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Mucinous epithelial cysts of the spleen associated with pseudomyxoma peritonei

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Aims: We report two rare cases of neoplastic pseudomyxoma peritonei associated with splenic mucinous epithelial cysts and review previously reported cases of splenic mucinous lesions in order to investigate the extent and implications of such an association.
Methods and results: The majority of mucinous lesions of the spleen appear to be associated with pseudomyxoma peritonei. The clinicopathological profile of these cases conforms to that of neoplastic pseudomyxoma peritonei, showing a similar age of onset, outcome and histological features. Most of the cases were associated with a confirmed or suspected appendiceal primary. The immunophenotype (cytokeratin 7 negative; cytokeratin 20 and CEA positive) of the lesions of both our cases, including those in the ovary, was suggestive of a gastrointestinal origin.
Conclusions: Splenomegaly due to cystic intrasplenic mucinous epithelial lesions may occasionally be the presenting feature of pseudomyxoma peritonei or herald tumour recurrence. Mucinous epithelial cysts of the spleen may also precede the development of pseudomyxoma peritonei. All cases of pseudomyxoma peritonei should be investigated for splenic involvement and, conversely, a primary mucinous neoplasm sought elsewhere in the abdomen in all cases of splenic mucinous cysts.

Keywords: cysts, pseudomyxoma peritonei, spleen

Introduction

The term ‘pseudomyxoma peritonei’ has been variously defined, but generally refers to the presence of localized or diffuse masses of mucinous material in the peritoneal cavity.[1,2] It may either follow rupture of a benign, mucus-filled visceral cyst with simple spillage or leakage of mucin into the abdominal cavity or, more ominously, be due to the growth of a mucinous neoplasm in the peritoneal cavity. The latter situation has generated considerable controversy with respect to the site of the primary tumour, the appendix now being favoured in the majority of cases.[2–4]

The variable histogenesis, appearances and outcome of ‘pseudomyxoma peritonei’ has lead to the suggestion that the term should not be used as a histological diagnosis, but rather as a description for a clinical appearance as defined above, requiring additional qualification of its histological features and origin.[1,2]

Neoplastic pseudomyxoma peritonei very infrequently involves abdominal viscera other than the ovary (which is now thought to be secondarily involved in the majority of cases) and rarely spreads beyond the diaphragm.[5] Primary mucinous epithelial cysts of the spleen are also exceptionally rare.[6,7] Splenic mucinous cysts have been reported in association with pseudomyxoma peritonei, the majority of which appeared to be related to an appendiceal primary tumour.[5,8–10] We report two additional cases of splenic involvement by pseudomyxoma peritonei showing an immunophenotype also supportive of an appendiceal or other gastrointestinal origin and review the clinicopathological features of these and the previously reported cases. Recognition of this association, albeit rare, may

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influence the management of both pseudomyxoma peritonei and splenic mucinous epithelial cysts.

Case reports

Case 1
A 52-year-old woman with cognitive impairment since infancy presented with a history of abdominal distention and pain of 6-months duration. She apparently had a hysterectomy for a fibroid uterus many years previously. Laparotomy revealed a right adnexal mass adherent to the appendix. The uterus, left ovary and left Fallopian tube were absent with evidence of a previous hysterectomy. The abdominal cavity was filled with mucinous material with an appearance consistent with that of pseudomyxoma peritonei. The right adnexal mass, appendix and 2 L of the mucinous material were removed. The spleen was reported as being mildly enlarged. A diagnosis of ovarian involvement by a 'well differentiated mucinous cystadenocarcinoma' with pseudomyxoma peritonei was made at the time. No clinical or pathological reference to the condition of the appendix other than that given above could be traced. She was discharged with no further treatment.

Five years later she presented at our hospital with the complaint of vague pain in the left hypochondrium of 2 years duration. On examination the spleen appeared enlarged. Ultrasound examination revealed multiple cystic areas associated with calcifications within the spleen. A splenectomy was performed. No tumour was observed in the abdominal and pelvic cavities and the remaining viscera appeared normal. The patient made an uneventful recovery and has been disease-free for the past 4 years.

Case 2
A 61-year-old man presented with abdominal distention due to an upper abdominal mass. A diagnostic laparotomy revealed extensive involvement of the upper abdominal cavity by pseudomyxoma peritonei. Histology confirmed the presence of a 'well-differentiated mucinous adenocarcinoma'. Further investigations failed to demonstrate a primary tumour. The patient was given chemotherapy. Over the next year and a half the tumour continued to show slow progressive growth with filling of the rest of the abdominal cavity. Malignant ascites necessitated periodic taps to alleviate abdominal distention. Four month before his death the patient developed subtotal intestinal obstruction. He died 2 years after the diagnosis of pseudomyxoma peritonei. An autopsy was performed.

Methods and results

Sections of formalin-fixed and wax-embedded tissue blocks were stained with haematoxylin and eosin, Best's mucicarmine and periodic acid–Schiff (PAS) with and without diastase. Immunohistochemistry was performed using the streptavidin–biotin–peroxidase technique and employing the following panel of antibodies: CEA (dilution 1 : 500, Dako, Ely, UK); low molecular weight cytokeratin 8, dilution 1 : 200, Dako); high molecular weight cytokeratins 1, 5, 10 and 14, dilution 1 : 200, Dako); cytokeratin 7 (dilution 1 : 50, Dako); and cytokeratin 20 (dilution 1 : 50, Dako). Positive and negative controls stained appropriately.

GROSS FINDINGS

Case 1
The specimen consisted of a spleen measuring $200 \times 110 \times 80$ mm and weighing 960 gm (Figure 1). The splenic capsule was smooth and intact. The cut surface revealed the presence of an intraparenchymal multicystic tumour surrounded by a peripheral rim of splenic tissue of varying thickness. The cysts were filled with yellowish, mucinous material. The largest cyst measured 80 mm in diameter. No solid tumour areas were observed. The tumour extended into the splenic hilum.

Case 2
The autopsy revealed extensive intra-abdominal pseudomyxoma peritonei entrapping the abdominal viscera and infiltrating the mesentery and retroperitoneum. The appendix could not be identified. An old surgical scar on the abdominal wall in the right iliac fossa region and suturing material in the vicinity of the caecum were, however, strong evidence for a previous appendicectomy (a history confirming such a procedure

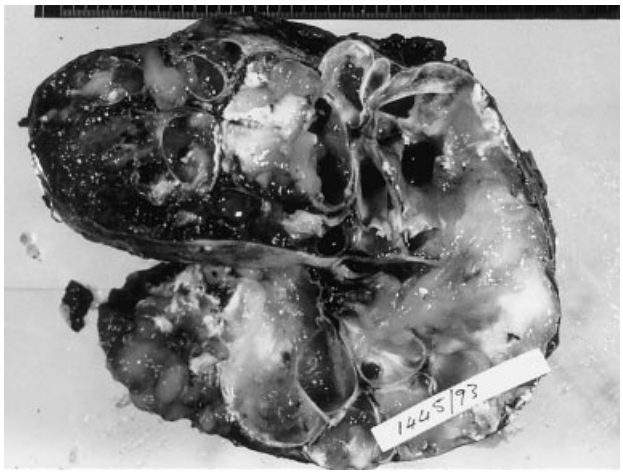

Figure 1. Case 1. Splenectomy specimen showing mucinous cysts of variable sizes displacing most of the parenchyma.

and the time thereof could not be obtained). The rectum was encased and constricted by tumour with resultant subtotal obstruction. No primary tumour was, however, identified within the whole of the gastrointestinal tract. The spleen was slightly enlarged and on section revealed multiple mucin-filled cysts, which in the hilar region appeared to be in continuity with the pseudomyxomatous deposits covering an apparently intact splenic capsule. The liver, biliary tract and pancreas were also surrounded by tumour but showed no invasion or the presence of a possible primary tumour. The ureters were both dilated, but it, the kidneys and lower urinary tract were otherwise uninvolved by tumour. Direct or metastatic spread of the tumour beyond the abdominal cavity was not observed.

MICROSCOPIC FINDINGS

Case 1

Multiple sections of the tumour showed cysts of varying sizes lined by a single layer of columnar to cuboidal mucinous epithelium of an intestinal type with goblet cells. The epithelium focally showed early budding with mild stratification and focal mild cytological atypia. No mitoses or stromal invasion were present. A collagenous fibrous wall of varying thickness supported the epithelium (Figure 2). The surrounding splenic parenchyma was unremarkable apart from fibrosiderotic nodules and pools of mucin unassociated with epithelial cells immediately adjacent to the tumour. The mucin here and within the tumour stained strongly with mucicarmine and PAS after diastase digestion.

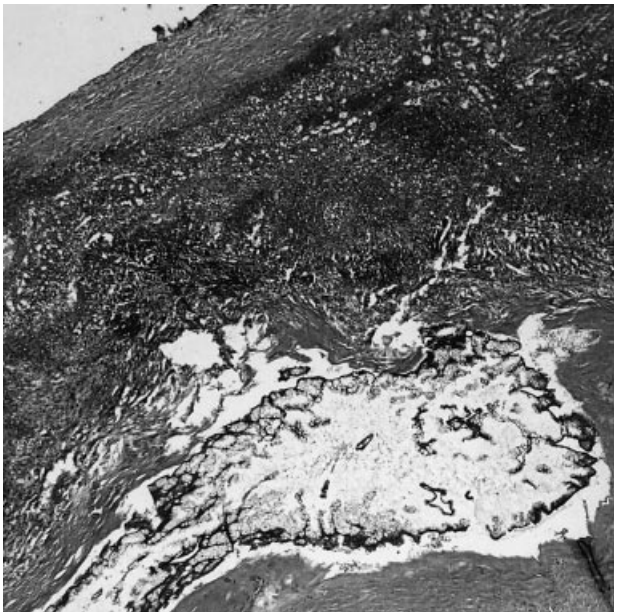

Figure 2. Case 1. Compressed rim of splenic parenchyma (centre) between epithelium-lined cyst (bottom) and intact capsule (upper left) (H & E).

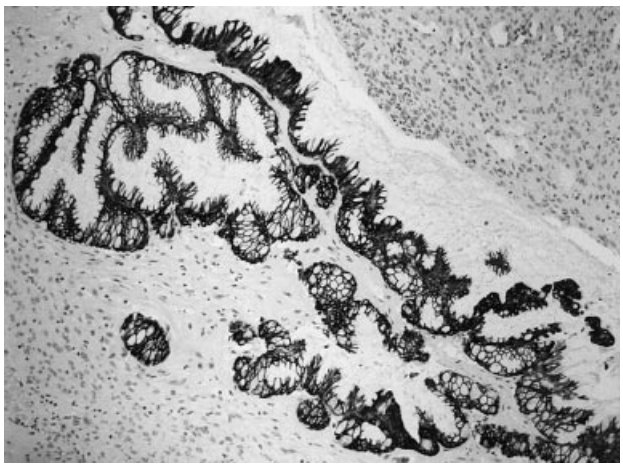

Figure 3. Case 1. Intestinal type mucinous cystic tumour with borderline features in right ovary showing strong cytoplasmic staining for cytokeratin 20.

Review of the paraffin-embedded tissue specimens taken at the time of the earlier right adnexectomy and tumour debulking showed the presence of an ovarian borderline mucinous tumour (Figure 3) and pseudomyxoma ovarii. Omental and peritoneal biopsies showed the presence of pseudomyxomatous tumour deposits consisting of mucin-filled cystic spaces sometimes lined by a single layer of benign to slightly atypical appearing mucinous epithelium. One of the blocks reviewed contained two cross-sections of an appendix showing involvement by a typical carcinoid tumour with no mucinous component. Unfortunately the rest of the appendix could not be traced.

Case 2

Sections representative of the intra-abdominal pseudomyxomatous tumour deposits showed multiple mucin-filled cysts of variable diameter, often lined by a single layer of mucinous epithelium lacking atypical cytological and architectural features (Figure 4). The epithelial cytoplasm as well as the intracystic mucoid material showed strong staining with mucicarmine and PAS after diastase digestion. The intrasplenic cysts were of similar appearance and continuity with the perisplenic pseudomyxomatous tumour deposits via the hilum was confirmed histologically with an apparently intact splenic capsule elsewhere. The other intra- and extra-abdominal viscera showed no evidence of a primary tumour. The lungs showed extensive thrombo-emboli with associated infarction, which was considered the final cause of death.

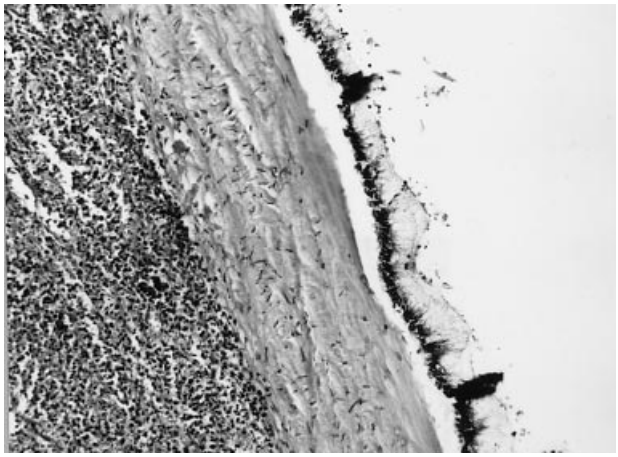

Figure 4. Case 2. Intrasplenic mucinous cyst lined by a single layer of well-differentiated mucinous epithelium (H & E).

IMMUNOHISTOCHEMICAL FINDINGS

The mucinous epithelium in the pseudomyxomatous tumour deposits and intrasplenic cysts of both patients showed strong staining for low molecular weight cytokeratin 8, CEA and cytokeratin 20. Cytokeratin 7 and the high molecular weight cytokeratins 1, 5, 10 and 14 consistently failed to stain the same epithelia. The epithelium lining the ovarian borderline mucinous tumour in Case 1 also showed cytokeratin 20 and CEA positivity with no staining for cytokeratin 7 (Figure 3).

Discussion

The majority of cystic lesions of the spleen are of parasitic origin. Rarely encountered nonparasitic cysts are classified as either true (epithelial, primary) or false (pseudo, secondary) based on the presence or lack of an epithelial lining on their inner surface.[11] The most common epithelial cysts are of a mesothelial and more often a so-called epidermoid type.[11,12] The light and electron microscopic demonstration of a transition between squamous epithelium and mesothelium in many of these cysts has led to the suggestion that epidermoid type splenic cysts are the result of squamous metaplasia in mesothelial derived inclusion cysts.[11,13] A study of the cytokeratin profile of one cyst has alternatively suggested that the squamous epithelium is of either teratomatous derivation or originates from inclusions of fetal squamous epithelium.[14] Dermoid type cysts with hair follicles and sebaceous glands are very rare.[15]

Exceptional cases of otherwise typical epidermoid type splenic cysts with a focal transitional lining of mucinous or mucoepidermoid type epithelium have been reported.[16,17] This should be distinguished from nonmucinous degenerative mesothelial cells with a pseudo-signet-ring cell appearance.[11] The transitional mucinous epithelium has variously been ascribed to intrasplenic rests of mesonephric origin,[16] or metaplastic change in mesothelium.[11] Two examples of apparently benign, simple splenic cysts with a complete lining of mucinous epithelium have been described.[6,15] A case of a low-grade mucinous cystadenocarcinoma of the spleen was reported more recently.[7] The patient was a 69-year-old male who had an appendicectomy for acute appendicitis 36 years previously. The intrasplenic tumour shared the macro- and microscopic features of our two cases, but was not associated with pseudomyxoma peritonei. Focal continuity with a suprasplenic acellular mucinous mass was, however, documented. The gastrointestinal tract and other possible sites of a primary tumour appeared normal clinically and radiologically. It was therefore regarded as a tumour of primary splenic origin.

Theories explaining the presence of intrasplenic mucinous epithelium include the following: the presence of a focal mesothelial-like lining in the previously described case as well as the epidermoid type cysts with a focal mucinous transitional-type lining referred to earlier, suggests the possibility of mucinous metaplasia in a pre-existing mesothelial lining.[7,11] A sequence of congenital or traumatic invagination of splenic capsular mesothelium followed by cystic dilatation, mucinous metaplasia and very rarely, ultimate neoplastic transformation has been proposed.[7] Splenic cystic mucinous lesions can therefore be regarded as analogous to primary cystic mucinous tumours of the mesentery and retroperitoneum which are also thought to develop through mucinous metaplasia in pre-existing mesothelial cysts known to exist in these locations.[18,19] A tumorigenic potential of mesothelium which has undergone mucinous metaplasia may also fit in with the theory of the female peritoneum as a secondary Müllerian system which may give rise to the same spectrum of epithelial types as seen in epithelial tumours of ovarian origin.

A derivation from ectopic intrasplenic tissue due to developmental displacement of endodermal epithelial tissue (e.g. pancreatic or intestinal)[6,7] or mesonephric structures[16] has also been proposed. Although heterotopic pancreatic rests have been found in the spleen none of the mucinous lesions discussed above have shown transition between them and remnants of any type of rest.

Most importantly, direct extension or metastasis from a mucinous neoplasm elsewhere, however rare, should be ruled out before entertaining a diagnosis of a primary

Table 1. Clinicopathological features of cases of pseudomyxoma peritonei involving the spleen

Reference	Age (years)/ Sex	Primary tumour site	Secondary spread	Clinical presentation	Treatment	Survival from diagnosis	Histology
Holder *et al*.[5]	38/F	Appendix	Peritoneal cavity, spleen	Splenomegaly	Surgery, chemotherapy	34 months, alive, disease free	Borderline features all lesions
Mets *et al*.[8]	47/M	Appendix suspected*	Peritoneal cavity, spleen, pleura, pericardium	Acute abdomen, splenomegaly	Surgery, chemotherapy	4½ years, died of disease	'Single-layered well-differentiated epithelium with no atypia' all lesions
Roulet[9]	45/M	Appendix	Peritoneal cavity, spleen, liver, chest wall, pleura	Abdominal pain and distention	Surgery, radiotherapy	8 years, died of disease	'Single-layered cubic to high cylindrical epithelium' all lesions
Karak *et al*.[10]	40/F	Unknown†	Peritoneal cavity, spleen	Abdominal pain and distention, hernia	Surgery, chemotherapy	Not reported	Not reported
Present case 1	52/F	Appendix suspected‡	Peritoneal cavity, ?right ovary, spleen	Abdominal pain, splenomegaly (recurrence)	Surgery	9 years, alive, disease free	Benign to borderline features all lesions
Present case 2	61/M	Appendix or another GIT site suspected‡	Peritoneal cavity, spleen	Abdominal distention	Surgery, hemotherapy	2 years, died of disease	Benign, single layered epithelium all lesions

*Appendix not identified at surgery. Gastrointestinal, biliary and urogenital tracts otherwise normal.
†Both ovaries removed 4 years before for bilateral mucinous cystadenomas. Appendix not described in report. ‡See text.

splenic tumour. Neoplastic pseudomyxoma peritonei is rarely associated with secondary visceral involvement or extension above the diaphragm regardless of the site of origin.[5] Apart from our two cases, four examples of pseudomyxoma peritonei with splenic involvement have been reported in the literature (Table 1).[5,8–10] The clinicopathological features of all these cases mirror that of neoplastic pseudomyxoma peritonei in general.

In the majority of these an appendiceal primary tumour was confirmed or suspected. Two of the three female patients had prior or concurrent involvement of the ovaries by benign to borderline mucinous tumours, but in both an appendiceal primary cannot be ruled out as the appendix was either not described or incompletely examined. The possibility of an appendiceal primary in the latter case (our case 1) is raised by recent immunohistochemical studies. These have suggested that the evaluation of CK7, CK20, CEA and vimentin expression may be useful to distinguish primary ovarian carcinoma or metastases thereof from metastases originating from the gastrointestinal tract. A coordinate immunophenotype of CK20 and CEA immunopositivity, and in particular, CK7 negativity appears consistent with a nonovarian (and most likely colorectal) origin.[20–22] The ovarian mucinous lesions found in Case 1 shared this immunophenotype with the splenic and pseudomyxomatous lesions.

Where given, descriptions or illustrations of the histology of the mucinous lesions were compatible with those of benign or borderline mucinous epithelial tumours. Two of the patients presented with palpable splenomegaly and in another this was the presenting symptom heralding recurrence. The prognosis of patients with pseudomyxoma peritonei with secondary visceral involvement (including spleen) or supradiaphragmatic spread does not appear to be adversely affected regardless of the site of origin.[5] Three of the patients under discussion died of their disease after a fairly indolent course ranging from 2 to 8 years. Another two were symptom free and alive 34 months and 9 years, respectively, after being diagnosed with pseudomyxoma peritonei. Male patients seemed to fare worse, but the numbers are too small to make meaningful conclusions.

Various mechanisms may explain splenic involvement in cases of pseudomyxoma peritonei. Haematogenous metastatic spread to the spleen by nonhaematolymphoid neoplasms is not as rare as is still generally believed. It occurs, however, at an advanced stage of the disease and is almost always accompanied by metastases to other organs.[23] Direct invasion from adjacent viscera by an obviously malignant tumour is more commonly described. Extension of surface implants of pseudomyxoma peritonei into the splenic parenchyma may be a more plausible explanation in situations where the primary tumour shows a benign or borderline appearance. Our findings and those of some of the other cases suggest that the splenic hilum may serve as a site of entry.

Although the focus of the pseudomyxoma peritonei debate has been on an ovarian vs. an appendiceal origin, the alternative theory of multicentric independent primary mucinous tumours has not been ruled out as an additional mode of pathogenesis in some cases.[1,24] If some tumours do arise on this basis, perhaps as the result of a neoplastic field effect, it is possible that mesothelial or other types of epithelial inclusions in the spleen may also be subject to this effect.

Whatever the histogenesis of the majority of cases of pseudomyxoma peritonei, the list of other less common, undisputed primary tumour sites may be extended to include rare acceptable cases of primary mucinous tumours of the spleen. The primary splenic low-grade mucinous cystadenocarcinoma described above[7] showed continuity with an extrasplenic mucinous mass, which could perhaps represent early pseudomyxomatous spread. Lauder also mentions an unpublished case of pseudomyxoma peritonei, which followed accidental rupture of a splenic mucinous epithelial cyst.[15]

In conclusion, mucinous epithelial cysts of the spleen assume importance because the majority of these appear to be related to pseudomyxoma peritonei. Splenomegaly due to cystic intrasplenic mucinous epithelial lesions may on occasion be the presenting feature of pseudomyxoma peritonei or herald tumour recurrence. Mucinous cysts of the spleen may also precede the development of pseudomyxoma peritonei. All cases of pseudomyxoma peritonei should therefore be investigated for splenic involvement and splenectomy considered as part of the treatment. Conversely, a mucinous neoplasm elsewhere in the abdomen should be ruled out before contemplating a diagnosis of a primary splenic mucinous tumour. This may necessitate appendicectomy even in cases where the appendix appears macroscopically normal.

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