

Correspondence

A migrating granuloma

Sir: Granulomas both of the foreign body and delayed hypersensitivity (immune) type are usually part of tissue-based inflammatory processes.¹ In some diseases such as sarcoidosis, which are characterized by granuloma formation, an association with lymphatic vessels does not appear to be a feature. In Crohn's disease, it is a frequent occurrence.² In addition, granulomatous lymphangitis of the scrotum and penis, granulomatous cheilitis and Melkersen–Rosenthal syndrome are also associated with peri- and intralymphatic granulomas.³ These latter conditions are considered by some to be a *forme fruste* of Crohn's disease. Migratory, non-inflammatory intralymphatic granulomas are a separate and presumably rare entity and the statement that 'granulomas are not static' would appear to be true in more ways than one.¹

Examination of the gastrectomy specimen, from a 70-year-old male with a 100 × 70-mm infiltrating moderately differentiated adenocarcinoma, was found to have 13 of 23 lesser curvature nodes and 32 of 45 greater curvature nodes replaced by metastatic carcinoma. One uninvolved lymph node contained a very poorly formed granuloma with, in one of the adjacent afferent lymphatic vessels, a small and apparently 'in transit' well-formed, non-caseating granuloma (Figures 1 and 2). Granulomas were not present in the stroma of the carcinoma. It would seem that granulomas should have the property of exhibiting migratory capabilities due to the wealth of cytokines involved in their initiation and maintenance. However,

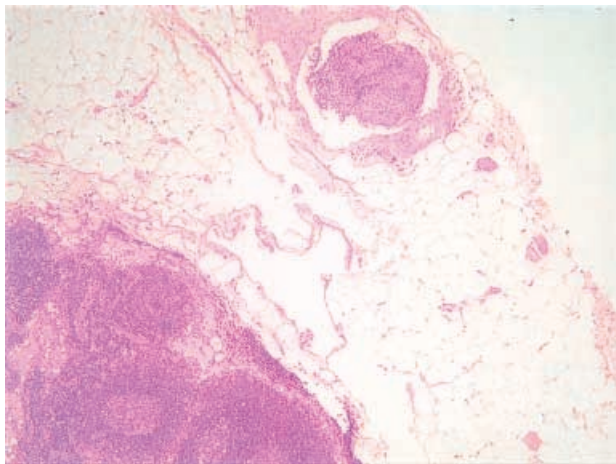


Figure 1. Intralymphatic granuloma.

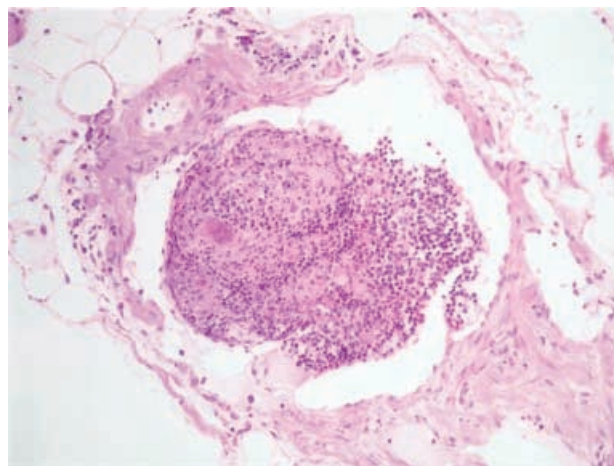


Figure 2. Intralymphatic granuloma.

the presence of a granuloma within a lymphatic channel as an isolated event is an extremely unusual occurrence. In cancer, granulomas are rarely found within the stroma but somewhat less commonly present within the draining lymph nodes. It is possible that this occasional process is initiated within the stroma as an immune surveillance response but retreats to the lymph nodes if this response is overwhelmed. Alternatively, and probably more likely, it may represent transport of a displaced tissue granuloma similar to the recently discussed mechanism of dislodgement and transportation of benign epithelium to lymph nodes.⁴

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Malignant epithelioid mesothelioma of the pleura with hyaline globules

Sir: Malignant epithelioid mesothelioma is classically composed of large eosinophilic cells disposed in a solid, tubulopapillary or microcystic pattern. However, several histological variants are recorded, including examples in which the cells are small, pleomorphic, deciduoid, rhabdoid, vacuolated, signet ring, clear, foamy, lipid-rich and glycogen-rich.¹ This extreme morphological variability may lead to confusion with other neoplastic and non-neoplastic conditions. We describe a malignant epithelioid mesothelioma of the pleura with hyaline globules, a finding which, to the best of our knowledge, has not previously been reported.

The patient, a 61-year-old smoking male, plumber with a long history of asbestos exposure, presented with dyspnoea and thoracic pain. A chest X-ray and a total body computed tomography scan showed a left pleural effusion, with diffuse nodularities of the ipsilateral pleura; no lesions were found in other locations. A left thoracoscopy confirmed the presence of several nodules of variable dimensions, greyish in colour and fleshy in consistency, involving the parietal pleura and the diaphragm. Multiple biopsies were obtained. The patient was subsequently treated with six cycles of chemotherapy (carboplatin and gemcitabine), and he is alive with progressive disease 6 months after diagnosis.

Microscopically, the neoplasm was extensively necrotic and haemorrhagic, and infiltrated the soft tissues of the thoracic wall. A small, benign-looking pleural plaque was also included in the biopsy material. The tumour was composed of markedly atypical epithelioid cells with abundant eosinophilic-to-pale cytoplasm, irregular nuclear contours and prominent nucleoli (Figure 1). Mitoses, including atypical forms, were numerous. Neoplastic cells were disposed in solid sheets surrounded by collagen bundles and by a rich inflammatory infiltrate. The most striking feature was the presence of many intracytoplasmic, brightly eosinophilic globules of variable size, which sometimes indented the nuclei (Figure 2). The globules were strongly positive for periodic acid–Schiff (PAS) with and without diastase digestion. Mucin was absent.

Immunohistochemically, the neoplastic cells were diffusely positive for cytokeratin (CAM5.2) and epithelial membrane antigen, focally positive for calretinin (Figure 1, insert) and vimentin, and negative for TTF-1, CD31, carcinoembryonic anti-

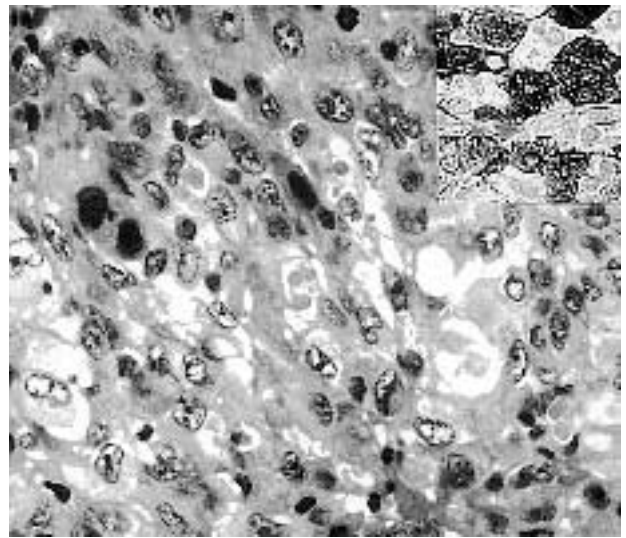


Figure 1. The tumour is composed of atypical epithelioid cells, with abundant eosinophilic-to-pale cytoplasm. Many intracytoplasmic hyaline globules are present (H&E). Neoplastic cells are immunoreactive for calretinin (insert, ABC).

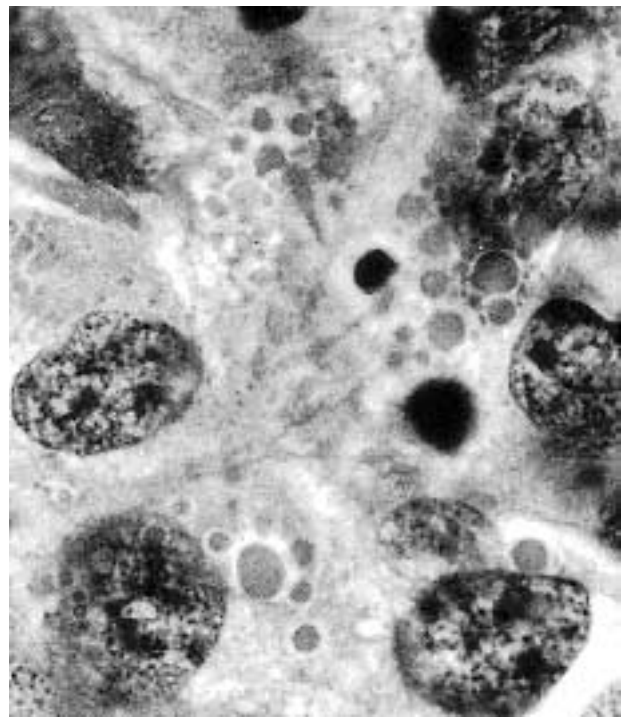


Figure 2. Higher magnification on the hyaline globules. In the right upper corner, the nucleus of a neoplastic cell is indented by several globules (H&E).

gen, BER-EP4, CD15 and α -fetoprotein. The hyaline globules were negative for all these antibodies.

This case represents a pleural tumour with the classical clinical, histological and immunohistochemical features of malignant epithelioid mesothelioma. The peculiarity consists in the presence, in the cytoplasm of the neoplastic cells, of numerous PAS-positive hyaline globules. Similar structures have been described in a variety of lesions, including single cases of multicystic mesothelioma² and ovarian/juxtaovarian adenomatoid tumour,³ but never, as far as we know, in malignant mesothelioma. Their presence in the latter neoplasm raises several differential diagnostic considerations, particularly metastatic adenocarcinoma and yolk sac tumour: both can occasionally grow on the pleural surface, mimicking the clinical and macroscopic appearance of mesothelioma.^{4,5} The correct diagnosis is based on the careful evaluation of the clinico-radiological, histological and immunohistochemical findings.

In our case, the hyaline globules were negative for a variety of immunoreactions, and their nature remains elusive. As suggested by Lamovec and Sinkovec,² they may be a secretory product of mesothelial cells or, alternatively, they may represent degenerated erythrocytes.

Our observation further expands the morphological spectrum of this protean neoplasm.

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High-grade thymic carcinoma other than basaloid or mucoepidermoid type could be associated with multilocular thymic cyst: report of two cases

Sir: Multilocular thymic cysts (MTC) are thought to be acquired lesions that are sometimes associated with thymic neoplasms, namely thymoma and thymic carcinoma.¹ Most thymic carcinomas can be classified as squamous cell carcinomas,² but several histological variants exist, among which basaloid carcinoma or mucoepidermoid carcinoma constitute the rarest variants of thymic carcinoma.^{1–5} An association between MTC and these particular types of thymic carcinoma has been reported.^{1–5} We present two cases of thymic carcinoma associated with MTC, with neither predominant basaloid or mucoepidermoid features.

Both patients were males aged 56–59 years. They underwent thymectomy. The former patient died of disease 35 months after the operation. In both cases a mass occupied the central portion of the right lobe of the thymus measuring 80 × 70 × 20 mm for case 1 and 60 × 50 × 30 mm for case 2. The central areas of the specimens were solid in consistency and yellowish white in colour, while peripheral areas were predominantly cystic. Histologically, the tumours showed a vaguely lobular structure, each lobule being separated by a broad fibrous band. In case 1, each lobule-like structure was composed of multiple relatively non-cohesive irregular cords and nests of anaplastic cells with a high nuclear–cytoplasmic ratio. The nuclei were pleomorphic, hyperchromatic, irregular in shape, and had mostly single prominent eosinophilic nucleoli. In case 2, cords and nests were composed of polygonal cells with relatively abundant cytoplasm and inconspicuous cell borders. A basaloid pattern was observed only very focally. Tumour at the periphery was composed of both invasive nests and *in-situ* involvement of the lining epithelium of the cysts. Individual tumour cells within the *in-situ* component were morphologically similar to those of invasive nests (Figure 1). In both cases alcian blue and periodic acid–Schiff stain identified no intra- or extracellular mucin. Immunohistochemically, most of the tumour cells were positive for AE1/AE3. There were no CD1a+ lymphocytes mixed with them. They were also positive for CD5 but negative for thyroid transcription factor-1.

Basaloid carcinoma of the thymus is characterized by proliferation of basaloid cells forming cords and nests, showing prominent peripheral palisading reminiscent of basal cell carcinoma of the skin. A close association between MTC and thymic neoplasia, in particular

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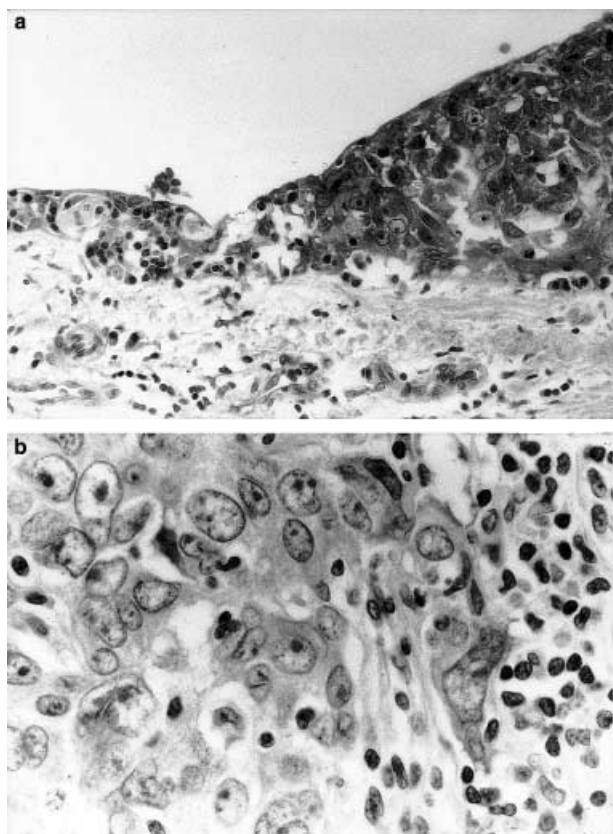


Figure 1. a, The tumour involving the lining epithelium of multilocular thymic cyst (case 1). b, High-power view of an invasive nest accompanied by lymphoid infiltration. The nuclei are pleomorphic, irregular in shape, and have mostly single prominent eosinophilic nucleoli (case 1).

basaloid carcinoma of the thymus, has been described.^{1–5} Recently, Moran and Suster reported six cases of mucoepidermoid carcinoma of the thymus. Interestingly, four cases were associated with MTC.⁵ They also reviewed a case reported by Leong *et al.* describing thymic squamous cell carcinoma associated with MTC⁶ and argued that it was in fact a mucoepidermoid carcinoma. Thus, a particular association between basaloid or mucoepidermoid thymic carcinoma and MTC may exist. Since the lining epithelium of MTC is considered to be not very different from normal thymic epithelium, tumour arising from MTC could presumably assume the histological features of every type of thymic neoplasm, including thymoma and thymic carcinoma. Thus, there may be no histogenetic link between MTC and particular types of thymic carcinoma, as exemplified by the present two cases, case 1 being poorly differentiated squamous cell carcinoma and case 2 being moderately differentiated squamous cell carcinoma. One could perhaps explain

the apparent frequent coexistence of MTC and basaloid or mucoepidermoid carcinoma by taking into account the invasiveness or stage of the lesion arising from MTC. In our cases the tumour had mostly replaced the central portion of the thymus and the remains of MTC occupied only a minor area. It is possible that slow-growing tumours, such as low-grade basaloid carcinoma or mucoepidermoid carcinoma, are more likely to preserve the structure of MTC, while in high-grade lesions MTC might be seen only focally or even be totally replaced by the tumour so that its presence could be overlooked without thorough sampling.

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Brenner tumour with carcinoma *in situ*: evidence for a spectrum from benign to malignant?

Sir: We report a case of Brenner tumour (BT) with a cystic component comprising severely dysplastic transitional epithelium amounting to carcinoma *in situ*. To our knowledge this has not been previously described and this observation suggests that malignant BT may arise from benign BT.

A 50-year-old woman presented with a 2-month history of post-menopausal bleeding. CA125 and CEA were normal.

Pelvic ultrasound scan showed a left-sided partly solid, partly cystic ovarian mass measuring 80 ×

70 × 70 mm with a 30-mm solid right ovarian mass. She proceeded to laparotomy which showed a smooth and mobile left ovarian cyst with normal uterus, right ovary, pelvis and omentum. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and peritoneal washings were performed. Macroscopically, the left ovary measured 100 × 90 × 70 mm. On sectioning it was partly solid, partly cystic, with the largest cyst measuring 60 mm in maximum dimension. This had a smooth surface and contained serous fluid. Within the cyst wall was a solid grey-white fibrous area measuring 45 × 23 × 20 mm. The right ovary measured 35 × 25 × 22 mm and was solid grey-white and fibrous throughout. The uterus, fallopian tubes and omentum were normal. On microscopic examination, the solid area in the left ovary showed nests of cytologically bland transitional-type cells lying in a fibrous stroma, in keeping with benign BT (Figure 1a). The cysts described macroscopically were lined by transitional epithelium showing severe dysplasia with atypical cells occupying the full thickness of the epithelium (Figure 1b). In addition there were atypical mitotic figures present. There was no invasion and the atypical cysts were internal to the ovary. The right ovarian tumour showed the classical appearance of a benign BT. The uterus, fallopian tubes, omentum and peritoneal washings were unremarkable.

Benign BT is a well-recognized ovarian tumour comprising 2% of ovarian epithelial tumours.¹ These tumours have the microscopic appearances described above. In addition, microcysts lined by transitional cells or metaplastic columnar endocervical-like mucinous cells occasionally develop within cell nests and occasionally foci of squamous metaplasia are seen. Borderline (proliferating) BTs are characterized by proliferating epithelium resembling low-grade transitional cell carcinoma of urinary tract origin. Occasional mitoses and nuclear atypia may be seen. The severity of nuclear atypia is the main determinant between low-grade and high-grade proliferating BT. By definition, malignant BT must include areas of benign BT and have an additional malignant component, normally squamous, transitional or adenocarcinoma. When BTs are composed of entirely malignant transitional epithelium, they are called transitional cell carcinomas. In the case described, the malignant potential of the lesion was difficult to determine, as the lack of proliferating areas precluded its diagnosis as a proliferative BT with high-grade features.² However, the presence of carcinoma *in situ* does not allow this lesion to sit comfortably in the 'benign' category.

The main differential diagnoses of malignant/proliferating BT include metastatic carcinoma from cervix

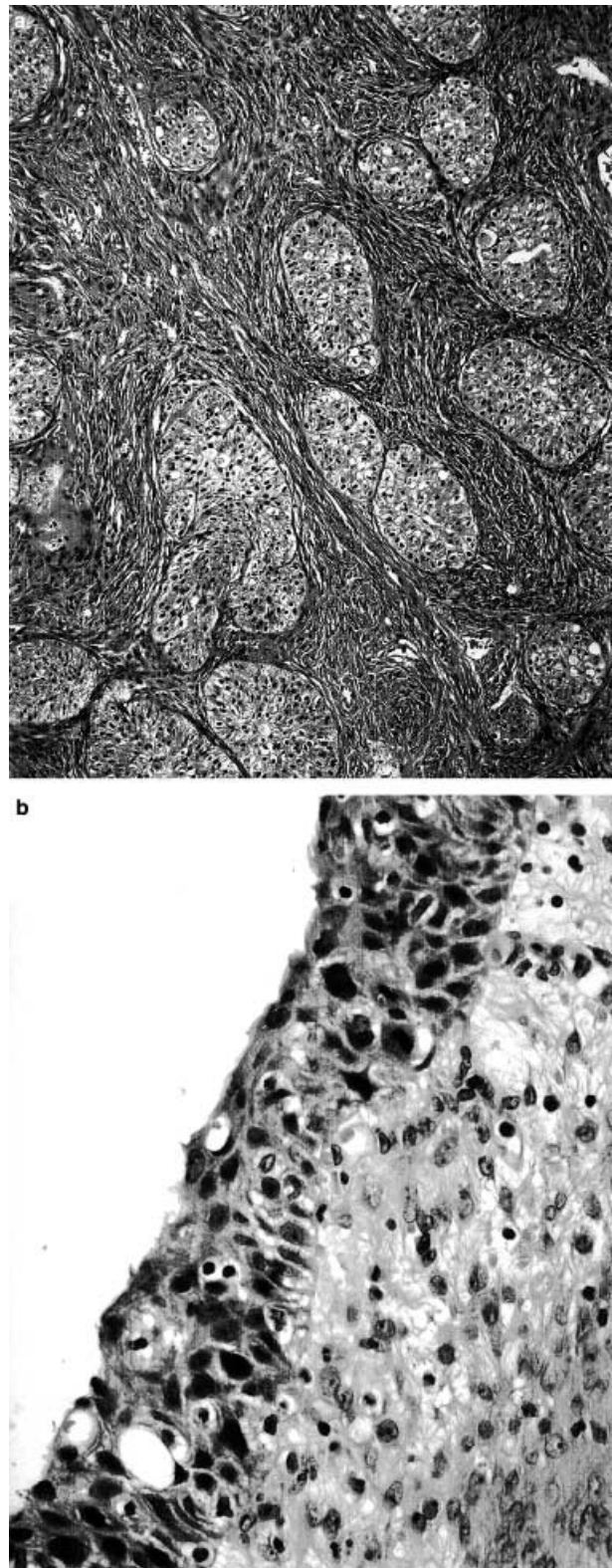


Figure 1. a, Nests of cytologically bland transitional cells lying in fibrous stroma. H&E. b, Severe dysplasia in thin epithelium lining the cyst. H&E.

or bladder. However, a distinguishing feature is that metastatic carcinoma from the bladder tends to be CK20+.³

In other organs such as the cervix, bronchus and oesophagus, carcinoma develops via a well-defined pathway from normal epithelium undergoing metaplasia, then dysplasia and finally invasion. This case supports the hypothesis that BT may undergo a similar stepwise progression. To our knowledge this is the first case of benign BT showing *in situ* transitional cell carcinoma. This provides further evidence of a spectrum in Brenner tumours ranging from benign, through squamous, transitional or intestinal metaplasia to malignant BT.

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Frozen section diagnosis of fibrotic sclerosing pneumocytoma with psammomatous calcification

Sir: We enjoyed reading the recent article by Drs Chan¹ with regard to frozen section diagnosis of sclerosing pneumocytoma. We agree with the authors that diagnosis is possible on frozen section, particularly if characteristic histological features or multiple differentiation patterns are evident on the sections taken. We also agree that a percentage of sclerosing pneumocytomas may defy confident identification at frozen section, particularly if only one pattern of differentiation is present. With this in mind, we wish to highlight a recent case that illustrated the difficulty facing the pathologist in frozen section diagnosis of this tumour.

Following a chest infection, a 63-year-old female was found to have a rounded mass on the mediastinal aspect of the left lower lobe. At operation, a 48-mm

diameter rounded firm beige tumour was confirmed, prompting a 11-mm diameter sample being sent for frozen section analysis to determine the resection required. Histological analysis (Figure 1) revealed a relatively bland fibrotic piece of tissue with spindle cells and scattered psammoma bodies. No epithelium was identified, and definitive diagnosis was deferred until paraffin section, thereby prompting lobectomy.

The lobectomy specimen revealed all four characteristic patterns of sclerosing pneumocytoma, with haemorrhagic, papillary, fibrotic and solid elements within the tumour. These appeared to be relatively well demarcated from one another. Overall, the tumour showed a rounded and pushing margin with adjacent compressed lung parenchyma.

This case highlights the difficulty in determining the nature of spindle cell proliferations at frozen section, and emphasizes that multiple frozen section samples may be required for the diagnosis of sclerosing pneumocytoma. On the basis of this case, our future policy will be to request more than one sample for frozen section from such lesions.

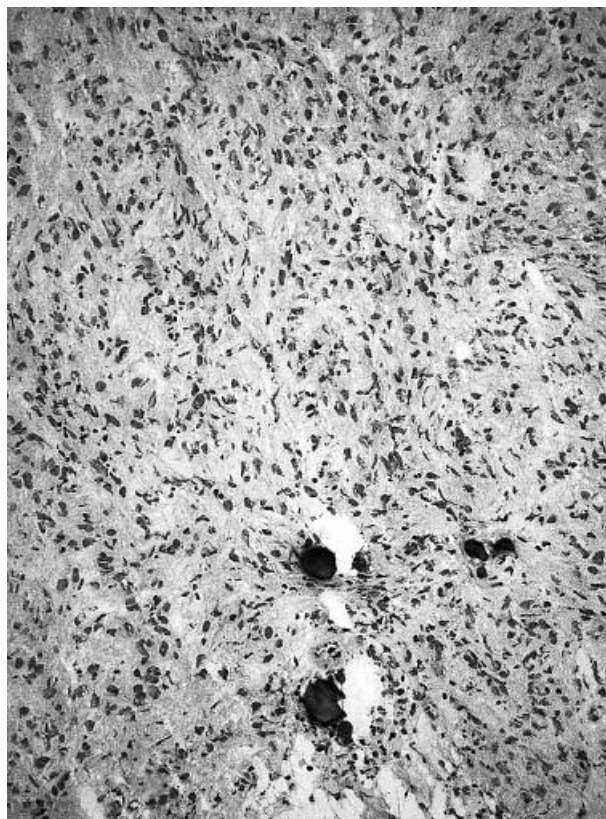


Figure 1. Bland spindle cells are seen in a collagenized background. Focal psammomatous calcification is noted.

The case also serves to remind pathologists of the difficulty in differential diagnosis of fibrotic/spindle cell processes solely on the basis of frozen section. The finding of foci of psammoma bodies was a further confounding factor in our diagnosis—these are not a common component of sclerosing pneumocytoma.²

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