

## Correspondence

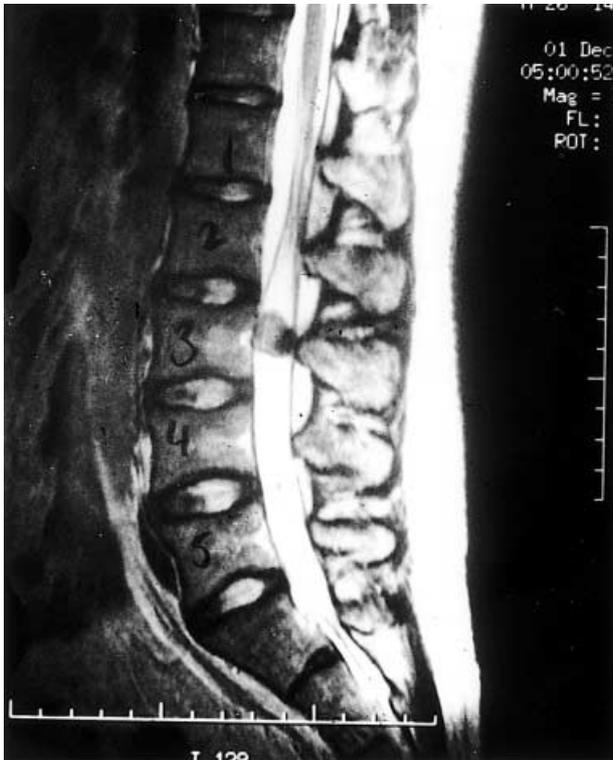
### Melanoma arising in and limited to a spinal nerve root of the cauda equina

*Sir:* A total of 39 cases of primary spinal cord melanoma have been described in the English language literature, but there are only two examples<sup>1,2</sup> of a melanoma arising in and limited to the spinal nerve root. We present a case of primary melanoma located in a spinal root of the cauda equina which was totally intradural, a peculiarity previously unreported.

A 26-year-old man with a 3-month history of progressively worsening left sciatica, which failed to respond to medical treatment, was admitted for evaluation by the Department of Neurosurgery. Neurological examination showed no spinal cord compression. Magnetic resonance imaging revealed a single intradural mass at the level of the L3 vertebra, with no associated compression of the conus medullaris (Figure 1). An L3 laminectomy was performed, and after the dura was opened the tumour was exposed. It was a firm, nodular, black, apparently encapsulated

mass arising in a spinal nerve root of the cauda equina. The tumour was totally excised together with proximal and distal segments of the involved spinal nerve root. Soon after surgery the sciatic pain disappeared.

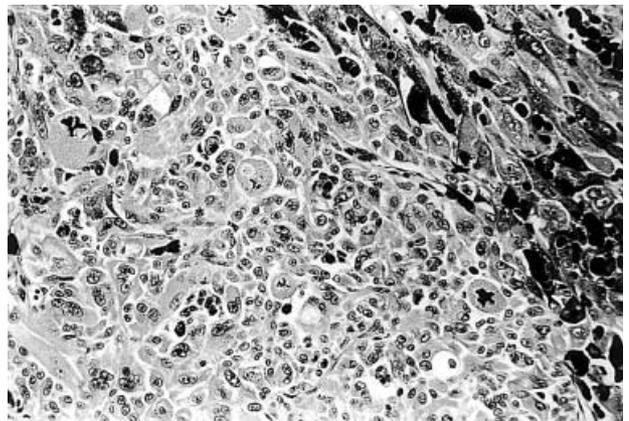
Macroscopically the tumour, which was 20 mm in diameter, was a rubbery, well-demarcated, round mass, with alternating black and white areas on section. Microscopically, it consisted of a diffuse proliferation of epithelioid and fusiform neoplastic cells showing marked nuclear atypia, with prominent eosinophilic nucleoli. Atypical mitoses were very frequent (16 mitoses/10 high-power field), but there was no necrosis (Figures 2, 3 and 4). There was abundant



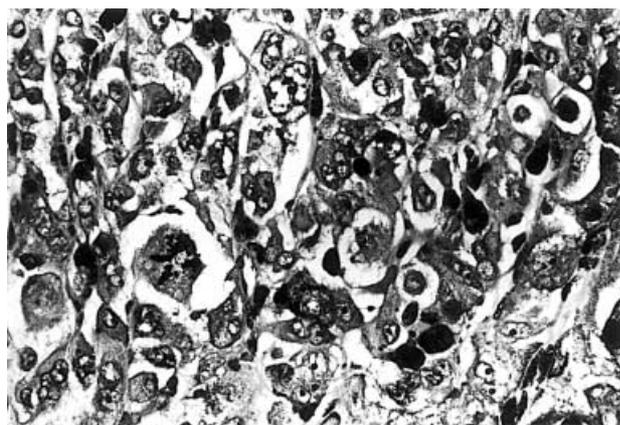
**Figure 1.** Magnetic resonance image. Intradural mass at the level of the L3 vertebra.



**Figure 2.** Low magnification. Well-demarcated nodular tumour with lobular pattern. Alternating pigmented and non-pigmented areas.



**Figure 3.** Neoplastic non-cohesive cells with nuclear atypia and abundant atypical mitoses. Intracytoplasmic melanin pigment (top right corner).



**Figure 4.** High magnification. Neoplastic cells with nuclear anaplasia, evident nucleoli and prominent cytoplasmic melanin granules.

intracytoplasmic melanin pigment. Immunohistochemically, the neoplastic cells were intensely positive for protein S100 and HMB45. Two small segments of normal spinal root were attached to the tumour. The pathological diagnosis was malignant melanoma. The malignant histological features excluded the possibility of a meningeal melanocytoma.

After surgery, the patient underwent further radiological studies, including computed tomography, of the head and body, as well as dermatological and ophthalmological examinations, none of which revealed any other foci of melanoma, either inside or outside the central nervous system. No adjuvant chemotherapy or radiation therapy was administered. Twenty-four months after surgery the patient remains well, with no symptoms of note. Subsequent investigations during this period have failed to find any other melanotic lesions or primary melanoma. Repeated imaging of the craniospinal axis has been normal.

This case fulfils all the necessary criteria to be classified as a primary melanoma arising in a spinal nerve root. In the two other cases of melanoma arising in and limited to a spinal root, with follow-up of 3 and 7 years, the course was benign, with no recurrences or metastases, despite the malignant histological features. This is a similar situation to that of the present patient, although the follow-up in this case is shorter (2 years). This is in stark contrast to the prognosis for primary spinal cord melanoma, for which the average survival of patients after surgery and radiotherapy is only 5–6 years. We believe that the good prognosis is related to the well-defined borders of the tumour in each of the three cases, which have enabled the whole tumour to be excised integrally, prior to local extension or dissemination. However, since definite conclusions

concerning the prognosis for these tumours cannot be made from only three cases, further reports of cases are necessary.

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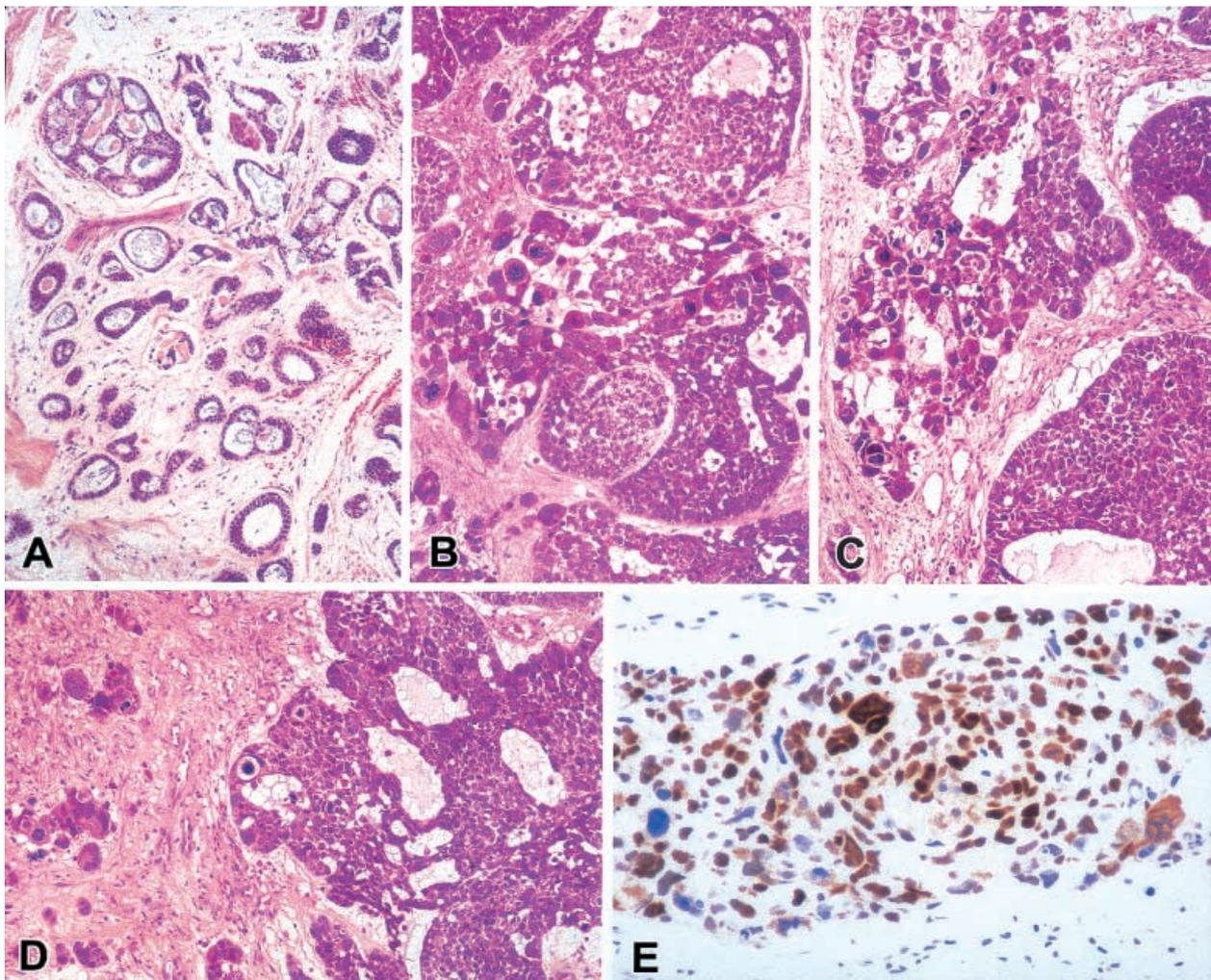
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### Small foci of high-grade carcinoma cells in adenoid cystic carcinoma represent an incipient phase of dedifferentiation

*Sir:* The concept of dedifferentiated adenoid cystic carcinoma as an entity was first described in 1999 by Cheuk *et al.*<sup>1</sup> We would like to complement their report with an interesting case of conventional adenoid cystic carcinoma containing small clusters of high-grade carcinoma cells. This may represent incipient dedifferentiation.

A 62-year-old man presented with a rapidly growing, 22 × 15 mm polypoid tumour of the soft palate. After excision, no follow-up information was available. Areas of typical adenoid cystic carcinoma with a tubulo-cribriform pattern were identified (Figure 1A). Scattered among the fairly uniform basaloid cells were variable numbers of anaplastic cells with bizarre pleomorphic nuclei and numerous abnormal mitoses (Figure 1B,C). These cells were scattered throughout the hyalinized stroma (Figure 1D). These high-grade carcinoma cells expressed pancytokeratin (AE1/A3) but were negative for cytokeratin 14 (LL002), muscle-specific actin (HHF35), S100 protein and glial fibrillary acidic protein (6F2). In contrast to the patchy reactivity of small adenoid cystic carcinoma cells, they showed strong and diffuse immunopositivity for p53 protein (DO7, Figure 1E) and Ki67.

Progression (i.e. increasing grades of malignancy) in the strict sense of dedifferentiation is extremely unusual in salivary gland carcinomas.<sup>2</sup> In adenoid cystic carcinoma, the usual finding is that of transformation from a low-grade tubular or cribriform phenotype to a high-grade solid type in keeping with adenoid cystic



**Figure 1.** A, Initial biopsy showing typical tubulo-cribriform adenoid cystic carcinoma . B, Pleomorphic carcinoma cells among uniform basaloid cells. C, High-grade carcinoma component. D, Scattered carcinoma cells within stroma. E, Diffuse and intense nuclear staining for p53 protein in anaplastic carcinoma cells.

carcinoma morphology. True dedifferentiated adenoid cystic carcinoma is rare and only five examples have been documented.<sup>1,3,4</sup> Except for a single example seen at recurrence,<sup>1</sup> this type of adenoid cystic carcinoma appears to have arisen *de novo*.

The dedifferentiated component has consisted of poorly differentiated adenocarcinoma, not otherwise specified (three cases),<sup>1,4</sup> large-cell undifferentiated carcinoma (one case)<sup>3</sup> and sarcomatoid spindle-cell carcinoma (one case).<sup>1</sup> Interestingly, our tumour had only small foci of high-grade carcinoma cells. Bicellular (ductal and myoepithelial) differentiation was still apparent and the gradual increase in anaplasia was evident. Since the possibility of radiation- or chemotherapy-induced bizarre epithelial atypia was ruled out due

to the absence of previous therapy, these histological features probably represent *de novo* incipient dedifferentiation.

Our immunohistochemical findings together with previous observations<sup>1,4</sup> and the lack of myoepithelial-positive markers in the undifferentiated components suggest that neoplastic myoepithelial cells are not involved principally in this process of dedifferentiation. Similar results have been reported in dedifferentiated epithelial–myoepithelial carcinomas.<sup>5</sup> Over-expression of p53 protein in the dedifferentiated areas suggests that a second primitive cell clone, perhaps of ductal origin, can give rise to high-grade carcinoma as a result of accumulation of mutations of the *p53* gene.<sup>1,4</sup>

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### Cytokeratin-positive malignant solitary fibrous tumour of the pleura: an unusual pitfall in the diagnosis of pleural spindle cell neoplasms

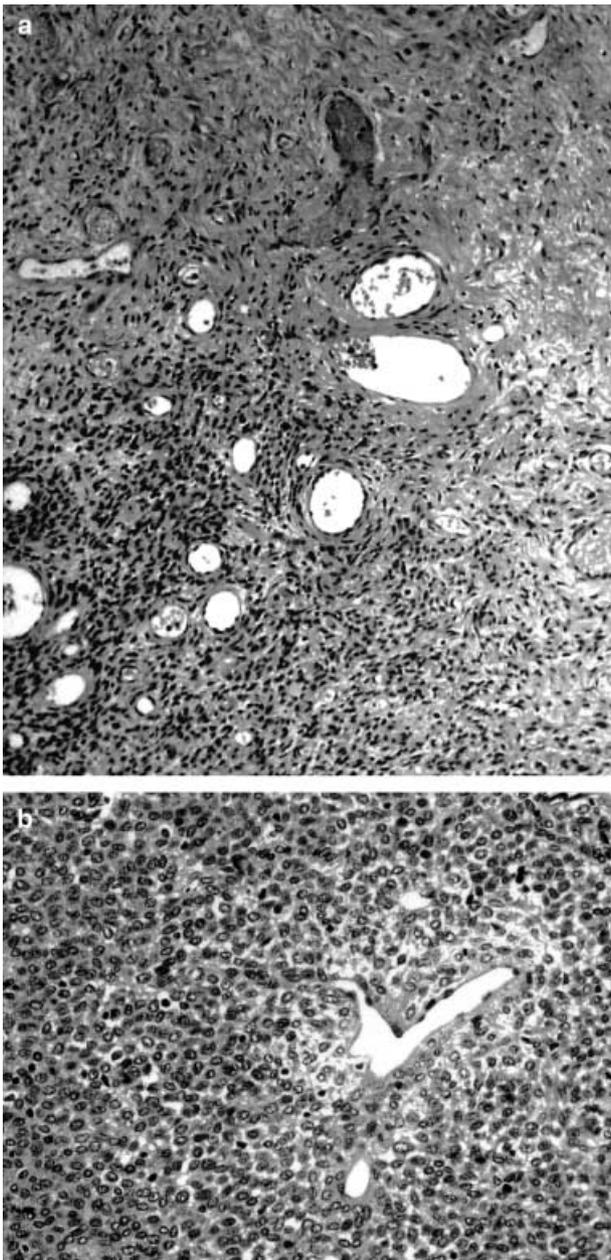
*Sir:* Solitary fibrous tumour (SFT) is a mesenchymal neoplasm that most often involves the pleura, although it can occur in numerous extrapleural locations.<sup>1</sup> The diagnosis by routine light microscopy is generally straightforward, but it can be difficult, particularly in its malignant form. In problematic situations, the characteristic immunophenotype of SFT (positivity for vimentin, CD34, Bcl-2 and CD99, negativity for cytokeratin<sup>2</sup>) is useful to exclude other spindle cell neoplasms. Although a few cases with rare cytokeratin-positive cells have been reported in the literature,<sup>3–7</sup> SFT is traditionally considered to be a cytokeratin-negative neoplasm. Moreover, because in the positive cases the staining was limited to a few cells, some authors have suggested that the latter were probably entrapped non-neoplastic mesothelial elements.<sup>2</sup> We describe a malignant SFT of the pleura in which the majority of the neoplastic cells strongly expressed cytokeratin, a phenomenon that, to the best of our knowledge, has not previously been reported.

The patient was a 74-year-old woman, with an unremarkable past clinical history, presenting with

seizures secondary to recurrent hypoglycaemia. A chest X-ray and a subsequent total-body computed tomography scan revealed a large mass located in the right thorax, compressing the lung parenchyma. Pulmonary function tests showed a restrictive pattern and bronchoscopy was negative. At thoracotomy, a well-circumscribed rounded mass, 220 mm in diameter, greyish in colour and elastic in consistency, was found attached with a thin pedicle to the parietal pleura. The mass was excised. Four years after surgery, the patient presented with multiple right thoracic nodules. An explorative thoracotomy showed numerous pleural masses of variable dimensions, infiltrating the lung and the thoracic wall. Multiple large biopsies were performed. No further therapy was instituted and the patient died of disease 1 month after surgery. No autopsy was requested.

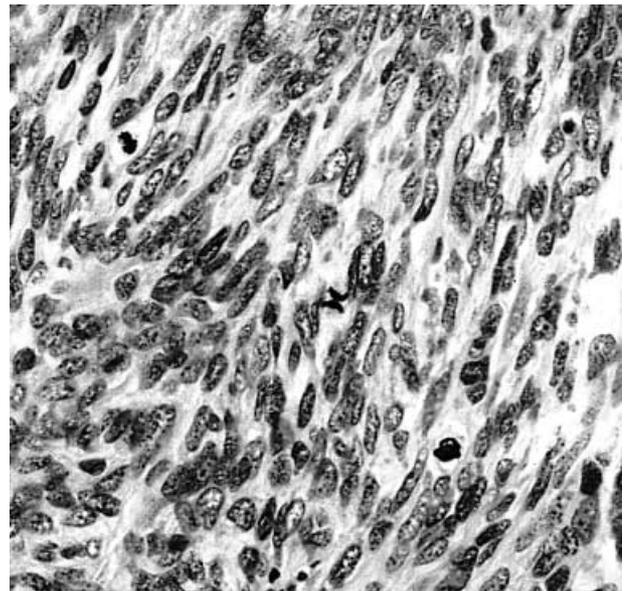
Histologically, the original tumour was well circumscribed. Hypercellular areas predominated, and alternated with hypocellular, densely fibrotic and oedematous foci (Figure 1). Numerous vessels were present, sometimes with a haemangiopericytoma-like appearance. Neoplastic cells were epithelioid to spindle-shaped, and were disposed in short fascicles, in sheets and in a disorderly pattern. In the fibrotic areas, they were surrounded by thick collagen bundles. The cytoplasm was quite abundant and eosinophilic-to-pale, and the nuclei were moderately atypical, with open chromatin and inconspicuous nucleoli. Mitotic activity was low [two mitoses/10 high-power fields (HPF)] and necrosis was absent. Immunohistochemically, tumour cells were strongly positive for vimentin, CD34, Bcl-2 and CD99, negative for EMA, cytokeratin (CK) (CAM5.2), CK7, CK20, CK5/6, calretinin, smooth muscle actin, desmin and S100 protein. A few scattered neoplastic elements reacted with CK AE1/AE3. At ultrastructural examination, lesional cells were fusiform-to-round, with prominent, dilated rough endoplasmic reticulum and randomly distributed cytoplasmic filaments. Polymerase chain reaction for the presence of a SYT-SSX1 or SYT-SSX2 fusion transcript was negative.

The recurrent tumour (Figure 2) was histologically similar to that previously resected: however, lesional cells were more atypical, with a much higher mitotic activity (30 mitoses/10 HPF). Immunohistochemically, the neoplasm retained a diffuse positivity for vimentin, CD34, Bcl-2 and CD99, and negativity for EMA, CK7, CK20, CK5/6, calretinin, desmin and S100 protein. Seventy percent of the tumour cells strongly expressed CK AE1/AE3 (Figure 3), and a few elements reacted with CK CAM5.2 and smooth muscle actin.

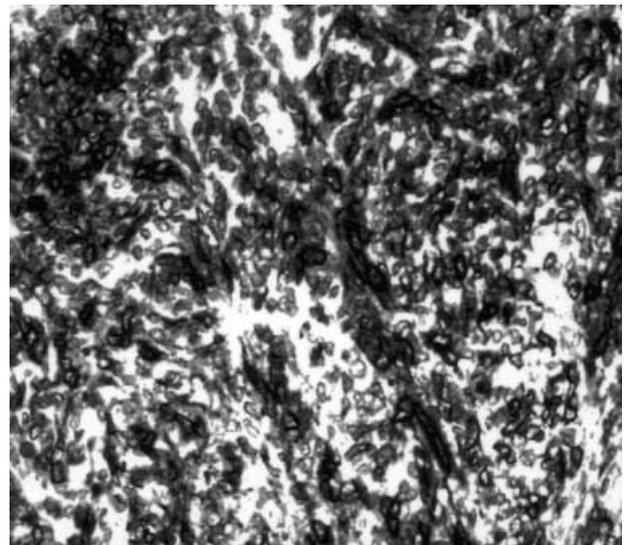


**Figure 1.** a, The original tumour is composed of cellular areas, merging with fibrotic foci (haematoxylin & eosin). b, The neoplastic cells have a pale-to-eosinophilic cytoplasm and an atypical, oval nucleus. The vessels impart to the lesion a haemangiopericytoma-like appearance (haematoxylin & eosin).

This case shows the classical clinical and morphological features of malignant SFT of the pleura.<sup>2</sup> What makes the present lesion apparently unique is the strong and diffuse immunoreactivity of the recurrent tumour for pan-cytokeratin: this exceptional finding is not surprising, since it is well known that cytokeratin



**Figure 2.** In the recurrence, neoplastic cells are more atypical and mitoses are numerous (haematoxylin & eosin).



**Figure 3.** Immunoreactivity of the recurrent tumour for cytokeratin AE1/AE3 (ABC).

can be expressed in a variety of sarcomas, sometimes when they dedifferentiate or recur, as in our case.<sup>8,9</sup>

A cytokeratin-positive malignant SFT poses several diagnostic problems, particularly in the pleura. Sarcomatoid mesothelioma generally presents as a diffuse pleural thickening, although a few examples of localized lesions are recorded.<sup>10</sup> Histologically, sarcomatoid mesothelioma is quite different from SFT. Immunohistochemically, it can be positive for calretinin

and CK5/6, and it lacks CD34, Bcl-2 and CD99 expression.<sup>2,11</sup>

The most difficult differential diagnosis is probably with monophasic synovial sarcoma, which occasionally may arise in the pleural cavity.<sup>12</sup> Synovial sarcoma tends to occur in a younger age group than SFT. Clinically, it is not generally associated with hypoglycaemia, and macroscopically it is not pedunculated. Histologically, a considerable overlap exists, and immunohistochemistry and molecular biology are useful in difficult cases: reactivity for CD34 and negativity for the SYT-SSX fusion transcripts, as in our study, strongly favour the diagnosis of SFT.

Finally, differences in histological and immunohistochemical features generally allow one to distinguish cytokeratin-positive malignant SFT from other spindle cell neoplasms that occasionally develop in or spread to the pleura, such as thymoma, sarcomatoid carcinoma or smooth muscle tumours.<sup>13,14</sup>

In summary, it is important to be aware that, albeit rarely, SFT can express cytokeratin, as may other mesenchymal neoplasms. Our observation emphasizes the importance of an appropriate immunohistochemical panel in the differential diagnosis of spindle cell tumours of the pleura.

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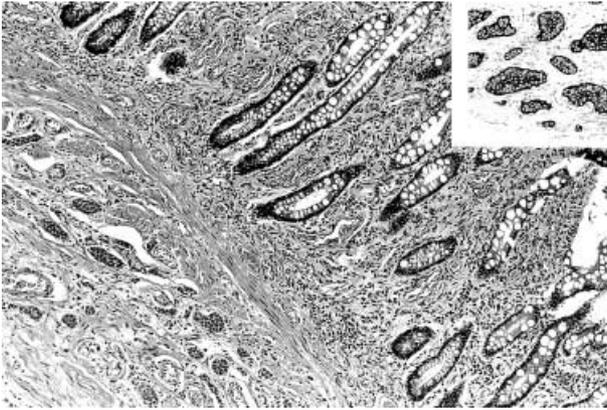
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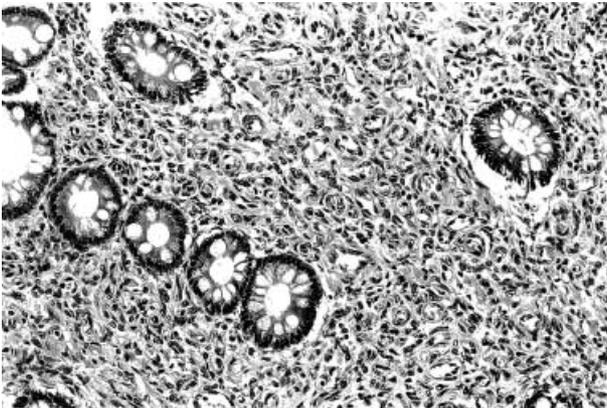
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### Ileal intussusceptus containing a Meckel's diverticulum showing florid localized mucosal angiogenesis and microcarcinoidosis

Sir: A 35-year-old male presented with intestinal obstruction due to intussusception; the intussuscepted bowel was excised. The specimen consisted of caecum 300 mm in length containing the intussusceptus (ileum measuring 80 mm in length) with a Meckel's diverticulum 70 × 30 mm proximal to the intussusceptus. Microscopic examination showed haemorrhagic ischaemic necrosis of the terminal ileum. The Meckel's diverticulum showed florid angiogenesis of the mucosa with patchy, vascular proliferation within the submucosa and in the muscularis propria (Figure 1). Fibrosis of the lamina propria was also a feature. In addition, in three pieces of tissue (of a total of approximately 50) small microscopic foci of carcinoid tumour were present, each consisting of scattered small nests of cells linearly disposed and the largest extending to 2 mm in maximum dimension (Figure 2). Immunohistochemistry showed strong positivity within the carcinoid tumour for chromogranin A and patchy reactivity for vascular endothelial growth factor (VEGF). Transforming growth factor-alpha (TGF- $\alpha$ ), TGF- $\beta$ , p53 and thrombospondin were negative.



**Figure 1.** Meckel's diverticulum submucosa containing microcarcinoid with adjacent mucosa in which there is vascular proliferation expanding the lamina propria. Inset shows chromogranin A immunopositivity within the microcarcinoid cells.



**Figure 2.** High-power photomicrograph showing mucosal angiomatosis.

Four cases of florid and sometimes polypoid mucosal angiogenesis associated with ileal carcinoids have been published.<sup>1–3</sup> In the first two reported cases the aetiology was thought to be multifactorial and due to growth factors and subsequent mechanical factors,<sup>1</sup> while the two more recent cases were ascribed to the angiogenic factors TGF- $\alpha$  and TGF- $\beta$ .<sup>2,3</sup> TGF- $\alpha$ , however, is present in a wide variety of endocrine cells and in intestinal carcinoids, most of which are unassociated with florid angiogenesis. VEGF has also been reported in mid-gut carcinoids unassociated with mucosal angiogenesis. Recently, Abrahams *et al.* found mucosal angiogenesis adjacent to 61% of ileal carcinoids, in 26% of which it was florid and adjacent to 72% of non-carcinoid ileal neoplasms, in 35% of

which it was florid.<sup>4</sup> In 83% of the former and in 100% of the latter cases this change was associated with features of mucosal prolapse leading them to suggest prolapse as the inducing aetiology. We reviewed six cases of Meckel's diverticulum and two showed the usual features of mucosal prolapse focally and one showed mild angiogenesis, illustrating that mucosal prolapse may not be an uncommon finding in such diverticula. Also, a case of florid vascular proliferation in the caecum of a patient with ileocolic intussusception due to a submucosal lipoma has been described.<sup>5</sup> Although distinctive glomeruloid vascular lesions in neuroendocrine carcinomas have been described,<sup>6</sup> and while the interplay of multiple (and perhaps unknown or unidentified) cytokines may play some role in the angiogenesis reported here, we consider that prolapse associated with possible recurrent intussusception is likely to have been the main cause in this case.

#### ACKNOWLEDGEMENTS

We thank Mrs Sandra Thompson for excellent secretarial assistance and Alan Curry PhD for photomicrographs.

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