CASE REPORT

Squamous Cell Carcinoma of the Lung With Microsatellite Instability in a Patient With Lynch Syndrome: A Case Report

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Received 31 May 2023; revised 9 October 2023; accepted 14 October 2023
Available online - 19 October 2023

ABSTRACT

Lynch syndrome is the most common autosomal dominant inherited cancer predisposing syndrome, due to mutations in DNA mismatch repair genes. The key feature of cancers in Lynch syndrome is microsatellite instability and a high risk of developing mainly colorectal and uterine cancers. However, cancers with microsatellite instability outside this spectrum, for example, lung cancer, are extremely rare. Here, we report a case of squamous cell carcinoma of the lung with microsatellite instability in a patient with Lynch syndrome.

Keywords: Lynch syndrome; Microsatellite instability; Squamous cell carcinoma of the lung; Case report

Introduction

Lung cancer is one of the most common cancers worldwide. Lynch syndrome is the most common autosomal-dominant inherited cancer-predisposing syndrome increasing the risk of several types of cancer, especially colorectal and uterine, but usually not lung cancer.[1] Here, we report a case of squamous cell carcinoma of the lung with microsatellite instability (MSI) in a patient with Lynch syndrome.

Case Presentation

A 68-year-old white man with a 25-pack-year smoking history (cessation since 2014) presented with a lung

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***Disclosure:** Dr. Piton reports receiving personal fees from Boehringer Ingelheim and AstraZeneca outside of this work. The remaining authors declare no conflict of interest.*

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Cite this article as: Haddad E, Bottet B, Thiebaut PA, et al. Squamous cell carcinoma of the lung with microsatellite instability in a patient with Lynch syndrome: a case report. *JTO Clin Res Rep*. 2024;5:100595.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2023.100595

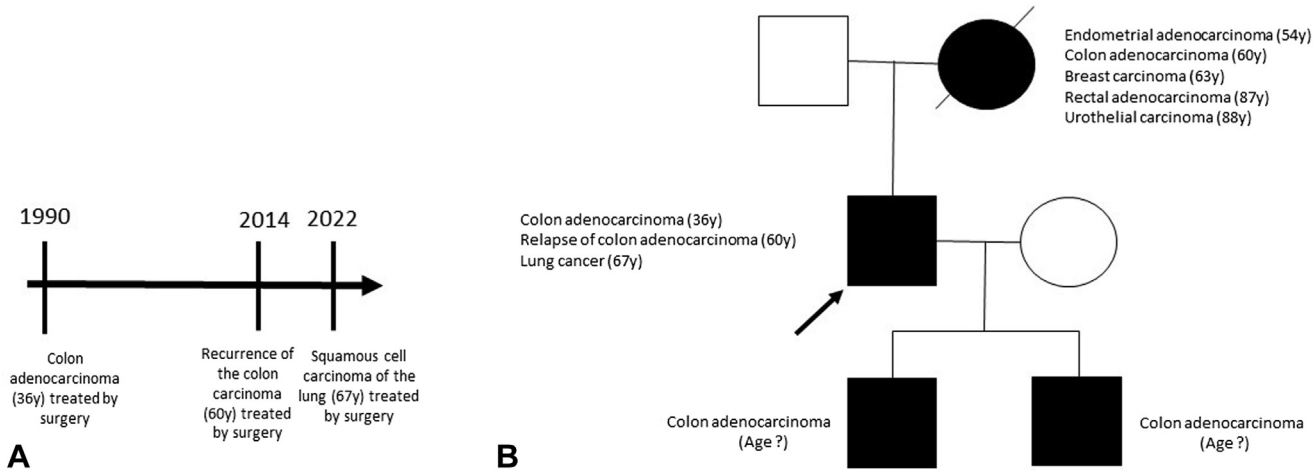

Figure 1. Family tree of the patient. The index case is indicated by a black arrow. The black circle indicates an individual with a cancer history. The white square indicates an individual without a cancer history. Circle indicates male individual, whereas square indicates female individual. Oblique line indicates deceased individual.

tumor in the right upper lobe. In 1990 (at the age of 36 y), he developed an adenocarcinoma of the right colon treated with surgery, recurring in 2014 (Fig. 1*A*).

In addition to the occurrence of cancer at a young age, his family medical history was suggestive of an inherited cancer-predisposing syndrome, with cancers occurring in his mother and his two sons (Fig. 1*B*). In this context, Lynch syndrome was suspected and confirmed by detection of a germline mutation in MLH1 (c.1943C>T, p.Pro648Leu), classified as "likely pathogenic" according to ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/RCV000075433/). It is uncertain whether the relatives were tested for this mutation because we did not have access to this family information. In parallel, a deficient mismatch repair (dMMR) status with a loss of MLH1, PMS2, and MSI was retrieved in his colon cancer. Unfortunately, we did not have access to the MSI status of cancer in his relatives.

The patient did not report any symptoms and the clinical examination was normal.

In August 2022, as part of the follow-up of his colon cancer, a computed tomography scan was performed, which revealed a nodule on the right upper lobe measuring 32 mm. A hypermetabolic tumor was identified on positron emission tomography–computed tomography with a maximum standardized uptake value not exceeding 22 (Fig. 2*A*). A transparietal needle biopsy of this lesion was performed, which revealed squamous cell carcinoma.

In December 2022, the patient had a robotic-assisted thoracic surgery of the right upper lobe with radical lymph node dissection (stations 7, 10, 2R-4R, and 11). Pathologic examination confirmed the diagnosis of squamous cell carcinoma, with the expression of p40 in tumor cells and a programmed death-ligand 1 tumor proportion score estimated at 40% (Fig. 2*B–D*). Tumor cells did not express GATA3, excluding a lung metastasis of urothelial carcinoma. No lymph node metastasis was retrieved, and all surgical margins were tumor-free. In addition, no vascular invasion of the pleura or spread through airspaces was observed. The cancer was staged as IB according to the eighth Union for International Cancer Control classification of lung cancer (pT2aN0).

The assessment of MMR status in the surgical specimen was performed by immunohistochemistry, revealing a loss of MLH1 and PMS2 expression in tumor cells, with a remaining expression of MSH2 and MSH6 (Fig. 3*A–D*). MSI was confirmed by polymerase chain reaction, with 11 tested microsatellite markers, revealing four with clear instability (Fig. 3*E*). In summary, the patient with Lynch syndrome was diagnosed with a dMMR invasive squamous cell carcinoma of the right upper lobe of the lung, stage IB (pT2aN0).

The postoperative course was uneventful. Adjuvant chemotherapy with carboplatin-paclitaxel was decided during a multidisciplinary meeting.

Discussion

We report here, to our knowledge, the first recorded case of a dMMR squamous cell carcinoma of the lung to be identified in a patient with Lynch syndrome. Clinically, the Amsterdam II criteria and Bethesda guidelines for the diagnosis of Lynch syndrome were fulfilled, with both personal and familial cancers in the spectrum of Lynch syndrome.[1] Lynch syndrome was confirmed by a germline pathogenic mutation of MLH1.

Lynch syndrome is caused by constitutional mutations impairing the mismatch repair system, which

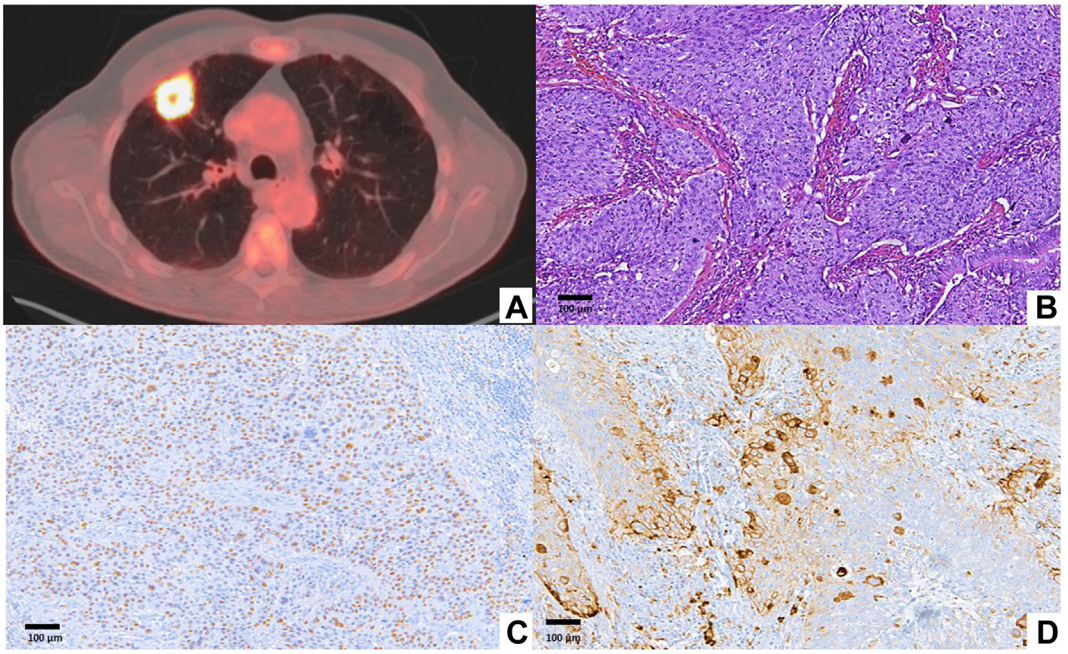

Figure 2. Images of the lung tumor. (*A*) Positron emission tomography–computed tomography scan revealing a lung nodule in the right upper lobe, with hypermetabolism. (*B*) Hematoxylin and eosin–stained tumor tissue sections revealing an infiltrative nonkeratinizing squamous cell carcinoma. (*C*) Immunohistochemical staining of the tumor illustrating positivity of p40, confirming the diagnosis of squamous cell carcinoma (Roche Ventana, Clone BC 28). (*D*) Immunohistochemical staining illustrating positivity of programmed death-ligand 1: tumor positivity score is evaluated at 40% (Diagomics, clone QR1). The bar scale indicates 100 μm.

results in tumor MSI. Patients with this condition are at a high risk of developing colorectal, uterine, ovarian, stomach, small bowel, pancreatic, kidney, and brain cancers, but the risk of lung cancer is considered the same as in the general population. In the literature, three cases of lung dMMR adenocarcinoma of the lung have been reported in patients with Lynch syndrome, including a Muir-Torr syndrome (a form of Lynch syndrome); but, to the best of our knowledge, no dMMR squamous cell carcinoma of the lung has ever been described.[2–4] The risk of squamous cell carcinoma of the lung in Lynch syndrome is the same as that in the general population, but the MSI status reported above clearly indicates that this cancer is not sporadic but directly linked to Lynch syndrome, and it is even uncertain that smoking played a role in carcinogenesis.

The dMMR status is a strong predictive biomarker for the efficacy of immune checkpoint inhibitors. Interestingly, a recent study reported a durable response to toripalimab in a dMMR squamous cell cancer of the lung.[5] In our patient, this very special characteristic shall raise the opportunity of immunotherapy in case of recurrence.

Conclusion

We report here a case of a dMMR squamous cell carcinoma of the lung in a patient with Lynch syndrome. This report highlights the importance of testing for MSI in all cancers among patients with Lynch syndrome, and even outside the spectrum because of major clinical implications, especially regarding the choice of treatment.

CRediT Authorship Contribution Statement

Emna Haddad: Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Writing – original draft, Writing - review & editing, Project administration.

Benjamin Bottet: Validation, Investigation, Resources, Writing - review & editing.

Pierre-Alain Thiebaut: Validation, Investigation, Resources, Writing – original draft, Writing - review & editing.

Samira Morin: Validation, Investigation, Resources, Writing - review & editing.

Hélène Dreysfus: Validation, Investigation, Resources, Writing - review & editing.

Élise Vannier: Validation, Investigation, Resources, Writing - review & editing.

Colette Vincent: Resources, Writing – review & editing.

Florent Marguet: Resources.

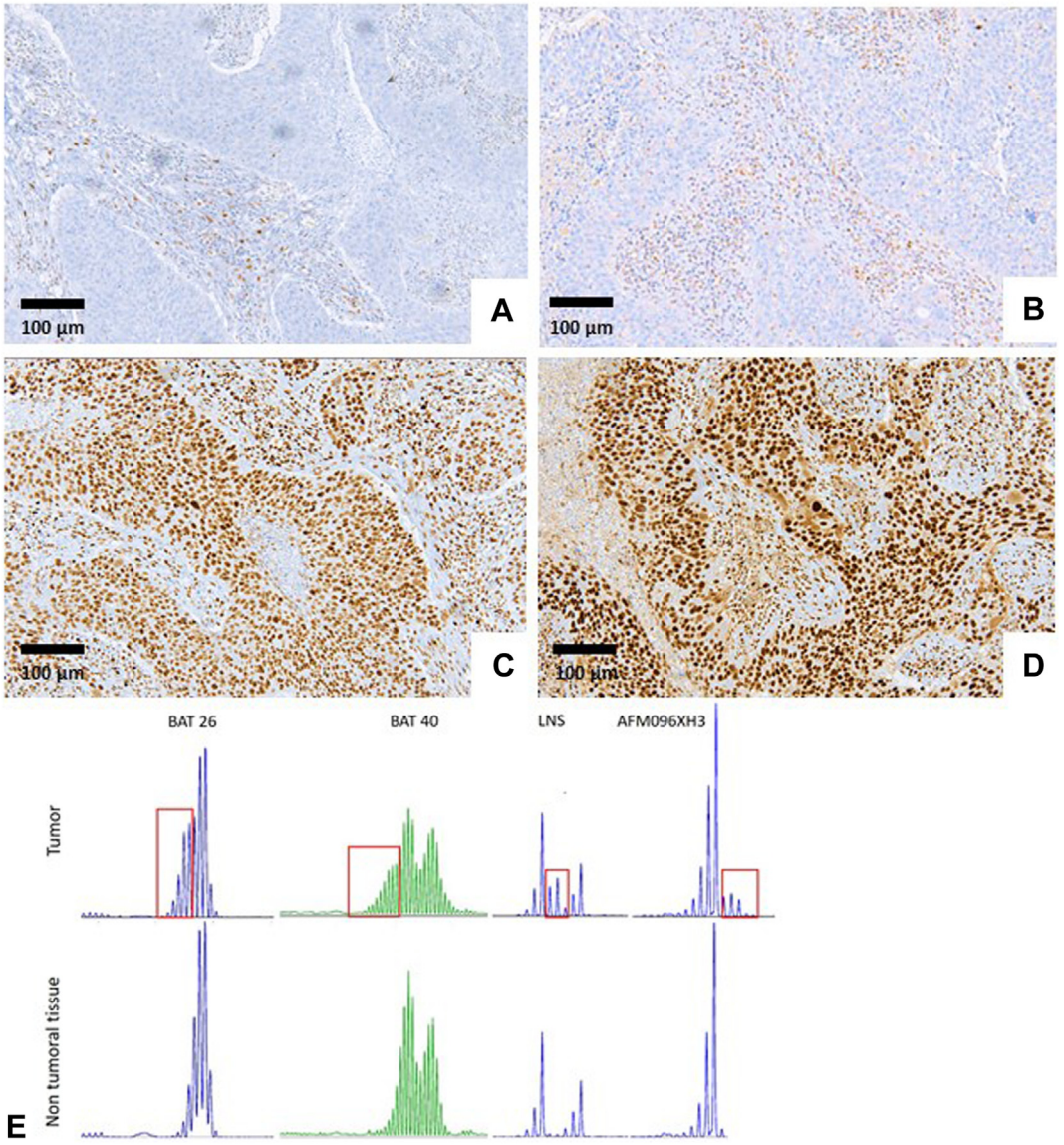

Figure 3. Evidence of a dMMR tumor. (*A*) Immunohistochemical staining illustrating a loss of MLH1 expression in tumor cells but not in normal adjacent cells (Roche Ventana: M1). The bar scale indicates 100 μm. (*B*) Immunohistochemical staining illustrating a loss of PMS2 expression in tumor cells, but not in normal adjacent cells (Agilent, clone: EPS1, dilution: 1/40ème). The bar scale indicates 100 μm. (*C*) Immunohistochemical staining illustrating nuclear positivity of MSH2 both in tumor and normal cells. The bar scale indicates 100 μm. (*D*) Immunohistochemical staining illustrating nuclear positivity of MSH6 both in tumor and normal cells (Roche Ventana, clone: G219-1129) (*E*) Electrophoresis migration of PCR products after amplification of the microsatellites BAT26, BAT40, LNS, and AFM096XH3 revealing an instability in tumor cells (red rectangles) compared with normal tissue. dMMR, deficient mismatch repair; PCR, polymerase chain reaction.

Aude Lamy: Resources, Investigation, Writing - review and editing.

Hagay Sobol: Validation, Investigation, Resources, Writing - review & editing.

Jean-Marc Baste: Validation, Investigation, Resources, Writing - review & editing.

Florian Guisier: Validation, Investigation, Resources, Writing - review & editing.

Jean-Christophe Sabourin: Writing - review & editing, Funding acquisition.

Nicolas Piton: Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing – original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Acknowledgments

The authors thank the patient for his kind cooperation, and Ms. Nikki Sabourin-Gibbs, CHU Rouen, for her help with editing the manuscript. Written informed consent was

obtained from the patient for the publication of any potentially identifiable images or data included in this article.

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