Catching a shark while looking for flounders

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Lung cancer screening (LCS) programs have been shown to reduce lung cancer-related mortality.1,2 In a subset of LCS participants, incidental findings are reported in 28% to 67% of cases, which can lead to unnecessary further evaluations, increasing patient anxiety, the risk of complications, and healthcare costs.1 Occasionally, incidental findings other than lung cancers may be detected. Moreover, in rare cases, the interval between 2 consecutive CT scans could exceed the time for development of the neoplastic disease, precluding early detection. Here we report a case of an unexpectedly rapid onset of malignant pleural mesothelioma (MPM) detected in an LCS program.

Written informed consent for publication of clinical details and clinical images was obtained from the patient. Institutional Review Board approval was not required.

CASE PRESENTATION

A 77-year-old female, a former smoker without any known exposure to asbestos, was enrolled in LCS program at our institution in 2013. Her first low-dose CT scan revealed a 2-cm ground-glass opacity (GGO) in the right upper lobe. During radiological follow-up, this finding has always been stable. In September 2022 (Figure 1, A), a high-resolution CT scan confirmed that the right GGO was unaltered, without any other noteworthy findings. Three months after that last CT scan, the patient complained of shortness of breath, at which time a new CT scan revealed a massive left pleural effusion (Figure 1, B). She underwent left thoracotensis, and the cytologic examination revealed atypical mesothelial cells. In January 2023, 18F-fluorodeoxyglucose positron emission tomography/CT was performed, which highlighted multiple and diffuse tracer uptakes within left pleural field (maximum standardized uptake value [SUVmax] 15) but negligible uptake in the known right GGO (SUVmax <1) (Figure 1, C).

After a multidisciplinary discussion, CT-guided transthoracic left pleural biopsy was performed. The histologic examination revealed an epithelioid MPM, with foci of necrosis and a high MIB-1 proliferation index of 35% (Figure 2). Further molecular profiling revealed PD-L1+ (TPS 10%), LKB1+. Next-generation sequencing did not identify any known fusions of genes. Detected variations are reported in Table E1 and Figure E1. The tumor mutation burden was 5.67 mutations/Mbp.

After a multidisciplinary discussion, chemotherapy was proposed, but the patient refused. She returned to our institution 3 months later, after receiving 4 cycles of chemotherapy (pemetrexed and carboplatin) at another center, with severe dyspnea and radiological progression of disease (Figure E2). The patient refused any further treatment, due to her worsening clinical condition.

DISCUSSION

We have presented the case of a patient undergoing annual screening for a stable GGO of the lung who developed a rapidly progressive symptomatic MPM in 3 months only. LCS programs likely will soon revolutionize lung cancer prognosis. On the other hand, incidental findings during...
LCS, when properly reported, could provide an opportunity to assess other benign or malignant diseases that can be monitored by CT scan in a periodic workup. The prevalence of incidental findings in LCS programs ranges widely, most being benign and clinically insignificant. Concerning the pleura, most common incidental findings are plaques (3.8%) and effusions (1.2%), that should always be reported and eventually investigated in high-risk patients or in the event of radiological changes, since they could be the expression of pleural malignancy.

Our case has 2 meanings. First, it underscores the limits of CT scans in early identifying some malignant thoracic diseases different from lung cancer. Moreover, the case plainly shows that MPM might rarely occur with an extremely aggressive pattern, even in the epithelioid subtype. The high MIB-1 proliferation index seen in our case, which has been associated with poor survival in MPM, testifies to the aggressive behavior of this disease, explaining its rapid progression. Irrespective of the histology, MPM is known to have early slow development, with a latency of 40 years from exposure, and subsequent faster growth, leading to an overall survival of <1 year. Relying on these assumptions, the poor results achieved in MPM screening programs are hardly surprising. Considering the absence of known asbestos exposure reported by our patient, genetic alterations may have had a role in such an abrupt onset. While the specific role of PD-L1 in MPM is still debated, higher expression levels may be associated with poorer overall survival.

The literature is still lacking definitive large-scale molecular studies on MPM, but MPM appears to be characterized by biological diversity and high heterogeneity, preventing detection of a single specific biomarker. Therefore, we evaluated PD-L1 expression as well as next-generation sequencing profiling of the tumor to explain the unexpected tumor spread.

Although no fusion of known genes has been found, variations in several genes have been highlighted, albeit without known prognostic significance. Specifically, BAP1 and NF2 have been reported in a high percentage of MPM (almost one-half of cases) and are thought to have a role in the pathogenesis of the neoplasm, with involvement in cellular proliferation, differentiation, apoptosis, and metabolism. Actually, the dismal prognosis of MPM could be related to the scant available information on its molecular development. MPM has a distinctively low tumor mutation burden, as our case shows, but different genes may be mutated.

This case report has 2 main limitations. The diagnosis was made through transthoracic tru-cut needle biopsy, which could have sampled only a limited area of epithelioid growth within a field of a biphasic subtype. The patient could have had radiologically undetectable low-burden disease for decades that later arose abruptly on CT scan. Although anecdotal cases of rapidly progressive MPM are reported in literature, with either epithelioid or sarcomatoid histology, to our knowledge, we report for the first time an epithelioid MPM developing in 3 months, recorded by radiological imaging, without any imputable genetic mutations. This case underscores the difficulty of reaching an early diagnosis of MPM relying on radiologic

**FIGURE 1.** Radiological imaging. A, Computed tomography (CT) scan performed in September 2022. The pulmonary ground-glass opacity (GGO) can be seen in the right upper lobe. B, CT scan performed in December 2022. The pulmonary GGO is stable, whereas massive pleural disease has affected the left hemithorax. C, 18F-fluorodeoxyglucose positron emission tomography/CT performed in January 2023, highlighting multiple and diffuse tracer uptakes within the left pleural field (maximum standardized uptake value [SUVmax] 15), together with left basal pleural effusion, whereas the uptake in the known right GGO was negligible (SUVmax <1).
methods, given that the radiologic appearance of “early mesothelioma” remains a topic of debate. Further analyses of LDCT-based screening programs are awaited to better evaluate this issue. In addition, deeper genetic profiling is advocated to better understand the dismal prognosis of this disease.

References
E-References


FIGURE E2. Last follow-up radiological imaging. *A*, Computed tomography scan performed in May 2023 showing progression of the left pleural disease, with the right lung ground-glass opacity remaining unaltered. *B*, $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography performed in May 2023 showing metabolic progression of disease.
TABLE E1. Genetic variations detected through next-generation sequencing

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<tr>
<th>Gene</th>
<th>Location</th>
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