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An early lesion of pulmonary carcinosarcoma: possible diagnostic problem in frozen section interpretation

Sarcomatoid carcinoma is a rare malignant neoplasm of the lung.¹ Its definition was ambiguous until the recent establishment of World Health Organisation (WHO) criteria, according to which it is classified into carcinosarcoma, pleomorphic carcinoma, and spindle cell carcinoma.¹ Most of the reported cases of carcinosarcoma or pleomorphic carcinoma of the lung have been large tumours. We present a case of an extremely small carcinosarcoma of the lung with an unfavourable course.

An asymptomatic 69 year old man was admitted to our hospital because of a coin lesion that was detected on a medical examination. He had smoked 20 cigarettes a day for 48 years. Computed tomography showed an irregular shadow of 19 mm maximum diameter in contact with the pleura, situated in the S3 region of the right lung. Neither transbronchial biopsy nor percutaneous needle biopsy yielded positive results. Because thoracoscopic biopsy with frozen section interpretation could not entirely rule out malignancy (fig 1), right upper and middle lobectomy with lymph node dissection was performed. Nine months after surgery he developed a pleural effusion, a cytological preparation of which showed the presence of malignant cells.

The tumour measured 19 × 15 × 7 mm, and was situated just beneath the pleural surface of the middle lobe of the right lung. On cut section it was firm, whitish, and uniform in appearance.

Microscopically, most of the tumour was composed of a pure sarcomatoid region, and the remainder comprised a biphasic region. More than two thirds of the sarcomatoid area was collagenous and showed a deceptively well differentiated appearance. A small focus showing apparent chondroid differentiation was seen within the collagenous area. The remaining sarcomatoid area was composed of atypical spindle cells with pleomorphic nuclei and eosinophilic cytoplasm, in which cross

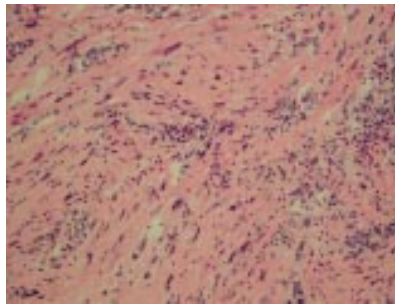


Figure 1 Frozen section of the tumour, which was composed of moderately atypical spindle cells with an inflammatory infiltrate, resembling reactive fibroblastic proliferation. The carcinomatous element was not conspicuous (haematoxylin and eosin stain; original magnification, ×100).

striations were not readily observed. The carcinomatous component showed varying degrees of distinct gland formation, the dimensions of which ranged from large cystic spaces to small tubular structures. The tumour invaded the pleura. There were no positive lymph nodes.

Immunohistochemically, the carcinomatous cells were positive with antibodies to various cytokeratins, including AE1/AE3 (prediluted; Dako, Carpinteria, California, USA). They were negative for vimentin (prediluted; Dako). Sarcomatous cells were negative for cytokeratins and strongly positive for vimentin. S-100 (prediluted; Nichirei, Tokyo, Japan) was positive in the foci with cartilaginous differentiation.

It is important to know just how small a carcinosarcoma of the lung can be, because the existence of small carcinosarcomas suggests that the sarcomatoid transition could take place relatively early. In the literature, small carcinosarcomas of the lung are encountered extremely rarely. Koss *et al* reviewed the literature and found 34 cases that fit the WHO definition of pulmonary carcinosarcoma, among which only two cases were 2 cm in size.² Early lesions of carcinosarcoma of the lung may necessitate intraoperative diagnosis. Care should be taken in the interpretation of a frozen section because insufficient sampling could lead to an erroneous diagnosis, such as reactive fibroblastic proliferation.

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Caution should be taken in using CD31 for distinguishing the vasculature of lymph nodes

When interpreting lymph node biopsies it is sometimes necessary to distinguish the different compartments of the lymph node. In normal lymph nodes the task may be easily accomplished, but it can be difficult for effaced lymph nodes. We compared the usefulness of routinely used endothelial markers for distinguishing sinuses from vascular channels in the lymph node.

Eighteen lymph nodes—seven normal lymph nodes from a patient with colonic cancer (patient 1), eight from a patient affected by diffuse large B cell lymphoma of the stomach (patient 2), and three from a patient with anaplastic large cell lymphoma (ALCL) (patient 3)—were selected from the archives of the department of pathology, Kariya General Hospital, Japan. The tissues were fixed in 10% formalin and embedded in paraffin wax. Standard tissue sections, 6 µm thick, were stained with haematoxylin and eosin. Immunohistochemical staining was performed by means of the Ventana immunostainer (Ventana, Tucson, Arizona, USA). The primary antibodies used were commercially available antibodies directed against factor VIII (prediluted; Dako, Carpinteria, California, USA), CD31 (prediluted; Dako), and CD34 (prediluted; Dako). Positive and negative controls were used in each assay. For anti-CD34, dewaxed sections were pretreated in a microwave for 15 minutes, in 95°C 10mM citrate buffer at pH 6.0. For anti-CD31, sections were pretreated in two ways, either with trypsin or by the microwave method.

Anti-CD34 was applied to the sections of all lymph nodes from patients 1 and 2, but only decorated vascular channels. For anti-factor VIII, background staining was very intense in the sinuses. Anti-CD31, when pretreated with either trypsin or in the microwave, was positive not only for the endothelium of vascular channels but also for the lining cells of sinuses. When applied to the lymph nodes from patient 3, all the tumour cells were confined within spaces that were lined by CD31 positive cells (fig 1). The application of anti-CD34 suggested that these spaces were in fact sinuses (fig 2), leading to the conclusion that this case represented ALCL with a sinus pattern of involvement.

The sinuses of the lymph node are different from vascular channels in that they are not lined with endothelium.¹ CD31 is believed to be a highly specific marker for endothelial cells.² Recently, however, McKenney and associates showed that the expression of CD31 by macrophages could easily be detected on formalin fixed, paraffin wax embedded sections, causing misdiagnosis in surgical pathology practice.³ This characteristic of CD31 may also be important in distinguishing the compartments of the lymph node or spleen. The presence of CD31 cannot be used to distinguish sinuses from capillaries or venules because specific dendritic cells that line the sinuses of lymph nodes are also positive for CD31.^{3,4} Apparent positivity for CD31 could lead to the misinterpretation of sinuses as vascular channels. CD34 is expressed by a variety of cells, and can be detected not only in endothelial cells, but also in reactive fibroblasts and some types of benign and malignant mesenchymal neoplasms.² Applying



Figure 1 Applied to an anaplastic large cell lymphoma (ALCL) case, CD31 decorates both vascular channels and sinuses that are filled with ALCL cells (diaminobenzidine reaction; haematoxylin counterstain; original magnification, $\times 100$).

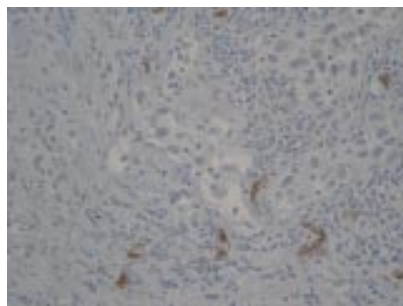


Figure 2 Staining for CD34 verifies that these channels are in fact sinuses (diaminobenzidine reaction; haematoxylin counterstain; original magnification, $\times 100$).

anti-CD34 to routinely processed lymph nodes can help to distinguish vascular channels from sinuses because all the sinuses, including peripheral sinuses, would be negative for CD34. In conclusion, it is highly recommended that anti-CD34 should be used together with anti-CD31 to distinguish the vasculature of lymph nodes.

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Cirrhosis with steatohepatitis following longterm stilboestrol treatment

Diethylstilboestrol, which is chemically related to the female hormone oestrogen, was the main form of androgen suppression in the treatment of advanced prostate cancer up until the late 1980s.¹ Although luteinising hormone releasing hormone (LHRH) analogues have superseded diethylstilboestrol over the past 10 to 15 years, it is relatively common in clinical practice to encounter patients who are still taking diethylstilboestrol. Adverse hepatic reactions involving diethylstilboestrol have been reported in animal models,² but are still relatively uncharacterised in humans.

We describe a case in which a patient was started on stilboestrol (1 mg twice daily) at age 65, after a diagnosis of prostatic adenocarcinoma of Gleason grade 3 (1+2). There was no evidence of metastatic spread, despite locally advanced disease. After 11 years of stilboestrol treatment, he was transferred to three monthly injections of LHRH analogue (Zoladex) to reduce the risk of developing the cardiovascular side effects associated with stilboestrol. At this time, liver function tests were abnormal, with γ glutamyl transpeptidase at 208 U/litre (normal range, 5-50) and aspartate aminotransferase at 63 U/litre (normal range, 10-35), but other liver enzymes were normal. The patient's alcohol intake was minimal. Liver ultrasound showed a diffuse nodular pattern suggestive of metastatic malignancy. Liver biopsy showed established cirrhosis with a steatohepatitis comprising steatosis, nuclear glycogenation, hepatocyte ballooning, and scanty hepatocyte necrosis (fig 1). There was no evidence of primary or metastatic malignancy.

The most common cause of steatohepatitis is alcohol excess, which should be excluded clinically. Causes of non-alcoholic steatohepatitis include obesity, diabetes mellitus, nutritional imbalance, and drugs including amiodarone and tamoxifen.³ Because no other contributing factors were identified,

the liver disease in our patient was thought most likely to be the result of treatment with stilboestrol.

Although the effect of stilboestrol on the liver has been investigated, research has centred on animal models.² One human study described parenchymal damage, in the form of non-alcoholic steatohepatitis, in six post-mortem cases with a history of diethylstilboestrol treatment for prostate cancer.⁴ In addition, two documented cases of hepatocellular carcinoma have been reported following longterm stilboestrol treatment.^{5,6} Interestingly, non-alcoholic steatohepatitis is seen not only with oestrogenic drugs such as stilboestrol, but also with the partial agonist drug tamoxifen.⁷ It is known that steatohepatitis inducing drugs such as stilboestrol accumulate within mitochondria, resulting in ATP depletion and lipid peroxidation of hepatocytes.²

Diethylstilboestrol was once the main alternative to orchiectomy in the treatment of prostate cancer.¹ However, its potential side effects, which include breast enlargement and cardiotoxicity, mean that it has been largely superseded by LHRH analogues with superior safety profiles. Although the use of stilboestrol has declined, its reintroduction to large scale clinical use has recently been proposed, particularly for early hormone refractory disease.¹ This case report emphasises the need for regular monitoring of liver function tests in those receiving such treatment. It also serves as a further example of a steatohepatitis inducing drug.

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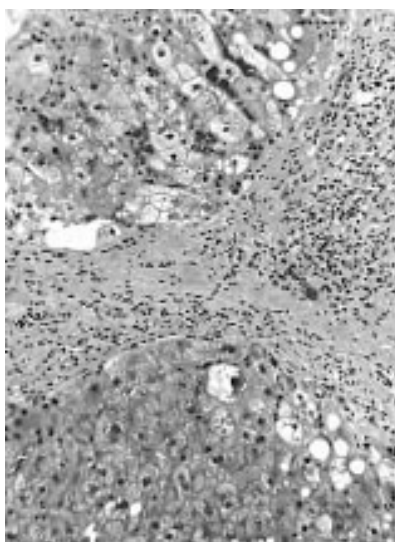


Figure 1 A needle biopsy of liver showing pronounced steatosis and hepatocyte ballooning, together with architectural abnormalities amounting to cirrhosis.

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BOOK REVIEWS

Cytopathology of the Breast

McKee GT. (£130.00.) Oxford University Press, 2002. ISBN 0 19 514006 0.

Grace McKee's recent publication provides an extremely comprehensive overview of breast entities. Although it is entitled "Cytopathology" it encompasses much more, providing clinical and histopathological details, in addition to cytological features of a very wide range of breast entities.

The initial chapters provide detailed discussions of normal breast histology and cytology, methods of aspiration, smear preparation, and laboratory techniques, including sections on the reporting of cytological specimens and the limitations of cytology. Although concentrating on fine needle aspiration biopsy material, exfoliative cytology of nipple secretions and ductal lavage specimens are also included. Subsequent chapters are organised such that entities are introduced with clinicopathological descriptions followed by gross, histological, then cytological features. For many entities this is followed by a summary of cytological findings. There are numerous photomicrographs of both histological and cytological features, which are of excellent quality, the discussions are detailed, and references are extensive. The very comprehensive nature of the text is perhaps a slight weakness, for even the numerous photographs cannot fully illustrate the features of some of the lesions discussed, and although the limitations of cytological diagnoses are described, it is not always clear whether the diagnosis of some entities from the cytological specimen is practically feasible.

The book is splendidly written and beautifully illustrated. In the context of the recent changes in breast diagnosis and the increased complexity of breast lesions, an in depth review of breast from the cytological and histological perspectives is timely. This book will be a useful reference text for those involved in

diagnosing breast lesions by either cytology or histology, and may also be recommended to clinicians who take their own cytological breast specimens

N A Miller

The Diagnosis of Lymphoproliferative Diseases: An atlas

Gatter K, Delsol G. (£145.00.) Oxford University Press, 2001. ISBN 0 19 850 891 3.

The authors set out clearly in their preface how and why this atlas came into being. An atlas in pathology is usually a compendium or analecta of illustrations attended by short annotations. As a rule, atlases don't make the "go for" book list when it comes to a diagnostic crunch. This book is more than an atlas. Condensed into a mere 262 (258 if one really wants to be pedantic) pages, crammed with excellent colour illustrations, this book is also full of facts, suggestions and guidelines. From the introduction (where one of the authors indulges himself with a military reference!) which contains very useful tables of antibodies used in haematopathology through to the index at the back, I found the book extremely user friendly and written in an almost conversational style. This book has everything a general surgical pathologist is ever likely to encounter by way of lymphoproliferative diseases. I daresay the card carrying haematopathologist will be hard pressed to find an entity that is not covered. The book addresses all the diagnostic dilemmas that cause non-afficionados of matters lymphoproliferative to become weak kneed about in a concise, coherent, and informative manner. There is no doubt that this is an essential benchbook for any department of pathology. With all the colour pictures, the price is competitive and not exorbitant. Professors Gatter and Delsol are to be congratulated on their pithy, epigrammatic offering, which really does prove that size doesn't really matter.

R Chetty

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Further details: Ms Valerie Wood, ACP Central Office, 189 Dyke Road, Hove, East Sussex, BN3 1TL, UK. (Tel: +44 01273 775700; Fax: +44 01273 773303; Email: valerie@pathologists.org.uk)

Dermatopathology Update

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Further details: Tel: +1 617 384 8600; Email: hms-cme@hms.harvard.edu; website: www.cme.hms.harvard.edu

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Further details: Professor Ian A Cree, Translational Oncology Research Centre, Department of Histopathology, Michael Darmady Laboratory, Queen Alexandra Hospital, Cosham, Portsmouth PO6 3LY, UK. (Tel: +44 (0)23 92 286378; Fax: +44 (0) 23 92 286379; Email: ian.cree@porthosp.nhs.uk)

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**Cytopathology of the Breast : McKee GT.
(£130.00.) Oxford University Press, 2002. ISBN
0 19 514006 0.**

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