Primary gynaecological tumours mistaken for metastases: report of two cases with review of literature

P.A. Menon[1], G. Kousparos[2], G.A. Culora[1]

[1]Department of Cellular Pathology, Guy's & St. Thomas' NHS Foundation Trust
[2]Department of Cellular Pathology, St. George's Hospital, Blackshaw Road, London (UK)

Summary

We describe two neoplasms of rare occurrence, one of ovarian and the other of uterine origin that were sent for consultation. Both lesions were diagnosed as metastatic carcinomas by pathologists with special interest in gynaecological pathology. The cases were referred for a second opinion because of subsequent failure to identify the primary source. We discuss the differential diagnoses, the need for generous sampling particularly in ovarian mucinous neoplasms and the value of including particular antibodies in the panel to aid the diagnostic process. Metastatic tumours mimicking primary tumours are always challenging. These two cases illustrate the need to be vigilant against the reverse scenario as well.

Key words: Ovary; Mucinous neoplasms; Uterus; Neoplasms; Sex cord-like differentiation.

Introduction

The distinction between primary and metastatic carcinomas is not always straightforward even with the application of an exhaustive panel of immunohistochemical markers. The existence of metastatic tumours that mimic native tumours and vice versa, adds to the diagnostic challenge. This is an all too familiar dilemma for a gynaecological pathologist who is confronted with an ovarian mucinous tumour. We describe two cases to highlight this issue in a gynaecological pathology setting. Both cases were sent for consultation on account of a previous diagnosis of metastatic carcinoma and subsequent failure to identify the primary tumour.

Case Reports

Case 1

A 39-year-old woman with no significant past or current medical history presented with menorrhagia and abdominal swelling. She was found to have multiple uterine fibroids on ultrasound scan. Abdominal myomectomy was performed and three fibroids were removed.

Pathological findings revealed the specimen consisted of three firm circumscribed nodules with diameter ranging from 17 mm to 70 mm. The cut surface all three lesions showed a pale tan whorled appearance characteristic of leiomyomas.

The two larger nodules were composed of fascicles of benign smooth muscle, in keeping with leiomyomas. The smallest of the nodules was described by the referring pathologist as having 'nests of epithelial cells in a cellular stroma' (Figure 1) with 'positive expression for cytokeratin, oestrogen and progesterone receptors' (Figure 2). A metastatic carcinoma with a possible primary origin from the breast was indicated based on the morphology and immunoprofile.

Revised manuscript accepted for publication June 8, 2011

Case 2

A 52-year-old woman presented with a 30-week in size abdominal mass. Ultrasound (US) and computed tomography (CT) scan revealed a right ovarian mass with likely mucinous contents. A total abdominal hysterectomy with bilateral salpingo-oophorectomy, pelvic lymphadenectomy and omentectomy was performed. At laparotomy, a smooth surfaced, intact, mobile right ovarian cystic mass was noted. A normal appendix was also visualised.

Pathological findings showed the right ovary contained a 210 mm intact cystic mass with mucinous contents. The cyst was described as multiloculated with a single focus of solid whitish nodule (25 mm). The left adnexae, omentum and uterus were unremarkable except for the presence of a soft polyp in the endometrial cavity.

The cystic mass was described as containing 'mucinous columnar epithelium with atypia and an infiltrative growth pattern'. The 'glands were positive for CK20, CDX2 and CEA and negative for CK7': the left ovary was normal as were the uterus and cervix. Based on these observations, a diagnosis of metastatic mucinous adenocarcinoma was made. The large intestine including the appendix was cited as a possible site of the primary lesion.

Case Review

Case 1: The smallest nodule had a well circumscribed margin and contained a mixture of smooth muscle cells and epithelioid cell nests with the latter being the predominant component. Further immunohistochemistry revealed positive expression for calretinin, inhibin (Figures 3, 4, 5) CD10, CD99, melan A and CD56 in the epithelioid nests. H-caldesmon staining showed diffuse strong expression in the entrapped smooth muscle elements and patchy positivity in the epithelioid cells. The epithelioid elements were negative for CK7, CK20, CEA and S100 protein. A diagnosis of uterine tumour resembling ovarian sex cord tumour (UTROSCT) was made.

The patient is well with no evidence of recurrence 24 months following the procedure.

Case 2: The sections revealed a mucinous neoplasm of

Fig. 1

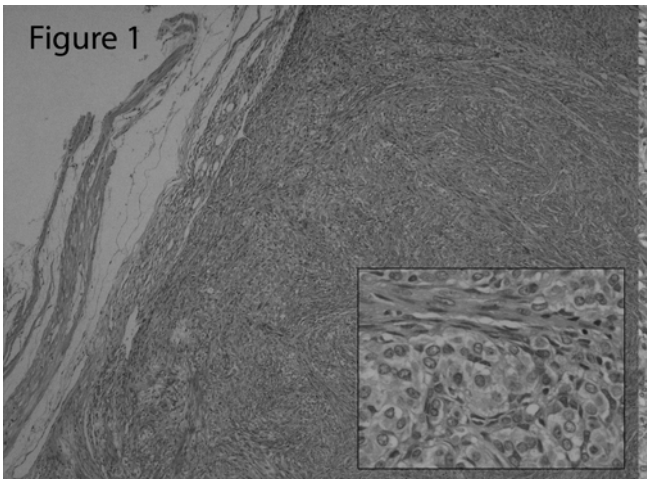


Fig. 2

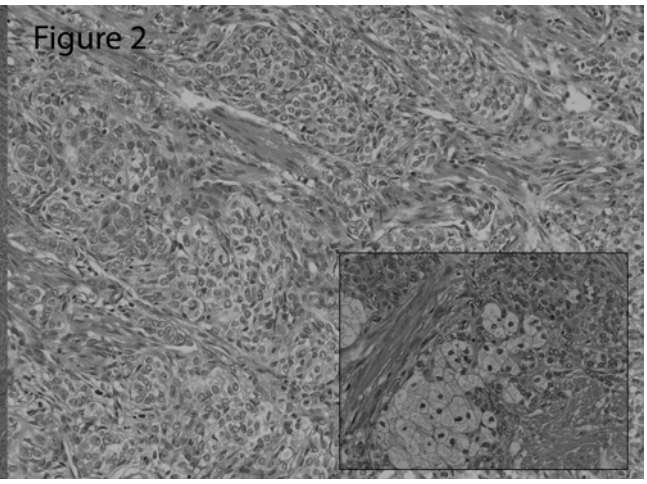


Figure 1. — Lesion with a well circumscribed margin; inset – 'epithelioid' cells (case 1).
Figure 2. — Nests of epithelioid cells separated by entrapped bundles of smooth muscle Inset – groups of cells with foamy cytoplasm – a feature of sex cord differentiation (case 1).

enteric type with epithelial stratification and moderate to severe cytological atypia. Also noted, were the prominent presence of mucin pools dissecting the tumour stroma (pseudomyxoma ovarii) (Figure 5). The epithelial atypia amounted to intraepithelial carcinoma and there were focal areas with stromal infiltration in keeping with the original diagnosis of mucinous carcinoma. The tumour was diffusely positive for CK20, CEA and CDX-2 and negative for CK7 (Figures 6a, 6b). An additional observation in two of the 20 tumour sections included presence of keratin and hair shafts and parts of a cyst wall lined by squamous epithelium, indicating a co-existing teratoma. A florid lipogranulomatous reaction was also noted adjacent to the teratomatous elements (Figure 7). In the absence of a demonstrable extra ovarian pathology, a diagnosis of primary ovarian mucinous adenocarcinoma (enteric type) arising in a teratoma was made. Postoperative CT scan of the pelvis and abdomen was normal. The patient is well and free of symptoms 12 months following laparotomy.

Discussion

Case 1: Uterine tumours resembling ovarian sex cord tumours (UTROSCTs) were originally described by Clement and Scully more than 30 years ago [1]. However they still offer a particular challenge owing to the relative rarity, a complex and varied immunophenotype [2, 3], and appearances that show a considerable degree of overlap with endometrial stromal tumours (EST) [4]. They occasionally get thrown into the path of an unsuspecting histopathologist as an incidental finding in a fibroid uterus, as happened in our case.

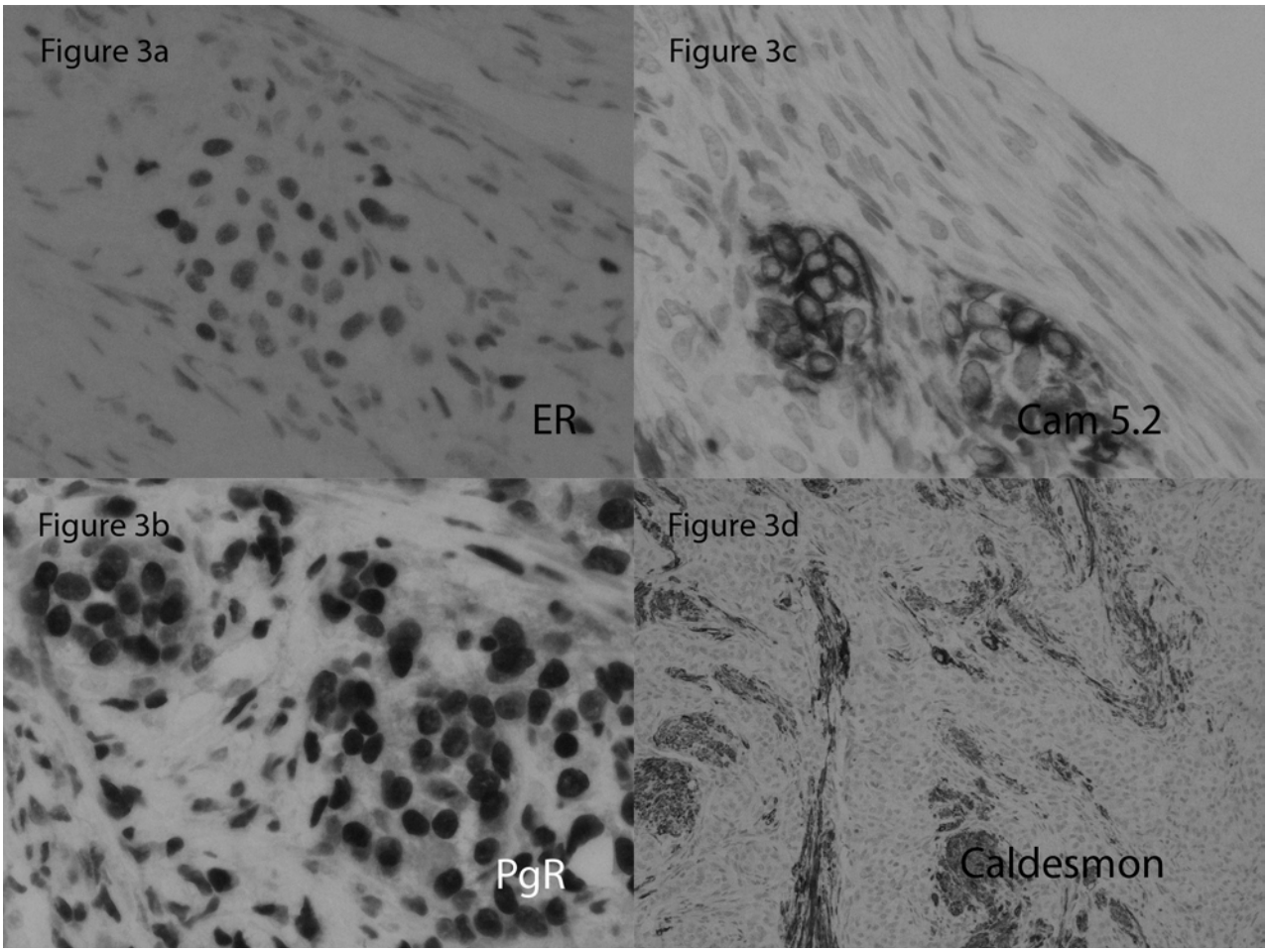
UTROSCTs were originally described as tumours with prominent sex cord-like differentiation in which there is no conspicuous endometrial stromal background [1]. In the recent version of the World Health Organisation classification of tumours, this is recognised as an entity separate from EST [5].

UTROSCT typically appears as a circumscribed myometrial or submucosal mass. The tumour cells are epithelioid in appearance and are often arranged in cords, trabeculae and nests, occasionally with interspersed cells with pale foamy cytoplasm. They sometimes form well-formed tubules with lumens [1, 4, 5]. These features in light of a positive cytokeratin stain can be mistaken for a metastatic or even a primary carcinoma [6]. The other differential diagnoses include epithelioid smooth muscle tumours, endometrial stromal tumours with sex cord differentiation and rarely sertoliform endometrioid carcinoma. The unique combination of positive expression with cytokeratin and sex cord markers such as calretinin and alpha inhibin helps to eliminate carcinoma from the list of differential diagnoses [7]. UTROSCTs are also known to show variable positive expression with CD56, EMA (epithelial membrane antigen), and oestrogen and progesterone receptors [2].

Various studies have focussed on the diverse immunohistochemical profiles of UTROSCTs [2, 3, 8-10]. There is evidence pointing to divergent differentiation as shown by co-expression of epithelial, myoid and sex cord markers [2, 3, 9, 10]. Based on emerging new evidence, a panel of four markers including calretinin, alpha inhibin, CD99 and melan A has been identified [4, 8]. These antibodies have been shown to be consistent with their expression indicating sex cord differentiation in UTROSCTs, a pattern different to ESTs that tend to show positive expression with mostly calretinin and CD10. Positivity with calretinin and at least one additional marker from the panel is considered diagnostic of UTROSCTs [8].

There is uncertainty regarding the histogenesis of UTROSCTs. Although the diverse immunophenotype points towards an origin from pluripotential mesenchymal cells [2, 8], more supportive molecular evidence is yet to emerge [10].

UTROSCTs are believed to have a largely benign course, but occasional cases of recurrences and metas-



Figures 3a, 3b, 3c, 3d. — Epithelioid cells with positive expression for CAM 5.2, ER and PgR and mostly negative expression with caldesmon (case 1).

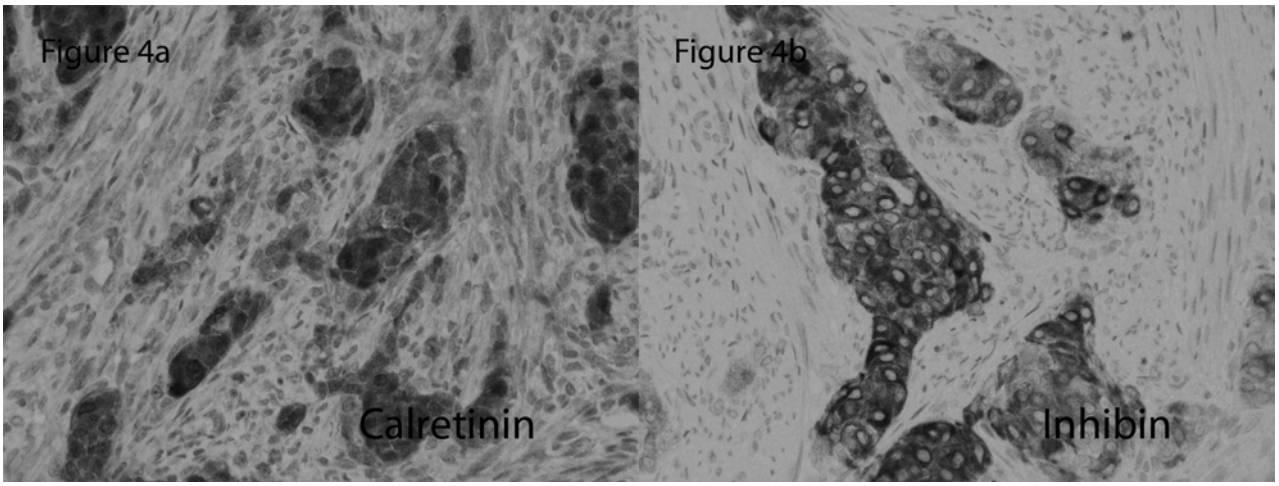
tases have been reported [8, 11]. In the absence of clear evidence from long-term follow-up studies, the current view is to consider these as tumours to be of uncertain, but low malignant potential [2, 8].

Case 2: Distinction between primary ovarian mucinous epithelial neoplasms and metastatic involvement of ovaries by primary gastrointestinal tumours is a well recognised problem. In response to this awareness, several studies have been published focussing on the differences in morphological patterns and immunohistochemical profiles between the two [12-14]. As a result there has been greater clarity on the subject and pathologists have a better understanding than ever of the histological differences and the role that immunohistochemistry can play in resolving this issue.

It is well established now that CK7 and CK20 expression profiles are helpful in differentiating primary ovarian mucinous tumours from tumour metastases from the lower gastrointestinal tract including the appendix [15, 16]. Although primary ovarian tumours are known to show expression with CK7 and CK20, the staining is more diffuse with the former and patchy with variable intensity with the latter. Metastatic tumours from the large intestine and appendix including ovarian involvement by low-grade appendiceal mucinous tumours show a diffuse expression with CK20 and negative to focal faint positivity with CK7. CK7/CK20 profiles are of limited value in differentiating primary mucinous tumours from metastases from the stomach (intestinal type adenocarcinomas), pancreas, gall bladder and breast.

There is also ample published evidence to support an appendiceal origin of ovarian mucinous tumours associated with pseudomyxoma peritonei (PMP) [17, 18].

This greater awareness about metastatic mimics in the ovary is reflected in the dramatic drop in the incidence of primary ovarian mucinous carcinomas over the years [19, 20]. In a study looking at the relative incidences of various types of ovarian carcinomas, Seidman et al noted that primary ovarian mucinous carcinomas constituted < 3% of all carcinomas [19]. Previous studies had quoted an incidence ranging from 6% to 25% with a mean of 12%. Another study looking at a series of 52 consecutive ovar-



Figures 4a, 4b. — UTROSCT with positive expression for calretinin and inhibin (case 1).

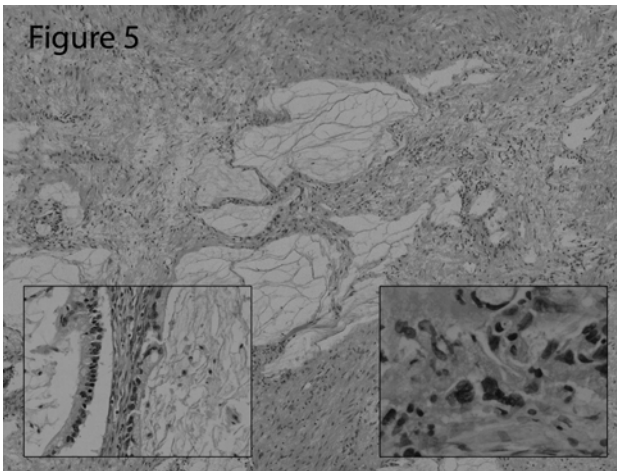


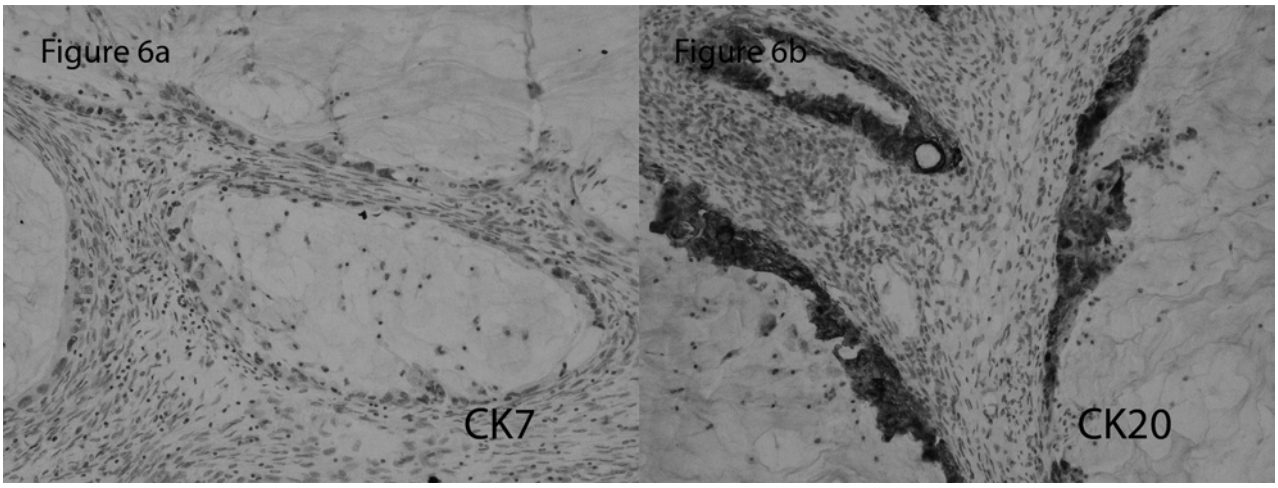
Figure 5. — Mucinous tumour with prominent pseudomyxoma ovarii; inset – benign, borderline and malignant enteric epithelium (case 2).

ian mucinous carcinomas identified 40 (77%) of them to be metastatic. Gastrointestinal tract (45%) was the single most common site of primary origin in this series [21].

Thus in light of all the statistical evidence, an ovarian mucinous tumour with CK20+/CK7-ve profile is most likely to be a metastasis from a primary tumour in the appendix or large intestine. It is essential to indicate this in a report so that all appropriate measures can be taken to track down the extra-ovarian source. In this context, we would like to highlight the occurrence of a rare converse scenario that is also worth consideration. As illustrated by this case and several other publications including studies on two major series [22-28], primary ovarian mucinous carcinomas with lower gastrointestinal phenotype and immunoprofile (CK20+, CK7-ve) are known to exist. These tumours of teratomatous origin are much rarer than their surface epithelial counterparts and metastatic tumours [22]. These are also known to be heterogeneous depending on the chosen line of germ cell differentiation. Teratomatous mucinous tumours showing sinonasal or upper gastrointestinal line of differentiation share many features that overlap with primary mucinous surface epithelial tumours including a CK7+/CK20-ve profile. Whereas mucinous tumours derived from lower intestinal germ cell lines display histological features and immunoprofiles that are indistinguishable from metastatic colorectal and appendiceal mucinous neoplasms [22-24]. It is also evident that this subset of ovarian mucinous neoplasms is more frequently associated with the clinical syndrome of PMP, another feature that is shared by appendiceal mucinous tumours but not tumours of surface epithelial origin [22-28].

There have been studies on two major series (44 and 42 patients) [22, 23] and one short series of three cases (24) of ovarian teratomatous mucinous tumours focussing on the histomorphological features, immunohistochemical spectrum and clinical association with PMP. Emerging evidence has indicated that these neoplasms are morphologically and immunohistochemically diverse with benign (cystadenomatous), borderline (low malignant potential) and malignant (intraepithelial and invasive) histology and varied patterns of CK7 and CK20 expression. In both series, cystadenomas and proliferative (borderline) mucinous tumours comprised the majority with invasive carcinomas forming 12%-14% [22, 23]. It has also been observed that compared with adenomas a greater proportion of borderline tumours (with or without intraepithelial carcinomas) and invasive carcinomas express an enteric immunoprofile (CK20+, CK7-ve). Pseudomyxoma ovarii (dissecting pools of extracellular mucin within the stroma) is also described as a recurring feature in these neoplasms. This has been observed with greater frequency in borderline tumours and invasive carcinomas, and an association with a CK20+, CK7-ve profile is also described. The aforementioned studies failed to establish any predictive link between pseudomyxoma ovarii and PMP [22, 23].

As pointed out by Vang *et al*., the germ cell components in these mucinous tumours tend to get overgrown by mucinous areas resulting in a need for careful sampling to



Figures 6a, 6b. — Mucinous tumour with negative CK7 and positive CK20 expression (case 2).

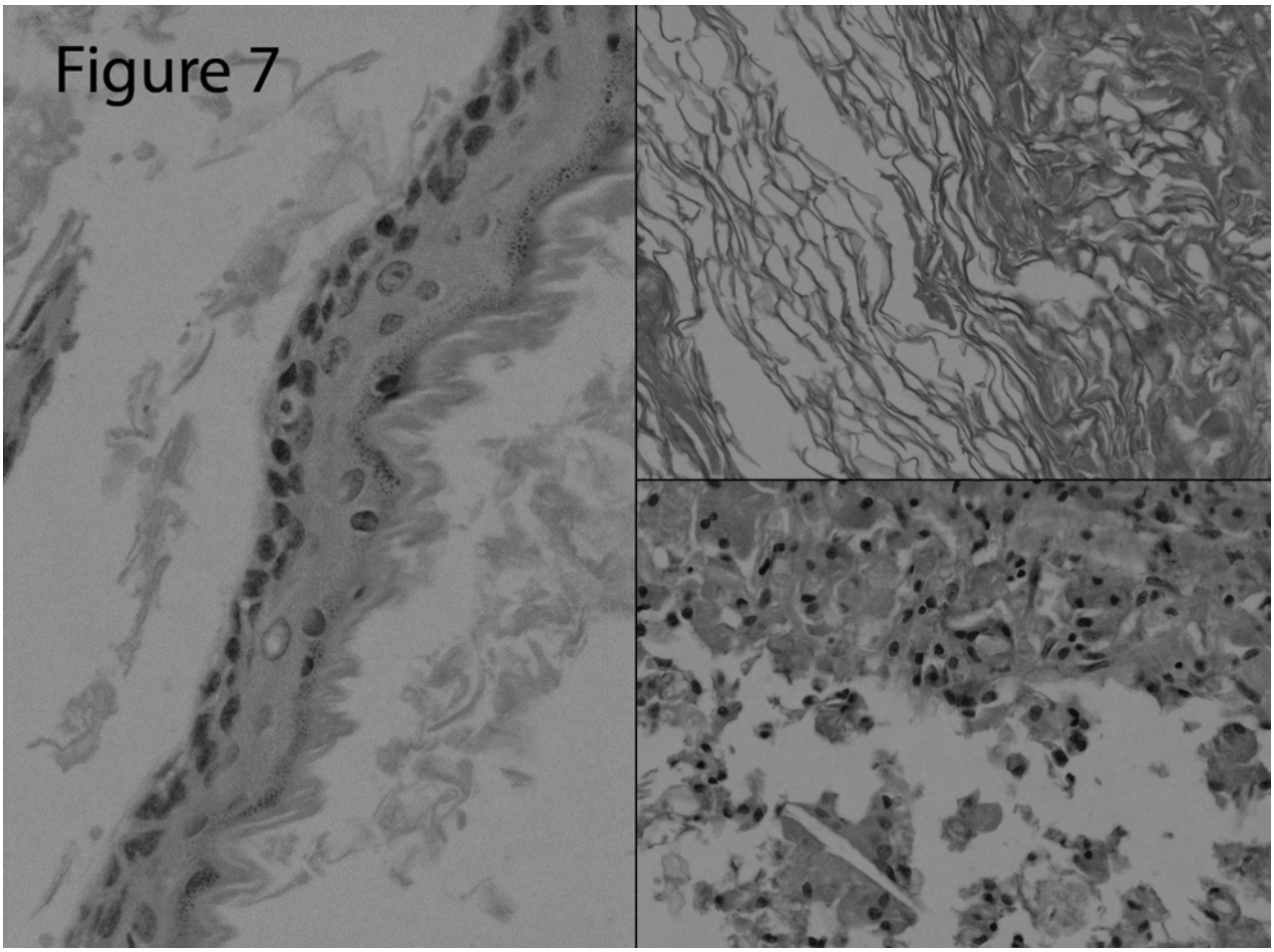


Figure 7. — Evidence of teratomatous origin – keratin, lipogranulomas and squamous epithelium lined cyst (case 2).

demonstrate the teratomatous origin [22]. Cases have been described in the literature where evidence of teratomatous origin was limited to finding keratin flakes and fragments of squamous epithelium-lined cysts in one or two sections [23], an observation identical to our case.

In a young woman with unilateral ovarian mucinous tumour with prominent pseudomyxoma ovarii and a lower gastrointestinal type immunoprofile (CK7-, CK20+ve), the pragmatic approach should include a detailed examination of sections and generous sampling of the tumour with the aim of identifing a possible teratomatous origin. The positive identification of teratoma-

tous elements in the absence of clinical or pathological evidence of a nonovarian (appendiceal) primary tumour is sufficient to confirm the primary nature of this neoplasm. Although it is theoretically possible to have a collision tumour comprising a teratoma and a metastatic adenocarcinoma, the evidence from previous studies does not support this. The majority of the cases from the previously quoted series were accompanied by histologically confirmed normal appendices [22-24].

A teratoma may not be uncovered in spite of extensive sampling in a scenario when the tumour has arisen in a monodermal teratoma that has been completely replaced and overgrown by it [22]. In such an event, if an extra ovarian primary is absent, it is worth stating in the report that a primary tumour is still a possibility [23, 24].

In view of the more common occurrence, every effort should be made to exclude a possible metastasis from the lower gastrointestinal tract including appendix. This should ideally involve a detailed clinical and intraoperative evaluation, an appendicectomy and thorough histological sampling of the specimen [22]. However due consideration should be given to the alternate possibility of a primary ovarian origin in a teratoma. This will reduce the element of uncertainty and distress for the patient. From the surgeon's perspective, this provides the much needed assurance for not pursuing further investigative procedures such as a surgical re-exploration at significant expense, which some of the patients in the previous studies [23] had to endure.

Invasive mucinous adenocarcinomas arising in teratomas have the potential to metastasise and hence need consideration for adjuvant chemotherapy and close clinical follow-up [22, 23]. A close watch is equally warranted for borderline mucinous neoplasms of teratomatous origin because of their increased predisposition to PMP [24-28].

Conclusion

In summary, we have described two distinctive cases with rare histological diagnoses in a gynaecological pathology setting. Both cases were mistakenly diagnosed as metastatic carcinomas for various reasons. In recent years, much attention has been given to metastatic tumours mimicking primary tumours. These two cases illustrate that pathologists should equally well guard themselves against the reverse scenario.

Acknowledgements

We would like to thank Miss Shanti Raju (Guy's & St. Thomas' Hospital (GSTT), London) and Mr. Frank Lawton (Kings College Hospital & GSTT, London) for referring the cases and providing clinical follow-up.

References

[1] Clement P.B., Scully R.E.: "Uterine tumors resembling ovarian sex-cord tumors. A clinicopathologic analysis of fourteen cases". *Am. J. Clin. Pathol*., 1976, *66*, 512.

[2] Hurrell D.P., McCluggage W.G.: "Uterine tumour resembling ovarian sex cord tumour is an immunohistochemically polyphenotypic neoplasm which exhibits coexpression of epithelial, myoid and sex cord markers". *J. Clin. Pathol.,* 2007, *60*, 1148.

[3] Irving J.A., Carinelli S., Prat J.: "Uterine tumours resembling ovarian sex cord tumours are polyphenotypic neoplasms with true sex cord differentiation". *Mod. Pathol.,* 2006, *19*, 17.

[4] Baker P., Oliva E.: "Endometrial stromal tumours of the uterus: a practical approach using conventional morphology and ancillary techniques". *J. Clin. Pathol*., 2007, 60, 235.

[5] Nogales F., Tavassoli F.A.: "Sex cord like tumours". In: Tavassoli F.A., Devilee P. (eds.). World Health Organization classification of tumours. Pathology and genetics. Tumours of the breast and female genital organs. Lyon, IARC Press, 2003, 255.

[6] Kabbani W., Deavers M.T., Malpica A., Burke T.W., Liu J., Ordoñez N.G. *et al*.: "Uterine tumor resembling ovarian sex-cord tumor: report of a case mimicking cervical adenocarcinoma". *Int. J. Gynecol. Pathol*., 2003, *22,* 297.

[7] McCluggage W.G.: "Value of inhibin staining in gynaecological pathology". *Int. J. Gynecol. Pathol.,* 2001, *20,* 79.

[8] Czernobilsky B.: "Uterine tumors resembling ovarian sex cord tumors: an update". *Int. J. Gynecol. Pathol.,* 2008, *27,* 229.

[9] Zámecník M., Staník M.: "Uterine tumor resembling ovarian sex cord tumor (UTROSCT). Report of case suggesting neoplastic origin of intratumoral myoid cells". *Cesk. Patol*., 2006, *42,* 145.

[10] Gupta M., de Leval L., Selig M., Oliva E., Nielsen G.P.: "Uterine tumors resembling ovarian sex cord tumors: an ultrastructural analysis of 13 cases". *Ultrastruct. Pathol*., 2010, *34,* 16.

[11] Biermann K., Heukamp L.C., Büttner R., Zhou H.: "Uterine tumor resembling an ovarian sex cord tumor associated with metastasis". *Int. J. Gynecol. Pathol*., 2008, *27*, 58.

[12] Lee K.R., Young R.H.: "The distinction between primary and metastatic mucinous carcinomas of the ovary: gross and histologic findings in 50 cases". *Am. J. Surg. Pathol.,* 2003, *27*, 281.

[13] McCluggage W.G., Wilkinson N.: "Metastatic neoplasms involving the ovary: a review with an emphasis on morphological and immunohistochemical features". *Histopathology,* 2005, *47,* 231.

[14] Dionigi A., Facco C., Tibiletti M.G., Bernasconi B., Riva C., Capella C.: "Ovarian metastases from colorectal carcinoma. Clinicopathologic profile, immunophenotype, and karyotype analysis". *Am. J. Clin. Pathol.,* 2000, *114*, 111.

[15] Chu P., Wu E., Weiss L.M.: "Cytokeratin 7 and cytokeratin 20 expression in epithelial neoplasms: a survey of 435 cases". *Mod. Pathol*., 2000, *13,* 962.

[16] McCluggage W.G., Young R.H.: "Immunohistochemistry as a diagnostic aid in the evaluation of ovarian tumors". *Semin. Diagn. Pathol*., 2005, *22,* 3.

[17] Ronnett B.M., Zahn C.M., Kurman R.J., Kass M.E., Sugarbaker P.H., Shmookler B.M.*:* "Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis: a clinicopathologic analysis of 109 cases with emphasis on distinguishing pathological features, site of origin, prognosis and relationship to 'pseudomyxoma peritonei'". *Am. J. Surg. Pathol.,* 1995, *19,* 1390.

[18] Ronnett B.M., Shmookler B.M., Diener-West M., Sugarbaker P.H., Kurman R.J.*:* "Immunohistochemical evidence supporting the appendiceal origin of pseudomyxoma peritonei in women". *Int. J. Gynecol. Pathol*., 1997, *16,* 1.

[19] Seidman J.D., Horkayne-Szakaly I., Haiba M., Boice C.R., Kurman R.J., Ronnett B.M.: "The histologic type and stage distribution of ovarian carcinomas of surface epithelial origin". *Int. J. Gynecol. Pathol.,* 2004, *23,* 41.

[20] McCluggage W.G.: "My approach to and thoughts on the typing of ovarian carcinomas". *J. Clin. Pathol.,* 2008, *61,* 152.

[21] Seidman J.D., Kurman R.J., Ronnett B.M.: "Primary and metastatic mucinous adenocarcinomas in the ovaries: incidence in routine practice with a new approach to improve intraoperative diagnosis". *Am. J. Surg. Pathol.,* 2003, *27,* 985.

[22] Vang R., Gown A.M., Zhao C., Barry T.S., Isacson C., Richardson M.S., Ronnett B.M.: "Ovarian mucinous tumors associated with mature cystic teratomas: morphologic and immunohistochemical analysis identifies a subset of potential teratomatous origin that shares features of lower gastrointestinal tract mucinous tumors more commonly encountered as secondary tumors in the ovary". *Am. J. Surg. Pathol.,* 2007, *31,* 854.

[23] McKenney J.K., Soslow R.A., Longacre T.A.: "Ovarian mature teratomas with mucinous epithelial neoplasms: morphologic heterogeneity and association with pseudomyxoma peritonei". *Am. J. Surg. Pathol.,* 2008*, 32,* 645.
[24] Ronnett B.M., Seidman J.D.: "Mucinous tumors arising in ovarian mature cystic teratomas: relationship to the clinical syndrome of pseudomyxoma peritonei". *Am. J. Surg. Pathol.,* 2003, *27,* 650.
[25] Marquette S., Amant F., Vergote I., Moerman P.: "Pseudomyxoma peritonei associated with a mucinous ovarian tumor arising from a mature cystic teratoma. A case report". *Int. J. Gynecol. Pathol.,* 2006, *25,* 340.
[26] Mandal S., Kawatra V., Khurana N.: "Mucinous cystadenocarcinoma arising in mature cystic teratoma ovary and associated pseudomyxoma peritonei: report of a case". *Arch. Gynecol. Obstet.,* 2008, *278,* 265.
[27] Hwang J.H., So K.A., Modi G., Lee J.K., Lee N.W., Lee K.W., Kim I.: "Borderline-like mucinous tumor arising in mature cystic teratoma of the ovary associated with pseudomyxoma peritonei". *Int. J. Gynecol. Pathol.*, 2009, *28*, 376.
[28] Pranesh N., Menasce L.P., Wilson M.S., O'Dwyer S.T.: "Pseudomyxoma peritonei: unusual origin from an ovarian mature cystic teratoma". *J. Clin. Pathol.,* 2005, *58,* 1115.

Address reprint requests to:
P.A. MENON, M.D.
Department of Cellular Pathology
Guy's & St. Thomas' NHS Foundation Trust
Westminster Bridge Road
SE1 7EH, London, UK
e-mail:Padma.Menon@gstt.nhs.uk