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Diffuse pleural thickening and thoracic contraction: An indistinguishable case from malignant pleural mesothelioma

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Abstract

The differential diagnosis of reactive mesothelial hyperplasia and mesothelioma is difficult. We present a rare case of diffuse pleural thickening with thoracic contraction that was indistinguishable from mesothelioma. A 66-year-old woman with no history of asbestos exposure visited our hospital with a complaint of dyspnea. The clinical findings included circumferential pleural thickening on chest computed tomography image and a high concentration of hyaluronic acid in the pleural fluid. Pleural biopsies obtained by thoracoscopy under local anesthesia were pathologically consistent with mesothelioma, but the patient refused to take any kind of mesothelioma treatments. Four months later, she consented to a surgical pleural biopsy under general anesthesia to obtain larger tissue samples, which included typical proliferating polygonal cells positive for CAM5.2, calretinin, WT-1, D2-40, CK5/6, epithelial membrane antigen, and glucose transporter-1 and negative for carcinoembryonic antigen, BerEP4, and MOC31. The analysis was consistent with diagnosis of epithelioid mesothelioma. Fluorescence in situ hybridization, however, showed the presence of p16 gene, and the expression of BRCA1-associated protein-1 was detected by immunohistochemistry. Our final diagnosis was diffuse pleural thickening unrelated to asbestos exposure. Differential diagnosis of diffuse pleural thickening and malignant mesothelioma is thus difficult and routine immunohistochemical examinations are often insufficient for accurate diagnosis. Multiple diagnostic methods are required for correct diagnosis in a clinically marginal case.

Keywords

Diffuse pleural thickening, malignant pleural mesothelioma, homozygous deletion of p16

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Introduction

Patients of mesothelioma, benign asbestos pleural effusion, and diffuse pleural thickening increase worldwide because many people were previously exposed to asbestos. Mesothelioma has a long latent period and is not clinically apparent until several decades after the asbestos exposure. It, however, rapidly progresses once developed and has a poor prognosis with overall survival of about 1.5 years even with an intensive treatment.[1] In contrast, benign asbestos pleural effusion and diffuse pleural thickening develop 3–4 years after the exposure.[2] Benign asbestos pleural effusion often precedes the diffuse pleural thickening. However, non-asbestos-related diseases such as pneumonia-associated pleural effusion, tuberculous pleurisy, and heart failure are occasionally followed by diffuse pleural thickening.[3,4] A current mesothelioma treatment includes surgery, chemotherapy, irradiation, and their combination or multi-modality

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therapy, but invasiveness of the procedures needs an accurate diagnosis for benefits of the patients. Nevertheless, differential diagnosis of reactive mesothelial hyperplasia and malignant mesothelioma in terms of pathology is often difficult.[5]

We present in this report an interesting case of diffuse pleural thickening not related to evident asbestos exposure, which was initially diagnosed as mesothelioma based on the pathological and immunostaining features. The diagnosis was challenged with characteristic genetic markers and the patient in fact survived long time more than 11 years.

Clinical summary

A 66-year-old Japanese woman with complaint of chest dullness was referred to Chiba University Hospital. She was a housewife with no history of smoking or any other complications. She had not been exposed to asbestos in her life, not even for a short period of exposure. Her residential area has not been contaminated with asbestos and her family had not been engaged to any works dealing with asbestos. These suggest the para-exposure or environmental exposure to asbestos was quite unlikely. Until the first visit to our hospital, she had no previous medical history of pneumonia, tuberculosis, or thoracic trauma that may cause pleural effusion. At the first visit, she complained left-sided dull pain, extending from lateral chest to back (grade 2 of the Numerical Rating Scale)[6] and slight dyspnea on effort (grade 1 of the MRC dyspnea scale).[7] These complaints continued thereafter for 11 years without any deterioration. Weight loss, continuous fever, and nocturnal sweat were not observed.

Chest X-ray showed left-sided pleural thickening and pleural effusion. The mild pleural effusion of unknown etiology was already detected 7 years ago before her visit to the hospital. Chest computed tomography (CT) on admission demonstrated left-sided thickened pleural of 13 mm at the lower thorax with some pleural effusion. Pleura thickening was not extended to the mediastinal side and there was no finding of fissure thickening or lung parenchyma involvement. Pleural plaques, pleural implantation, and thoracic wall invasion were not detected. Typical radiological finding of malignant pleural mesothelioma was therefore absent. Nevertheless, it is sometimes difficult to make differential diagnosis between malignant pleural mesothelioma and non-mesothelioma diseases, since mesothelioma does not demonstrate these typical features, especially in the earlier stage.

Even though she had no history of asbestos exposure, malignant pleural mesothelioma was suspected based on CT scan findings and an abnormally high concentration of hyaluronic acid (2,030,000 ng/mL) in the pleural fluids. A pleural biopsy was performed with video-assisted thoracoscopic surgery (VATS) under local anesthesia and the pathological diagnosis with the specimens was epithelioid malignant pleural mesothelioma. The patient refused to take surgery and chemotherapy and was carefully monitored in the outpatient clinic. Four months after the VATS biopsy, the pleural effusion increased (Figure 1) and the CT scan detected a nodule with 4 cm in size (Figure 2(a)), which were compatible with mesothelioma or dissemination of lung cancer into the thoracic cavity. The patient then consented to a surgical pleural biopsy under general anesthesia in order to obtain an additional tissue

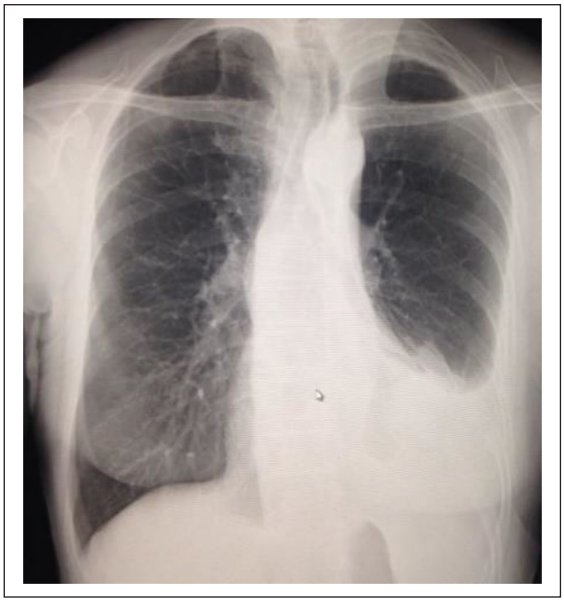

Figure 1. Chest X-ray showing a left-side pleural effusion.

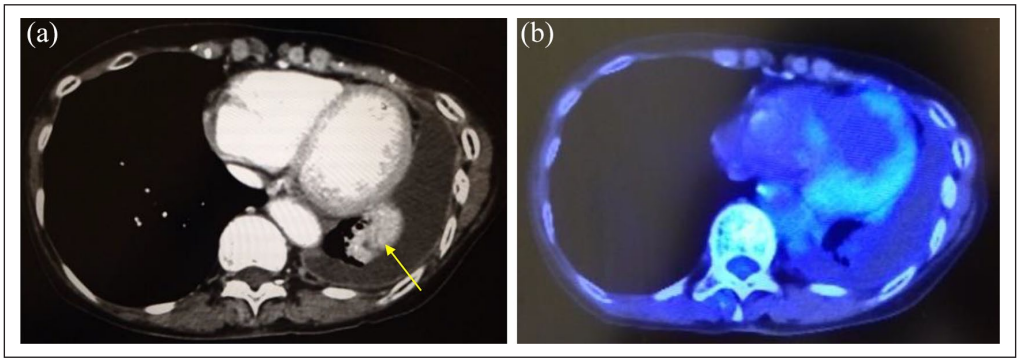

Figure 2. (a) The chest CT shows pleural thickening and a 4 cm mass (arrowhead) in the pleural fluid and (b) The PET scan is negative for FDG accumulation in the mass.

for further analysis, and we conducted several examinations as described below. A positron emission tomography (PET) scan did not show fludeoxyglucose (FDG) accumulation in the nodule, but detected a round-shaped atelectasis (Figure 2(b)). The patient survived 3 years after the last biopsy without any respiratory symptoms and more than 11 years from the first manifestation of pleural effusion.

Pathological findings

Twenty-five samples were obtained from the surface of the parietal pleura during the VATS-guided biopsy under local anesthesia. The maximum diameter of these samples was 2 mm. The parietal pleura was thickened by the proliferation of spindle cells and accumulation of collagen fibers and atypical cells with eosinophilic cytoplasm (Figure 3(a)). Zonation was not detected. The atypical cells were positive for CAM5.2, calretinin, WT-1, D2-40, and CK 5/6, but negative for carcinoembryonic antigen (CEA), thyroid transcription factor-1 (TTF-1), and claudin 4 expression. Immunohistochemical staining analyses showed that epithelial membrane antigen (EMA) was positive with a strong membranous staining pattern (Figure 3(b)) and glucose transporter-1 (Glut-1) was also positive, but desmin was negative (Figure 3(c)). Positive EMA and Glut-1 staining and negative desmin staining were consistent with epithelioid mesothelioma, but the tissue was not adequate to evaluate the invasive lesion in the biopsy samples.

The surgical pleural biopsy samples under general anesthesia were large and yielded serial sections that covered a 13 mm × 9 mm glass slide (Figure 4(a)). The tissue included striated muscle of the thoracic wall in addition to the thickened parietal pleura. The pleura was rich in spindle cells and collagen fibers, and the fibrosis extended into striated muscle of the thoracic wall. Some spindle cells were hyperchromatic in the nuclei (Figure 4(b)), and there were foci of proliferating atypical polygonal cells with eosinophilic cytoplasm (Figure 4(c)). These foci were confined to the pleura and did not invade the endothoracic fascia or striated muscle. The spindle cells were diffusely positive for CAM5.2 (Figure 4(d)) and zonation was not observed. The atypical polygonal cells were positive for CAM5.2, calretinin (Figure 4(e)), WT-1, and D2-40 and were negative for CEA, BerEP4, and MOC31. All polygonal cells were positive for EMA and Glut-1 (Figure 4(f)), desmin, and BRCA1-associated protein-1 (BAP1), but negative for IMP3 and CD146 (data not shown). The fluorescence in situ hybridization (FISH) analysis of 100 atypical polygonal and spindle cells did not show homozygous deletion (HD) of the p16 gene (Figure 5). Fibrosis of the pleura was marked, but proliferation of the atypical polygonal cells was not extensive partly because of marked fibrosis of the pleura and there was no invasion of mesothelial cells into chest wall. These data collectively indicated that the pathological diagnosis based on the surgical pleural biopsy tissue was fibrous pleuritis with reactive mesothelial hyperplasia.

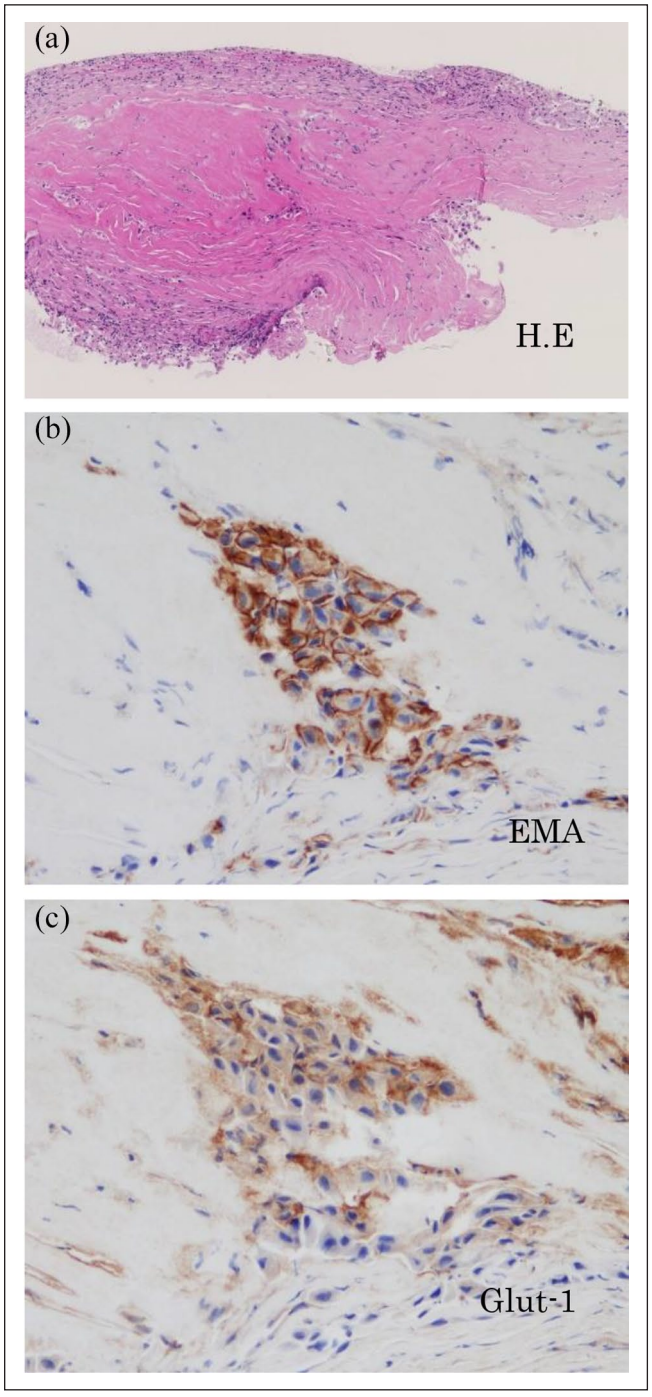

Figure 3. VATS pleural biopsy tissue with (a) thickened parietal pleura, proliferation of spindle cells, depositions of collagen fibers, and no zonation. (b) Strong EMA membrane staining pattern and (c) Glut-1 positivity.

Discussion

In this study, we showed a case with diffuse pleural thickening that was initially diagnosed as mesothelioma. A further analysis with the second specimens denied the diagnosis of mesothelioma and the patient survived for more than 11 years after the manifestation of pleural effusion.

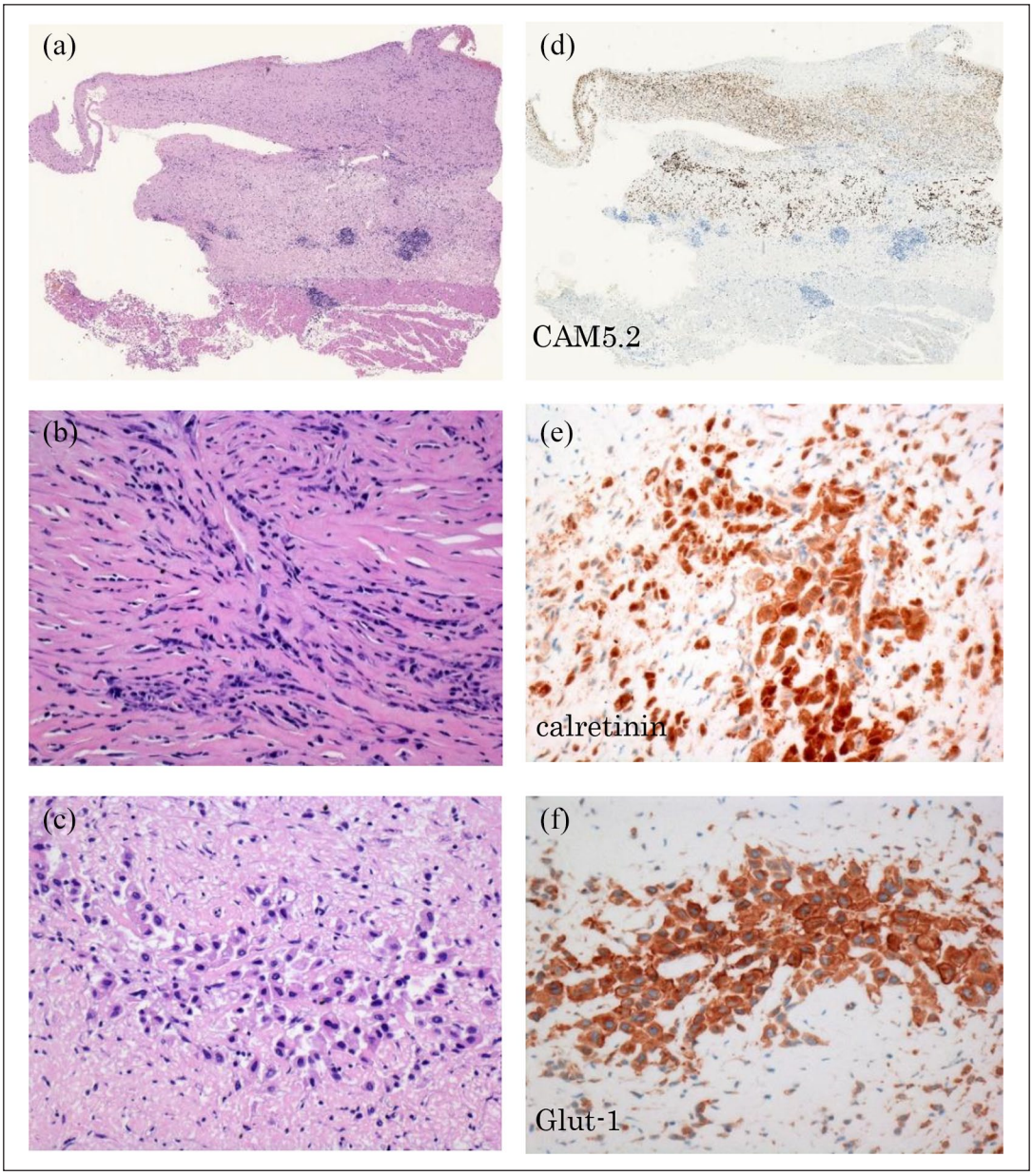

Figure 4. Surgical pleural biopsy tissue showing (a) thickened parietal pleura with the proliferation of spindle cells and deposition of collagen fibers, with fibrosis extending into the striated muscle of the thoracic wall, (b) spindle cells with hyperchromatic nuclei, and (c) foci of proliferation of atypical polygonal cells with eosinophilic cytoplasm in the thickened parietal pleura. (d) Spindle cells were diffusely positive for CAM5.2. (e) Atypical polygonal cells were positive for calretinin. (f) Some polygonal cells were positive for Glut-1.

In most cases with mesothelioma, the CT findings include the presence of nodular pleural thickening, pleural rind, mediastinal or chest wall invasion, and loss of lung volume.[8] Pleural effusion alone can be a feature in some of early-stage mesothelioma. Right-side predominance of malignant pleural mesothelioma in the order of 1.6:1 is reported,[9] but this case had left pleural thickening and pleural effusion. This case showed pleural effusion and loss of lung volume, but other features suggestive of malignant mesothelioma were not evident.

Diffuse pleural thickening can be one of the characteristics of the benign asbestos-related diseases and manifests as broad of ipsilateral or bilateral broad pleural thickening. Pathologically, it is described as chronic fibrous pleuritis of the visceral pleura. It can extend and adhere to the parietal side, resulting in the insidious development of constrictive pulmonary dysfunction.[10] A differential diagnosis between diffuse pleural thickening and mesothelioma is often difficult, and analysis of open surgery-mediated biopsies including substantial amounts of all layers of pleura is therefore required.

In this case, expression of CAM5.2 and the mesothelioma markers including calretinin, WT-1, D2-40, and CK5/6 were all positive, but that of carcinoma markers, including TTF-1,

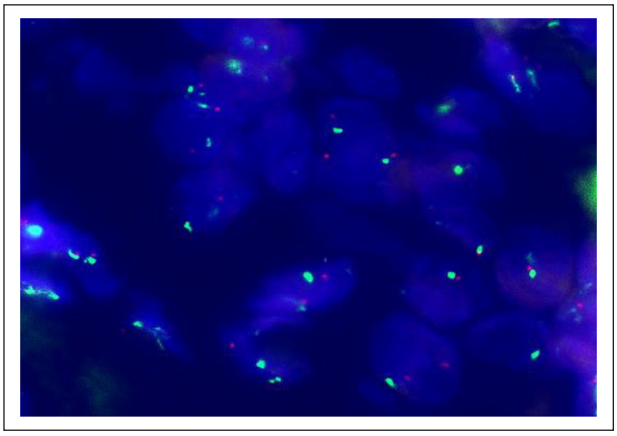

Figure 5. FISH assay showing that the atypical polygonal cells and spindle cells did not harbor HD of p16.

MOC31, CEA, BerEP4, and claudin 4 were negative. Zonation was not found in the biopsy tissue. These results were consistent with the diagnosis of mesothelioma. The results with the initial VATS biopsy under local anesthesia were reproduced in the tissue specimens obtained by the open surgery. In contrast, further analysis with the tissue specimens showed that mesothelial cells were confined to the pleura and did not invade into the endothoracic fascia or striated muscle, which supported a diagnosis of fibrous pleuritis.

The Japan Mesothelioma Panel Meeting consisting of professional clinicians, radiologists, and pathologists is regularly held twice a year to discuss difficult mesothelioma disease cases. This case was discussed at the meeting and 9 out of 15 pathologists gave a diagnosis of epithelial pleural mesothelioma, with 3 of the 9 agreed the case being early mesothelioma. Three other pathologists mentioned that the case was atypical mesothelial proliferation favoring mesothelioma. Overall, 80% of the pathologists regarded the case as mesothelioma. Extensive pleural thickening over 1 cm in width, high concentration of hyaluronic acid in the pleural effusion, and the pathologic findings with the VATS biopsy were consistent with the diagnosis of mesothelioma. However, the negative FDG-PET scan findings, absence of malignancy-related symptoms, and survival without progression over 11 years negated the possibility of mesothelioma. This case indicated that immunostaining of markers, routinely accepted as diagnostic tools,[11] is not effective for differential diagnosis between mesothelioma and reactive mesothelial proliferation when the case showed absence of morphologic invasion.

The HD of p16 gene is detected in up to 80% of pleural mesotheliomas with FISH, but not at all in reactive mesothelial hyperplasia.[11,12] In the present case, the FISH assay did not show HD of p16 gene. Lack of BAP1 expression with immunostaining is an excellent biomarker for malignant mesothelioma with 100% specificity in the context of mesothelial proliferation,[13] but the cells in this case were positive for BAP1. These data collectively indicated that the case was not malignant mesothelioma. The negative voters for malignant mesothelioma in the Japanese mesothelioma panel focused on the atypical clinical course and radiographic findings for the pleural mesothelioma and emphasized their importance of the differential diagnosis of malignant pleural mesothelioma.

The current treatment of malignant pleural mesothelioma is often highly invasive with a high recurrence rate and sometimes worsens patient's activity of daily life. We often do not pay much attention to a diagnostic procedure of the mesothelioma in daily clinical practice and make a diagnosis of mesothelioma incorrectly. There are some cases with benign pleural thickening in a patient group of long survivors who were once diagnosed with mesothelioma. We presumed that a large biopsied sample with open surgery and additional investigations with the p16 FISH analysis and the BAP1 staining are at least essential for a differential diagnosis between mesothelioma and benign disease.

Conclusion

In summary, we presented a rare case of diffuse pleural thickening that was indistinguishable from mesothelioma with routine immunohistochemical examinations. Number of this type of marginal case will increase in the future according to expansion of asbestos-related disease. We presume that large biopsied samples by open surgery and p16 FISH analysis and BAP1 immunohistochemistry are crucial for differential diagnosis between mesothelioma and the benign diseases, in order to avoid misdiagnosis which leads to highly invasive medical interventions.

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Author contributions

All authors have contributed significantly and that all authors agree with the content of the manuscript. This manuscript has not been published elsewhere and it is not under consideration by another journal. We have approved the manuscript and agree with submission to SAGE Open Medical Case Reports.

Declaration of conflicting interests

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Ethical approval

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Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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