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Synchronous Dual Primary Malignancies of Lung and Colon: A Case Report with Review of Literature Emphasizing the Role of Molecular Profiling in Diagnostic Differentiation

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Abstract

Multiple primary malignant tumors (MPMT), particularly when presenting synchronously—defined as two or more distinct primary malignancies diagnosed within 6 months—are rare and present considerable diagnostic and therapeutic challenges. We report a case of a 75-year-old male patient with no considerable comorbidities who presented with exertional dyspnea and was diagnosed with synchronous adenocarcinomas of the lung and rectosigmoid colon. Comprehensive diagnostic evaluation—including imaging, histopathology, immunohistochemistry, and next-generation sequencing—confirmed the independent origin of both tumors, revealing a shared KRAS (p.G12V) mutation along with distinct additional genomic alterations in each lesion. This case underscores the critical role of integrated molecular and pathological assessment in accurately distinguishing synchronous primary malignancies from metastatic lesions. This report highlights the need for a multidisciplinary strategy in the diagnosis and management of synchronous MPMTs, particularly in elderly individuals with complex disease biology.

Keywords
- colorectal cancer
- KRAS mutation
- lung adenocarcinoma
- multiple primary tumors
- synchronous malignancy

Introduction

Multiple primary malignant tumors (MPMT), first described by Billroth in 1889 and later detailed by Warren and Gates in 1932, refer to the occurrence of two or more distinct malignancies in the same patient. Synchronous MPMT refers to a second malignancy developing within 6 months of the original tumor, while metachronous MPMT occurs when a second tumor develops more than 6 months after the primary tumor.[1] The development of multiple primary malignancies (MPMs) is not fully understood and is likely multifactorial, with identified risk factors including prior cancer treatment, smoking, diet, and genetic mutations.[2] Here, we present a case of a 75-year-old male patient presenting with synchronous double primary lung and colon cancer, incidentally discovered during staging, highlighting rare concurrent malignancies with distinct pathological and molecular profiles. Ruling out metastatic lung lesions

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originating from the colon is essential, as they account for 20% of cases.[3] The findings underscore the importance of comprehensive imaging, histopathology, and molecular diagnostics in guiding the management of patients with dual primary malignancies.

Case Report

A 75-year-old male patient with a notable smoking history, no known comorbidities, and no family history of malignancy presented with Grade II dyspnea on exertion and an ECOG performance status of 2. Physical examination revealed bilateral crepitations with reduced air entry, while chest CT showed multiple right lung lesions; PET-CT further identified abnormalities including a 4.1 cm × 1.6 cm rectosigmoid junction mass (SUVmax 19.2), a 4.8 cm × 4.9 cm right lung mass (SUVmax 7.7) involving the pleura with moderate to massive pleural effusion, enlarged lymph nodes (SUVmax up to 7.5), and a small hypoenhancing liver lesion in segment VIII (SUVmax 6.2).

A CT-guided biopsy of a pleural nodule confirmed metastatic adenocarcinoma of lung origin, with immunohistochemistry showing CK7 and TTF-1 positivity with CK20 and CDX2 negativity. In light of the rectosigmoid mass detected on imaging, a colonoscopy was conducted, and it revealed a rectal neoplasm, colonic polyps, and cecal diverticuli, with biopsy confirming rectosigmoid adenocarcinoma; immunohistochemistry showed CK20 and CDX2 positivity.

A comprehensive panel of next-generation sequencing (NGS) was performed to evaluate SNVs, CNVs, and indels spanning over 15,000 loci for 1,080 tumor-specific genes in both the lung and rectosigmoid tumor tissue-derived DNA and RNA. The genomic analysis of the lung adenocarcinoma revealed mutations in KRAS (p.G12V, Exon 2; variant allele frequency [VAF] 11%), ERCC2 (p.E300, Exon 10), SMO (p.G288D, Exon 4), and NF1 (p.Y1689F, Exon 37). PD-L1 testing using the Dako 22C3 assay showed a tumor proportion score (TPS) of 70%, while, NGS of the rectosigmoid adenocarcinoma identified mutations in KRAS (p.G12V, Exon 2; VAF 11%), TP53 (p.E286D, Exon 8), PIK3CA (p.E542K, Exon 10), and APC (p.R499*, Exon 12 and p.Q223, Exon 7). PD-L1 testing for this site revealed a TPS of 2%.

Given the patient's age, ECOG performance status, and disease status, oral metronomic chemotherapy with capecitabine (1,000 mg) and cyclophosphamide (50 mg) was initiated, along with low-dose nivolumab administered biweekly. The patient has demonstrated good tolerability to the regimen, and on subsequent clinical follow-up, continues to demonstrate clinical stability with sustained therapeutic benefit.

Discussion

The widespread adoption of comprehensive screening strategies, along with advancements in cancer therapies that have extended survival, has led to an increasing frequency of MPM in a single patient, a phenomenon first recognized over a century ago.[4] MPM can be synchronous or metachronous, with the latter occurring over 6 months after the first; SEER database analysis reports MPM incidence ranging from 1% in liver cancer to 16% in bladder cancer,[5] with a 2.5% occurrence in lung cancer patients.[6] Liu et al reported that the most common tumors associated with lung cancer were in the aerodigestive tract (larynx, nasopharynx, esophagus, oral cavity, and hypopharynx), followed by colorectal and cervical cancers.[7] Double primary malignancy is more prevalent in cases of colorectal cancer (CRC). The common sites for the second primary malignancy in CRC include the stomach, urinary system, liver, and lungs. The incidence of synchronous colorectal and lung cancer is reported to range between 0.1 and 0.6%, with Evans et al identifying 801 cases of primary lung cancer (0.6%) among 127,281 patients with CRC, underscoring the rarity of this co-occurrence and its potential for underdiagnosis.[8,9]

The diagnosis and treatment of MPM remain contentious, as there is currently no established method available to differentiate between multiple primary cancers and metastatic disease. Timely detection of hidden secondary malignancies presents a significant challenge in managing synchronous dual malignancies. Additionally, there are notable variations in the driving genes across different tumors in patients with MPM. Identifying the driving mutations in each lesion is critical for accurate pathological staging and the formulation of effective treatment strategies. Combining this with immunohistochemistry to trace the source may offer a more comprehensive approach.[10] In this case, the patient presents with cancers in two distinct organs—lung and colon—each having a distinct immunohistochemical and NGS profile, which aids in differentiating them as two primary malignancies.

The management of synchronous dual malignancies necessitates a personalized, multidisciplinary approach, integrating considerations of tumor biology, disease stage, molecular profile, and patient performance status.[11] NGS technology has enabled a genetic approach to defining multiple primary cancers, and it was conducted on tumor samples from both the lung adenocarcinoma and rectosigmoid adenocarcinoma to delineate their distinct genomic landscapes and inform therapeutic decision-making. The lung adenocarcinoma harbored mutations in KRAS and other genes, with a PD-L1 TPS of 70%, indicating a high likelihood of response to immune checkpoint inhibitors. In contrast, the rectosigmoid adenocarcinoma also exhibited a KRAS mutation along with other genomic alterations, but with a lower PD-L1 TPS of 2%. The shared KRAS mutation, alongside unique mutation profiles, supports the classification of these tumors as independent primary malignancies rather than metastatic disease. KRAS mutations are established drivers in CRC and increasingly recognized in nonsmall cell lung cancer. Their presence in both primary tumors raises the possibility of a clonal relationship, potentially indicating a common progenitor cell or shared environmental trigger. Identical KRAS mutations across synchronous malignancies have been reported, supporting the hypothesis of clonal evolution rather than independent events. This underscores

the importance of comprehensive molecular profiling in distinguishing metastatic disease from synchronous primary malignancies.[12] A potential central role of KRAS mutation exists in altering the tissue microenvironment. Hence, in MPM, KRAS alteration also exhibits a unique immune signature characterized by elevated PDL-1 expression and occasionally elevating tumor mutational burden beyond its intrinsic pro-tumorigenic role. KRAS mutation shapes an immune suppressive microenvironment by impeding effective T cell infiltration and recruiting suppressive immune cells, including myeloid-derived suppressor cells, regulatory T cells, and cancer-associated fibroblasts. This tumor microenvironment-modifying role of KRAS may affect multiple organs simultaneously within the same individual, thus promoting MPM.[13] Should the presence of a KRAS mutation at presentation of a malignant neoplasm cause alarm to screen other organs. This may be another topic of research.

In this case, surgical intervention was deferred due to the presence of multiple lesions and the patient's overall disease burden. This decision aligns with established guidelines that recommend nonsurgical management necessitating chemotherapy or other palliative treatments as the primary therapeutic strategy. The decision to select a low-intensity systemic treatment regimen was influenced by the patient's advanced age, ECOG performance status, overall disease burden, and a TPS score exceeding 10%. This approach aimed to optimize therapeutic efficacy while mitigating treatment-related toxicity through the combination of OMCT and immunotherapy.

This case report highlights the importance of a multidisciplinary approach, integrating imaging, histopathology, and molecular diagnostics to differentiate synchronous primary malignancies from metastatic disease. A key strength is the comprehensive molecular analysis, including NGS, which provided valuable insights into distinct tumor profiles. Additionally, the case emphasizes individualized treatment strategies, particularly in elderly patients with advanced disease. However, as a single-patient study, its findings may not be broadly generalizable, and the lack of long-term follow-up limits conclusions on treatment outcomes. The absence of a surgical perspective due to stage IV disease further restricts discussions on curative interventions.

Conclusion

This case highlights the diagnostic challenge of synchronous dual primary malignancies, emphasizing the role of comprehensive diagnostics, including immunohistochemistry and NGS, in distinguishing independent tumors from metastatic disease. The patient's favorable response to a low-intensity systemic regimen underscores the importance of personalized treatment strategies in elderly patients with advanced disease.

Patient's Consent

The authors confirm that all necessary patient consent forms have been obtained. The patient has provided written permission for their medical images and clinical details to be included in this publication. They have been informed that their identity will be protected by withholding their name and initials.

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Conflict of Interest

None declared.

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