median duration of symptoms was 3 months (range 1 to 24 months), with two further cases reported as undergoing “rapid growth”. The most common site on the vulva was anterior/clitoral (n=8) with further cases occurring on the labia minora (n=2) and labia majora (n=2), with one site not specified. Eleven cases were described as exophytic, nodular or polypoid, and 12 were ulcerated. The tumours ranged in size from 15mm to 120mm with a median of 39.5mm. Six tumours were at least FIGO (2009) stage III at presentation. To date, none of the five vulval cases tested for HPV has been positive (1 case tested by Santos-Briz et al7 and four cases from our series), although similar cases in the cervix11 and penis12 have shown HPV on PCR analysis.

Histologically 10 of the cases of spindle cell carcinoma of the vulva were biphasic2,3,5,6,7,8,9, one monophasic1 and a further two (current case included) composed of spindle cells with malignant heterologous elements4. The biphasic tumours showed conventional SCC, sometimes very focal and superficial, merging with spindle cell areas. The two cases with heterologous elements both showed osteosarcoma. Our case also showed malignant cartilaginous differentiation. Metastases of either component may occur. Seven women had lymph node metastases, with three showing conventional SCC6, two spindled SCC1,7, and one with both conventional and spindled SCC6. The morphology of the metastasis was not described in remaining case.

The histiogenesis of this group of tumours has been debated for over two decades, with robust evidence now supporting the view that in most cases the sarcomatous cells are derived from metaplastic transformation of malignant epithelial cells (“conversion” theory)13,14. This theory is supported by embryological, ultrastructural, immunohistochemical, molecular and in vitro evidence. Molecular evidence includes studies of patterns of X chromosome inactivation,15,16 demonstration of identical mutations of P53 and k-ras mutations in both components,15,17 loss of heterozygosity
using polymorphic microsatellite markers, and demonstration of the same genetic alterations in both epithelial and sarcomatous elements, all suggesting the tumour is monoclonal.

Cases of sarcomatous transformation have followed radiation, and solar damage is postulated to account for a subset of cutaneous tumours. Previous radiation is commonly documented in patients presenting with MMMT of the uterus. One woman in our series developed recurrent SCC with a spindled morphology following radiotherapy for a previous conventional SCCV. There are nevertheless many cases without antecedent exposure to radiation, and the trigger for sarcomatous change is unknown. Sarcomatous transformation is postulated to be a relatively late development, accounting for the history of rapid growth so frequently elicited from these patients. There has been considerable research and debate in the experimental pathology literature over the last decade regarding the concept of “Epithelial to Mesenchymal Transition (EMT)”. EMT describes a loss of epithelial features such as loss of intercellular junctions and resultant loss of intercellular adhesion, and contact inhibition accompanied by increased cell motility. This occurs during embryogenesis as a natural phenomenon, but is also postulated to be the mechanism by which some, but not all epithelial tumours acquire a more motile phenotype, and therefore greatly enhanced capacity for invasion and metastasis.

The immunohistochemical profile of spindle cell carcinoma reflects the metaplastic conversion from epithelial to sarcomatous phenotype. With progressive loss of the epithelial phenotype, there is loss of the cytokeratin filaments within the cytoplasm, and expression of mesenchymal filaments. While many tumours may show some evidence of residual CK immunopositivity following a wide panel of CK markers, others may not. This is important in the consideration of differential diagnoses. Where there is residual conventional squamous cell carcinoma, or non-ulcerated epithelium showing vulval intraepithelial neoplasia, the diagnosis is relatively straightforward. Diagnostic problems usually arise where the lesion is monophasic and overlying epithelium ulcerated. Differential diagnosis should include melanoma, sarcoma and metastatic spread from another site. Melanoma is relatively easily excluded with S100, melan A or HMB45 immunohistochemistry. Primary sarcomas of the vulva are rare and account for between 1.5 and 5% of all malignant vulval tumours. In a series recently completed at our centre, the incidence was 5.4% of all malignant vulval tumours. Leiomyosarcoma comprise the largest subgroup. Other sarcomas reported at this site include synovial sarcoma, rhabdomyosarcoma, clear cell sarcoma, DFSP, peripheral nerve sheath tumour, liposarcoma, myofibroblastic sarcoma, proximal-type epithelioid sarcoma, Ewing’s sarcoma and poorly differentiated sarcoma, not otherwise specified. Further, we have observed a case of generalized Kaposi’s sarcoma with involvement of the vulva. Sarcomas are usually located in the deeper planes of tissue rather than in the dermis.

Spindle cell carcinoma is reportedly more aggressive than conventional SCC. The rarity of this tumour in the vulva, and the limited period of follow up in reported cases hampers meaningful analysis. Series of similar tumours with follow up in the penis (n=9), cervix (n=9) and vagina (n=10) showed distant metastasis or death from disease, usually within one year, in 56%, 60% and 70% of patients. Follow up was available in 12 women with vulval tumours. An adverse outcome was experienced in five patients (42%), four of whom died of disease with a median
A survival time of 4 months (range = 1-32.5 months). A further woman is alive with disease. One woman died of unknown causes at 5 months, and a further woman (the current case) died at 1 month of other causes. The remaining five women for whom follow up is available were well without evidence of disease with follow up periods between 24 and 84 months. The presence of heterologous elements has not been shown to be prognostically significant at other sites.

References

CASE 2

Presenter: Dr Anita Achan
ICPMR, Wesmead Hospital, Sydney, NSW.

Adenoid cystic carcinoma of vagina.

CLINICAL HISTORY:
Thirty-four year old female presented with heavy PV discharge and lower 1/3rd vaginal wall polyp. At surgery, this was a superficial soft polypoid mass located 10 - 15mm from the introitus, which appeared completely excised. Previous pap smears were negative.

GROSS FINDINGS:
A piece of mucosa bearing a tan coloured polypoid lesion measuring 22 x 12 x 11mm.

MICROSCOPIC FINDINGS:
Sections contained a polypoid lesion abutting and ulcerating the overlying squamous epithelial lining. Tumour was composed of invasive nests of atypical basaloid cells arranged in an adenoid cystic growth pattern with peripheral palisading of nuclei. Smaller more compact cells rimmed the punched out cystic spaces. These cells showed round nuclei, 2 – 3indistinct nucleoli, scanty amount of amphophilic cytoplasm and frequent mitotic figures. Alcian blue/PAS positive diastase resistant hyalinised basement membrane-like material or cellular mesenchymal tissue was seen in the cribriform spaces. Overlying squamous epithelium showed full-thickness dysplasia equivalent to VAIN III. No lymphovascular space/perineural invasion was noted. Tumour was incompletely excised.

Differential diagnoses generally considered include adenoid cystic carcinoma, basaloid squamous cell carcinoma, adenoid basal carcinoma, polymorphous low-grade adenocarcinoma, neuroendocrine carcinoma, basal cell carcinoma, metastatic atypical carcinoid, small cell carcinoma and carcinosarcoma.

IMMUNOHISTOCHEMISTRY FINDINGS:
AE1/AE3 & Cam5.2: patchy positivity in the majority of tumour cells
S-100, P63 & SMA: diffuse positivity predominantly in periphery of tumour nests
Ki-67 index: elevated up to 80% particularly in periphery of tumour nests
CD117: positivity in >50% of cells
P16: strong diffuse nuclear positivity in tumour + surface dysplastic epithelium, probably implicates high-risk HPV in the genesis of the lesion
CEA & synaptophysin: negative

Studies have shown that collagen type IV and laminin stains are strongly positive in the relation to the extracellular basement membrane-like material. EMA is positive in glandular lumens and periluminal cell membranes.

The most important differential diagnosis of cervico-vaginal adenoid cystic carcinoma (ACC) is adenoid basal carcinoma (ABC). However, ACC has several clinico-pathological features that will allow distinction from ABC. The differentiation is important, as unlike ACC, the overwhelming majority of cases of ABC are benign owing to the lower potential for recurrence and metastasis. Both tumours are common...
in postmenopausal women, but patients with ABC are usually asymptomatic, without a gross abnormality of the cervix. Histologically, ABC has been described as a proliferation of nested uniform, cytologically bland basaloid cells with a peripheral palisading pattern. Mild nuclear chromatin abnormalities are present with small nucleoli and rare mitoses. Clusters of basaloid cells may demonstrate focal glandular or central squamous differentiation. ABCs are frequently associated with CIN or small invasive SCCs. Features commonly identified in ACC such as cellular pleomorphism, mitoses, necrosis, stromal hyalinization and metastases, are rare or absent in ABC. Although both tumours exhibit positive reactivity to CEA, EMA, CK7, CK20 and CAM5.2, ACC shows positive reactivity to actin, collagen IV and laminin, while in contrast these stains are negative in ABC. Divergent neoplastic epithelial differentiation has been described in both tumours including keratinizing squamous cell carcinoma, adenosquamous carcinoma and basaloid nonkeratinizing squamous cell carcinoma.

Polymorphous low-grade adenocarcinoma (PLGA) consists of cellular lobules with cribriform, papillary, cystic patterns and “single –Indian file arrays” comprising of cytologically bland cells with low mitotic count. Perineural invasion is usual. In contrast, ACCs lack filing pattern and is mitotically active. Diffuse expression of smooth muscle actin and smooth muscle myosin heavy chain is seen in 20 cases of ACCs versus one out of 24 cases of PLGA, and has a positive predictive value of 95% for ACCs. CD117 (c-kit) is positive in more than 50% of tumour cells (cytoplasm of luminal cells) in ACC vs less than 50% in PLGA, and is not useful in equivocal cases. P63 is positive in both. Distinguishing between these tumours is important for prognosis and management.

Basaloid squamous cell carcinoma is composed of poorly differentiated basaloid type cells with some keratinization in the centre of tumour nests. Basal cell carcinoma is composed of aggregates of uniform basaloid cells with peripheral palisading and arises from the basal layer of the overlying squamous epithelium. Squamous differentiation may occur in the centre of the tumour nests.

DIAGNOSIS: ADENOID CYSTIC CARCINOMA OF VAGINA

Adenoid cystic carcinoma (ACC) is more common in salivary and lacrimal glands. It is a rare but highly specific undifferentiated cervical neoplasm due to its distinct morphology and different biological behaviour. Aetiology of the tumour is unknown. However, Yang and Gordon reported a case of cervical adenoid cystic carcinoma coexisting with a variety of human papilloma virus (HPV) – related lesions including condyloma acuminate, vulvar intraepithelial neoplasm, cervical intraepithelial neoplasm and invasive basaloid squamous cell carcinoma, which raises the speculation that HPV may also be the causative factor for adenoid cystic carcinoma of uterine cervix. Integration of high-risk HPV, in particular HPV 16, has recently been implicated in pathogenesis of both ACC and ABC.

The tumour probably originates from the cervical multi-potent reserve cells. Adenoid cystic carcinoma, adenoid basal carcinoma and basaloid squamous cell carcinoma are part of a morphological and biological spectrum of basaloid cervical neoplasms and a putative reserve cell origin has been suggested. Combined ABC-ACC tumours have been described and that ABC may be a precursor of ACC has been suggested. Given
that the majority of the tumour cells are positive for S-100 and HHF35, a myoepithelial line of differentiation has been suggested, probably an aberrant differentiation of neoplastic epithelial cells towards myoepithelium. In this case, Professor Russell described the tumour as an adenosquamous variant within a cribriform adenocarcinoma arising from, or merging with, extensive VAIN III. Vaginal cytology is abnormal in most cases comprising of small cells arranged in cribriform pattern and dysplastic or malignant squamous cells with presence of hyaline material in the background (suggestive of remnants of lamina densa of basement membrane of malignant cells). Despite the tumour’s architectural similarity to adenoid cystic carcinoma of the salivary gland, the cervico-vaginal adenoid cystic carcinomas show necrosis, a high mitotic rate and greater nuclear pleomorphism than its salivary counterpart. A solid variant has been described. EM studies show multiple cylinders of redundant basal lamina material enveloped by the tumour cells (positive for laminin & collagen IV). Tumour cells shows high N:C ratio, irregular round to oval nuclei, coarse chromatin, several well-formed desmosomes between cells, glycogen in cytoplasm and tonofilaments.

Adenoid cystic carcinoma of the vagina and cervix are associated with poor prognosis due to widespread lymph node and vascular metastases, especially to the lungs, which is the commonest site of metastases.

Treatment of ACC in cervix is a judicious combination of radical pelvic surgery, radiotherapy and chemotherapy (especially those with histological features associated with a higher risk of recurrence), except in patients with stage 1 who should receive aggressive local therapy alone. Our patient underwent a wide local excision of base of the vaginal polyp one month later, which was clear of tumour. PET scan and MRI of pelvis done preoperatively showed no residual tumour or remote metastases. A small vaginal skin tag was excised three months after the initial surgery, which showed scar tissue only. No adjuvant therapy was given. The follow-up of the patient is so far uneventful.

References


Case 3

Presenter: Dr Jane Nankervis
Southern IML Pathology, Wollongong, NSW.

Mixed trophoblastic tumour (Choriocarcinoma and Epithelioid trophoblastic tumour).

CASE HISTORY:
A 41 year old woman, G3P3 presented with heavy irregular painful periods. A Mirena IUD had been inserted six months before, without resolution of symptoms. A second gynaecologist requested an ultrasound before surgery and fibroids were reported. Her last pregnancy was 12 years previous (daughter). The hysterectomy specimen showed a heterogeneous nodule in the lower uterine segment, 55 x 48 x 40 mm, from which the Mirena device protruded. The cut surface appeared haemorrhagic, necrotic and cystic, and invaded the myometrium, clear of the anterior parametrial surface by 5 mm.

The tumour had a variety of microscopic appearances. The central area had necrosis and undifferentiated carcinoma appearance. There was also Choriocarcinoma, of typical morphology. The deepest tumour component (epithelioid trophoblast tumour: ETT) was composed of glands, tubules and cords. Immunoperoxidase stains showed uniform staining for AE1/AE3, CAM5.2, CK7, βHCG and CD10. Calretinin positivity was seen in the ETT component and less strongly in the choriocarcinoma (CC). CEA, CD34, CK20, Vimentin and chromogranin were negative. Human placental lactogen (HPL) stained the syncytiotrophoblast and inhibin-α stained the deep component. Afp showed weak focal staining.

A second opinion was sought from Dr. Catherine Camaris, who also sent the case to Dr. Robert Kurman for confirmation. The opinion was that this was a mixed trophoblastic tumour containing Epithelioid Trophoblastic Tumour and Choriocarcinoma.

The patient had her BHCG measured post-operatively and CT scans of brain, thorax and abdomen, which were clear. The initial BHCG level was 2223 and took 2 months to fall to 4. She had adjuvant chemotherapy and is now 2 years post completion of treatment with no evidence of disease and BHCG at normal levels. MRI scans of brain, abdomen and pelvis are normal.

DISCUSSION:

Gestational trophoblastic disease covers many different trophoblastic tissue proliferations. The WHO classification of 2003 includes the neoplasms choriocarcinoma (CC) epithelioid trophoblastic tumour (ETT) and placental site trophoblastic tumour (PSTT)(1). These neoplasms include tumours of cytotrophoblast, intermediate trophoblast and syncytiotrophoblast. Intermediate trophoblast (IT) is divided into three groups depending on their site in the pregnant uterus; the ETT is said to derive from chorionic-type IT from the chorionic laeve (foetal membrane) on histological appearance, immunohistochemistry and PCR analysis (1)(2). It is possible that CC is related to IT cells in the trophoblastic column ‘villous type IT‘. (19)
These 2 tumours (ETT and CC) are derived from different types of trophoblast and the importance lies in the different response to chemotherapy and malignant potential. ETT is often organ confined and thought unlikely to respond to chemotherapy, however, CC is chemoresponse and more likely to metastasise (15). ETT has such a low incidence that only a small number of cases have been studied. It is likely that ETT has been under-reported due to both misdiagnosis and ignoring ETT-like areas when surrounded by conventional CC. ETT are / were categorised as choriocarcinoma or as squamous cell carcinoma of the cervix or other epithelioid tumours (4)(5)(6)(7). Spread along the surface mucosa of the cervix is possible (5)(6) mimicking SCC, and the morphological appearance means determining ETT in metastatic sites may be very difficult.

ETTs were described in 1989 by Kurman (6) but had been identified earlier by different names (atypical choriocarcinoma, nodules of intermediate trophoblast) (4). They now number over 50 in the literature (3)(4), mostly arising in the uterus or cervix, but occasionally in the lung (10).

Initially it was postulated that ETT was caused by an inadequate response of CC or moles to chemotherapy (15). Just over one third of cases are seen after a mole (4)(6) and there are cases where a mixed pattern CC/ETT is seen (15). However, many cases are seen after a normal pregnancy and some are many years later. The postulated aetiologies include drug effect on tumour cells phenotype (15), or dedifferentiation of CC so that the two trophoblastic components are lost and trophoblastic differentiation is altered (4). Chorionic-type IT may be resistant to chemotherapy (15).

Genetic studies have confirmed paternal genetic Y chromosome material (2)(16)(17) i.e. foetal trophoblastic origin. It has also been postulated that PSN is the precursor to ETT (12) because of shared immunohistochemistry and morphology. Two cases have been reported with features intermediate between PSN and ETT (13).

Many CC are composed predominantly of mononuclear trophoblastic cells (10) and a recent study reported large IT populations in CC (18). There are many descriptions of ETT with foci of CC (10)(5)(3)(6). Multinucleated IT cells may also be seen in ETT haphazardly or in small clusters (round or polygonal cells compared to elongated, admixed multinucleated cells in CC) (10). There is also overlap in some immunohistochemical features (3)(11).

Immunoperoxidase studies confirm some staining for trophoblastic markers HPL, hCG and placental alkaline phosphatase (pLAP) in ETT, but they are often weak. The epithelial markers are positive, and CK18, pankeratin, CD10, CAM5.2, EMA and E-Cadherin have been mentioned in reports (6)(4)(8)(20). CD10 is negative in the mullerian epithelia of the female genital tract but positive in mesonephric tissues, syncytiotrophoblasts, cytotrophoblast, IT, moles and some metastatic tumours (CRC, RCC, melanoma) (6)(20). CK18 is useful when differentiating ETT from cervical SCC, especially when used in conjunction with p16 (21) and inhibin-α (12). Other commonly seen positive histochemical markers are MelCAM, inhibin-a, HLA-G and p63 (6)(8)(14). MelCAM is positive in PSTT (implantation site IT) but only a few cells are positive in ETT. Similarly p63 is said to be positive in chorionic-type IT of ETT but negative in implantation- site IT of PSTT (3)(25). Therefore, these markers may be useful when considering the diagnosis of ETT/PSN vs PSTT/EPS (8)(14). Cyclin E (15) is also useful for separating PSN and ETT. ETT lacks staining for p16 (11), actin and desmin (12) and CK5/6. Cell cycle markers may also be useful. Ki67 will
help differentiate areas of PSN vs ETT vs CC, as there is little overlap in the proliferative index. (8)

In summary, this case illustrates a mixed trophoblastic tumour with both ETT and CC. ETT are rare tumours and little studied. Some mixed cases have been described, although they arise from a different type of trophoblast. It is important to recognise both components, so that appropriate treatment is given. Morphology and immunohistochemistry are both important.

REFERENCES:

Case 4

Presenters: Dr Raghwa Sharma, Dr Hema Mahajan.
ICPMR, Westmead Hospital, Sydney, NSW.

Thymic neuroendocrine carcinoma metastatic to the ovaries.

A 23 year old lady presented with complaints of abdominal pain and per vaginal bleeding. On CT scan, she was found to have right ovarian mass. Past history included a thymic tumor for which she had undergone surgery and received adjuvant chemotherapy and radiotherapy, a few months ago. The right ovary was resected and retroperitoneal lymph node dissection was performed. Gross examination of ovarian mass showed a tumor measuring 14 cm in maximum dimension, with pale homogenous, lobulated appearance.

Histological examination showed ovary replaced by a tumor composed of islands and nests of small to medium-sized cells with scant cytoplasm and hyperchromatic nuclei. Some nuclear moulding was noted. Frequent mitoses were present as well as scattered apoptotic bodies. Pseudorosettes were present in many islands. Focal necrosis and haemorrhage were present. The tumor stroma was dense and fibrotic in some and loose in others. Focal endothelial-lined space invasion was present. There was a thin rim of ovarian cortex around the tumor and no involvement of the ovarian surface was seen.

The immunohistochemical stains showed positive punctuate cytoplasmic staining for pan cytokeratin and CAM 5.2, positive cytoplasmic staining for synaptophysin, chromogranin and neuron specific enolase. CD99 showed faint focal cytoplasmic staining. Desmin, smooth muscle actin, inhibin, S-100, LCA, TTF1, placental alkaline phosphatase, neurofilament and vimentin were negative in tumor cells. The cytogenetics result on tumor cells showed unbalanced translocation t(11;22) (q13;p13) in all analysed cells, compatible with rearrangements involving 11q13, which have been reported in neuroendocrine carcinomas.

Based on histological and immunohistochemical features and previous history of thymic neuroendocrine carcinoma, a diagnosis of metastatic thymic small cell neuroendocrine carcinoma was made. A few months later, the patient died after metastases to left ovary, peritoneal cavity and cervical vertebrae.

Thymic location is one of the rarest sites for neuroendocrine carcinomas to occur. They account for 2-4% of all mediastinal tumors. Earlier pathology literature referred many of these tumors as thymic carcinoid tumors. However, unlike carcinoid tumors in other organs such as the lung, these tumors were clinically malignant in the majority of cases. Thus, the present WHO classify these tumors as part of the spectrum of the neuroendocrine carcinomas. The high grade tumors show areas indistinguishable from small cell carcinoma.

Neuroendocrine tumors of thymus were first described by Rosai and Higa (prior to that they were grouped with other epithelial neoplasms) who proposed a three tier classification for these tumors into low grade, intermediate and high grade neuroendocrine carcinoma 25 years ago. This is roughly equivalent to the typical carcinoid, atypical carcinoid and large cell neuroendocrine carcinoma and small-cell neuroendocrine carcinoma of the World Health Organization (WHO) classification.

There appears to be a different cytogenetic oncogenesis between the thymic and foregut neuroendocrine tumors as exemplified by their differing pathologic and clinical presentation. A few thymic neuroendocrine tumors have occurred in
association with multiple endocrine neoplasia type 1 syndrome (MEN1). Pan et al looked at the cytogenetic and molecular events underlying the development of thymic neuroendocrine tumor with comparative genomic hybridization (CGH) analysis. They found gross chromosomal abnormalities chiefly involving chromosome 6, 8, 13, 18 and X in thymic neuroendocrine tumors, which are not usually seen in foregut neuroendocrine tumors.

These tumors may present with symptoms of thoracic structure displacement or compression. About a third are incidentally discovered. Occasionally, thymic neuroendocrine tumors secrete adrenocorticotropic hormone leading to Cushing’s syndrome. Gal et al found that p53, MIB-1 (cellular proliferation), and Bcl-2, Bcl-x (antiapoptosis markers) and Bax (proapoptosis marker) correlate with survival in thymic neuroendocrine tumors.

The major problem in the differential diagnosis of metastatic small cell carcinomas is their distinction from primary ovarian small cell carcinomas of pulmonary type. In this case, presence of extragenital tumor compatible with a primary tumor favored metastasis to the ovary. Primary ovarian small cell carcinomas of pulmonary type are more likely to show cytoplasmic and membranous cytokeratin positivity and rarely are chromogranin positive. Primary ovarian small cell carcinomas of hypercalcemic type resemble only superficially to the metastatic small cell carcinomas. The cells in the former have abundant eosinophilic cytoplasm and occasional hyaline globules; they contain mucinous cells in 10% of the cases and follicle-like structures lined by tumor cells are seen in the majority of the cases of the primary ovarian small cell carcinomas of hypercalcemic type. They also demonstrate vimentin positivity in about half the cases, in contrast, vimentin is rarely, if ever, positive in small cell carcinomas of metastatic or pulmonary type. Other tumor to be considered in differential is intra-abdominal desmoplastic small round blue cell tumor which shows prominent desmoplasia and typically shows positive immunohistochemical staining for cytokeratin and vimentin and paranuclear globular staining for desmin. On cytogenetic analysis, desmoplastic small round blue cell tumors almost always have translocation t(11;22)(p13;q12) whereas neuroendocrine carcinomas show rearrangements of 11q13. Lymphomas and high grade undifferentiated sex cord stromal tumors can be differentiated from small cell carcinomas on the basis of immunohistochemical staining for LCA and inhibin respectively.

Thymic small cell neuroendocrine tumors behave more aggressively than the conventional nonthymic neuroendocrine tumors. It is reported that around half of the cases invaded the surrounding mediastinal structures, and 30–40% metastasized. However, there is conflicting data as to whether the degree of tumor differentiation correlates with survival. Fukai et al did not find an association between histological grade and outcome in a group of 15 patients. In a larger study, Moran and colleagues showed an inverse correlation between survival and tumor differentiation in thymic neuroendocrine tumors. Wick et al found that thymic neuroendocrine tumors associated with endocrinopathy proved fatal in 65% of cases, whereas those unaccompanied by an endocrinopathy had 30% mortality. Nonetheless, it is important to diagnose and treat these tumors aggressively because of the high incidence of local recurrence of metastatic disease.

References


Case 5

Presenter: Dr Lyndal Anderson
ICPMR, Westmead Hospital, Sydney, NSW.

Psuedoactinomycotic radiate granules.

Psuedoactinomycotic radiate granules (PAMRAGs) should be recognized in the gynaecological tract where they are a harmless mimic for actinomyces infection.1 Actinomyces israelii is a Gram positive anaerobic filamentous bacterium frequently found in the oral cavity and often found in gynaecological specimens where it is associated with prolonged intrauterine contraceptive device (IUD) usage.2,3 Complications of pelvic actinomycosis include endometritis, salpingo-oophoritis and tubo-ovarian abscess2 which may masquerade as malignancy.3 Actinomycosis is treatable with penicillin but is often not diagnosed until after surgery.3 It is imperative to distinguish PAMRAGs from infection and avoid unnecessary treatment.

Epidemiology:

PAMRAGs are typically incidental findings in uterine curettings from patients using an IUD.4 Rarely they are found without a history of IUD usage.5 They are occasionally seen in material from the cervix, and vulva.6 They were recognized in uterine curettings by O’Brien et al in 1981 who examined 235 curetting specimens taken at the time of IUD removal and found PAMRAGs in 16 patients and actinomyces in 1 patient,7 suggesting they are more frequent finding in the gynaecological tract than true actinomycosis. PAMRAGs have also been reported in association with true actinomyces infection; radiating around a bacterial nidus.6

Composition:

O’Brien et al speculated that the granules were synthetic fragments from an IUD.7 Since then, they have been found to contain variable amounts of neutral glycoproteins, lipid, calcium, copper, phosphorus, iron, chloride and sulphur.5,6 They are now thought to be a form of Splendore–Hoeppli phenomenon5, after original descriptions by the authors in 1908 and 1932 respectively, typically as a host mediated immune response forming around a central nidus.4 The nidus may consist of inspissated mucus from endocervical glands and nabothian cysts4, fungi, bacteria, nematodes, inert materials8 or leukocyte products.6

Histological appearance:

PAMRAGs consist of radiating thick irregular eosinophilic club-like projections.6 They are refractile but not birefringent and often exhibit ‘tide-water’ marks.1 They are rounded or seen in strips and, in contrast to accumulations of actinomyces (or sulfur granules) or actinomyces-like organisms such as nocardia, they lack radiating filaments and are negative on silver and acid-fast bacilli stains.4 They exhibit intense
non-specific Gram staining\(^1\) and may be associated with a surrounding neutrophilic inflammatory response.\(^4\)

**Conclusion:**

PAMRAGs are a form of Splendore-Hoepli phenomenon around a central nidus. They can be seen in gynaecological tract specimens associated with IUD usage where they may mimic actinomyces infection; from which they should be distinguished.

**References:**