REVIEW

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Metachronous Multiple Primary Lung Cancer: A Case Report and Review of the Literature

Metakron Çoklu Primer Akciğer Kanseri: Bir Olgu Sunumu ve Literatür Derlemesi

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ABSTRACT

Multiple primary lung cancers (MPLC) may develop either synchronously or metachronously. While synchronous MPLC involves the simultaneous occurrence of histologically distinct tumors, metachronous MPLC arises over time following the treatment of an initial lung cancer. To highlight the diagnostic and therapeutic challenges, we present a rare case of triple metachronous primary lung cancer, accompanied by a systematic review of case reports and reviews published between 2010 and 2024, focusing on clinical, pathological, and radiological aspects. In the presented case, three distinct histopathological subtypes of primary lung cancer developed over an eight-year period. Genetic analysis revealed TP53 and PTEN mutations, potentially contributing to metachronous tumor development. The literature emphasizes the importance of timely imaging and histological confirmation in distinguishing metachronous tumors from recurrence or metastasis. This case represents one of the rare reports of triple metachronous primary lung cancer in the literature and underscores that the diagnostic process necessitates the integrated use of radiological, histopathological, and molecular methods. High clinical vigilance is essential for identifying MPLC in patients with a previous history of lung cancer, and aggressive surveillance strategies—such as low-dose computed tomography—and a multidisciplinary approach are critical for improving patient outcomes.

Keywords: Multiple primary lung cancer, metachronous lung cancer, lung adenocarcinoma, squamous cell carcinoma, small cell lung carcinoma

ÖZ

Çoklu primer akciğer kanserleri (ÇPAK), senkron ya da metakron şekilde gelişebilir. Senkron ÇPAK, histolojik olarak farklı tümörlerin eş zamanlı ortaya çıkmasını ifade ederken; metakron ÇPAK, ilk akciğer kanserinin tedavisini takiben zaman içinde gelişir. Tanısal ve tedaviye ilişkin zorlukları vurgulamak amacıyla, üçlü metakron primer akciğer kanseri olgusunu ve 2010-2024 yılları arasında yayımlanan olgu sunumları ile derlemeleri klinik, patolojik ve radyolojik açıdan inceleyen sistematik bir derlemeyi sunmaktayız. Sunulan olguda, sekiz yıl içinde üç farklı histopatolojik alt tipte primer akciğer kanseri gelişmiştir. Genetik analizde TP53 ve PTEN mutasyonları saptanmış olup, bu mutasyonların metakron tümör gelişimine katkıda bulunabileceği düşünülmektedir. Literatürde, metakron tümörlerin nüks veya metastazdan ayırt edilmesinde zamanında yapılan görüntüleme ve histolojik doğrulamanın önemi vurgulanmaktadır. Bu olgu, literatürde nadiren bildirilen üçlü metakron primer akciğer kanseri olgularından biri olup, tanı sürecinin radyolojik, histopatolojik ve moleküler yöntemlerin bütüncül kullanımıyla yürütülmesi gerektiğini göstermektedir. Akciğer kanseri öyküsü olan hastalarda yüksek klinik farkındalık esastır ve düşük doz bilgisayarlı tomografi gibi agresif izlem stratejileri ile multidisipliner bir yaklaşım, hasta sonuçlarının iyileştirilmesi açısından büyük öneme sahiptir.

Anahtar Kelimeler: Çoklu primer akciğer kanseri, metakron akciğer kanseri, akciğer adenokarsinomu, yassı hücreli karsinom, küçük hücreli akciğer karsinomu

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INTRODUCTION

Lung cancer continues to represent the leading cause of cancer-related mortality worldwide. Based on the latest GLOBOCAN 2022 estimates, approximately 2.5 million new cases and 1.8 million deaths were reported globally in that year[1]. Key risk factors for lung cancer include tobacco smoke exposure, environmental carcinogens, and genetic predisposition[2]. Patients with lung cancer may present with multiple primary tumors either simultaneously [synchronous multiple primary lung cancer (MPLC)] or sequentially following the treatment of the initial tumor (metachronous MPLC). This phenomenon has emerged as a significant clinical challenge, with the classification and management of these tumors remaining complex[3]. Crucially, distinguishing whether a subsequent tumor is an independent primary malignancy or a recurrence/metastasis of the initial tumor is essential for determining staging, therapeutic strategies, and prognosis.

The first documented case of two distinct primary lung cancers was reported by Beyreuther[4] in 1924. In 1975, Martini and Melamed[5] proposed clinicopathological criteria for the diagnosis of MPLC. Over time, these criteria have been refined and integrated into clinical guidelines. Lung tumors arising at different times are classified as metachronous if they exhibit distinct histologies or, in cases of similar histology, if there is no evidence of systemic metastasis between tumors over a period of four years or longer[6]. In this report, we present a rare case of triple metachronous primary lung cancer in a long-term smoker, characterized by three distinct histopathological subtypes: adenocarcinoma, squamous cell carcinoma, and small cell carcinoma, diagnosed at different time intervals. The second primary lung cancer was detected four years after the initial diagnosis, followed by a third tumor four years later. In addition to this unique case presentation, a comprehensive literature review was performed through PubMed, MEDLINE, and Scopus databases to identify case reports and reviews published between 2010 and 2024. Articles were evaluated for clinical, pathological, and radiological findings, emphasizing diagnostic innovations and management strategies in MPLC. This integrated analysis aims to highlight both the diagnostic and therapeutic challenges of metachronous MPLC and to provide a concise synthesis of recent evidence in this field.

A 63-year-old male patient was referred to our clinic in May 2012 due to a pulmonary mass. The patient had an 80 pack-year smoking history and had worked as an office clerk for 30 years. There was no family history of lung cancer, and the patient had no chronic illnesses.

Computed tomography (CT) imaging revealed a mass measuring 5.0×3.5 cm in the right upper lobe. A biopsy performed under CT guidance was consistent with non-small cell lung cancer (NSCLC). Clinical staging, conducted using transbronchial needle biopsy and F-18 fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET), was determined as cT2N0M0. The patient underwent a right upper and middle lobectomy. Pathological examination revealed well-differentiated adenocarcinoma (Figure 1) with a pathological stage of pT2N0. Molecular analysis based on next-generation sequencing (NGS) was performed on the primary lung adenocarcinoma specimen to evaluate potential hereditary or somatic predispositions. The targeted panel included 54 cancer-related genes and 26 microsatellite loci. The analysis revealed pathogenic variants in the *TP53* gene (c.734G>T, p.G245V) and the *PTEN* gene (c.380G>T, p.G127V). Both mutations were classified as Tier 2C alterations, indicating potential clinical significance. Adjuvant treatment with four cycles of cisplatin and vinorelbine combination therapy was administered. The patient was subsequently placed under routine follow-up.

Four years after the initial diagnosis, in October 2016, follow-up thoracic CT and ^{18}F-FDG PET/CT imaging revealed a lobulated, malignant mass lesion measuring 27×27 mm in the posterobasal segment of the left lower lobe of the lung (maximum standardized uptake value: 8.5). No distant metastases were observed. The patient underwent wedge resection of the left lower lobe. Pathological examination revealed squamous cell carcinoma (Figure 2) (TTF-1 negative, p63 positive) with a pathological stage of pT1cN0. The patient was followed up without adjuvant therapy.

Four years after the second primary tumor, in January 2020, thoracic CT revealed an endobronchial lesion extending from the left lower lobe to the secondary carina. A punch biopsy was performed. Pathological examination revealed findings consistent with small cell carcinoma (Figure 3), characterized by p63 negativity, synaptophysin positivity, chromogranin positivity, and CD56 positivity. PET-CT imaging demonstrated limited-stage disease, and concurrent curative chemoradiotherapy was administered. Follow-up CT scans showed a complete response to therapy. The patient has been under surveillance for the past four years without evidence of malignancy (Table 1).

DISCUSSION

MPLC can present either synchronously (simultaneously) or metachronously (at different times)[7]. According to the criteria for synchronous lung cancer defined by Martini and Melamed[5], synchronous tumors are secondary tumors observed concurrently with a primary tumor but with a different histology. If the tumors share the same histology, they must be located in different segments or lobes.

The definition of metachronous MPLC includes secondary tumors histologically distinct from the primary tumor or tumors of the same histology arising after a tumor-free

interval of at least two years, located in a different lobe, and without extrapulmonary metastasis at the time of diagnosis[8].

Antakli et al.[9] made modifications to Martini and Melamed's[5] criteria, adding a definition for metachronous lung tumors with the same histology as the primary tumor. These revised criteria require the presence of two or more of the following: anatomical distinction from the primary tumor, association with a premalignant lesion, different DNA ploidy, and absence of systemic metastasis or mediastinal spread. The rate of developing a second primary lung cancer after curative treatment of NSCLC is reported to be 1-2% per patient per year, whereas this rate rises to 6% per patient per year after curative treatment of SCLC[10]. Retrospective studies indicate that the median interval between the primary and new lung cancer is 38 to 48 months, with approximately two-thirds of the tumors sharing the same histology[11]. Triple primary lung cancer is extremely rare, even within the MPLC category. This case represents one of the few reports of triple primary lung cancer with three distinct histological types[12,13].

Smoking is a major etiological factor in the development of metachronous multiple lung cancers[2]. While the development of metachronous tumors in patients who continue smoking after the initial diagnosis is not surprising, the occurrence of metachronous tumors many years later in patients who quit smoking raises questions about the persistent epigenetic effects of smoking. Carcinogens in cigarette smoke are known to cause genetic damage, leading to mutations in tumor suppressor genes such as *TP53* and *PTEN*. TP53 mutations impair tumor suppressor function, inhibit apoptosis, and disrupt DNA repair mechanisms, leading to genetic instability and cellular malignant transformation, and are therefore widely recognized as markers of poor prognosis in various malignancies, including NSCLC[14]. PTEN mutations activate the PI3K/AKT/mTOR pathway, promoting cellular proliferation, growth, and metastatic potential. The coexistence of both mutations supports tumor heterogeneity, allowing the development of independent clones and potentially triggering the formation of metachronous tumors[15]. In our case, despite smoking cessation at the time of initial diagnosis, the development of two additional primary lung tumors four and eight years later may be attributed to the persistent mutagenic effects of smoking. The coexistence of TP53 and PTEN mutations in this patient may explain the mechanisms underlying the emergence of three distinct metachronous primary tumors.

Approximately two-thirds of metachronous lung cancers are resectable, and about one-third of these patients undergo limited resections[6]. In metachronous MPLC, the American College of Chest Physicians recommends surgical treatment as the first choice when the tumor is detected in its early stages, as surgical resection can provide long-term survival[16]. One of the greatest challenges in treating a second primary lung cancer is determining the feasibility of surgical resection. Patients who have undergone prior lung cancer resection may not be suitable candidates for a second lobectomy or pneumonectomy due to limited pulmonary reserves[17].

The use of high-resolution CT has significantly increased the detection of small lung cancers, which correlates with the rising incidence of MPLC[18,19]. According to the 8th edition of the TNM classification for NSCLC, a second tumor in the same lobe is categorized as T3, tumors in different ipsilateral lobes as T4, and tumors in the contralateral lung as M1[20]. As a result, most MPLC cases are reclassified as stage III or IV, which are

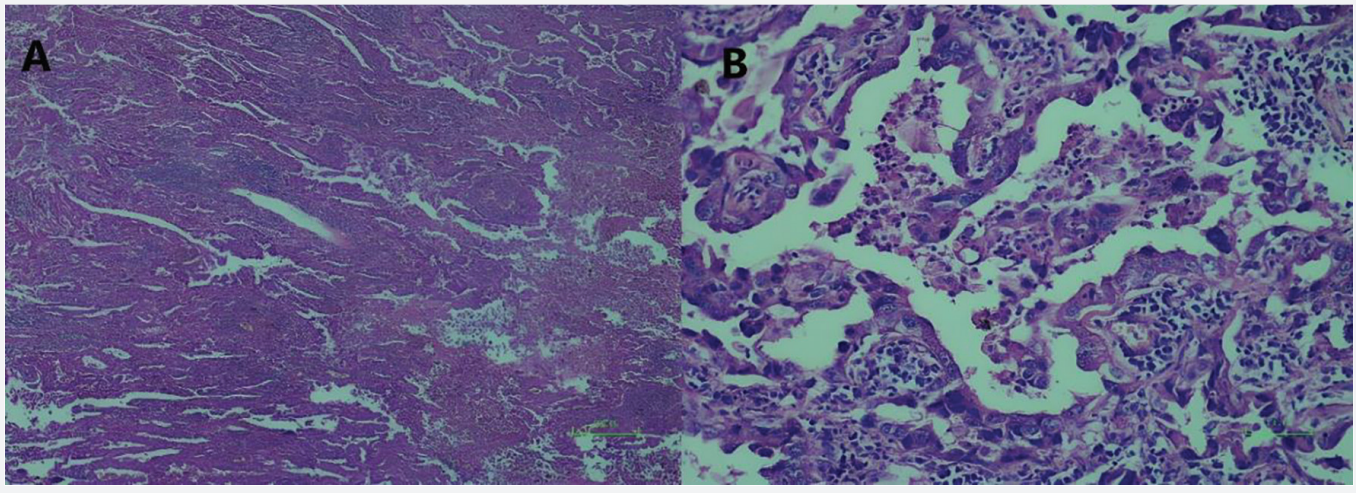

Figure 1. (A) Tumoral infiltration exhibiting lepidic and papillary growth patterns (hematoxylin and eosin ×40) (B) Tumoral infiltration forming papillary structures with fibrovascular cores, composed of cells with large nuclei and prominent nucleoli (hematoxylin and eosin ×200)

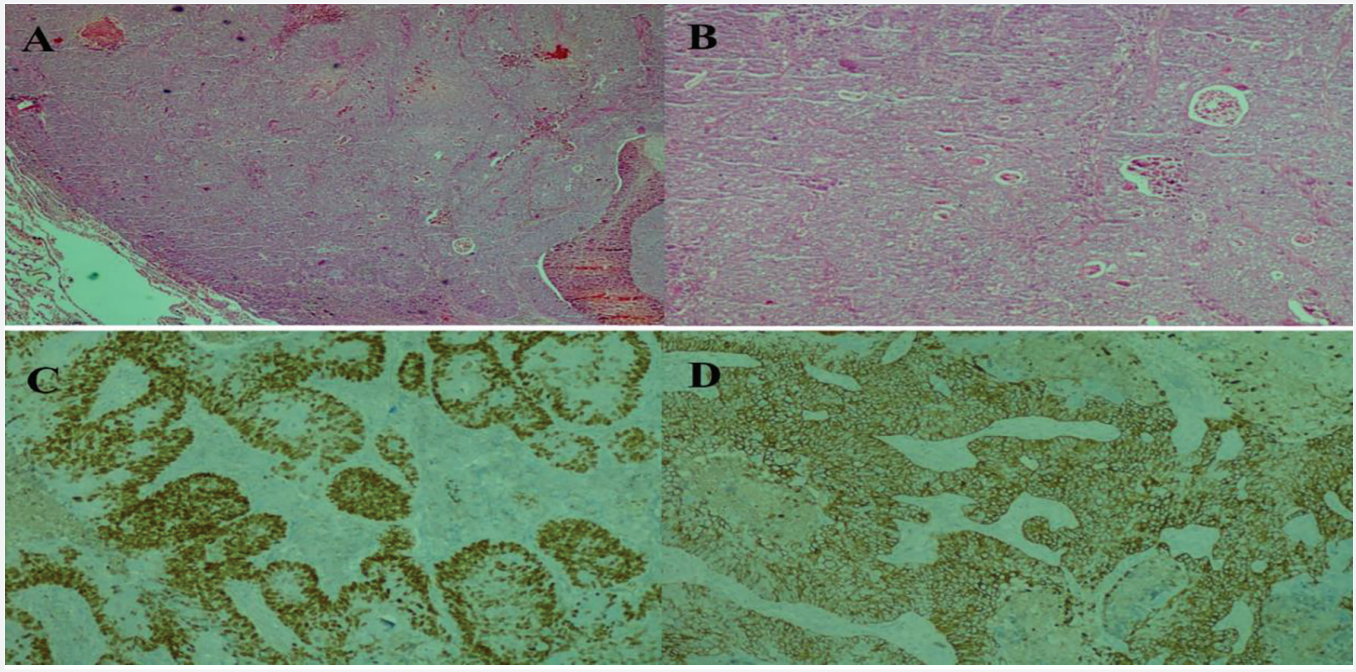

Figure 2. (A) Tumoral infiltration in a solid pattern invading the lung parenchyma (hematoxylin and eosin ×40) (B) Tumoral infiltration in a solid pattern, composed of cells with vesicular nuclei, prominent nucleoli, and eosinophilic cytoplasm (hematoxylin and eosin ×200) (C) Nuclear positivity with p63 immunohistochemistry (×200) (D) Cytoplasmic positivity with CK5 immunohistochemistry (×200)

Table 1. Characteristics of the patient's multiple primary lung tumors

Histological type	Well-differentiated adenocarcinoma	Squamous cell carcinoma	Small cell carcinoma
Year of diagnosis	2012	2016	2020
Tumor location	Right upper lobe	Posterobasal segment of the left lower lobe	Central part of the left lung
Tumor size (radiological)	50x35 mm	27x27 mm	40x30 mm
Disease Stage (based on the 8th TNM staging system)	pT2N0	pT1cN0	Limited-stage disease
Curative treatment	Right upper lobectomy	Wedge resection of the left lower lobe	Concurrent chemoradiotherapy

typically associated with poorer prognoses and are managed with systemic therapies such as chemotherapy or radiotherapy. However, van Bodegom et al.[21] reported significantly better survival outcomes in MPLC patients compared to those with advanced-stage single tumors. Similarly, Pairolero et al.[22] demonstrated more favorable prognoses in patients with multiple primary tumors compared to those with local recurrence or metastatic disease. A comprehensive meta-analysis by Jiang et al.[23] confirmed that MPLC patients show superior 3- and 5-year overall survival rates compared to those with intrapulmonary metastases. The same analysis concluded that histological type (similar or different) and laterality (unilateral or bilateral) were not significantly associated with differences in overall survival[23].

Furthermore, the prognosis of metachronous NSCLC has been specifically evaluated in dedicated surgical cohorts. A meta-analysis by Hamaji et al.[16] revealed a five-year overall survival rate of 46% following resection of a second metachronous NSCLC, underscoring the potential benefit of surgical intervention in patients with good performance status who are eligible for resection. Supporting this, Haraguchi et al.[24] found that patients with the same histologic subtype in both primary tumors had significantly improved outcomes, reporting five-year survival rates of 71% versus 47% (p=0.0174). These findings suggest that histological similarity may serve as a positive prognostic indicator in metachronous NSCLC and reinforce the rationale for aggressive surgical approaches in well-selected patients. Interestingly, despite the presence

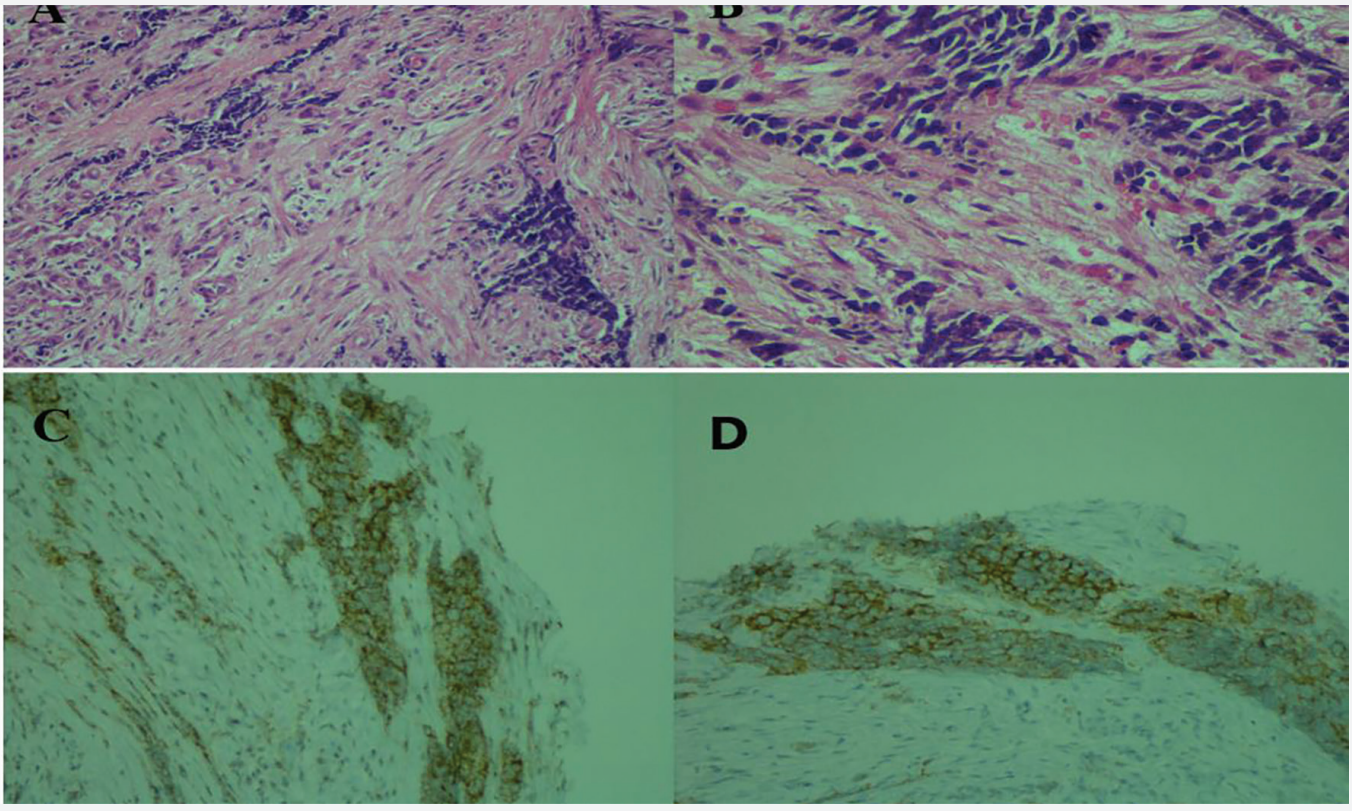

Figure 3. (A) Tumoral infiltration with crush artifacts, small hyperchromatic nuclei (hematoxylin and eosin ×100) (B) Tumoral infiltration with crush artifacts, small hyperchromatic nuclei, and nuclear irregularities (hematoxylin and eosin ×400) (C) Cytoplasmic positivity with CD56 immunohistochemistry (×400) (D) Cytoplasmic positivity with synaptophysin immunohistochemistry (×400)

of three distinct histologic subtypes in our case, the patient exhibited a favorable long-term outcome. This may reflect the potential influence of early detection, individualized treatment planning, and close radiologic follow-up in modifying the expected prognostic trajectory.

In conclusion, the prognosis of MPLC—both synchronous and metachronous—is considerably better than that of patients with intrapulmonary metastases. Despite the tumor-free interval in metachronous cases, no significant survival difference was noted between synchronous and metachronous MPLC in existing analyses[23]. When new suspicious pulmonary lesions arise during surveillance of patients with a prior lung cancer history, multidisciplinary evaluation is essential. Nevertheless, hesitation by clinicians to perform re-biopsies—due to procedural risks such as anticoagulation needs—and patient anxiety regarding recurrence, treatment delays, or invasive procedures continue to pose challenges in timely diagnosis and management of metachronous MPLC.

Despite the diagnostic challenges, advanced imaging technologies and multidisciplinary strategies significantly enhance the detection accuracy of metachronous MPLC. Such integrative approaches, as demonstrated in our case, enable the timely differentiation of second primary tumors from recurrences or metastases, allowing patients to benefit from curative interventions and improved long-term outcomes.

The follow-up of metachronous MPLC remains controversial, particularly in patients who have undergone previous curative resections. However, the American Association for Thoracic Surgery (AATS) guidelines emphasize the need for aggressive surveillance strategies in this population[25]. These include annual low-dose computed tomography (LDCT) screening up to age 79, and more intensive imaging every six months during the first 2-3 years post-resection, when recurrence risk is highest. Such structured monitoring protocols may facilitate earlier detection of new malignancies, particularly in high-risk individuals, and ultimately contribute to improved survival outcomes.

Understanding the molecular profile of metachronous MPLC is equally essential for developing personalized surveillance and therapeutic strategies. Genomic analysis using NGS can identify actionable somatic mutations such as TP53 and PTEN, which are associated with an increased risk of recurrence. These findings may support more aggressive treatment planning and

closer follow-up algorithms in genetically predisposed patients.

Finally, integration of radiological, pathological, and molecular data remains pivotal in enhancing diagnostic precision, informing prognosis, and optimizing clinical management of patients with MPLC.

CONCLUSION

Metachronous MPLC represents a complex and diagnostically challenging clinical entity that necessitates a comprehensive multidisciplinary approach. In patients with a history of lung cancer, the emergence of new suspicious pulmonary lesions during follow-up should raise clinical suspicion for metachronous MPLC. This case, involving three distinct histopathological subtypes over an 8-year period, contributes uniquely to the limited literature by illustrating the natural history and management complexities of triple metachronous MPLC. Our report emphasizes the need for high clinical vigilance and the critical role of serial imaging and histological confirmation in distinguishing new primary tumors from recurrence or metastasis. Whenever feasible, molecular analysis of the initial tumor using NGS should be performed to assess for potential hereditary or somatic predispositions. Notably, in our case, concurrent TP53 and PTEN mutations were identified, which may indicate an increased risk for metachronous tumor development and further underscores the importance of integrating molecular profiling into individualized follow-up strategies. Early detection and aggressive curative interventions, including surgical resection when appropriate, may improve clinical outcomes in selected patients diagnosed with MPLC. Histopathological confirmation remains essential to guide optimal therapeutic decision-making. While regular follow-up is universally important, the AATS recommends annual LDCT until the age of 79 in long-term lung cancer survivors, with semiannual imaging during the first 2-3 years after resection due to peak recurrence risk. However, these recommendations are not personalized and may not fully address the needs of patients with high-risk molecular profiles. In this context, more frequent surveillance—every 3 months during the first 2 years, followed by 3-6 month intervals during years 3 to 5—may facilitate timely identification of new lesions. Notably, despite our patient harboring high-risk prognostic factors such as somatic TP53 and PTEN mutations and three distinct histologic subtypes, the case demonstrated an unexpectedly favorable long-term clinical outcome. This observation suggests that intensified surveillance algorithms could be beneficial in selected high-risk MPLC populations. Prospective studies are warranted to validate whether personalized follow-up strategies improve early detection and overall survival in such patients. This case highlights the potential value of individualized surveillance strategies that integrate radiologic and molecular evaluation to enhance early detection, inform prognosis, and improve overall survival and quality of life in patients with MPLC.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.B.K., Concept: G.Ö.,A.F.A., T.İ.A., Design: G.Ö., G.B.K., M.B.H., Data Collection or Processing: M.A.M.,G.B.K., Analysis or Interpretation: A.F.A.,T.İ.A., G.B.K.,B. E., Literature Search: B.E.,S.T., Writing: G.Ö.,M.A.M., M.B.H.,S.T.

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