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Case report

The impact of SMARCA4 loss in non-small cell lung cancer therapy

Mariano Lombardi [a], Marianna D'Ercole [a], Valeria Midolo De Luca [a], Matteo Chiari [b], Lorenzo Spaggiari [b,c], Luca Bertolaccini [b,*]

[a] Department of Pathology, IEO, European Institute of Oncology IRCCS, Milan, Italy
[b] Department of Thoracic Surgery, IEO, European Institute of Oncology, IRCCS, Milan, Italy
[c] Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy

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ABSTRACT

This case report explores the therapeutic impact of SMARCA4 loss in a 63-year-old female patient with a history of smoking, hypertension, hypercholesterolemia, and prior surgeries for breast and pancreatic carcinomas, who presented with a new pulmonary nodule. On February 23, 2024, a CT scan identified a solid pulmonary nodule in the right lower lobe. A PET scan confirmed the nodule's metabolic activity. By May 8, 2024, follow-up imaging revealed disease progression and central cavitation in the nodule. Following admission on June 14, 2024, the patient underwent a multidisciplinary evaluation, and a lobectomy of the right lower lobe was performed. Pre-operative assessments indicated good general health and no respiratory distress. Post-surgical histology demonstrated a SMARCA4-deficient non-small cell lung cancer with loss of Brahma-related gene 1. Immunohistochemical analyses showed positive expressions of Cytokeratin-7, focal cytoplasmic positivity for Hepar-1 and loss of BRG-1. The surgery successfully removed the neoplasm, and the patient remained alive and disease-free post-operation. The follow-up plan includes tri-annual visits with contrast-enhanced chest and abdomen CT scans to monitor for recurrence. The case underscores the significance of identifying SMARCA4 deficiencies in NSCLC and advocating for tailored therapeutic strategies. Enhanced awareness and understanding of SMARCA4-deficient NSCLC can guide future treatment protocols and improve patient outcomes.

1. Introduction

The management of neoplastic diseases, particularly those involving the pancreas and lungs, presents significant challenges in clinical practice due to their complex nature and potential for metastasis. The interplay between primary tumours and metastatic disease necessitates a thorough understanding of diagnostic modalities, treatment options, and the implications of surgical interventions.

2. Case/case series presentation

1. Description of Patient

A 63-year-old female patient with a history of smoking, hypertension, hypercholesterolemia, and previous surgeries for ductal

* Corresponding author. Division of Thoracic Surgery IEO, European Institute of Oncology IRCCS Via Ripamonti 435, 20141, Milan, Italy.
E-mail address: luca.bertolaccini@gmail.com (L. Bertolaccini).

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breast carcinoma and pancreatic adenocarcinoma.

2. Case History

The timeline of the case began on February 23, 2024 when an initial CT scan revealed a solid pulmonary nodule in the right lower lobe along with signs of bilateral emphysema (Fig. 1) PET positive. On June 14, 2024, the patient was admitted for further evaluation and treatment. The initial assessment indicated that the patient was in good general condition, with no signs of respiratory distress. The multidisciplinary decision was made for surgical intervention due to the presence of a neoplasm. The planned surgical intervention was a lobectomy of the right lower lobe.

3. Diagnostic Assessments

The physical examination results indicated no signs of stasis or bronchial stenosis, and the patient exhibited good functional capacity. Pathological examination results are pending post-surgery. Other investigation results included a CT scan performed on February 23, 2024, which showed a solid pulmonary nodule in the right lower lobe with no pleural or pericardial effusion. A follow-up CT scan on May 08, 2024 indicated progression of the pulmonary disease with new central cavitation in the nodule.

4. Therapeutic Interventions

The treatment plan included surgical lobectomy of the right lower lobe, with post-operative monitoring and follow-up imaging to assess treatment efficacy. The procedure was performed through a standard posterolateral thoracotomy. Intraoperative findings included a solid tumour with surrounding inflammation. The tumour and a margin of healthy tissue were carefully excised to ensure complete removal. The pulmonary resection was followed by meticulous haemostasis and closure of the thoracic cavity with a chest tube placed to monitor for post-operative complications. The patient's recovery was uneventful, with a gradual improvement in respiratory function. The patient was advised to continue antihypertensive and cholesterol-lowering medications.

2.1. Pathological features

This was a case with a biopsy diagnosed at another centre as carcinoma with hepatoid features. The macroscopic examination of the right lower lobectomy revealed a solid mass measuring 5.5 cm along its major axis, with well-defined and multilobulated margins, greyish-white in colour with a necrotic appearance, which upon the histological examination of the surgical specimen showed a proliferation of large, round or rhabdoid, discohesive cells with vesicular chromatin and prominent nucleolus, with the presence of extensive "geographic" necrosis (Figs. 2, 3 and 4a, 4b, 5). Immunohistochemical analysis showed only rare nuclei positive for TTF-1 and negativity for Napsin and p40. We then expanded the immunohistochemical panel with the following results: intense and diffuse positivity for cytokeratin 7 (Fig. 6), focal cytoplasmic positivity for Hepar-1 (Fig. 7), and negativity for Alpha-Fetoprotein, Glypican-3, estrogen, and progesterone receptors. Considering the morphological appearance and immunohistochemical profile, we performed the immunohistochemical test for BRG-1, whose nuclear expression was predominantly absent (Fig. 8). The diagnosis of SMARCA4-deficient non-small cell lung carcinoma (NSCLC) was then made. In accordance with the WHO 2021 guidelines, the immunohistochemical loss of BRG-1 is considered sufficient to make the diagnosis, with no need for molecular analysis. Given the patient's history of multiple cancers, including breast, pancreatic, and now lung cancer, the possibility of a SMARCA4 germline mutation was considered. However, no clinical evidence or family history suggested an inherited cancer syndrome at the time of diagnosis.

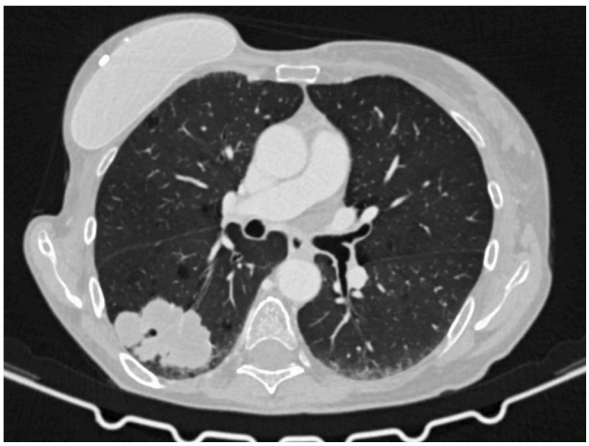

Fig. 1. An initial CT scan revealed a solid pulmonary nodule in the right lower lobe with signs of bilateral emphysema.

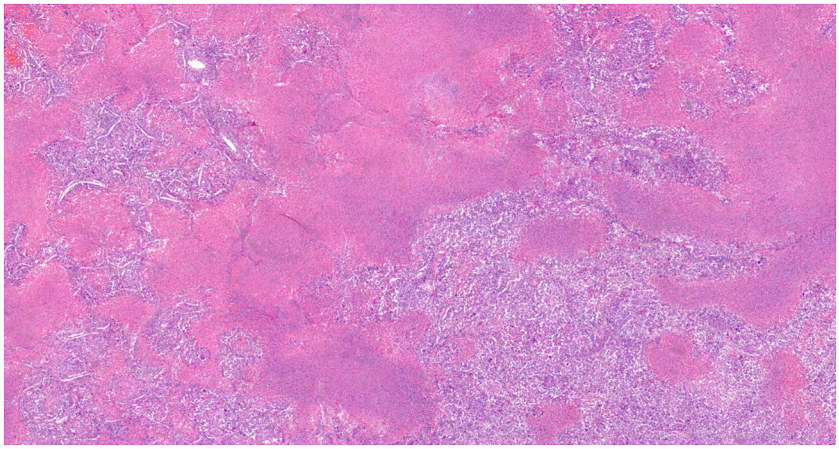

Fig. 2. Neoplasm with extensive necrosis in a geographic map pattern (magnification: 0.4×).

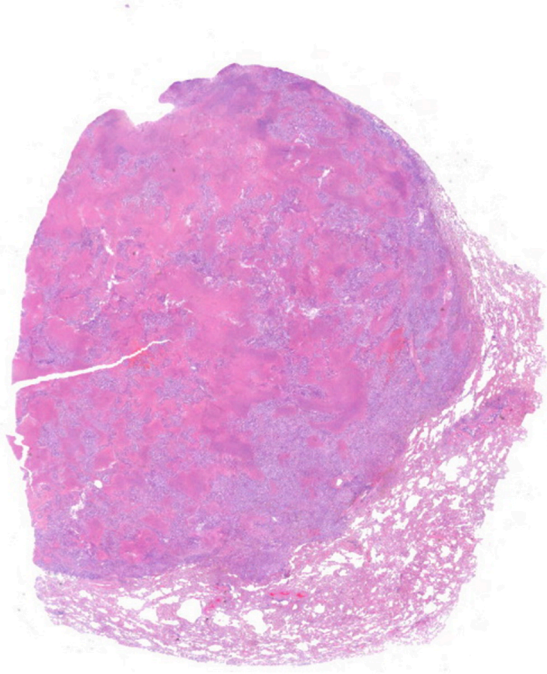

Fig. 3. Neoplasm within the lung parenchyma (magnification: 0.4×).

5. Expected Outcome and Actual Outcome

The expected outcome of the surgical intervention was the successful removal of the neoplasm, leading to an improvement in respiratory function and a reduction in tumour burden. The actual outcome is with a patient alive and without evidence of disease.

6. Description about Follow-Up

The follow-up strategy involved tri-annual visits, including contrast-enhanced chest and abdomen CT scans. In addition to imaging, the patient was monitored for symptoms and underwent periodic pulmonary function tests to assess recovery and detect potential complications. All follow-up imaging has been negative for recurrence. The patient's quality of life post-surgery has been good, with no significant respiratory issues or other complications.

7. Adverse Effects

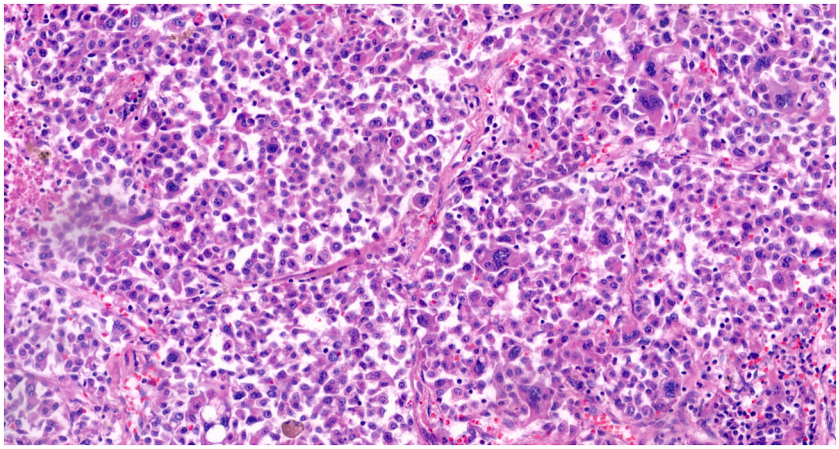

Fig. 4a. Sheets of variably discohesive, large round to epithelioid or rhabdoid cells with vesicular chromatin and prominent nuclei (magnification: 20×).

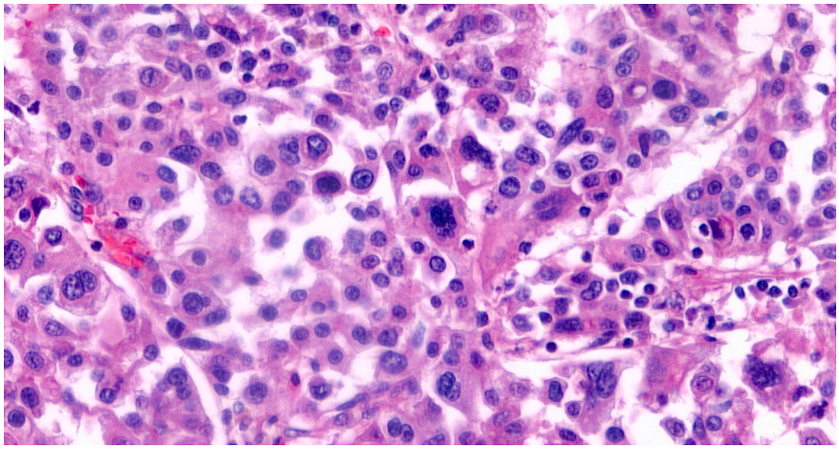

Fig. 4b. Sheets of variably discohesive, large round to epithelioid or rhabdoid cells with vesicular chromatin and prominent nuclei (magnification: 60×).

No significant adverse effects were reported during the hospitalisation.

3. Discussion

The significance of this case series lies in its exploration of SMARCA4-deficient non-small cell lung cancer (NSCLC), a distinct entity characterised by poor responses to conventional treatments and a challenging clinical course. SMARCA4 alterations, which occur in approximately 5–10 % of NSCLC cases, have been associated with aggressive tumour behaviour, resistance to standard therapies, and a worse prognosis compared to SMARCA4-intact counterparts [1]. This case highlights the importance of recognising this entity, which can sometimes show immunohistochemical expression of Hepar-1 and be mistaken for other neoplasms [2]. Additionally, it is essential to emphasise that in a patient with a smoking history, the diffuse and intense immunohistochemical expression of cytokeratin 7 supports the epithelial origin of the neoplasm, distinguishing it from its sarcomatous counterpart, SMARCA4-deficient thoracic sarcomatoid tumours [3]. Recent studies have elucidated the clinicopathological characteristics of SMARCA4-deficient NSCLC, revealing that these tumours often present with larger sizes, higher proliferation indices, and increased metastatic potential [4,5]. Immunohistochemical analyses typically show a negative expression of thyroid transcription factor-1 and a positive expression of cytokeratin 7, which aids in distinguishing these tumours from other NSCLC subtypes [5]. The prognosis for patients with SMARCA4-deficient tumours is notably poorer, with studies indicating significantly reduced overall survival rates compared to those with intact SMARCA4 [1,4,5].

Current therapeutic approaches for SMARCA4-deficient NSCLC are limited, with conventional chemotherapy yielding suboptimal results. Investigations into immunotherapy and targeted therapies are ongoing, with promising findings suggesting that these patients may benefit from immune checkpoint inhibitors and combination therapies [1,5]. SMARCA4-deficient NSCLC presents unique

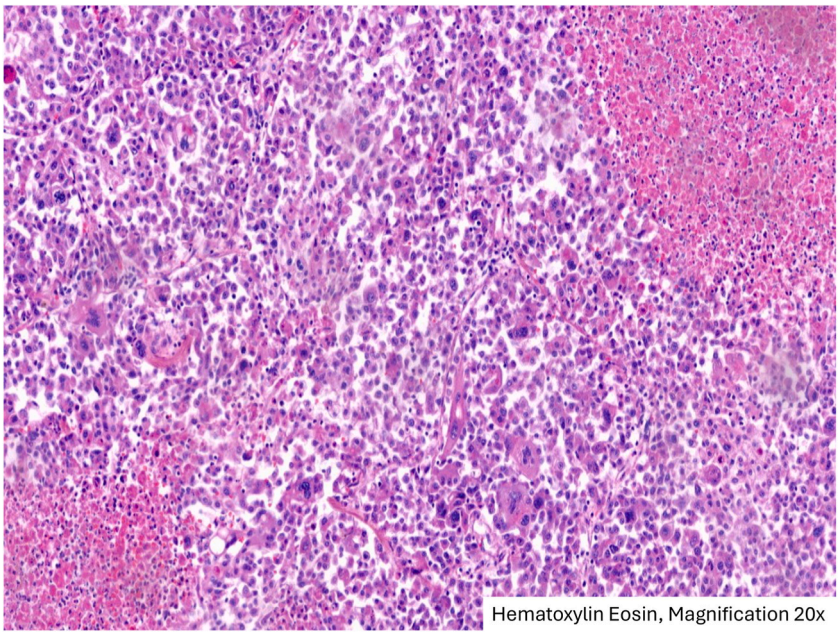

Fig. 5. Haematoxylin – Eosin staining of a poorly differentiated NSCLC.

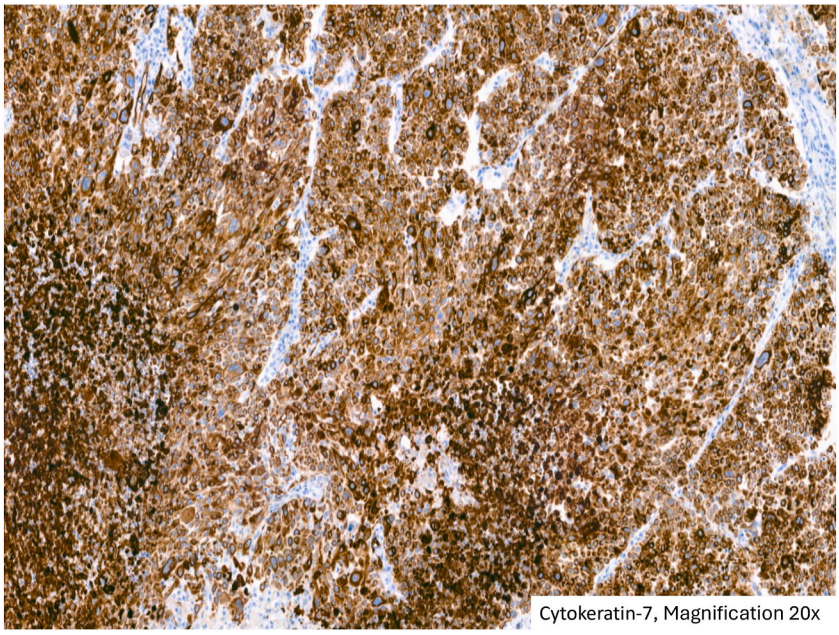

Fig. 6. Immunohistochemical expression of Cytokeratin 7 in the tumour cells further confirms the presence of NSCLC.

treatment challenges due to its poor response to conventional therapies and aggressive clinical course. SMARCA4 alterations in 5–10 % of NSCLC cases correlate with resistance to standard treatments and a worse prognosis. The case emphasises the need for personalised treatment strategies and the importance of molecular profiling in managing this subtype since this histotype does not positively respond to conventional treatments. Although immune checkpoint inhibitors offer promise in various cancers, their efficacy in SMARCA4-deficient NSCLC remains variable. The decision to proceed with surgical resection was influenced by the patient's overall health and the tumour's aggressive nature. Post-operative monitoring remains crucial, given the high risk of recurrence. This case highlights the importance of integrating molecular insights into treatment planning and underscores the need for ongoing research into novel therapeutic approaches for SMARCA4-deficient NSCLC. The management of SMARCA4-deficient NSCLC presents several challenges. The inherent resistance to standard chemotherapy necessitates a shift towards innovative treatment modalities. In this

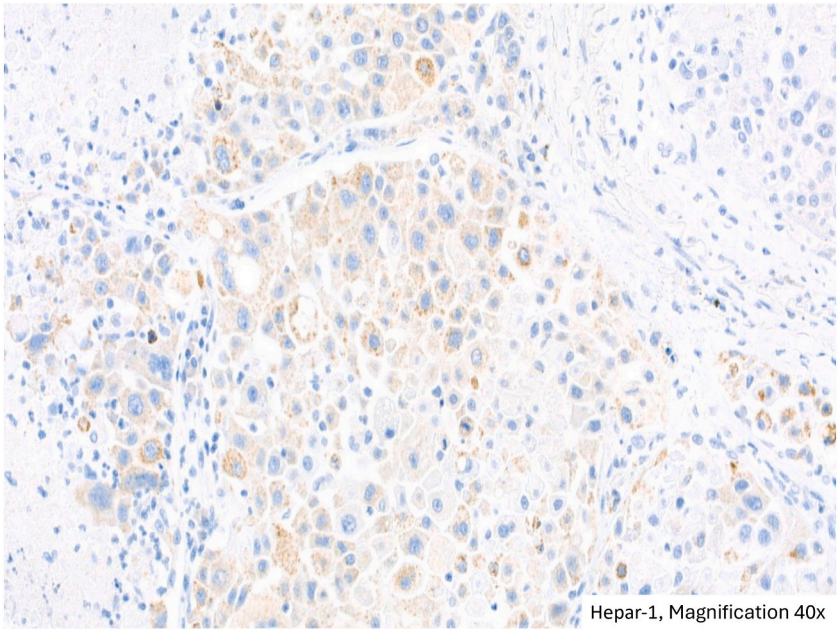

Fig. 7. Focal cytoplasmic positivity for Hepar-1

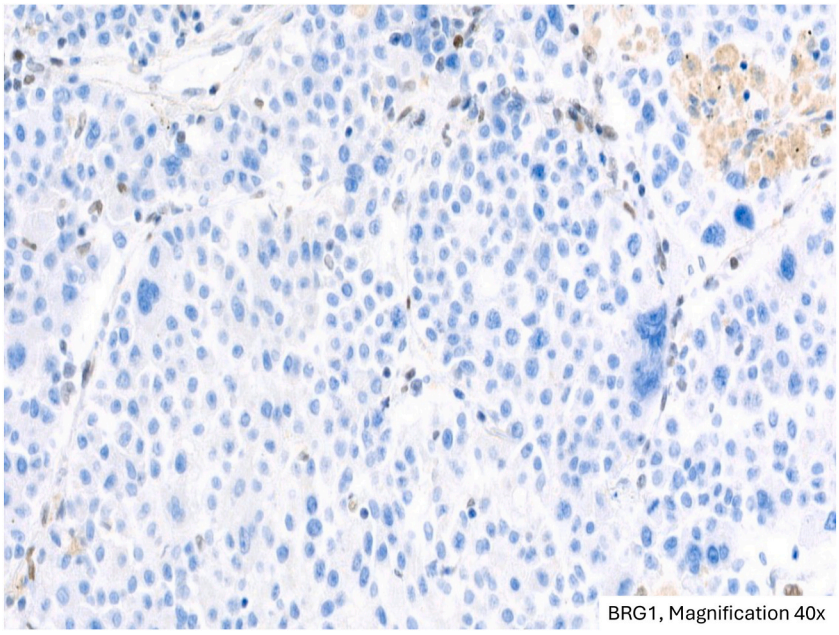

Fig. 8. Immunohistochemical staining for SMARCA4 (BRG1) demonstrates a deficiency in the tumour cells, indicative of SMARCA4-deficient NSCLC.

case, the multidisciplinary approach involving surgical resection was pivotal, given the patient's overall good health status and the absence of significant comorbidities during surgery. The decision to proceed with lobectomy was informed by the patient's tumour characteristics and the potential for improved respiratory function post-surgery.

Research into targeted therapies for SMARCA4-deficient NSCLC has gained traction, with trials exploring the efficacy of drugs that target specific molecular pathways altered by SMARCA4 loss. For example, inhibitors of the PI3K/AKT/mTOR pathway and other downstream signalling pathways are under investigation, as these pathways are often upregulated in SMARCA4-deficient tumours. Although traditional immunotherapy has shown mixed results in SMARCA4-deficient NSCLC, ongoing trials evaluate immune checkpoint inhibitors (e.g., PD-1/PD-L1 inhibitors) combined with other therapeutic agents. The potential benefits of combining

immunotherapy with targeted therapies or chemotherapy are being explored to enhance treatment efficacy. Newer agents targeting chromatin remodelling pathways or correct epigenetic alterations are being tested. These agents aim to restore the function of the SWI/SNF complex or modify the tumour's response to existing treatments [6]. The successful outcome in this case suggests that surgical intervention is still a viable option for some patients, offering better short-term outcomes than systemic therapies alone. In this case, the detailed follow-up and quality-of-life assessment highlight the importance of long-term surveillance and supportive care. Unlike many cases where follow-up is less thoroughly documented, this report provides insight into the patient's post-surgical recovery and ongoing monitoring, which may be crucial for identifying and managing potential recurrences. The findings from this case underscore the need for continued research into SMARCA4-deficient NSCLC. Future studies should focus on Developing and validating personalised treatment approaches based on molecular profiling to optimise outcomes for SMARCA4-deficient patients, investigating the efficacy of combining surgical interventions with targeted and immune-based therapies to address the high risk of recurrence and improve overall survival, conducting longitudinal studies to understand better the long-term outcomes and survival benefits of different treatment strategies, including novel agents and combinatorial therapies [7].

4. Conclusion

This case report highlights the successful management of SMARCA4-deficient NSCLC through surgical resection, demonstrating that personalised treatment strategies can yield positive outcomes even for this aggressive cancer subtype. Clinicians should apply insights from this case by adopting individualised treatment plans incorporating multidisciplinary approaches, including surgical intervention when feasible, targeted therapies and rigorous surveillance protocols. Enhanced monitoring, such as tri-annual imaging and functional assessments, should be adopted to detect and address recurrences promptly. The case also underscores the importance of integrating novel therapies, such as emerging targeted treatments and immunotherapy, into patient care. Future research should focus on evaluating combination therapies, conducting longitudinal studies to understand survival and recurrence patterns better, exploring the mechanistic roles of SMARCA4 loss, and refining patient stratification through advanced molecular profiling. By embracing these strategies and continuing to investigate new treatment modalities, clinicians can improve outcomes and quality of life for patients with SMARCA4-deficient NSCLC, paving the way for more effective and personalised cancer care.

CRediT authorship contribution statement

Mariano Lombardi: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Marianna D'Ercole:** Writing – review & editing, Investigation. **Valeria Midolo De Luca:** Writing – review & editing, Formal analysis. **Matteo Chiari:** Writing – review & editing, Investigation. **Lorenzo Spaggiari:** Writing – review & editing, Writing – original draft, Funding acquisition. **Luca Bertolaccini:** Writing – review & editing, Writing – original draft, Conceptualization.

Ethics statement

The authors have written informed consent to publish the clinical condition, study findings, de-identified images, clinical reports, and any other information pertinent to the patient discussed in the Case Report.

Data and code availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Luca Bertolaccini is an Associate Editor of Heliyon If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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