

Correspondence

Clear cell adenocarcinoma of the colon arising in endometriosis: a rare variant of primary colonic adenocarcinoma

Colonic adenocarcinomas composed predominantly or exclusively of cells with clear cytoplasm are extremely rare.^{1,2} Considerable diagnostic difficulties can arise in distinguishing primary colonic clear cell adenocarcinoma and metastatic carcinoma from sites such as ovary or kidney. Here, we describe a case of primary colonic clear cell adenocarcinoma that probably arose in endometriosis. The possible presence of endometriosis was only appreciated on review and after the examination of multiple levels and extra histological sections.

A 65 year old woman presented with crampy lower abdominal pain and the passage of blood and mucus from the rectum. Barium enema showed an apparently malignant stricture of the rectosigmoid and she underwent an anterior resection. Preoperative serum CA125 was not measured. At surgery, the clinical impression was of a primary colorectal tumour. Small haemorrhagic nodules were present on the pelvic and abdominal peritoneum, suggestive of endometriosis. There were multiple metastatic lesions within the liver. Both ovaries and kidneys appeared normal.

The surgical specimen consisted of a 30 cm length of colon. A polypoid ulcerated tumour involved the mucosa and infiltrated through the full thickness of the colonic wall.

Histology of the tumour showed an ulcerated surface. The tumour was composed entirely of cells with abundant clear cytoplasm and prominent cell membranes (fig 1A). Several growth patterns were present. Much of the tumour had a pronounced papillary pattern, with hyalinised cores covered by tumour cells (fig 1A). Tubular and solid areas were also identified. There was moderate nuclear pleomorphism and low mitotic activity, with a formal mitotic count revealing 1-2 mitoses/10 high power fields. Areas of necrosis were present and there was extensive lymphovascular permeation, both within the tumour and within submucosal and serosal lymphatics away from the tumour. Calcified psammoma bodies and intracytoplasmic periodic acid Schiff (PAS) positive eosinophilic hyaline inclusions were also present. The adjacent colonic mucosa showed no dysplastic features. The tumour infiltrated through the full thickness of the colonic wall into the surrounding fat.

Situated within the fat, on the external surface of the tumour, a cystic structure was present. This had an epithelial lining, which focally consisted of a single layer of plump cells with abundant eosinophilic cytoplasm (fig 1B). These cells merged with a single layer of cells with abundant clear cytoplasm, similar to those seen within the main tumour. Surrounding the cyst a fibrous stroma was present but no definite endometrial type stroma was identified. Histology of a liver biopsy taken at the time of laparotomy showed metastatic clear cell carcinoma.

Immunohistochemical staining showed diffuse strong positive membrane staining of tumour cells with CA125 (fig 2A) (CIS Bio

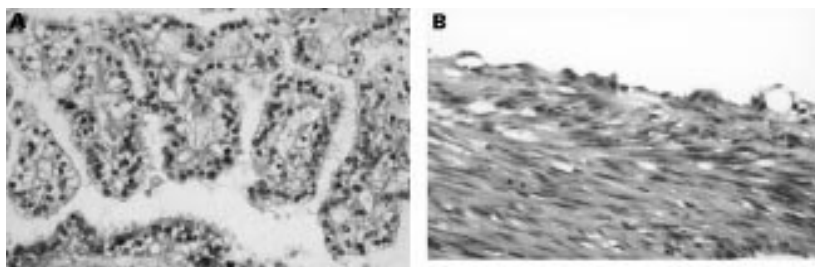


Figure 1 (A) Papillary area of tumour with hyalinised cores covered by tumour cells with clear cytoplasm. (B) Cystic structure with epithelial lining and surrounding fibrous stroma, suggestive of endometriosis.

International, High Wycombe, UK). There was also diffuse strong positivity for cytokeratin 7 (CK7; Dako, Ely, UK) (fig 2B), but no staining for CK20 (Dako), which stained adjacent normal colonic mucosa. Staining for type IV collagen (Dako) and laminin (Dako) showed positivity of the hyalinised cores within the papillary areas. The cells lining the cystic structure stained strongly with Ber-EP4 (Dako).

We consider it probable that the colonic clear cell carcinoma in this case arose in endometriosis. This is based on the presence of a cystic structure at the deep aspect of the tumour, which was lined by cells with eosinophilic cytoplasm. Although endometrial type stroma was not identified, the morphological findings are similar to those that can be seen in long standing endometriosis. In addition, at laparotomy, there was a clinical impression of endometriosis surrounding the tumour with multiple small haemorrhagic pelvic and abdominal peritoneal nodules. The possible importance of this cystic structure was only appreciated after review of the case and examination of multiple levels and extra histological sections. A possible transition was seen within the epithelial lining of the cyst from cells with eosinophilic cytoplasm, suggestive of endometriosis, to cells with abundant clear cytoplasm, similar to those seen within the main tumour. One of us (WGM) has previously observed similar features in ovarian clear cell carcinoma arising in endometriosis. It was thought possible that the cystic structure could have been a mesothelial lined cyst, but this was excluded by strong positivity of the lining cells for Ber-EP4.

Malignant transformation in endometriosis was first described by Sampson in 1925,³ who recommended that three criteria be met for a definitive diagnosis, namely: (1) there should be histological evidence of endometriosis in close proximity to the tumour; (2) no other primary site of malignancy should be identified; and (3) the histological appearance of the tumour should be compatible with an origin in endometriosis. In our patient, only the second and third of these criteria were fully satisfied. However, these

criteria are restrictive because in many cases the tumour may completely obliterate pre-existing endometriosis, making it impossible to confirm its presence unequivocally. Tumours that can arise in endometriosis include endometrioid adenocarcinoma, clear cell carcinoma, squamous carcinoma, endometrioid stromal sarcoma, adenosarcoma, and carcinosarcoma.^{4,5}

Clear cell adenocarcinoma of the ovary is associated with pelvic endometriosis in 50-70% of cases and a quarter of ovarian clear cell carcinomas can be shown to arise in endometriotic cysts. It should therefore be no surprise if occasionally a clear cell carcinoma of ovarian type should arise in extraovarian endometriosis, and several such cases have been reported.⁶⁻⁸ Endometrioid type adenocarcinoma has occasionally been described arising in colonic endometriosis,⁹ and we are aware of a single previous report of clear cell carcinoma arising in endometriosis of the sigmoid colon.⁸

In our patient, the strong positivity of tumour cells with CA125 provides evidence of Mullerian derivation. Although focal immunoreactivity can be present in primary colonic carcinoma, positivity to this extent is unusual. The strong immunoreactivity for CK7, combined with CK20 negativity, is also in keeping with an ovarian type primary, the converse pattern of staining being expected in a primary colonic neoplasm.¹⁰ A further histological pointer to an ovarian type tumour was the presence of calcified psammoma bodies. The ovaries and kidneys appeared grossly normal at laparotomy, helping to exclude the possibility of a colonic metastasis from an ovarian or renal primary.

In summary, we describe an unusual case of primary colonic clear cell adenocarcinoma that has probably arisen in extraovarian endometriosis. When confronted with an extraovarian tumour with the histological appearances described above, pathologists should consider a primary of ovarian type and an origin in endometriosis. The demonstration of endometriosis might require the examination of multiple levels and extra histological sections. Even then, residual endometriosis might not be definitely dem-

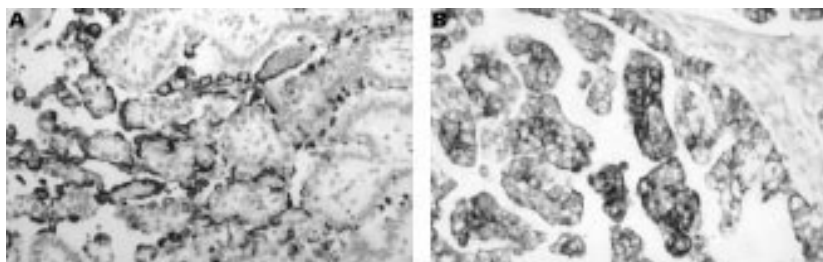


Figure 2 (A) Strong positive membrane staining of tumour cells with CA125. (B) Strong positive staining of tumour cells for CK7.

onstrated because it may be completely obliterated by tumour. Confirmation that a tumour is of ovarian type is of clinical importance, because chemotherapeutic regimens will differ from those administered for a typical colonic adenocarcinoma.

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Retroperitoneal extraskeletal osteosarcoma

Extraskeletal osteosarcomas are rare malignant mesenchymal neoplasms characterised by the direct production of osteoid or bone by tumour cells. By definition, they are located in the soft tissues without primary bone or periosteal involvement. The most common location of these tumours is the lower extremity, especially the thigh, followed by the upper extremity and the retroperitoneum.¹⁻⁴

We report the radiological presentation of a retroperitoneal extraskeletal osteosarcoma, which may be helpful in the consideration of its differential diagnosis.

A 68 year old man presented with a painless palpable mass in the right side of the abdomen. A previous trauma was denied. The patient was not on anticoagulant medication. Except for a cholecystectomy in 1986, his medical history was unremarkable. Physical examination revealed a firm mass measuring approximately 10 × 10 cm. Laboratory findings were within normal limits, with the exception of a slightly raised alkaline phosphatase concentration of 140 U/litre (normal range, 40-120).

Plain radiography of the abdomen demonstrated a large ill defined dense lesion projecting over the right side of the pelvis. Contrast enhanced helical computed tomography (CT) of the abdomen identified a large,

non-homogeneous soft tissue mass in the right side of the retroperitoneum (fig 1). The tumour measured 9 × 12 × 14 cm. The medial part of the mass was predominantly mineralised; the lateral side showed a large soft tissue mass with low density in the centre suggestive of necrosis or haemorrhage. The radiological features suggested an osseous, rather than chondroid, nature because of the poorly defined and homogeneous aspect of the mineralisation. The upper border of the mass was in close anatomical proximity to, but clearly separate from, the adjacent right kidney on three dimensional reformatting. The tumour definitely did not arise from adjacent osseous structures and the psoas muscle was compressed by the tumour.

Magnetic resonance imaging (MRI) demonstrated a mass surrounded by a pseudocapsule near but not originating from the lower pole of the right kidney. In addition to the ossified zone, the mass contained areas of necrosis, old haemorrhage, or secondary lacunae formation filled with protein substance indicated by intermediate signal intensity on T1 weighted sequences and very high signal intensity on T2 weighted images. Based on the clinical history and radiographic findings, the diagnosis of an extraskeletal osteosarcoma was suggested.

Macroscopic examination of the resected specimen revealed a 19 × 12 × 9 cm tumour including the resected margins, partly bony, partly firm, partly weak of consistency, with a white pink colour. There was a large cystic area, measuring 7 × 6 cm filled with serous fluid.

Microscopically the tumour was composed of storiform oriented bundles of spindle shaped tumour cells, admixed with areas of polygonal shaped tumour cells with abundant deposition of primitive osteoid matrix in between (fig 2). The osteoid matrix showed a trabecular arrangement and was focally admixed with chondroid forming areas. In these fields, the tumour cells showed lacunae. In all areas the tumour cells showed moderate pleomorphism and mitotic activity of up to eight mitosis/mm². Scattered areas of necrosis were seen. No relation with a pre-existing nerve could be documented. Immunohistochemically, the tumour showed diffuse reactivity with antibodies against vimentin and focal reactivity with antibodies against the S-100 protein in the chondroid containing fields and the spindle cells. Antibodies directed against neurofilaments and p53 showed no reactivity. The differential diagno-

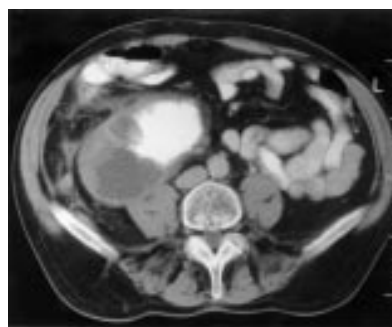


Figure 1 Axial contrast enhanced helical computed tomography (CT) scan compatible with the ultrasound image demonstrates a large mass with extensive mineralisation in the medial part of the tumour, as well as an area of decreased attenuation laterally compatible with necrosis. The psoas muscle is compressed. However, the tumour does not seem to arise from this structure.

sis included high grade extraskeletal osteogenic sarcoma, malignant peripheral nerve sheath tumour with heterologous elements, and dedifferentiated liposarcoma. A combined liposarcomatous part was not identified. Because of the lack of an identifiable nerve, the morphology of the spindle cells, focal reactivity only with S-100, and neurofilaments being negative, the diagnosis was extraskeletal osteogenic sarcoma.

Extraskeletal osteosarcoma is a rare tumour, constituting approximately 1% of all soft tissue sarcomas and approximately 4% of all osteosarcomas.¹⁻³ Although primary osteosarcomas of bone occur predominantly in the first decades of life, extraskeletal osteosarcomas are rarely encountered under 40 years of age.⁴

The pathogenesis of the tumour is unclear; the tumour may occur and be induced at sites that have received previous radiotherapy. In addition, a history of trauma has been reported in 12-30% of patients. There are cases described in which extraskeletal osteosarcoma is presumed to be preceded by myositis ossificans lesions.¹⁻³

Few reports of extraskeletal osteosarcoma have detailed the radiological findings of this rare neoplasm.⁵⁻⁹ The imaging techniques showed a large soft tissue tumour, for a large part demonstrating ossification, located in the retroperitoneum. Another primary osteosarcoma of bone was not found elsewhere in the body. On T1 weighted sequences the tumour was hypointense and isointense compared with muscle, and exhibited high signal intensity on T2 weighted imaging in the lateral part of the tumour, suggesting necrosis, haemorrhage, or secondary lacunae formation filled with protein substance. This latter correlated with the histological findings. Compression but no involvement of the psoas muscle, as visualised by CT, was confirmed.

The radiological differential diagnosis of extraskeletal osteosarcoma includes benign and malignant lesions that show mineralisation. The most important benign lesions are calcified haematoma and myositis ossificans. Several mesenchymal tumours can show reactive or metaplastic bone formation—for example, synovial sarcoma, epithelioid sarcoma, liposarcoma, and malignant peripheral nerve sheath tumour.⁴ Both possible benign lesions could be ruled out. The first because the patient definitely denied previous trauma. Furthermore, the patient did not use anticoagulant medication and the aorta was normal on all studies. Myositis ossificans was unlikely because there was no previous trauma and because of the large size of the lesion. Most myositis ossificans lesions measure 3-6 cm in

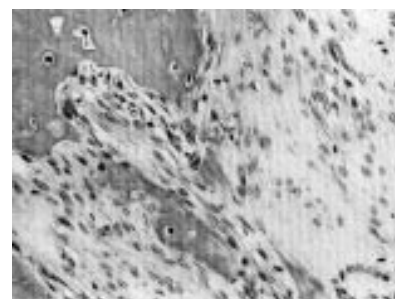


Figure 2 Photomicrograph of the tumour mass demonstrates the spindle shaped tumour cells with abundant deposition of osteoid matrix (haematoxylin and eosin stained; magnification, ×200).

diameter.⁴ Moreover, this lesion demonstrated ossification throughout a large part of the tumour and not at the periphery as is seen in myositis ossificans. Furthermore, the adjacent muscles were normal. Differentiating our patient's tumour from other malignant retroperitoneal sarcomas that can show bone formation is more difficult.

In conclusion, this case demonstrates that radiological imaging can help in the diagnosis of extraskelatal osteosarcoma. However, a biopsy is mandatory for a definitive diagnosis.

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Immunohistochemical demonstration of oestrogen and progesterone receptors

The excellent paper by Rhodes and colleagues¹ provides a valuable insight into the factors that might cause interlaboratory variability in the immunohistochemical demonstration of oestrogen receptors, now probably the most frequent histopathology result that determines specific patient treatment.² There is, however, one section of the paper where the statistical analysis may be causing confusion, rather than clarity.

In table 6, the degrees of agreement between the participant and organising laboratories for oestrogen receptor expression using the "Quick score" method are given. For each level of expression a κ statistic is given, and the values of all these statistics are less than zero, indicating a degree of agreement that is worse than chance alone. These κ statistics might be a reasonable reflection of the low levels of concordance, but it is unusual to calculate them for each level of expression, rather than all levels of expression together,³ and it is not clear which results have been included in each 2×2 contingency table to derive these statistics. A more usual way to assess the level of agreement would be to have a 4×4 contingency table with all levels of expression within it and to calculate a single κ statistic for the overall agreement.⁴ The authors may have done this in the final line of table 6 but it is not clear that this is the case. Because a misclassification between distant categories—such as the classification of a

high expressing tumour as a low expressing tumour—is more important than misclassification between adjacent categories, a weighted κ statistic might be appropriate.^{5,6} It should also be remembered that the quick method of scoring will be subject to observer variability,⁷ but the figures in the paper (for example, figs 8 and 9) demonstrate that it is an obvious difference in the intensity of staining, rather than interpretative variation, that accounts for the difference in the results.

None of these minor points should detract from the very important results of Rhodes *et al*,¹ which have important implications for any laboratory running an immunohistochemical service assessing oestrogen and progesterone receptor expression.

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The authors' reply

We would like to thank Dr Cross for his interest shown in our article and for his kind and constructive comments.

Cohen's κ statistic¹ was used in our study to compare the degree of agreement between the immunohistochemical (IHC) sensitivity for oestrogen receptors (ER) achieved by 152 laboratories on in house breast tumours, to that achieved by the UK National External Quality Assessment Scheme for Immunocytochemistry (NEQAS-ICC) organising laboratories' IHC assay on spare sections from the same cases, as evaluated by the "Quick score" method.² As quite rightly deduced by Dr Cross, the rationale behind using κ statistics for this part of the study, in addition to the Wilcoxon's matched pairs signed ranks test and the χ^2 goodness of fit test, was to emphasise the lack of agreement between the pairs of matching slides. This was reflected in the

negative κ scores, and the significant differences shown in the results of the other statistical tests, indicating a degree of agreement that was worse than would have occurred by chance alone.

In retrospect, we agree that the way the κ statistics were calculated and the way the results were expressed may have been confusing, and we welcome this opportunity to clarify the results by repeating the calculations using a 4×4 contingency table and by calculating a single κ statistic as suggested by Dr Cross, using the formula detailed by Robertson *et al* in 1981.³ Table 1 gives the results of this analysis.

This approach yields a κ coefficient of 0.19 when the Quick scores are evaluated by one of the authors (AR) and 0.20 when evaluated by a second (BJ). Although "yardsticks" are arbitrary and should not be slavishly adhered to,⁴ κ values less than 0.4 are generally considered to show poor agreement.^{5,6} As suggested by Dr Cross, a weighted κ statistic might be more appropriate, because a misclassification between distant categories is of greater importance than a misclassification of adjacent ones, and we have therefore also performed these calculations.⁷ Although the weighted κ statistics of 0.30 (AR) and 0.34 (BJ) are slightly higher than the unweighted κ values, they are still less than 0.4, confirming that agreement between the two assays is poor.

Lastly, to emphasise that the differences observed resulted predominantly from differences in the sensitivities of the IHC assays and not observer error, we have used the same weighted κ statistic to determine the degree of intra-observer (AR) and interobserver (AR and BJ) agreement. Fleiss recommends that κ values between 0.4 and 0.75 represent fair to good agreement, and values exceeding 0.75, excellent agreement.⁸ The weighted κ statistics for intra-observer agreement in our study for the evaluation of the Quick scores of the participants' assays and the organising laboratories' assay on the same in house tumours, are 0.70 and 0.74, respectively, indicating good agreement by the same assessor when evaluating the same slides on two different occasions. The weighted κ statistics for inter-observer agreement when assessing the participants' and organising laboratories' IHC results by Quick score evaluation in this study are 0.79 and 0.87, respectively, indicating excellent agreement. These findings support those of previous studies that have used the Quick score method of evaluation.^{8,9}

In summary, we conclude that the results of these additional tests suggested by Dr Cross support and clarify those published in our original study. They emphasise that the significant differences observed in the Quick score evaluations of the IHC assay results for ER on in house tumours are caused by differ-

Table 1 Contingency table showing the overall level of agreement between the participants' assays and the organising laboratory's assay, on 152 breast carcinomas

	Organising laboratory's IHC assay				Total
	Negative (0)	Low (2, 3)	Medium (4, 5)	High (6, 7)	
Participants' IHC assays					
Negative (0)	3	3	2	8	
Low (2, 3)		6	15	24	
Medium (4, 5)		1	7	34	42
High (6, 7)		6	6	72	78
Total	3	7	19	123	152

Negative, low, medium, and high refer to relative oestrogen receptor expression of the 152 in house breast carcinomas as evaluated by the "Quick score" method, with the Quick scores in parenthesis.

ences in the sensitivity of the assays in different laboratories and not by observer bias.

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Dietary dangers: ingestion of a bread bag clip

During a routine postmortem evisceration, a segment of jejunum of approximately 20 cm was noted to be doubled back upon itself, with fibrous adhesions joining the two halves of the loop creating a “U” shape. The segment of jejunum was opened along the antimesenteric border, and a bile encrusted foreign body was seen to be attached by a free bridge of mucosa where the bowel doubled back upon itself. The object was removed without damaging the mucosal bridge; removal of the encrusted bile showed the foreign object to be a plastic bread bag clip. There was no date on the clip. The bridge of free mucosa passed through the space behind the tooth-like pincers (fig 1). The amount of bile encrustation and the remarkable growth

of a mucosal bridge through the clip suggest that it had been present in this particular segment of jejunum for a considerable time. Its presence was unrelated to the cause of death, which was given as coronary artery atherosclerosis, and there was no evidence to suggest that the presence of the bread bag clip had caused problems during life.

The segment of jejunum removed was sliced across, the cut running parallel to the plicae circulares, to cut the mucosal bridge longitudinally. Sections were submitted for histopathological examination. A haematoxylin and eosin stain and an actin immunocytochemistry stain, to highlight muscle, were studied (fig 2). Although there was considerable postmortem autolysis, it was evident that the bread bag clip had been held within a mucosal lined eyelet. The actin stain showed the muscularis propria curving to run below the base of the eyelet; there was no muscularis propria running over the bridge of tissue that retained the clip. The muscularis mucosae similarly did not run in continuity across the top of the eyelet; the eyelet was within the lamina propria and the muscularis mucosae passes around and deep to it. There was a small amount of muscle within the tissue bridge itself but this did not appear to run in continuity across the top of the tissue bridge.

The mechanism of formation of this loop is difficult to determine. The bread bag clip has sharp tooth-like pincers, and would be expected to cause crushing and necrosis of the bowel wall if attachment occurred. Re-epithelialisation of the bowel wall is recognised to take place after crush injury; this phenomenon has been exploited in the past in double barrelled colostomy formation and closure in the Paul-Mikulicz surgical procedure (now obsolete).^{1–3} The patterns of the musculares propria and mucosae shown

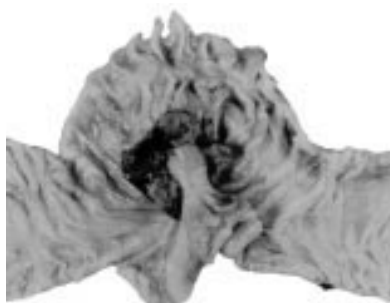


Figure 1 Bread bag clip attached to small bowel by a mucosal bridge.

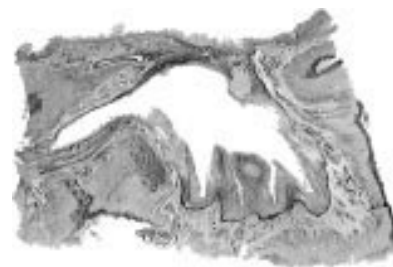


Figure 2 Section through mucosal bridge retaining bread bag clip (actin immunocytochemistry; magnification $\times 7$).

by actin immunocytochemistry suggest that the clip has “caught up” the small bowel wall in two places, bringing the “mucosal crest” of each into apposition, with apparent mucosal fusion to form a bridge.

Review of the literature has identified six previous reports of medical problems arising from the accidental ingestion of bread bag clips.^{4–8} Problems arising included gastrointestinal bleeding, small bowel obstruction, and intestinal perforation. Complications may arise long after ingestion,^{4,5,7} and there may be no recall of the ingestion.^{6,8} Although bread bags are now secured with plastic sticky tape, bread bag clips may still be encountered and the potential for late symptomatic presentation in relation to a retained bread bag clip remains.

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