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PII: S2666-2507(23)00261-4
DOI: https://doi.org/10.1016/j.xjtc.2023.06.020
Reference: XJTC 1450

To appear in: JTCVS Techniques

Received Date: 26 April 2023
Accepted Date: 29 June 2023

Please cite this article as: Orlandi R, Leuzzi G, Lorenzini D, Rolli L, Ferrari M, Conca E, Pastorino U, Catching a shark while looking for flounders., JTCVS Techniques (2023), doi: https://doi.org/10.1016/j.xjtc.2023.06.020.

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Catching a shark while looking for flounders.

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The authors have no conflicts of interest to declare that are relevant to the content of this article.

The authors did not receive support from any organization for the submitted work.

Written informed consent for publication of clinical details and clinical images was obtained from the patient.

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Word count: 853 words.
Glossary of abbreviation

LCS: lung cancer screening
MPM: malignant pleural mesothelioma
CT: computed tomography
GGO: ground-glass opacity
HRCT: high-resolution computed tomography
FDG: fluorodeoxyglucose
CKAE: cytokeratin AE
WT: Wilms tumor
TTF1: Thyroid transcription factor 1
BAP1: BRCA1 associated protein-1
PD-L1: Programmed death-ligand 1
TPS: Tumor Proportion Score
NGS: next generation sequencing
LKB1: liver kinase B1
MUTYH: mutY DNA glycosylase
RICTOR: RPTOR Independent Companion Of MTOR Complex 2
APC: adenomatous polyposis of colon
FANCM: FA Complementation Group M
CREBBP: CREB binding protein
KMT2B: Lysine Methyltransferase 2B
NF2: moesin-ezrin-radixin like (MERLIN) tumor suppressor
FAT1: FAT Atypical Cadherin 1
TMB: Tumor mutation burden
LDCT: low-dose computed tomography
Central Picture legend: CT scan of Sep 2022 and CT scan of Dec 2022: abrupt onset of left pleural mesothelioma.

Central message
Malignant pleural mesothelioma could occur in 3 months only, even in epithelioid subtype, without any imputable genetic mutation. Low-dose CT screening cannot reliably identify its early stage.

Introduction
Lung cancer screening (LCS) programs have been demonstrated to reduce lung cancer-related mortality [1s]. In the subset of LCS participants, incidental findings are reported in 28%-67% of cases, and can lead to unnecessary further evaluations, increasing patients’ anxiety, risk of complications as well as healthcare costs [1]. Occasionally, within incidental findings, other-than-lung cancers may be detected. As well, in rare cases, the time span between two consecutive CT scans could be longer than the development time of the neoplastic disease, thus preventing early detection.

Here we report a case of an unexpectedly rapid onset of pleural malignant mesothelioma, occurring during LCS program. Written informed consent for publication of clinical details and clinical images was obtained from the patient; IRB approval was not required.

Case presentation
A 77-year-old female, great former smoker without any known exposure to asbestos, was enrolled in LCS program at our Institution from 2013. The first low-dose CT-scan revealed 2 cm ground-glass-opacity (GGO) in the right upper lobe. During the radiological follow-up this finding has always been stable. In September 2022 [Figure 1A], HRCT scan confirmed that the right GGO was unaltered, without any other noteworthy finding. Three months after the last CT scan, the patient started complaining shortness of breath: a massive left pleural effusion was revealed [Figure 1B].
underwent left thoracentesis and the cytological examination showed atypical mesothelial cells. In January 2023, $^{18}$F-FDG-PET/CT was performed, highlighting multiple and diffuse tracer uptakes within left pleural field (SUVmax 15), whereas the uptake in the known right GGO was negligible (SUVmax < 1) [Figure 1C]. After multidisciplinary discussion, she underwent CT-guided trans-thoracic left pleural biopsy. The histologic examination revealed epithelioid malignant pleural mesothelioma, with foci of necrosis and high proliferation index (MIB1 35%) [Figure 2]. Further molecular profiling revealed PD-L1+ (TPS 10%), LKB1+. The next-generation sequencing (NGS) has not revealed any fusions of known genes. Detected variations are reported in Table S1 and Figure S1. Tumor mutation burden (TMB) has resulted 5.67 mutations/Mbp. After multidisciplinary discussion, chemotherapy was proposed, but the patient refused. She came back 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 S2]. The patient refused any kind of further treatment, due to worsening clinical conditions.

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 are likely going to revolutionize lung cancer prognosis soon. On the other hand, incidental findings during LCS, when properly reported, could give the opportunity to assess other benign or malignant diseases that can be monitored by CT scan as a periodic work-up. Prevalence of incidental findings widely range in LCS programs, most being benign and clinically insignificant [2s]. 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 case of radiological changes, since they could be the expression of pleural malignancies [2]. Our case has two meanings. First, it underlines the limits of CT scans in early identifying some malignant thoracic diseases different from lung cancer. Moreover, the case plainly proves that MPM rarely might occur with extremely aggressive pattern,
even in the epithelioid subtype. The high percentage of MIB1 proliferation index detected in our case, which have been associated with poor survival in MPM [3], testifies the aggressive behavior of this disease, explaining its rapid progression. Whatever the histology, MPM is known to have early slow development with latency time of 40 years from exposure, and subsequent faster growth leading to an overall survival of less than 1 year. Relying on these assumptions, poor results achieved in MPM screening programs are hardly surprisingly [3s]. Considering the absence of known asbestos exposure reported by our patient, genetic alterations may have had a role in such an abrupt onset. Whilst the specific role of PD-L1 in MPM is still debated, it seems that higher values of its expression could be associated with poorer overall survival [4]. Literature is still lacking definitive large-scale molecular studies on MPM, but it seems that MPM is characterized by biological diversity and high heterogeneity [5], which do not allow to detect single specific biomarker. Therefore, we evaluated PD-L1 expression as well as NGS profiling of the tumor to explain the unexpected tumor spread. Although no fusion of known genes has been found, variations in few genes have been highlighted, albeit without known prognostic significances. Specifically, BAP1 and NF2 have been reported in high percentages of MPM (almost half of cases) and are thought to participate in the pathogenesis of the neoplasm, being involved in cellular proliferation, differentiation, apoptosis, and metabolism [4s]. Actually, some reasons for the dismal prognosis of MPM could be associated with the poor information available about its molecular development: MPM has a distinctively low TMB, as our case shows, but different genes may be mutated. This report has two main limitations: the diagnosis was made through trans-thoracic tru-cut needle biopsy, which could have sampled a limited area of epithelioid growth, within a field of biphasic subtype; furthermore, the patient could have had radiologically undetectable low burden disease for decades, which has later arisen abruptly at CT scan. Although anecdotal cases of rapidly-progressive MPM are reported in literature, with either epithelioid [5s, 6s] or sarcomatoid [7s, 8s] histology, to our knowledge, we reported for the first time an epithelioid MPM developing in 3 months, recorded by radiological imaging, without any
imputable genetic mutations. This occurrence underlines the difficulty of reaching an early diagnosis of MPM, by relying on radiologic methods, since the radiologic appearance of “early mesothelioma” is still debated. Further analyses on LDCT-based screening programs are awaited to better evaluate this issue, as well as a deeper genetic profiling is advocated to understand the dismal prognosis of such disease.

References


Supplemental references


Figure 1. Radiological imaging of the patient. A: 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: $^{18}$F-FDG-PET/CT performed in January 2023, highlighting multiple and diffuse tracer uptakes within left pleural field (SUVmax 15), together with left basal pleural effusion, whereas the uptake in the known right GGO was negligible (SUVmax < 1).

Figure 2. Immunohistology of the left pleural core biopsy specimen (CKAE1-AE3+, WT180+, podoplanin+, calretinin+, claudin-, TTF1-; BAP1 loss). A: hematoxylin and eosin, original magnification 100x (400x, insert), smooth muscle and fibrous tissue involved by an epithelioid neoplasia with foci of necrosis (arrowhead). B: immunohistochemical stain showing positivity for calretinin. C: immunohistochemical stain showing positivity for WT1. D: loss of nuclear staining for BAP-1. E: negativity for claudin-4. F: Ki67/MIB1 proliferative index of 35%.

Figure S1. Next-generation sequencing results. Left: presence of pathogenic c.784-1G>T variant in BAP1 intron 9. Right: copy number variant analysis showed loss of CDKN2A and CDKN2B on chromosome 9.

Figure S2. Last follow-up radiological imaging of the patient. A: CT scan performed in May 2023, showing progression of the left pleural disease, whereas the right lung GGO is still unaltered. B: $^{18}$F-FDG-PET/CT performed in May 2023, showing metabolic progression of disease.