Unexpected diagnosis of multiple sclerosing pneumocytomas in a patient with chondrosarcoma of the hand

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SUMMARY

Sclerosing pneumocytomas are rare, benign pulmonary neoplasms that predominantly affect Asian female patients in the age category of 40–70 years, mostly non-smokers. We report on a 72-year-old Caucasian woman with chondrosarcoma of the hand who developed multiple bilateral progressive lung nodules suspicious of lung metastases. Staged lung resections were performed, and pathological diagnosis was confirmed by immunohistochemical analysis of the resected specimens. Next-generation sequencing (NGS) was used to detect gene mutations. Immunohistochemistry demonstrated sclerosing pneumocytomas, and NGS showed an IDH1 mutation. Eventually, the patient developed lung metastases for which rethoracotomy was performed. The differentiation of sclerosing pneumocytoma from lung cancer is a diagnostic challenge, and sclerosing pneumocytoma should be considered in the differential diagnosis of pulmonary nodules. Gene mutation analysis does not always show classical and common mutations, which should be kept in mind when interpreting its results.

BACKGROUND

Sclerosing pneumocytomas are rare, benign pulmonary neoplasms that predominantly affect Asian females 40–70 years of age, mostly non-smokers.[1–4] Multiple simultaneous lesions are particularly rare, and progression of the lesions is also not commonly seen.[4] Differentiation from lung cancer can prove to be a diagnostic challenge.[3 4] Patients can be asymptomatic or have general complaints, such as cough or sputum production.[2–4] We describe a 72-year-old patient with chondrosarcoma of the hand, with bilateral lung nodules suspicious of lung metastases. Pathological findings were quite unexpected.

CASE PRESENTATION

A 72-year-old retired Caucasian woman with a history of thromboembolic disease presented with progressive swelling of her right hand. CT and MRI showed a chondrosarcoma of the second metacarpal bone. A chest CT scan revealed multiple well-defined, small lung lesions in both upper lobes, suspicious of lung metastases. Positron emission tomography (PET) showed uptake in the hand, but not in the lung (figure 1). Resection of the second metacarpal bone showed a dedifferentiated chondrosarcoma.

A follow-up chest CT scan 3 months later showed progressive growth and development of new lung lesions. The patient was discussed at the thoracic oncology multidisciplinary team (MDT) meeting, where surgical treatment was recommended. By left thoracotomy, wedge resections were performed of all palpable nodules. Histopathological investigation showed a well-circumscribed, solid homogeneous tumour with few cystic areas and foci of haemorrhage (figure 2). There was a papillary architecture (figure 3). At high magnification, the tumour was composed of two cell types: epithelial (surface) cells lining the surface of the papillary structures and round cells, present within the papillary stalks in the sclerotic and solid areas (figure 4). Immunohistochemistry showed thyroid transcription factor-1 (TTF-1) positivity in the surface epithelial cells but not in the round cells (figure 5), whereas the round cells showed positivity for cluster of differentiation 99 (CD99) (figure 6). Both morphology and immunohistochemistry in all lesions were suggestive of sclerosing pneumocytoma. Lymph nodes were not involved. After discussion at the MDT meeting, a follow-up chest CT scan was planned.

On follow-up chest CT scan 2 months later, the right-sided lesion had doubled in size. Right thoracotomy was performed, and the lesion was removed by wedge resection. The histopathological diagnosis was again sclerosing pneumocytoma, and immunohistochemical analysis was similar to that of the lesions in the left lung. In addition, epithelial membrane antigen (EMA) and napsin A were positive in the surface epithelial cells, and EMA was also weakly positive in the round cells. Next-generation sequencing (NGS) showed an IDH1 (isocitrate dehydrogenase (NADP(+)) 1) c.394C>G p.Arg132Gly (mutant allele frequency: 4%) mutation, but no mutations in any other genes, including *BRAF* (B-Raf proto-oncogene, serine/threonine kinase) and *AKT1* (AKT serine/threonine kinase 1). The patient was once again discussed at the MDT meeting, and no further follow-up was recommended since all lesions were considered benign in nature.

INVESTIGATIONS

As mentioned earlier, the initial contrast chest CT scan revealed multiple sharply defined, small lung lesions in both upper lobes. The lesions had a maximum diameter of 7 and 9 mm in the left and

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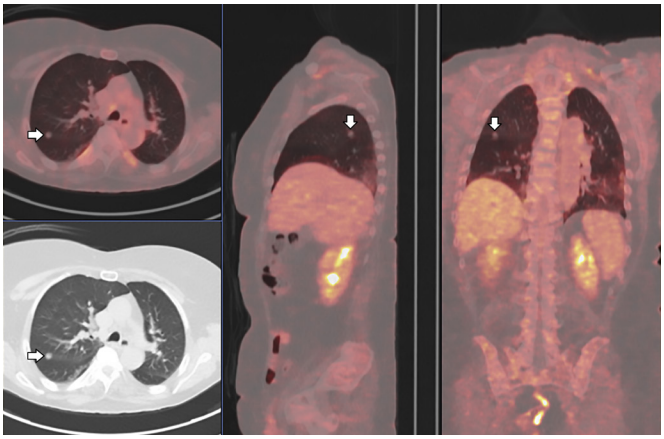

Figure 1 Computed tomographic and positron emission tomographic images show a well-defined lung lesion in the right upper lobe (arrow) with a maximum diameter of 9 mm. There was no fluorodeoxyglucose uptake.

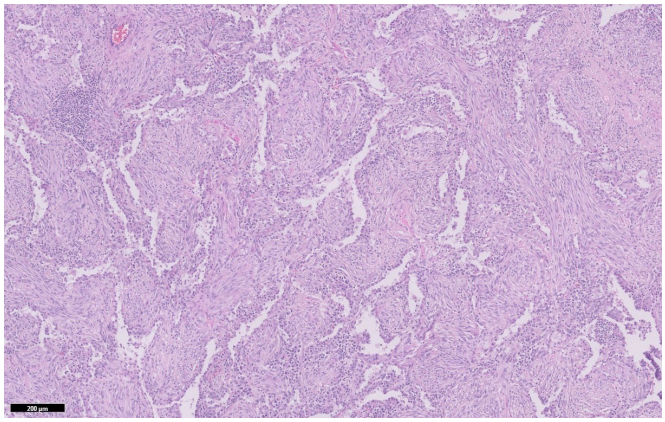

Figure 3 H&E staining of sclerosing pneumocytoma. The lesion is composed of distinct broad papillary structures, of which the lining epithelial cells are very uniform and not atypical (original magnification ×5).

right upper lobes, respectively. No enlarged lymph nodes were observed.

The PET/CT scan showed uptake in the chondrosarcoma of the hand, but not in any of the lung nodules (figure 1). Since this was a low-dose, non-contrast examination without breath-holding, the diagnostic value was somewhat limited.

Follow-up chest CT scans 3 and 5 months later showed progressive growth: the diameter of the left lesion increased to 13 mm and the diameter of the right lesion increased to 14 mm. Two new lesions were detected in the left lower lobe (up to 7 mm) and one in the left upper lobe (4 mm), which were also progressive in nature. Finally, 3 months later and after left thoracotomy, the right-sided lesion had almost doubled in size.

DIFFERENTIAL DIAGNOSIS

In this case, the differential diagnosis is that of incidentally found multiple lung nodules suspicious of lung metastases. Primary lung cancer was also considered in the differential diagnosis, but was less likely since there was no history of smoking or other risk factors.

Lung metastases were considered as the most probable diagnosis considering the oncological orthopaedic history and given the size and morphological characteristics on the chest CT scan. Also, the progressive nature of the lesions and the development of new lesions were quite suspicious. The absence of metabolic activity without any enlarged lymph nodes on the PET/CT scan was an argument to question this diagnosis.

Finally, despite the suspicious circumstances, benign or rarer pathology should not be overlooked. It is known that sclerosing pneumocytomas may present as incidentally found solitary, well-circumscribed nodules. Of course, the presence of multiple and progressive sclerosing pneumocytomas is very rare. Nevertheless, a broad view should be retained in case of incidentally found multiple lung nodules, and one should not be misguided solely by the oncological history of the patient.

TREATMENT

Considering the number and progression of the lesions, left thoracotomy was performed first. More lesions were palpated than those described on the CT scan. Wedge resections were performed of all five palpable nodules located at the posterior segment of the upper lobe, the anterior segment of the upper

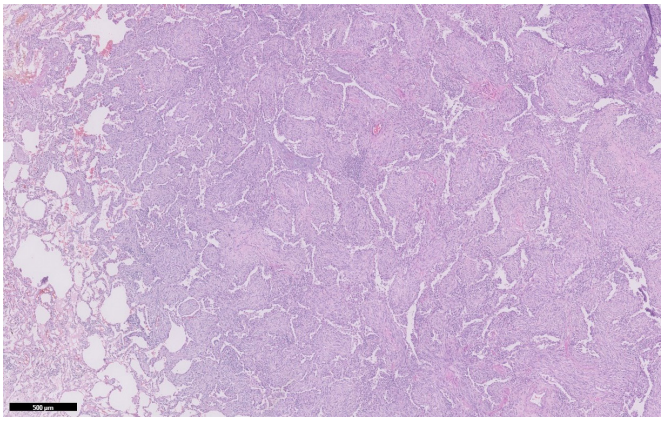

Figure 2 H&E staining of sclerosing pneumocytoma shows a lesion that is well circumscribed on low magnification. Some foci of haemorrhage are present in the tumorous lesion (original magnification ×2).

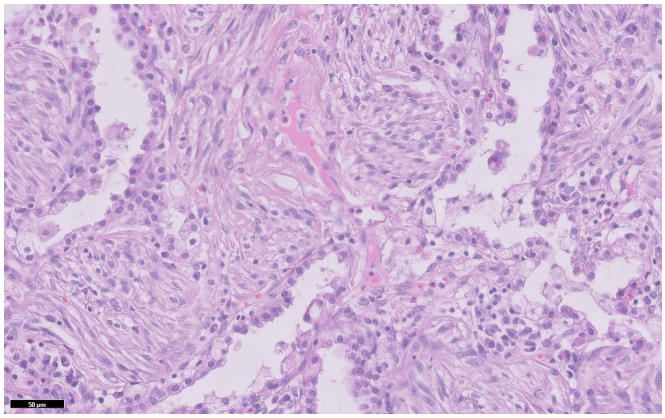

Figure 4 H&E staining of sclerosing pneumocytoma. A higher magnification of the tumour shown in the previous figure shows very monotonous cells, with two populations: the lining surface epithelial cells and the rounded tumour cells within the papillae. The round cells that are found within sclerosing areas sometimes impart a somewhat spindled appearance (original magnification ×20).

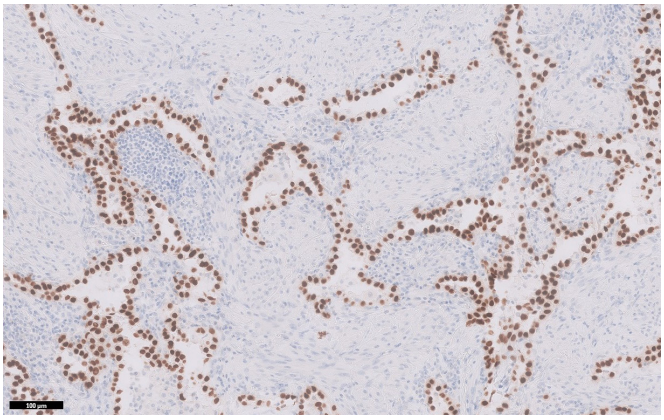

Figure 5 Thyroid transcription factor-1 (TTF-1) immunohistochemical staining of sclerosing pneumocytoma accentuating the surface epithelial cells of the lesion. As mentioned, the round cells are negative (original magnification ×10).

lobe, the anterobasal segment of the lower lobe and the apex of the lower lobe.

Three months later, right thoracotomy was performed, and the progressive nodular lesion in the right upper lobe was removed by wedge resection. In addition, an anthracotic lesion in the middle lobe and multiple tiny lesions in the lower lobe were also removed by wedge resections. These additional lesions were found to be calcifications and fibrosis.

Respiratory physiotherapy and progressive mobilisation were implemented during the postoperative periods.

OUTCOME AND FOLLOW-UP

Almost a year after the right thoracotomy was performed, the chondrosarcoma recurred, and the trapezoid bone was resected. A follow-up PET/CT scan showed progressive disease in the right upper, left upper and right lower lobe. Only the lesion in the right lower lobe was positive on the PET/CT scan; it was removed by rethoracotomy and intrapericardial lobectomy. This time, a diagnosis of pulmonary metastasis of a dedifferentiated chondrosarcoma was made (figures 7 and 8). Lymph nodes were negative. The patient was subsequently discussed at the MDT meeting, and the decision was made not to remove the other lesions due to severe adhesions and limited lung function after the previous interventions. Moreover, the patient had become oxygen-dependent. A chest CT scan 10 months later showed progressive disease and, considering the ambulatory oxygen therapy and the patient's wish not to receive further invasive treatment, palliative treatment was started. Unfortunately, the patient died 1 month later.

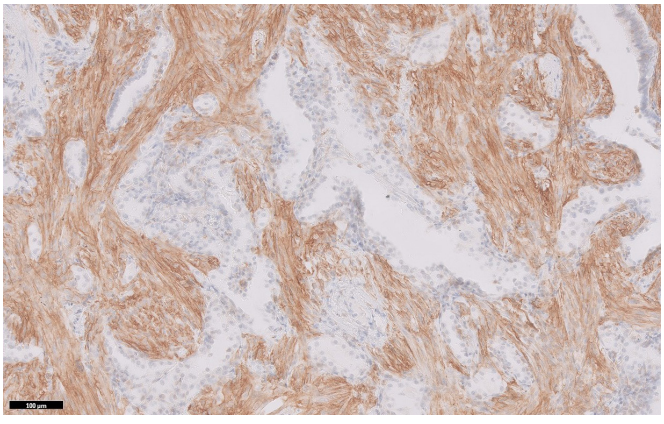

Figure 6 Cluster of differentiation 99 (CD99) immunohistochemical staining of sclerosing pneumocytoma showing positivity in the round cells of the lesion, located within the papillary stalks. As seen in the image, CD99 is negative in the surface epithelial cells (original magnification ×10).

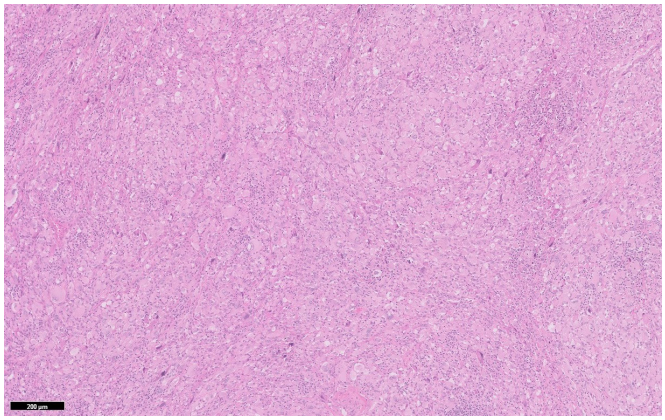

Figure 7 H&E staining of metastatic dedifferentiated chondrosarcoma. At low magnification, a solid tumorous lesion is seen. There are no papillary structures (original magnification ×5).

DISCUSSION

Sclerosing pneumocytoma was first described in 1956 by Liebow and Hubbell as sclerosing haemangioma, since it was assumed to be of endothelial and vascular origin.[5] More recent insights through immunohistochemical studies showed that it is more likely to arise from undifferentiated respiratory epithelial cells, more specifically type II pneumocytes.[6] On chest CT scan, they present as nodules or lumps, and they should be considered in the differential diagnosis of solitary or multiple pulmonary nodules.[2 7] Iyoda *et al* specifically described the difficult differentiation of sclerosing pneumocytoma from lung cancer. By using immunohistochemical staining, they showed that the Ki-67 labelling index was significantly lower in sclerosing pneumocytoma, and p53 expression was negative, indicating a low

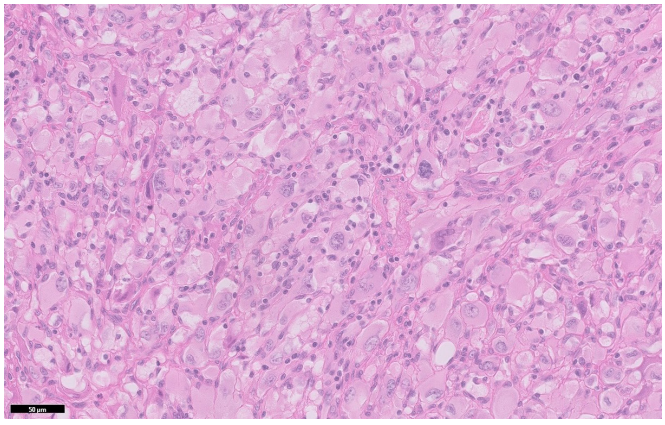

Figure 8 H&E staining of metastatic dedifferentiated chondrosarcoma on high magnification shows striking atypia. The tumour is composed of highly pleiomorphic, sometimes multinucleated cells with monstrous nuclei and abundant eosinophilic cytoplasm. Scattered within the tumour there are chronic inflammatory cells (original magnification ×20).

proliferative activity and thus rather benign character.[3] Chu *et al* also described a case in which the sclerosing pneumocytomas were initially misdiagnosed as pulmonary adenocarcinomas.[8] Furthermore, Goel *et al* reported a case of a young girl in whom sclerosing pneumocytoma was initially mistaken for pulmonary tuberculosis.[9] Typically, sclerosing pneumocytomas are solitary, well-circumscribed lesions of 10–20 mm; however, size may vary.[2 7] Final diagnosis is made by immunohistochemical analysis after resection.[2–4] In cases where there is a suspicion of lung metastases, it is generally accepted to perform lung parenchymal wide wedge resections with clear margins in order to spare as much functional lung parenchyma as possible. Patients may develop recurrent disease allowing subsequent resections, as demonstrated by our case. In a multicentre study by Maleki *et al*, fine-needle aspiration (FNA) was performed in nine cases to describe the cytomorphology and immunoprofile of sclerosing pneumocytoma.[10] Although FNA may provide cytological diagnosis of sclerosing pneumocytomas, removal of the whole lesion provides more material for the pathologist to perform detailed histochemical examinations and molecular genetic analysis.

The combination of multiple factors in our patient makes this an exceptional case. Zhu noted that 97.9% of the 187 patients studied had a single lesion, making the occurrence of multiple lesions, as in our case, extremely rare.[2] This is also described in a recent review of multiple sclerosing pneumocytomas. Certainly, the bilateral presence and the large number of lesions—at least six proven lesions in our case—is quite unusual.[4] The rapidly progressive nature of sclerosing pneumocytoma seen in this case, consisting of lesional growth as well as development of new lesions, is also a rare event.[4 7] Finally, NGS performed on the resected tissue did not show the highly frequent AKT1 mutation found to be a hallmark of sclerosing pneumocytomas.[4 11 12] Screening for BRAF mutation was performed, as suggested by Jiang *et al*, but was also found to be negative.[12] Instead of the previously described mutations in sclerosing pneumocytomas, only IDH1 mutation was found to be present in our patient.

In conclusion, this case of a 72-year-old woman describes a very unusual presentation of sclerosing pneumocytoma and suggests that, despite its rarity, it should be considered in the differential diagnosis of pulmonary nodules. Differentiation with primary lung cancer or pulmonary metastases proves to be a diagnostic challenge. This particular case shows that the oncological history can be quite misleading, and that a broad view should always be retained when pulmonary nodules are incidentally found. The results of NGS performed in this case also suggest that gene mutation analysis should be carefully interpreted, and that an absence of classical and common mutations should not lead to an alternative diagnosis when the right arguments for the diagnosis of sclerosing pneumocytoma are present.

Patient's perspective

Patient's daughter:

It all started when my mother noticed a swelling of her right hand. We weren't too worried about it at first, but over time it started to increase. When we found out it was cancer, that was a shock for both of us. Fortunately, my daughter and I lived with my mother, so we all had a lot of support from each other. When we heard that there were also lesions in the lungs, this was again a hard blow. After the operation, we received the news that the lesions were not malignant, and of course this was an enormous relief. Unfortunately, that was not the end of the story. When the tumour of the hand recurred and subsequently new lesions in the lungs were discovered, we knew there was not much hope left. In the time that was left us, we fully enjoyed life and we did as many things together as we possibly could.

I am sure that my mother would have liked to cooperate in writing this article. She would have really wanted to help others with a similar condition as much as she could have done. She has always been positive from the beginning until the end. That is really an attribute of her personality that I always admired and that also made me the person I am today. I am very glad that she was able to celebrate my own and my daughter's birthday with us; the final time we got to spend together will always be special and will always be kept in our hearts. As a message to other patients and their families, I would really recommend spending as much quality time together as possible. It is really important to be there for each other and to support each other in difficult times, but also to enjoy all the beautiful moments in life together with the ones you love most!

Learning points

- Differentiating sclerosing pneumocytoma from primary lung cancer or pulmonary metastases is a diagnostic challenge.
- Sclerosing pneumocytoma should be considered in the differential diagnosis of pulmonary nodules.
- Oncological history of the patient can be quite misleading.
- A broad view should be retained in case of incidentally found pulmonary nodules.
- Gene mutation analysis should be carefully interpreted.

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REFERENCES

1 Lovrenski A, Vasilijević M, Panjković M, *et al*. Sclerosing Pneumocytoma: a ten-year experience at a Western Balkan university hospital. *Medicina* 2019;55:27.
2 Zhu J. Analysis of the clinical differentiation of pulmonary sclerosing pneumocytoma and lung cancer. *J Thorac Dis* 2017;9:2974–81.
3 Iyoda A, Hiroshima K, Shiba M, *et al*. Clinicopathological analysis of pulmonary sclerosing hemangioma. *Ann Thorac Surg* 2004;78:1928–31.
4 Pal P, Chetty R. Multiple sclerosing pneumocytomas: a review. *J Clin Pathol* 2020;73:531–4.
5 Liebow AA, Hubbell DS. Sclerosing hemangioma (histiocytoma, xanthoma) of the lung. *Cancer* 1956;9:53–75.
6 Devouassoux-Shisheboran M, Hayashi T, Linnoila RI, *et al*. A clinicopathologic study of 100 cases of pulmonary sclerosing hemangioma with immunohistochemical studies: TTF-1 is expressed in both round and surface cells, suggesting an origin from primitive respiratory epithelium. *Am J Surg Pathol* 2000;24:906–16.

7 Morikawa K, Misumi S, Fukuda T, *et al*. Pulmonary sclerosing pneumocytoma presenting as slow-growing multiple nodules over a long period. *Radiol Case Rep* 2019;14:602–7.
8 Chu M, Kumari H, Salmah N, *et al*. Synchronous sclerosing haemangiomas of the lung: an unusual presentation of a rare tumour. *BMJ Case Rep* 2013;2013
9 Goel MM, Kumari M, Singh SK. Symptomatic sclerosing haemangioma: a rare case of solitary pulmonary nodule in a young girl. *BMJ Case Rep* 2013;2013.
10 Maleki Z, Muller S, Layfield L, *et al*. Pulmonary sclerosing pneumocytoma: Cytomorphology and immunoprofile. *Cancer Cytopathol* 2020;128:414–23.
11 Yeh YC, Ho HL, Wu YC, *et al*. AKT1 internal tandem duplications and point mutations are the genetic hallmarks of sclerosing pneumocytoma. *Mod Pathol* 2020;33:391–403.
12 Jiang G, Zhang M, Tan Q, *et al*. Identification of the BRAF V600E mutation in a patient with sclerosing pneumocytoma: a case report. *Lung Cancer* 2019;137:52–5.