atypia, hyperchromasia and nuclear stratification. HPV-independent endocervical adenocarcinoma *in situ* (AIS), such as well-differentiated gastric-type endocervical adenocarcinoma, could mimic this type of MH. However, gastric-type endocervical AIS would display mucinous differentiation, a single cell layer and the gland architecture would not be lobulated. Desmoplasia should be absent in MH but may be encountered in gastric-type AIS. Immunohistochemistry should prove contributory in this distinction as MUC6 and p53 positivity and PAX2, CD10 and GATA3 negativity would favour gastric-type AIS over ductal-type MH.^{5,6} Benign misplaced Skene's glands, such as the tubulosquamous polyp of the vagina or cervix, could mimic the bilayered aspect of ductal-type MH, but may be distinguished by absence of micropapillary tufting and presence of squamous differentiation.⁷

We contrasted the immunophenotype of our two cases of ductal-type MH with other histopathological types of MH (lobular and diffuse). Lobular or diffuse MH typically shows expression of EMA, CD10 (luminal), PAX2, PAX8, Bcl-2, AR, calretinin, GATA3 and at times TTF-1.^{6,8–10} Calretinin and TTF-1 may aid in distinguishing ductal-type MH as they were not expressed in both our cases. Additionally, the presence of a myoepithelial outer cell layer in ductal-type MH expressing myoepithelial markers is a characteristic finding. The absence of expression of prostatic differentiation markers (PSA, P501S and NKX3.1) allowed us to rule out misplaced Skene's glands.

Further supporting that ductal-type MH, as with lobular or diffuse-type MH, is derived from the mesonephric epithelium, is that it may have been described analogously in males. In a series by Chen *et al.* studying 10 cases of MH in the prostate or periprostatic tissue, four cases were reported as demonstrating a pattern of glands with 'papillary infoldings or micropapillary tufts' (their so-called 'Pattern 4').¹¹ PAX8 was positive in all instances, and p63-positive myoepithelial cells were present in the periphery.

To conclude, ductal-type mesonephric duct/remnant hyperplasia is an uncommon, and likely underdiagnosed, finding that may occur in the cervical or vaginal stroma. It is characterised by dilated ducts, with clefted contours, micropapillary tufting and the presence of an outer myoepithelial cell layer.

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Localised biphasic mesothelioma with prominent myxoid stroma

Sir,

Localised malignant mesothelioma (LMM) is an uncommon and poorly recognised neoplasm. We report an autopsy case of a patient with LMM of the biphasic myxoid type arising from the visceral pleura. This type of LMM has never been reported to date, and we present this exceptionally unusual, interesting tumour in detail.

An 81-year-old man had a pleural effusion on the right side and a tumour in the right chest wall measuring 11.3×4.6 cm with focal calcification on computed tomography (CT) scan. One month later, a CT scan revealed the mass had grown to 13.6×4.6 cm. The patient's dyspnoea progressed severely, and he was transferred to the National Hospital Organization Hakodate Hospital for an assessment to determine whether the mass could be surgically treated. Continuous drainage was performed for the large uncontrollable accumulation of pleural effusion throughout the entire period of hospital admission. Three months later, the patient died of renal failure and arrhythmia due to hyperkalaemia without surgery. An autopsy was performed 1 hour and 20 minutes after death. Gross examination of the tumour revealed a jelly-like, soft, translucent, polypoid mass that measured 17×16×6 cm and arose from the right pleura of the lung (Fig. 1). The tumour was localised in the pleural cavity without infiltration or metastasis to any other organs. Histologically, the cellularity was different from low to high cellular areas with abundant stromal mucinous substances in the background (Fig. 2A). The tumour cells had monotonous spindle-shaped nuclei with unclear cytoplasmic borders (Fig. 2B). Nuclear atypia was remarkable in limited

Fig. 1 (A) A jelly-like whitish, soft translucent, polypoid mass measuring 17×16×6 cm and arising from the right visceral pleura of the lung (arrow). (B) The tumour arises on the visceral pleura of the lung (arrow). (C) The cut surface of the tumour showed lobulated, mucinous nodules with heterogeneous density.

areas (Fig. 2C). There were focal small glandular structures among the myxomatous component (Fig. 2D,E). Alcian blue positive mucin in the background was completely digested with hyaluronidase. From these histopathological findings, LMM of the biphasic type was suggested; however, it was necessary to rule out biphasic synovial sarcoma and myxofibrosarcoma of the thorax.

Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissues using a Benchmark ULTRA auto-immunostainer (Ventana, USA) according to the manufacturer's protocol. The primary antibodies used were as following: cytokeratin CAM5.2 (prediluted; Becton Dickinson, USA), cytokeratin AE1/AE3 (prediluted; Dako, Denmark), vimentin (V9, prediluted; Dako), D2-40

(prediluted; Nichirei, Japan), calretinin (prediluted; Novocastra, UK), WT-1 (6F-H2, 1:25; Dako), thrombomodulin (M0617, 1:25; Dako), HMBE1 (N1594, prediluted; Dako), aSMA (1A4, prediluted; Dako), CD34 (prediluted; Dako), CD31 (prediluted; Dako), EMA (prediluted; Dako), Ki-67 (MIB1, prediluted; Ventana, USA), BAP1 (clone C-4, 1:200; Santa Cruz, USA), MTAP (clone 2G4, 1:100; ThermoFisher, USA).

The tumour cells of glandular structure were positive for cytokeratin AE1/AE3 (Fig. 2F), CAM5.2, and calretinin (Fig. 2G). In contrast to the glandular component, the spindle-shaped tumour cells were negative for cytokeratin and calretinin; however, these tumour cells were strongly positive for vimentin, aSMA and thrombomodulin (Fig. 2H), and focally and weakly positive for D2-40 but negative for, WT-1, HMBE1, CD31, CD34, EMA, BAP1 (Fig. 2I) and MTAP (Fig. 2J). The endothelial cells of vessels were only positive for BAP1 and MTAP and these were used as internal controls. The Ki-67 labelling index was only 5%. In addition, fluorescence *in situ* hybridisation (FISH) using a p16 (CDKN2A)/CEP9 probe (Abbott, USA) was performed, and 100% of 50 tumour cells counted showed homozygous deletion of p16 (Fig. 2K). Finally, this tumour was diagnosed as localised biphasic mesothelioma with prominent myxoid stroma.

LMMs originating from the parietal or visceral pleura or peritoneum are either sessile or pedunculated and are recognised as isolated nodules.¹ Of the 43 LMMs examined by Inagaki *et al.*, there were 24 cases of epithelioid type (56%), six cases of cytokeratin-positive biphasic type (14%), and 13 cases of sarcomatoid type (30%).² Shia *et al.* reported that 19 of 234 (8%) analysed pleural mesotheliomas were myxoid mesotheliomas with a pronounced myxoid stroma and that such myxoid mesotheliomas represent a group of epithelioid mesotheliomas that retain the secretory activity of normal mesothelium.³ Myxoid stroma is mainly composed of hyaluronidase-sensitive materials.³ In the previously reported cases, most myxoid mesotheliomas were diffuse epithelioid mesothelioma,^{3,4} and only two were localised epithelioid mesothelioma.^{5,6} The tumour cells in the previously reported cases of myxoid mesothelioma were cytokeratin positive but cytokeratin positive cells were limited in the glandular epithelioid components. However, in the present tumour all spindle-shaped cells in the myxomatoid component were cytokeratin negative.

Immunohistochemical analysis is important for differential diagnosis. However, no specific markers are recommended for cytokeratin-negative sarcomatoid mesothelioma. The myxomatous component of the present tumour was positive for vimentin, thrombomodulin and aSMA, and negative for cytokeratin (AE1/AE3, CAM5.2), calretinin, WT-1, HMBE1, CD31, CD34, EMA, BAP1 and MTAP. These results ruled out localised epithelioid mesothelioma, solitary fibrous tumour, biphasic synovial sarcoma and angiosarcoma; however, myxofibrosarcoma and cytokeratin-negative sarcomatoid mesothelioma should be considered for differential diagnosis. Lucas *et al.*⁷ investigated the utility of diagnostic immunohistochemistry for distinguishing sarcomatoid mesothelioma from its histological mimics, high-grade sarcoma and pulmonary sarcomatoid carcinoma, and reported that the distinction between sarcomatoid mesothelioma and sarcoma may become arbitrary with the exception of smooth muscle actin.

Fig. 2 (A) The tumour comprises a mixture of areas of low and high cellularity. Small tumour cells with round-to oval-shaped nuclei and indistinctive cytoplasmic borders are loosely present in abundant myxomatous background. (B) Some areas have high cellularity of tumour cell density. Nuclear atypia is not evident. (C) The tumour had partly large anaplastic cells in some areas. (D,E) Some glandular structures composed of cells with large, vesicular nuclei with prominent nucleoli appear in the myxoid area. These are epithelioid components. (F) The glandular structures are positive for calretinin. (G) The glandular structures are positive for AE1/AE3. (H) The tumour cells of myxoid component are strongly positive for thrombomodulin. (I) BAP-1 is completely negative in tumour cells. Only capillary endothelial cells are reactive for BAP-1 as internal controls. (J) MTAP is also completely negative in tumour cells. Only capillary endothelial cells are reactive for MTAP as internal controls. (K) FISH was performed using the p16 (CDKN2A)/CEP9 probe. Green arrows indicate the 9p centromere probe (CEP9), and no red signals indicate the p16 (CDKN2A) probe.

Myxofibrosarcoma is a tumour that comprises a spectrum of malignant fibroblastic neoplasm with variably prominent myxoid stroma,⁸ and it was highly suspected as a differential diagnosis. Although histology of the myxomatous component of the present tumour resembled myxofibrosarcoma of the thorax,⁸ the epithelioid component of our tumour was cytokeratin positive in glandular structure, in contrast to reports that neoplastic cells in epithelioid myxofibrosarcoma were negative for pan-keratin.⁹ In addition, negative CD34 immunohistochemistry was against myxofibrosarcoma.⁸

BAP1 is a BRCA1-binding protein, and loss of BAP1 expression has been frequently reported in malignant pleural mesothelioma.¹⁰ Although CDKN2A/p16 is useful for discriminating malignant mesothelioma from benign

mesothelial proliferation, it is proposed as a biomarker for poor prognosis in other soft tissue sarcomas.¹¹ Immunohistochemical detection of MTAP loss was 78% sensitive and 96% specific for CDKN2A homozygous deletion. MTAP immunohistochemistry is an accurate and reproducible surrogate for p16 gene (CDKN2A) FISH in diagnosis of malignant pleural mesothelioma.¹² Homozygous deletion of the p16 gene in the pleural malignant mesothelioma has been reported in up to 80% of cases depending on the histological subtype (90–100% of sarcomatoid type; 70% of the epithelioid and mixed types) and has also been reported in LMM. The myxomatous component was compatible with sarcomatoid mesothelioma. The present tumour was mainly composed of myxoid sarcomatoid mesothelioma with a very small glandular component.

Ultimately, the tumour was diagnosed as localised biphasic mesothelioma with prominent myxoid stroma.

Because of the unusual histology of pleural tumours which are composed of a large proportion of myxoid components and a small portion of epithelioid components, and also the rarity of LMM with prominent myxoid stroma, the differential diagnoses from other types of sarcomas, especially myxofibrosarcoma, are required for the diagnosis. The current 2021 World Health Organization classification has included myxoid stroma in the typing, indicating favourable prognosis;⁸ however, the present tumour was found at autopsy, and it is impossible to argue the prognosis in this case.

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Progression of mesothelioma *in situ* to invasive disease 4 years and 10 months after initial diagnosis

Sir,

In 2017¹ we reported the first case of mesothelioma *in situ* (MIS) that was diagnosed using the now accepted diagnostic criteria. MIS is a preinvasive mesothelial lesion which was recognised as a concept as early as 1992² but has only now been incorporated as a diagnostic entity into the current World Health Organization (WHO) classification of thoracic tumours.³ The patient at the time presented with recurrent pleural effusions over the space of several months, and a biopsy at the time showed non-invasive focally papillary mesothelial proliferation with minimal mesothelial atypia and loss of BAP1. At that time, MTAP labelling was not available, and CDKN2A by fluorescence *in situ* hybridisation was not readily available; also, it is important to remember that neither were recognised as a diagnostic tool at that time. The diagnosis of MIS at that time was not recognised in this context, but because of the molecular significance of the unequivocal loss of BAP1, we flagged the finding to the clinicians and a decision for close clinical follow up was made.

Since we reported this case there has been renewed interest in the concept of MIS,^{4,5} but only a handful of cases that have reported progression of MIS to invasive tumour.^{6,7} In a recent publication we noted that over 4 years later, there had been no progression in this case.⁸ This patient had originally presented with recurrent pleural effusions, which were not overly cellular but showed mild cytological atypia and deletion of BAP1, and some papillary proliferations in a later sample. Radiology at the time showed pleural effusion, with no plaques and no nodularity (Fig. 1A), and no nodularity was visualised at thoracoscopy. The patient underwent talc pleurodesis, and the effusion resolved. Monitoring was by 6-monthly computed tomography (CT) scans and the patient remained free of detectable tumour and asymptomatic. However, 4 years and 10 months after the initial presentation with mesothelioma *in situ*/BAP1 deleted atypical mesothelial proliferation on cytology, the patient presented again acutely with pleural effusion and radiologically rapid progression to invasive disease. The CT at this time showed multifocal nodular pleural thickening with the largest area of thickening being located in the right lateral costophrenic angle, indenting the surface of the right liver lobe (Fig. 1B).

Effusion cytology now showed highly cellular pleural effusion with morular and papillary proliferations, typical of mesothelioma with an epithelioid component (Fig. 2). A biopsy of the new tumour showed invasive epithelioid mesothelioma, with the typical immunohistochemical profile of an epithelioid mesothelioma, showing positive labelling for calretinin, WT1, HBME1, and D2-40, with BAP1 loss and