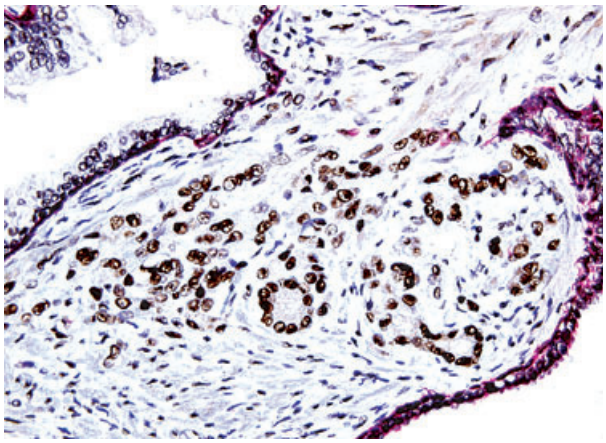

Figure 4. Double immunohistochemistry with an antibody cocktail containing MLH1 and 34bE12. Benign glands show strong pink 34bE12 cytoplasmic immunoreactivity and prostatic adenocarcinoma shows strong brown MLH1 nuclear reactivity.

Table 2. Proposed quadruple staining cocktail

	Nuclear	Cytoplasm
Adenocarcinoma	MLH1	AMACR
Benign glands	p63	34bE12

In summary, we have found a significant increase in MLH1 immunoreactivity in prostatic adenocarcinoma. The increased MLH1 expression in the precursor lesion HGPIN suggests a role of MLH1 in prostatic carcinogenesis. However, its expression may not be related to the aggressiveness of prostatic cancer, because the intensity of immunoreactivity is similar in both intermediate and high-grade prostatic adenocarcinoma. Lastly, we have demonstrated the feasibility of creating new cocktails containing antibodies specific for malignant (MLH1, AMACR) and benign (34bE12, p63) prostatic epithelia.

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Nodular histiocytic/mesothelial hyperplasia on transthoracic biopsy: another source of potential pitfall in a lesion frequently present in spontaneous pneumothorax

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Sir: 'Nodular mesothelial hyperplasia', 'lesions resembling histiocytoid (epithelioid) haemangioma', 'mesothelial/monocytic incidental cardiac excrescences (MICE)' and 'nodular histiocytic/mesothelial hyperplasia (NHMH)' are the designations used to describe an incidentally detected tissue consisting of small, discrete, nodular aggregates of numerous histiocytes with a minor component of closely intermingled mesothelial cells singly dispersed or disposed in clusters and/or strips.[1–7] These completely benign lesions are generally found during cardiac surgical procedures[2–4] and in hernial sacs,[1,7] but also on transbronchial biopsies,[5,7] pulmonary resections for pneumothorax or pelvic surgery.[7]

We describe a case of NHMH detected on transthoracic biopsy performed for a peripheral lung nodule. In this hitherto unreported setting, NHMH had some peculiar features that represent further potential pitfalls and should be highlighted to prevent misdiagnosis. In addition, we point out the frequent finding of NHMH in pneumothorax.

A 79-year-old man, an ex-smoker and retired building worker, presented in February 2007 with recurrent dry cough associated with exertional dyspnoea. The patient had a past medical history of chronic cardiac ischaemic, for which he had undergone a triple aorto-coronary by-pass 2 years previously. Standard

chest x-rays showed an irregular opacity of the left lower lobe. Chest computed tomography (CT) confirmed the presence of a 50-mm pleural-based mass in the left lower lobe involving the descending aorta and associated with concomitant pleural effusion and subcarinal lymph node enlargement. Since standard bronchoscopy was negative, a CT-guided transthoracic biopsy of the pulmonary mass using a 19-G needle was performed (Figure 1A). A 2-mm fragment of brownish tissue was obtained for histological examination (Figure 1B). It consisted of blood clot and a discrete nodular aggregate of cohesive polygonal round-to-oval

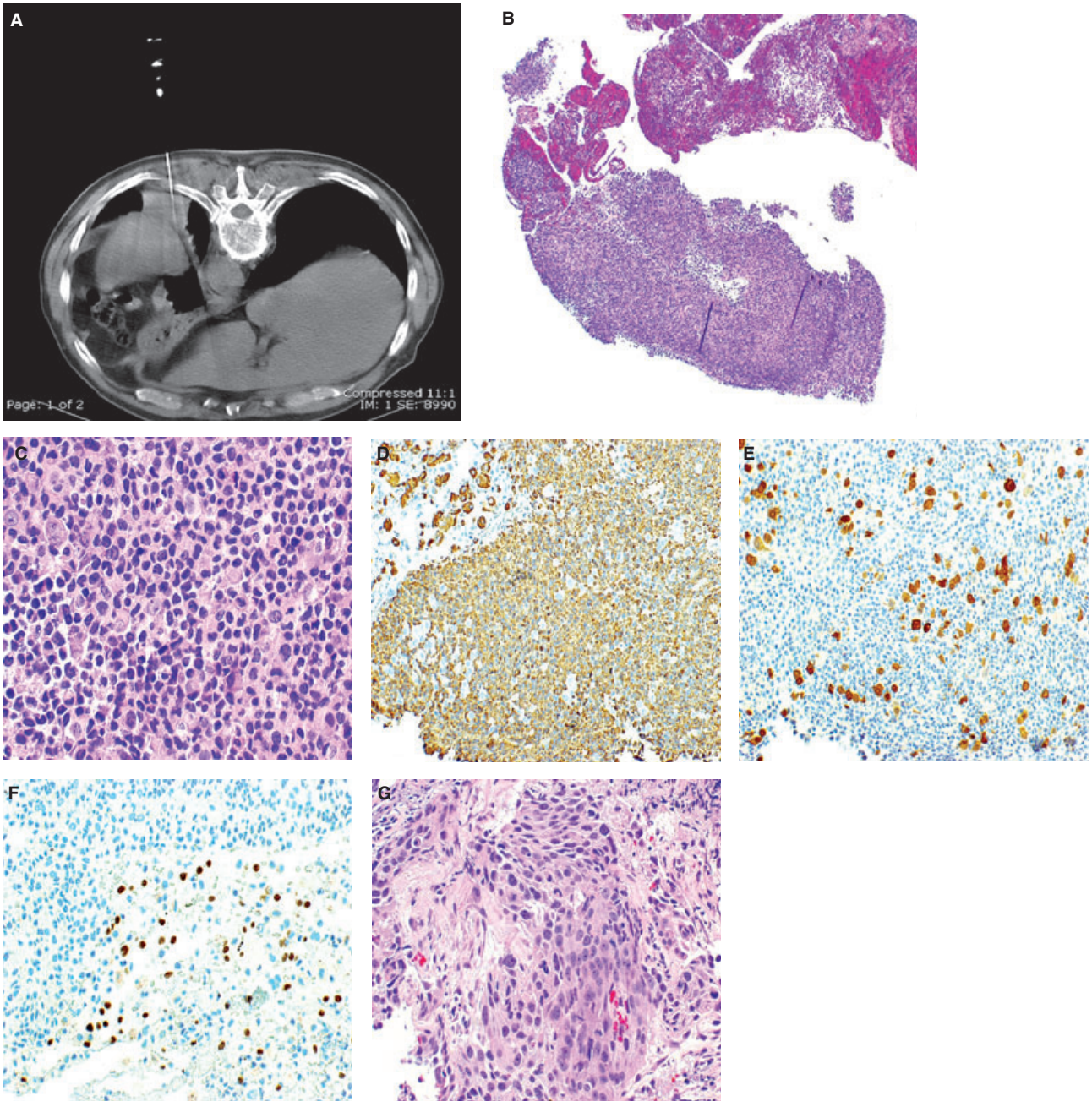

Figure 1. Chest computed tomography (CT) scan showing a left lower-lobe pleural-based mass with concomitant pleural effusion (**A**). During CT-guided transthoracic biopsy a discrete nodular fragment (**B**) consisting of a dense aggregate of polygonal cells with grooved nuclei (**C**) was obtained. The great majority of cells are CD68+ (**D**), whereas scattered cells react with an antibody to calretinin (**D**). At the periphery, dispersed thyroid transcription factor-1-positive (**F**) cells can be seen. Subsequent transbronchial biopsy revealed a poorly differentiated squamous cell carcinoma (**G**).

cells with ample pink cytoplasm and nuclei with prominent grooves, occasional nucleoli and moderate pleomorphism with a few mitotic figures, never atypical (Figure 1C). Immunohistochemically, most of the cells exhibited histiocytic differentiation immunoreactive for CD68 (PGM-1) (Figure 1D), whereas scattered poorly distinguishable cells were immunopositive for pan-cytokeratin (clone MNF-116) and calretinin (Figure 1E), thus appearing as mesothelial elements. No immunoreactivity was noted for S100, CD1a, p63, leucocyte common antigen or CD138. An insignificant MIB-1 labelling index was also observed.

This nodular mixture of histiocytes and mesothelial cells had the classic characteristics of NHMH. However, immunohistochemistry for cytokeratin and thyroid transcription factor (TTF)-1 (Figure 1F) revealed a few dispersed cells with moderate cytoplasm and small distinct nucleoli at the periphery of the nodule. These slightly atypical elements appeared suspicious for adenocarcinoma. However, in light of the inconclusive findings, a transbronchial biopsy was performed and revealed a poorly differentiated non-small-cell carcinoma (Figure 1G). Tumour cells were intensely immunoreactive with p63, but were negative for TTF-1, CD56/neural cell adhesion molecule and chromogranin, suggesting squamous cell differentiation. At this point, the previously described TTF-1+ cells in the NHMH were interpreted as hyperplastic/reactive pneumocytes rather than true neoplastic cells.

NHMH is more likely to be an artefactual/reactive proliferation of histiocytes and mesothelium secondary to pleural irritation, as previously suggested by Chan *et al.*[5] The presence of a pleural effusion in this case favours this interpretation, but, whatever the aetiopathogenesis of NHMH, it is clear that it represents an undeniable potential pitfall for pathologists. Of note, we found foci of NHMH in 34 out of 100 consecutive lung resections for spontaneous pneumothorax, and this fact further supports the reactive origin of such lesions.[5] It is therefore important to be aware of this lesion in order not to misinterpret NHMH as a malignant process. Controversial results have been reported using CD34 to highlight mesothelial cells in NHMH, implicating cell–cell adhesion molecules in such an occurrence.[8,9] We stress that NHMH can occur even in a transthoracic biopsy specimen and the probability of error in this setting may be higher than in other situations. In fact, transthoracic fine-needle aspiration biopsy is an invasive diagnostic procedure usually adopted in peripherally located pulmonary nodules that are unlikely to be accessible by standard bronchoscopy. Pathologists may consider this unusual nodular proliferation as a bizarre form of lung tumour. The probability of an erroneous diagnosis of adenocarcinoma becomes higher if the lesion is associated with scattered, slightly atypical cells (hyperplastic reactive pneumocytes) immunoreactive with TTF-1, as in our case. Of note, there is the possibility of a carcinoma occurring in a MICE, as previously described.[10]

In conclusion, NHMH is a frequent occurrence in pleura-damaging processes (such as pneumothorax), and knowledge of such an occurrence and the use of appropriate immunohistochemistry are the main clues to the correct diagnosis. MIB-1, demonstrating very low proliferative activity, may be a useful adjunct to the diagnosis.

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