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CASE REPORT

Successive Development of Three Histologically Distinct Primary Malignancies: Synovialosarcoma, Colorectal Adenocarcinoma, and Pulmonary Large Cell Neuroendocrine Carcinoma. A Case Report

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ABSTRACT

The coexistence of multiple primary malignant tumors is rare but represents a significant diagnostic and therapeutic challenge in oncology. This complexity is further heightened when tumors arise from different histological lineages, such as mesenchymal, epithelial, and neuroendocrine origins. We report an exceptional case of a 67-year-old man who sequentially developed three distinct primary malignancies over a six-year period: a biphasic synovial sarcoma of the ankle, a colorectal adenocarcinoma, and a primary pulmonary large-cell neuroendocrine carcinoma. The management of each malignancy required a tailored multidisciplinary approach, including surgery and adjuvant chemotherapy. This case underscores the importance of prolonged and individualized follow-up in patients with a history of malignancy and highlights the need to actively investigate potential underlying hereditary cancer syndromes through genetic testing, which may inform both preventive and therapeutic strategies. This study is a retrospective observational case report and does not constitute a clinical trial or involve experimental interventions. Data were collected from patient medical records during routine clinical follow-up. In accordance with national and international guidelines, formal approval by an Institutional Review Board or ethics committee was not required for this type of study. All procedures were conducted in compliance with the ethical principles of the 2013 Declaration of Helsinki, ensuring patient confidentiality, anonymity, and respect for dignity.

Keywords: Multiple primary tumors, Germline mutations, Synovialosarcoma, Colorectal adenocarcinoma, Large cell neuroendocrine carcinoma, Multidisciplinary tumor board.

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1. INTRODUCTION

The coexistence of multiple primary malignant tumors (MPMTs) in a single patient remains a relatively uncommon but clinically significant phenomenon in oncology [1]. While the incidence of MPMTs has increased in recent decades, likely due to improved diagnostic techniques and longer patient survival after a first primary cancer, their management presents a persistent challenge. The principal difficulty lies in distinguishing a true new primary tumor from a metastasis of the initial cancer, as this distinction has profound implications for staging, prognosis, and therapeutic strategy [2]. The established criteria for diagnosing MPMTs require that the tumors are histologically distinct and that the possibility of metastasis has been reasonably excluded, a task that can be diagnostically complex, especially when tumors present in close temporal or anatomical proximity [2].

This diagnostic and therapeutic complexity is further amplified when the multiple primary tumors arise from different embryological lineages, such as mesenchymal, epithelial, and neuroendocrine. The occurrence of such histologically diverse neoplasms suggests a broader underlying field of genetic or epigenetic instability, often referred to as "field cancerization," rather than a series of unrelated

sporadic events [3]. This phenomenon raises critical questions about shared etiological factors, which may include a combination of environmental exposures, lifestyle choices, and, most importantly, an underlying hereditary cancer predisposition. The potential presence of a germline mutation in a cancer susceptibility gene (e.g., TP53, MMR genes, APC) could create a systemic vulnerability, giving rise to various tumor types across different organ systems [4].

The study of such exceptional cases is therefore of paramount importance. While large-scale epidemiological studies can identify risk factors for single cancer types, individual case reports of MPMTs provide unique and invaluable insights into the complex interplay of carcinogenesis, genetic susceptibility, and the long-term effects of treatment. They serve as powerful clinical lessons that underscore the necessity for a high index of suspicion, prolonged surveillance, and a truly personalized approach to patient care [5].

Therefore, this case report aims to describe the exceptional clinical course of a patient who sequentially developed three distinct primary malignancies—a synovialosarcoma, a colorectal adenocarcinoma, and a pulmonary large-cell neuroendocrine carcinoma—over a six-year period. Through this case, we will discuss the formidable diagnostic and therapeutic challenges encountered, and we highlight the critical importance of a multidisciplinary approach and the systematic search for an underlying hereditary cancer syndrome to guide future management and counseling.

2. CASE PRESENTATION

Patient Information and Initial Presentation We report the case of a 67-year-old male patient with a known history of well-controlled hypertension. His baseline performance status was good (ECOG 1). His medical history began in July 2019 when he presented with a progressively enlarging mass on his left ankle.

First Primary Malignancy: Biphasic Synovialosarcoma of the Left Ankle The patient underwent an incisional biopsy of the ankle mass, followed by a wide local excision. The pathological examination revealed a biphasic synoviosarcoma. Staging work-up, including MRI of the ankle and a CT scan of the chest, abdomen, and pelvis, showed no evidence of metastatic disease. The tumor was classified as a primary high-grade sarcoma (Figure1). Following discussion in a multidisciplinary tumor board, the patient received four cycles of adjuvant chemotherapy with doxorubicin (75 mg/m²) and ifosfamide (10 g/m²) over 3 days. He tolerated the treatment well and was subsequently placed under routine surveillance.

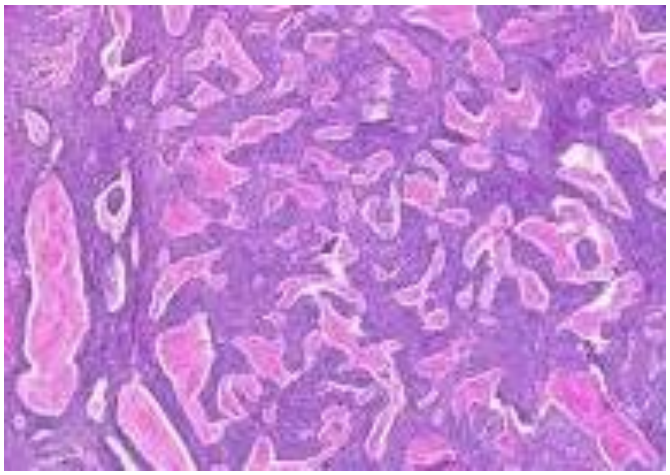

Figure 1. Hematoxylin and Eosin (H&E) staining of the synovial sarcoma.

Interval and Lost to Follow-Up After completing adjuvant treatment, the patient was lost to follow-up for approximately five years. This represents a total break in care, with no documented surveillance imaging or oncology visits at our institution during this interval.

Second Primary Malignancy: Left Colonic Adenocarcinoma In November 2024, the patient presented to the emergency department with signs and symptoms of acute intestinal obstruction. An abdominal CT scan revealed a left colonic mass causing a transition point. He underwent an emergency left hemicolectomy. Postoperative pathological analysis confirmed a moderately differentiated colonic adenocarcinoma (Figure 2). The final pathological stage was pT3N1bM0, Stage IIIB according to the AJCC 8th edition. The patient

recovered well from surgery and subsequently received 12 cycles of adjuvant chemotherapy with the FOLFOX regimen (5-FU, leucovorin, and oxaliplatin).

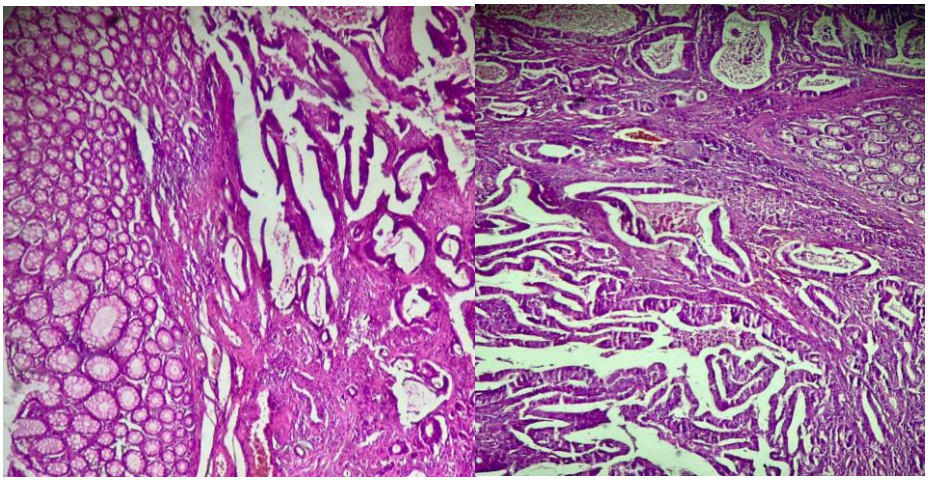

Figure 2. Moderately differentiated adenocarcinoma of the colon.

Third Primary Malignancy: Pulmonary Large-Cell Neuroendocrine Carcinoma A follow-up thoraco-abdomino-pelvic CT scan performed at the end of 2025, after the completion of adjuvant chemotherapy for his colon cancer, revealed a new, solitary 14 x 13 x 12.5 mm nodule in the middle lobe of the right lung. No new intra-abdominal or pelvic lesions were identified. A CT-guided percutaneous biopsy of the pulmonary nodule was performed. The pathology was consistent with a primary pulmonary large-cell neuroendocrine carcinoma. A PET-CT scan confirmed the solitary nature of the lesion with no other sites of metastasis (Figure3). The patient underwent a video-assisted thoracoscopic surgery (VATS) middle lobectomy. The final pathology confirmed a large-cell neuroendocrine carcinoma, staged as pT2aN0M0, Stage IB. Given his history of multiple primary malignancies, a multidisciplinary tumor board recommended adjuvant chemotherapy with carboplatin (AUC 5) and etoposide (100 mg/m²) for four cycles.

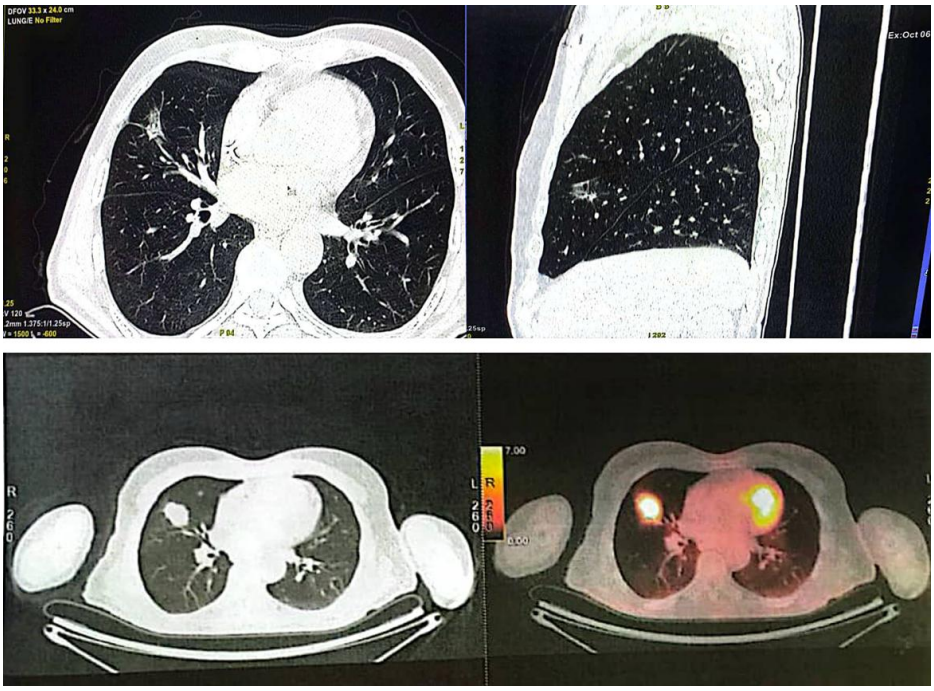

Figure 3. Pulmonary neuroendocrine carcinoma.

Table 1. Chronological Summary of the Patient's Three Primary Malignancies.

Timeline	Primary Tumor (Type, Location)	Key Diagnostic Findings	Staging (AJCC 8th Ed.)	Primary Treatment
July 2019	Synovialosarcoma, Left Ankle	Biphasic morphology on H&E. No metastases on CT/MRI.	High-Grade, pT2N0M0, Stage IIIA	Wide local excision + 4 cycles Doxorubicin/Ifosfamide
Nov 2024	Adenocarcinoma, Left Colon	Moderately differentiated adenocarcinoma. Obstructing mass on CT.	pT3N1bM0, Stage IIIC	Emergency left hemicolectomy + 12 cycles FOLFOX
Dec 2025	Large-Cell Neuroendocrine Carcinoma, Right Lung	Solitary nodule on CT. Positive for neuroendocrine markers on biopsy.	pT2aN0M0, Stage IB	VATS middle lobectomy + 4 cycles Carboplatin/Etoposide

Table 2. Key Pathological and Immunohistochemical (IHC) Profiles.

Primary Tumor	Histology	Positive IHC Markers	Negative IHC Markers
Synovialosarcoma	Biphasic (spindle cell & epithelioid)	Cytokeratin (AE1/AE3), EMA, BCL-2	S100, SOX10
Colorectal Adenocarcinoma	Moderately differentiated	CK20, CDX2, CEA	CK7, TTF-1
Pulmonary Neuroendocrine	Large-cell type	Synaptophysin, Chromogranin A, CD56 (NCAM)	TTF-1, PAX8, CK7/CK20 variable

3. DISCUSSION

The "Field Effect" and Etiological Considerations The successive development of three histologically distinct primary malignancies in our patient over a six-year period is a remarkable clinical phenomenon that strongly suggests a predisposed "field effect." This concept describes a field of tissue that has been preconditioned by genetic or environmental insults, making it susceptible to the development of multiple, independent neoplasms [3].The etiology of such a field effect is multifactorial, but in our patient, a genetic predisposition is the most compelling hypothesis. The specific combination of a sarcoma, a colorectal adenocarcinoma, and a pulmonary neuroendocrine carcinoma raises a high suspicion for a hereditary cancer predisposition syndrome, most notably Li-Fraumeni syndrome (LFS), which is classically associated with germline *TP53* mutations [6]. LFS significantly increases the lifetime risk of sarcomas, breast cancer, brain tumors, and adrenal cortical carcinoma, but other malignancies, including colon and lung cancer, have also been reported. Other potential genetic syndromes, such as Lynch syndrome (MMR gene mutations) or familial adenomatous polyposis (APC gene), could explain the colon cancer, but they do not typically account for the synovialosarcoma [7]. Furthermore, iatrogenic factors must be considered. The patient received doxorubicin and ifosfamide for his synovialosarcoma. Both agents are known carcinogens. Therapy-related solid tumors typically emerge after a latency period of 5 to 10 years.While their role in this specific case is speculative, they represent a potential contributor to the "field effect" and a known risk factor for secondary malignancies [8]. Finally, environmental and lifestyle factors, such as tobacco use (a known risk factor for lung cancer) and diet, may have acted as cofactors in a genetically susceptible individual.

Diagnostic and Therapeutic Challenges This case presented several formidable challenges. The primary diagnostic challenge was to definitively rule out metastatic disease at each new presentation. For the colonic mass, the distinction from a metastatic sarcoma was straightforward based on the distinct histology. For the pulmonary nodule, however, the possibility of a metastatic colon cancer to the lung had to be excluded. The final diagnosis was confidently established through a combination of clinical context (solitary nodule after a disease-free interval), distinct histology, and a unique immunohistochemical profile (TTF-1 negative, neuroendocrine markers positive), which is incompatible with a colorectal primary [9].

Therapeutically, the management was complex, requiring sequential treatments for three different malignancies. This raised significant concerns about cumulative toxicities, particularly cardiotoxicity from sequential anthracycline and oxaliplatin, and myelosuppression from multiple lines of chemotherapy. The decision to proceed with each adjuvant treatment was made by a

multidisciplinary tumor board (MDT), which carefully weighed the potential benefits against the risks of cumulative toxicity in a patient with a good performance status [10].

The Critical Role of the Multidisciplinary Tumor Board and the Imperative for Genetic Testing The successful navigation of this complex clinical course was entirely dependent on a robust multidisciplinary approach. At each juncture—the initial sarcoma, the colonic obstruction, and the pulmonary nodule—the MDT was essential for accurate diagnosis, staging, and treatment planning. This case underscores that the management of MPMTs is not a series of isolated events but a continuum of care requiring seamless integration between surgical oncology, medical oncology, pathology, radiology, and genetics. Most importantly, this case serves as a powerful argument for systematic germline genetic testing in any patient presenting with a second primary malignancy, especially when the tumors are of different histological lineages [11]. While genetic testing was not performed in our case, its systematic implementation in such clinical scenarios is crucial and would have significantly strengthened the scientific value of this report.

Identifying a pathogenic germline mutation (e.g., in *TP53*) would not only explain the patient's clinical history but would also have profound implications for his family members, enabling predictive testing and enhanced surveillance. Furthermore, a confirmed genetic diagnosis could influence future therapeutic choices, as certain targeted therapies or clinical trials may be available for specific hereditary syndromes.

The strengths of our study include the detailed longitudinal follow-up of a truly exceptional case. However, our study must be interpreted in light of several limitations. The primary limitation is the lack of genetic testing, which represents a missed opportunity to identify a potential hereditary cancer syndrome and provide comprehensive care. Additionally, the five-year loss to follow-up limits our understanding of the natural history of the patient's disease during that interval.

In summary, while the occurrence of multiple primary malignant tumors is rare, this case highlights the critical importance of maintaining a high index of suspicion and adopting a holistic, patient-centered approach. The successive triad of a synovialosarcoma, colorectal adenocarcinoma, and pulmonary neuroendocrine carcinoma is a dramatic illustration of a systemic predisposition to malignancy. It reinforces the concept that a diagnosis of cancer should prompt consideration of the entire patient, including their genetic background and prior treatments. Ultimately, the integration of comprehensive genetic counseling and testing into the standard of care for patients with MPMTs is no longer optional but is an essential component of modern, personalized oncology.

4. CONCLUSION

In conclusion, this exceptional case does not merely represent a medical curiosity; it serves as a dramatic and didactic illustration of the inherent complexity in managing patients with multiple primary tumors. It is a stark reminder that a diagnosis of cancer should never be viewed as an isolated event but should always prompt a holistic evaluation of the patient. The successive triad of three histologically distinct neoplasms in our patient underscores the imperative for a prolonged, multidisciplinary, and highly personalized follow-up, where seamless collaboration between surgical, medical, and radiation oncologists, pathologists, and radiologists is not merely an option, but an absolute necessity. Furthermore, this case makes a compelling argument for the systematic integration of genetics into oncology practice. It convincingly demonstrates that the search for germline mutations is no longer an academic exercise but an essential component of modern cancer care. Identifying an underlying hereditary predisposition redefines the therapeutic strategy, guides future preventive strategies for both the patient and their family, and informs the use of novel targeted therapies. It marks the critical transition from treating a single tumor to managing the patient's lifelong cancer risk. Ultimately, this report compels us to enact a paradigm shift in our oncological practice. It reminds us that we are treating individuals with a unique biological landscape, shaped by a complex interplay between their genetics, environmental exposures, and prior treatments. The future of oncology lies in our ability to integrate these multiple facets to deliver care that is not only effective but also truly holistic, predictive, and, ultimately, more human.

Competing interests: The authors declare that they have no competing interest.

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