Case Report

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Multiple primary malignancies: sequential development of Ewing sarcoma and carcinoid tumor in a single patient

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Introduction and importance: Multiple primary malignancies (MPMs) involve two or more distinct primary cancers in one individual, either simultaneously or at different times. The incidence of MPMs is rising due to advancements in cancer detection, improved survival rates, and long-term treatment effects. This case report, likely the first of its kind, highlights a rare instance of a 30-year-old female developing a carcinoid tumor 5 years after Ewing sarcoma, emphasizing the need for vigilant monitoring of cancer survivors.

Case presentation: A 30-year-old female with a history of Ewing Sarcoma diagnosed 5 years prior, initially presenting with a vascular, hard mass on her right shoulder, underwent neoadjuvant chemotherapy and surgical excision. She recently presented with high-grade fever, cough, weight loss, and severe chest pain. Imaging and biopsy confirmed a high-grade carcinoid tumor. Histopathology showed positive markers for Synaptophysin, CD56, and Chromogranin, with a Ki-67 index of 30–40%. The patient passed away after one cycle of chemotherapy.

Clinical discussion: Diagnosing and managing MPMs is challenging due to the complexity of distinguishing primary tumors from metastases. This case fits the Warren and Gates' criteria for MPMs. This case confirmed Ewing sarcoma and atypical carcinoid tumor as distinct primary malignancies. Delayed diagnosis worsens outcomes, especially for aggressive atypical carcinoids. This case underscores the importance of thorough diagnostics, long-term follow-up, and improved healthcare infrastructure.

Conclusion: This case report emphasizes the importance of a multidisciplinary approach, regular follow-ups, and timely detection for effective management of MPMs.

Keywords: carcinoid tumor, case report, Ewing sarcoma, multiple primary malignancies (MPMs), neuroendocrine tumor

Introduction

Multiple primary malignancies (MPMs) refer to the occurrence of two or more distinct primary cancers in the same individual, either simultaneously (synchronous) or at different times (metachronous). The incidence of MPMs is increasing due to advancements in cancer detection, improved survival rates, and the long-term effects of cancer treatments. Globally, the prevalence of MPMs varies, with studies reporting an incidence ranging from 0.7 to 17.2%[1,2]. MPMs pose significant diagnostic and therapeutic challenges, requiring a comprehensive understanding of the underlying genetic, environmental, and treatment-related factors that contribute to their development[3]. Ewing Sarcoma is a rare and aggressive bone and soft tissue cancer predominantly affecting children and young adults. It is characterized by a specific chromosomal translocation, most commonly t(11;22)(q24;q12), leading to the EWSR1-FLI1 fusion gene[4]. This malignancy typically presents in the pelvis, femur, and other long bones, but can also occur in soft tissues[5]. Carcinoid Tumors are slow-growing neuroendocrine tumors that typically arise in the gastrointestinal tract and lungs. They can metastasize and produce hormones causing systemic symptoms. Genetic mutations, such as those in the MEN1 gene, play a role in their pathogenesis[6].

HIGHLIGHTS

- First documented case of sequential Ewing sarcoma and carcinoid tumor in one patient.
- Emphasizes the need for vigilant monitoring of cancer survivors for secondary malignancies.
- Highlights the importance of a multidisciplinary approach for accurate diagnosis and treatment.
- Stresses the critical role of regular follow-ups and timely detection in managing secondary malignancies.
- Calls for further research into the mechanisms underlying multiple primary malignancies.

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Ewing sarcoma primarily affects children and young adults, with an estimated incidence of ~1.5 cases per million individuals in this age group worldwide, while carcinoid tumors occur at a rate of ~2.5–5 cases per 100 000 people annually with the highest incidence observed in individuals in their 50s–70s[7,8]. The occurrence of both malignancies in a single patient is unprecedented, with no previously documented cases in the literature, adding significant value to the medical field.

This case report discusses a 30-year-old female who was diagnosed with a new primary malignancy of carcinoid tumor 5 years after being treated for Ewing sarcoma. This case highlights the rarity of such occurrences and is likely the first of its kind to be reported, emphasizing the need for vigilance in monitoring cancer survivors for secondary malignancies. This case report is in line with the CARE guidelines for case reports[9]. The guardians provided all the data used for the case report and consent to the study.

Case presentation

A 30-year-old female presented with a history of Ewing sarcoma diagnosed 5 years prior, which was confirmed through patient history and treatment records, although detailed diagnostic evidence such as CT scans and histopathology slides were unavailable. According to that, she presented with a mass on the back of her right shoulder that had been present for 6 months. The mass was described as highly vascular and hard. An incisional biopsy revealed round cell tumor. A subsequent CT scan showed a large, well-defined, heterogeneously enhancing soft tissue density mass involving the soft tissue of the upper posterior cervical region, opposite the C5–T3 level, with no osseous or intrathoracic extension. The biopsy revealed a small round blue cell tumor. The immunohistochemical stain for CD99 was positive, suggesting a diagnosis of Ewing sarcoma at tumor stage of T4.N0.M0. At that time, there was no evidence of any additional malignancies, including the atypical carcinoid tumor. The patient underwent neoadjuvant chemotherapy followed by surgical excision of the tumor. Although she was counseled for regular follow-ups, she did not attend them due to living in a remote village and financial constraints, until her recent presentation with new symptoms.

Recently, the patient presented with high-grade fever, cough with serous sputum, and weight loss for 1 month, along with chest pain for 9 months, which had intensified in the past 15 days, and shortness of breath upon slight exertion. Clinical examination revealed a pale, emaciated patient with slight tenderness in the right hypochondrium. Respiratory examination showed decreased chest movement and expansion on the left side, a stony dull note on percussion, and decreased air entry on auscultation. The rest of the systemic examination was unremarkable. Preliminary workup revealed a hemoglobin level of 10.8 g/dl, TLC of 19 200/ul, platelet count of 562 000/ul, blood urea of 28.7 mg/dl, serum creatinine of 0.7 mg/dl, bilirubin level of 0.3 mg/dl, ALT of 15.6 U/l, and AST of 20.6 U/l. Ultrasonography of the abdomen revealed cholelithiasis and right-sided moderate pleural effusion, with no evidence of metastatic deposits in the liver and spleen.

A CT scan of the chest (with IV contrast) revealed a large, lobulated, heterogeneous enhancing soft tissue mass filling the lower two-thirds of the left hemithorax, medially infiltrating the mediastinal mass, encasing the left hilar vessels, and compressing the left lower lobe bronchus. Bronchoscopy revealed a lesion in the left lingular lobe with complete obstruction of the lumen (Fig. 1). An immunohistopathological study of a sample (1.1×0.3 cm) taken from the left bronchus after CT-guided core biopsy revealed an atypical carcinoid tumor with cores of lung tissue containing strands of atypical cuboidal cells with scanty cytoplasm and nuclei showing increased chromatin (Fig. 2). Histochemical staining showed expressions of Synaptophysin, CD56, and Chromogranin, and was negative for Cytokeratin AE1/AE3, TTF1, GATA-3, and PAX-8. The proliferative index

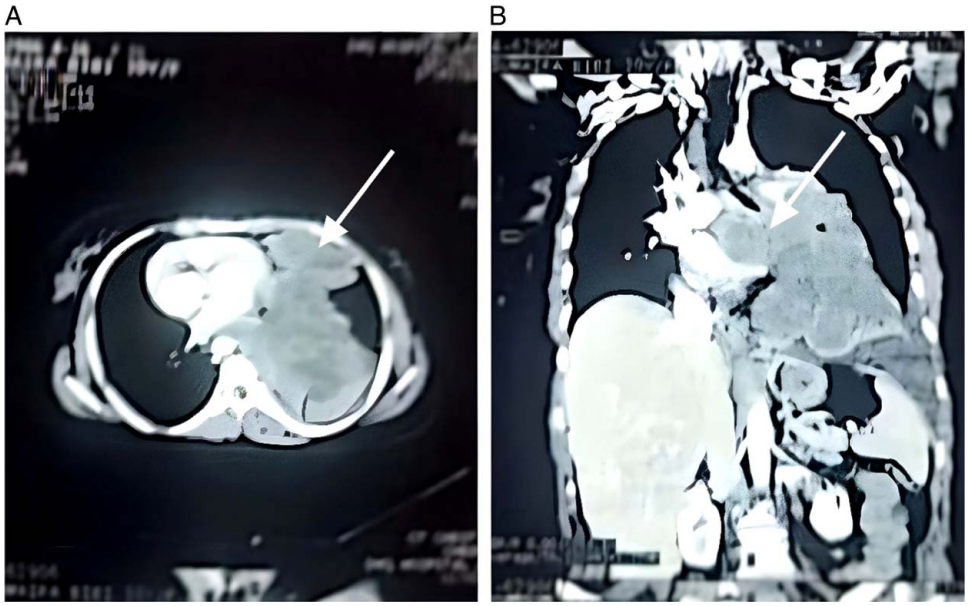

Figure 1. Axial (A) and coronal (B) images of contrast computed tomography chest showing a large lobulated heterogeneous enhancing soft tissue attenuation mass filling lower 2/3rd of left hemithorax, medially infiltrating mediastinal mass encasing left hilar vessels and compressing left lower lobe bronchus (white arrows).

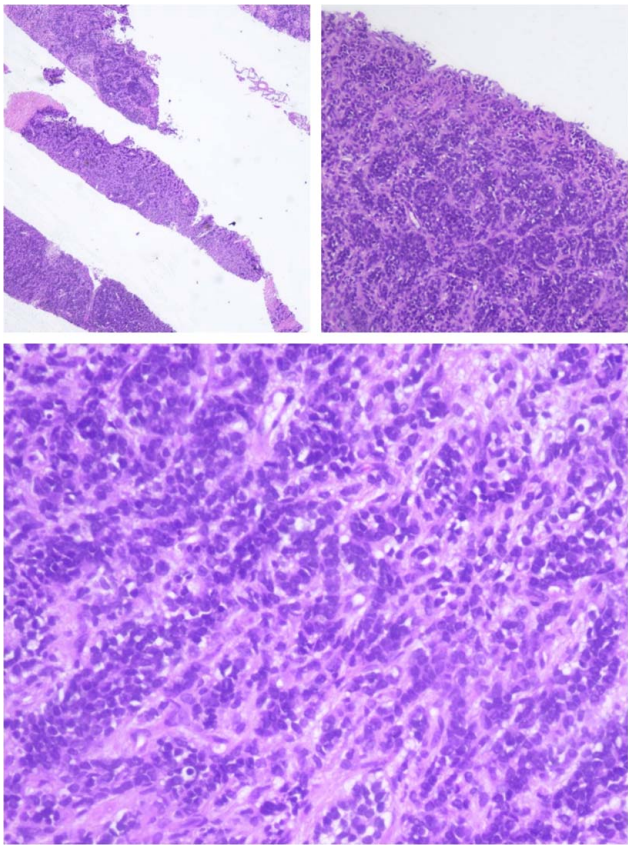

Figure 2. Hematoxylin and eosin images at different magnifications showing rounded cells with scant cytoplasm and variable size nuclei. Mitotic activity is also seen. Intervening areas of hyalinization are also noted.

(Ki-67) was 30–40% (Fig. 3). It was noteworthy that the features of the tumor were consistent with Neuroendocrine tumor Garde 2. CT abdomen and MRI spine revealed no metastasis.

Before the diagnosis of the atypical carcinoid tumor, the patient was managed conservatively by the pulmonology department. Treatment included nebulization and steroids to manage respiratory symptoms. After the diagnosis the patient was planned for three cycles of multi-agent chemotherapy (CEX regimen: Capecitabine, Epirubicin, and Cyclophosphamide). Unfortunately, the patient's condition deteriorated, passed away following one cycle of treatment.

Discussion

Diagnosing and managing MPMs presents significant challenges due to the complexity of distinguishing between primary tumors and metastatic lesions, the need for comprehensive patient history, and the requirement for advanced diagnostic techniques[10]. Warren and Gates set the criteria for defining MPMs as follows: (a) Each primary tumor must be histologically confirmed as malignant; (b) each primary tumor must be anatomically separate from the others; and (c) it must be verified that one tumor is not a metastasis or recurrence of another[11]. In this case, the diagnosis of Ewing Sarcoma was confirmed through patient history and treatment records. Extensive diagnostic workup and imaging revealed a large thoracic mass, and biopsy confirmed atypical carcinoid tumor. Histopathology showed positive markers for Synaptophysin, CD56, and Chromogranin, with a high Ki-67 index, indicating aggressive malignancy. This suggests a unique biological behavior, differing from typical Ewing sarcoma metastases[12]. The histological features and anatomical locations of the tumors confirmed that they were distinct primary malignancies, fitting the criteria for MPM and they are metachronous as they are diagnosed 5 years apart.

Neuroendocrine lung tumors, comprising 20–30% of all neuroendocrine tumors, are classified into typical carcinoids (TCs) and atypical carcinoids (ACs). TCs are slow-growing and rarely metastasize, while ACs grow faster, metastasize more often, and have a worse prognosis. Delayed diagnosis complicates treatment and worsens outcomes, making early detection crucial, especially for ACs[13].

This case report has several limitations. Detailed diagnostic evidence from the initial diagnosis of Ewing sarcoma was unavailable, and the report lacks detailed molecular analysis, which could provide insights into the genetic and molecular mechanisms underlying the development of multiple primary malignancies. A thorough literature search revealed no evidence or link explaining this finding, highlighting the need for further research in this area.

Despite these limitations, this case underscores the importance of thorough diagnostic workups and long-term follow-up for cancer survivors. Advanced imaging and histopathological techniques are crucial for accurate diagnosis and treatment. Maintaining comprehensive medical records, aided by electronic

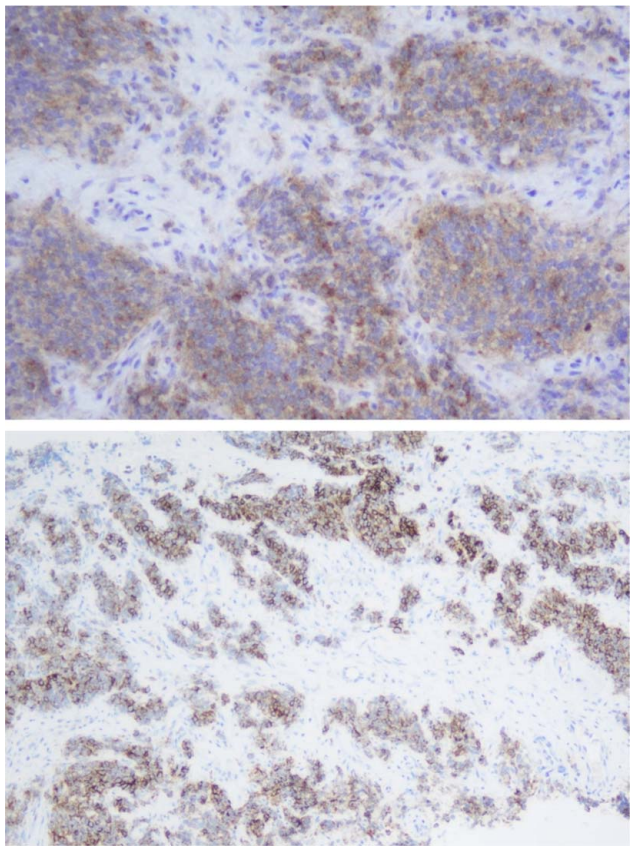

Figure 3. Immunostaining images: positive expression of immunostain synaptophysin (above), positive expression of immunostain CD56 (below).

systems, is vital for continuity of care. In developing countries, challenges like poor healthcare access, illiteracy, and financial constraints highlight the need for improved infrastructure and patient education.

Conclusion

This case report emphasizes the importance of a multidisciplinary approach to ensure accurate diagnosis and effective treatment. Additionally, it highlights the critical role of regular follow-ups and timely presentation in detecting and managing secondary malignancies early. This unprecedented case contributes valuable insights to medical literature and underscores the necessity for further research into multiple primary malignancies.

Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

H.A.: conceptualization supervision, data curation, methodology, writing—original draft, writing—review and editing. D.A.: conceptualization, data curation, methodology, writing—original draft, writing—review and editing. A.N.: data curation, investigation, writing—original draft, writing—review and editing. H.A.: conceptualization, investigation, data curation, writing—original draft. H.S.: writing—original draft, writing—review and editing. A.S.: conceptualization, writing—original draft. A.K.: conceptualization, supervision, writing—review and editing. N.N.: writing—original draft.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

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