Case Report

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A Rare Case of Concurrent Chromophobe Renal Cell Cancer with Lung Neuroendocrine Tumor: A Case Report and Literature Review

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Introduction: Multiple primary malignancies (MPM) may be in one organ or in multiple separate organs. They are categorized into synchronous and metachronous according to the time interval between the two malignancies. Multiple risk factors could be attributed to the development of second primary malignancy.

Case presentation: The authors report a case of a 51-year-old male patient with renal cell carcinoma. During his evaluation, he seemed to have a lung mass which revealed to be a carcinoid tumour. As the patient had two primary malignancies, he was managed according to the treatment options for each tumour.

Discussion: Although MPMs have been reported increasingly in the past decade, overall incidence is still very rare. Appropriate management and survival depend on distinguishing between dual primary tumours from metastatic disease.

Conclusion: Multidisciplinary approach is very crucial for diagnosis and management such rare cases.

Keywords: renal cell carcinoma, carcinoid, immunohistochemistry, case report

Introduction

Renal cell carcinoma (RCC) of chromophobe type is a rare subtype of renal cell carcinoma representing about 5–10% of all cases of renal cell carcinoma[1]. The mean age at presentation is 52 years[2] with a higher predilection for females. Patients with chromophobe renal cell carcinoma are usually asymptomatic without a palpable mass. If the classical triad of palpable abdominal mass, flank pain and haematuria is present, it suggests advanced local disease[3].

Pulmonary carcinoid tumours are rare tumours, accounting for 2% of primary lung neoplasms. They originally arise from Kulchitsky cells, which synthesize bioactive substances, such as serotonin and peptide hormones[4].

Bronchial carcinoid tumours may be asymptomatic in 25–39% or present with bronchial obstruction and recurrent infection. Cushing syndrome, acromegaly and carcinoid syndrome are all paraneoplastic syndromes associated with pulmonary carcinoid due to the release of corticotropin, growth hormone releasing hormone and vasoactive substance, respectively[5].

Unusual coincidence of chromophobe renal cell carcinoma with carcinoid tumour in the same kidney[2] or with carcinoid tumour in the gallbladder have been previously reported[6]. This is, to our knowledge, the first report of simultaneous occurrence of chromophobe renal cell carcinoma and bronchial carcinoid tumour. This case was written according to the SCARE (Surgical case report) criteria 2020[7].

HIGHLIGHTS

- Although multiple primary malignancies (MPM) have been reported increasingly in the past decade, overall incidence is still very rare.
- Since the incidence of multiple primary malignancies increases in the past decade, further research into the relationship between their coexistence is warranted.
- When one primary malignancy is diagnosed, more attention should be paid for the presence of other primary malignancy.
- Multidisciplinary approach is necessary in diagnosing these cases due to difficulty in diagnosis and variety of treatment options.
- Appropriate management and survival depend on distinguishing between dual primary tumours from metastatic disease.

Case presentation

A 51-year-old male with a 30-pack-year smoking history who worked as a hospice care assistant with an unremarkable medical

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history, presented in November 2022 at an outpatient clinic due to a 2-week history of hemoptysis. The patient denied at the time having any cough, dyspnoea, weight loss, chills, fever, night sweats, diaphoresis, headache, palpitation, flushing, changes in bowel movement, fatigue or other complaints.

Initial evaluation included a chest X-ray, revealing a right lung mass. Subsequent imaging in December 2022, via whole-body computed tomography (CT) scan with IV contrast, displayed a large, well-defined soft tissue lesion in the right middle lung zone, partially encasing the interlobar pulmonary artery and the right intermediate bronchus, measuring ~9.5 × 8.5 cm (Fig. 1). Additionally, a well-defined and heterogeneously enhanced soft tissue mass lesion in the right kidney was observed, displaying internal calcification suggestive of renal cell carcinoma (Fig. 2). His complete blood count and biochemical investigations were normal. One month later, a CT-guided lung biopsy was performed, resulting in a diagnosis of metastatic adrenocortical carcinoma. This diagnosis was confirmed by positive inhibin results and the absence of TTF1, PAX8, CD10, RCC, and HMB45 markers. Notably, all biochemical parameters, including plasma cortisol, testosterone, dehydroepiandrosterone (DHES), estradiol, Renin–aldosterone ratio, serum, and 24-h urinary metanephrine were within normal limits.

The mass's characteristics observed on CT imaging, combined with the patient's negative hormonal profile, created a diagnostic discrepancy. In an effort to address this diagnostic challenge, a case revision was initially attempted, but it yielded insufficient results. A new core-guided right lung biopsy was conducted in February 2023. This second biopsy revealed features consistent with a low-grade neuroendocrine tumour, devoid of necrosis or mitosis. Immunohistochemistry staining showed positivity for synaptophysin, chromogranin, CD56, and focal NSE, while testing negative for RCC, PAX8, vimentin, MelanA, HMB45, TTF1, and Napsin-A. Ki67 exhibited positivity in less than 2% of neoplastic cells. (Fig. 3).

In light of these findings, the case was reviewed in a multidisciplinary tumour board meeting, leading to the conclusion that there were two primary tumours. Subsequently, two surgeries were scheduled to remove these primary tumours.

In March 2023, the patient underwent a right radical nephrectomy, and the excised kidney measured 14 × 7 × 5 cm. The kidney tumour appeared as a solid, well-circumscribed, spherical mass measuring 5.5 × 5 × 4.5 cm (Fig. 4), occupying the lower pool and extending into the renal pelvis and renal capsule. Histologically, the tumour was characterized by nests, sheets, and trabeculae composed of pale cells with distinct cell borders. Fibrous scarring and significant calcification areas were present, with no evidence of lymphovascular invasion. Importantly, the tumour was confined to the kidney and did not involve the renal capsule, perinephric fat, or Gerota's fascia. Surgical resection margins were free of tumour involvement. Immunohistochemical staining revealed positivity for CK7 and C-Kit, while CD10 and vimentin were negative (Fig. 5) consistent with Chromophobe renal cell carcinoma (ChRCC).

In May 2023, a right lung pneumonectomy was performed, revealing a grade 1 typical carcinoid tumour with neuroendocrine features. This tumour, measuring 9 cm (pT4), was located in the right middle lobe, extending into the right upper lobe and compressing the lobar bronchi. It exhibited neuroendocrine characteristics with low mitotic activity and a Ki67 index of 1–2%. Immunohistochemistry confirmed positivity for synaptophysin, chromogranin, CD56, and CK, while being negative for TTF1, Napsin-A, S100, and CDX2. Lymphovascular invasions were noted, but perineural invasions were absent. Importantly, five hilar and peribronchial lymph nodes were tumour-free, as were vascular, bronchial, and pleural margins. The hilar parenchymal resection margin was also clear, resulting in a pathological TNM staging of pT4, pN0, and Mx.

The patient's recovery after surgery went smoothly, and regular follow-up was maintained. Three months later, a whole-body 18 F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan was performed and showed no evidence of disease.

Discussion

Definitions

Multiple primary tumours were first described in 1879 by Billroth. These neoplasms may be in one organ or in multiple

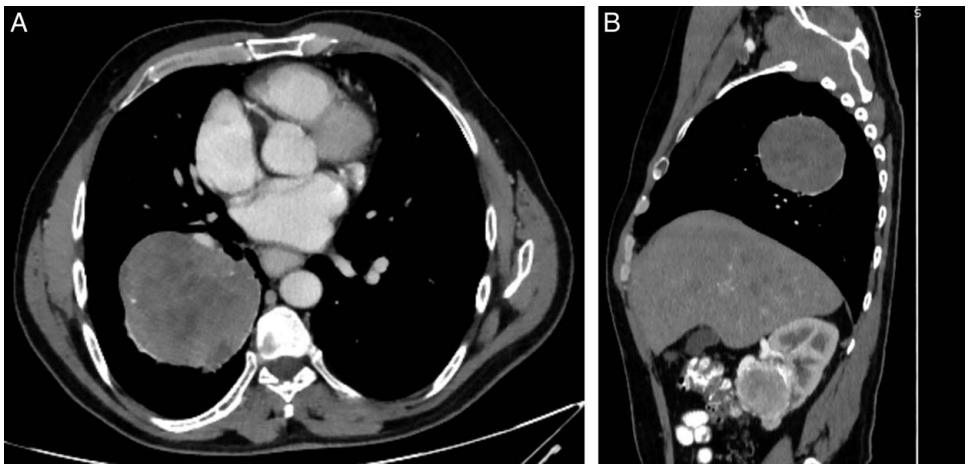

Figure 1. Axial and sagital computed tomography (CT) images showing right middle lobe lung mass. Axial (A) and sagital (B) CT images a large, well-defined soft tissue lesion in the right middle lung zone, partially encasing the interlobar pulmonary artery and the right intermediate bronchus, measuring ~9.5 × 8.5 cm.

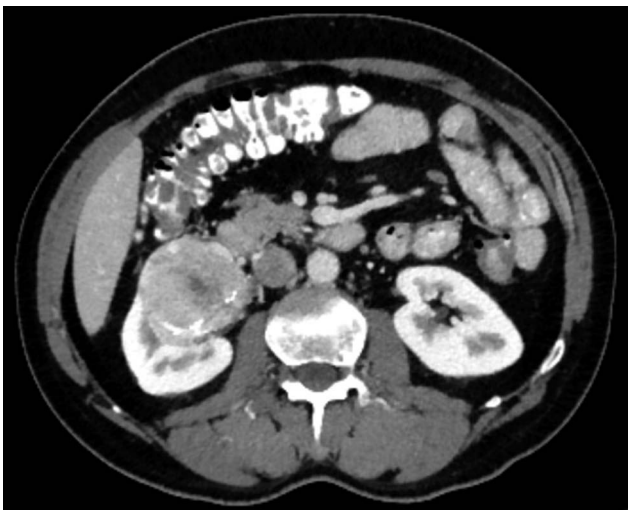

Figure 2. Axial computed tomography image showing a well-defined and heterogeneously enhanced soft tissue mass lesion with internal calcification in the right kidney suggestive of renal cell carcinoma.

separate organs as in our case[8]. Diagnosis of multiple primary tumours should fulfil he criteria as following: (1) definite picture of malignancy is needed for each tumour. (2) histologically distinct from each other. (3) each tumour should be ruled out as a metastatic of the other[9].

Synchronous and metachronous are the two types of multiple primary tumours according to the North American Association of Central Cancer Registries (NAACCR)[8]. If the tumours are diagnosed simultaneously or within 6-month interval, they are synchronous tumours. If the interval is longer than 6 months, they are metachronous tumours[10].

Epidemiology

Multiple primary tumours reported between 2.4 and 17%[11]. Many factors play an important role in increasing its incidence like improvement in cancer diagnosis, treatment, comprehensive screening protocol for cancer patients and prolong life expectancy[8].

Metachronous tumours slightly favors women compared with men but synchronous tumours have a greater risk for men. Patients with cancer had 1.29 times the risk of developing a new malignancy compared with those that were never diagnosed as found by Schoenberg *et al.*[10].

Head and neck, colorectal and breast cancers have been reported as the most common first primary malignancies. While the most common subsequent primary malignancies are lung cancer, breast cancer and colorectal cancer. The most common multiple primary malignancies pairs are head and neck with lung cancers as well as breast cancer with gynaecological cancers[12].

In a retrospective study conducted by Tanjak and colleagues included 109 054 adults patients diagnosed with first primary malignancy and then followed for period of 25 years for the occurrence of second primary malignancy. They defined a period of 2 months between the diagnosis of the two malignancies as synchronous multiple primary tumours. In addition, they defined metachronous tumours if the second tumour was diagnosed after 2 months of the primary tumour diagnosis. They found that 1.63% developed multiple primary tumours with 70.87% included as metachronous tumours. The highest metachronous association was reported as head and neck cancers followed by oesophageal cancer[13].

Renal cell carcinoma constitutes between 1 and 3% of all the cases of visceral malignant neoplasms and as the ninth most common neoplasm in women[14]. Renal cell carcinoma has various clinical characteristics, genetics and pathological backgrounds. Clear cell renal cell carcinoma is the most common histological variant which constitutes 75–85% of renal cell carcinoma cases. This is followed by papillary renal cell carcinoma and chromophobe renal cell carcinoma which represents, respectively, (10–15%) and (5–10%) of all kidney cancers patients[1]. On the other hand, bronchial carcinoid tumours constitute 1–2% of all lung tumours with no difference in incidence between males and females[15]. The incidence of synchronous cancers with renal cell carcinoma has been reported to be 3.7%[9]. This percentage increases to 30–42% in studies based on autopsy findings[16]. urological cancers, oesophageal carcinoma, colorectal carcinoma, lung cancer, breast cancer, gynaecological cancer and non-Hodgkin lymphoma have all been reported as subsequent primary malignancies[9].

In a study by Demir and colleagues, the incidence of second primary malignancy in 1129 patients with renal cell carcinoma is found to be 6.2%. In his study, clear cell renal cell carcinoma was the most common subtype that is associated with second primary malignancy in breast, lung, urinary bladder

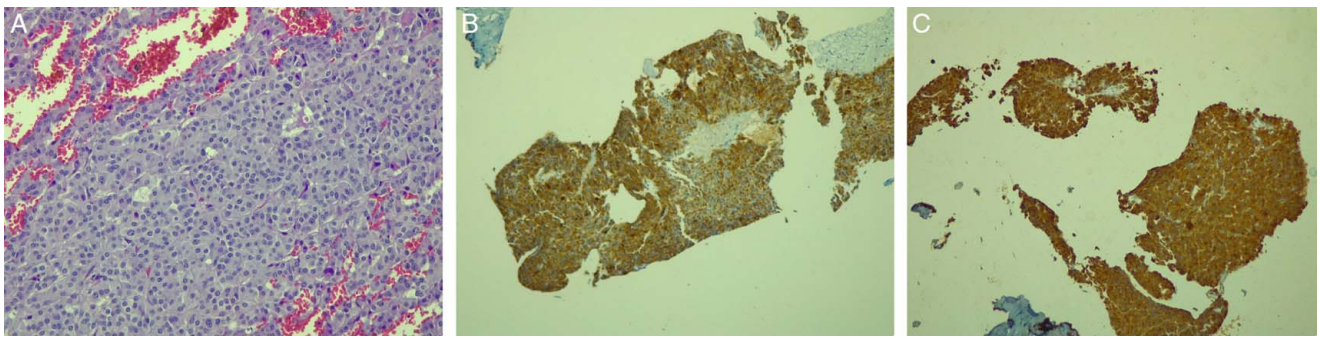

Figure 3. (A) Histological imagies (high power) shows features consistent with a low-grade neuroendocrine tumour, devoid of necrosis or mitosis with low mitotic activity and a Ki67 index of 1–2%. (B) Immunohistochemistry staining (low power) shows positivity for chromogranin. (C) Immunohistochemistry staining (low power) shows positivity for synaptophysin.

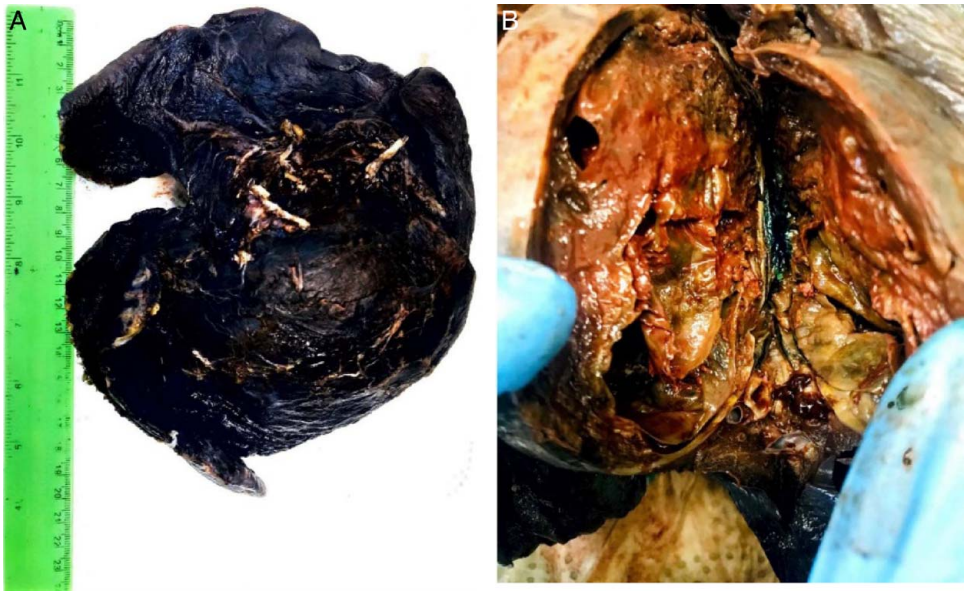

Figure 4. Macroscpoic examination. (A) The excised kidney measured 14 × 7 × 5 cm. (B) The kidney tumour appeared as a solid, well-circumscribed, spherical mass measuring 5.5 × 5 × 4.5 cm.

and pancreas. Other authors investigate the association between histological subtype of renal cell carcinoma and second primary malignancy. Abdel-Rahman and colleagues report that papillary renal cell carcinoma had the highest incidence for subsequent primary malignancies[17]. Other study conducted by Chen and colleagues found that 61.9% of patients with renal cell carcinoma diagnosed to have another primary tumour. According to this result, it is recommended to do full systematic examination in patients with renal cell carcinoma in order not to miss the diagnosis of other primary tumours[18].

Pathophysiology

Renal cell carcinoma has been frequently diagnosed as second primary malignancy and this could be explained by iatrogenic causes (particularly radiation), common risk factors like smoking, rare hereditary cancer syndromes that leads to multiple primary tumour development[19]. For example, the most known inherited condition for renal cell carcinoma and cancers in the adrenal gland, von Hippel-Lindau syndrome, an autosomal dominant disease characterized by tumours in the kidney, adrenal and lymphatics, hemangioblastoma in brain, spinal cord and retina[20]. In addition, greater access to surveillance imagining leads to increase the rates of detection of incidental renal masses which could be diagnosed later as secondary renal cell carcinoma. It is worth to mention that patients diagnosed with secondary renal cell carcinoma are found to have less symptoms and fewer tumour sizes than those diagnosed as primary renal cell carcinoma[18].

Diagnosis

The diagnosis of multiple primary tumours requires to distinguish between the presence of secondary primary tumours from metastatic lesions. During diagnostic workup, further investigations are recommended if clues for the presence of secondary primary tumours are revealed. This includes primary tumour

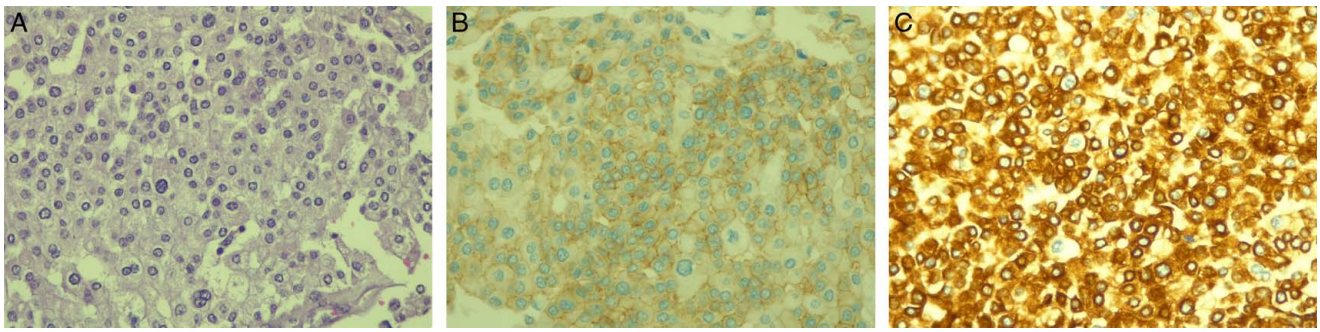

Figure 5. (A) Histological image (hematoxylin and eosin) shows nests, sheets and trabeculae composed of pale cells with sharply defined cell borders. (B) Immunohistochemical staining shows positivity for C-Kit. (C) Immunohistochemical staining shows positivity for CK7.

with atypical metastatic spread (e.g. prostate cancer with metastasis as radiologically lytic bone lesions). Low tumour marker load associated with high tumour burden (e.g. patient with low tumour specific antigen diagnosed with extensive liver metastasis). Moreover, a patient with a primary cancer revealed then to have a single metastatic lesion (a patient with head and neck cancer diagnosed then to have single pulmonary nodule). In such cases, a histological examination is required to confirm the presence of secondary primary tumour[21].

Chromophobe renal cell carcinoma microscopic appearance composed of two cell types in different proportion: eosinophilic cells and pale cells. The eosinophilic cells are smaller and have eosinophilic granular cytoplasm. On the other hand, pale cells are large, have prominent plant like cell membrane and an abundant flocculent cell membrane. Immunohistochemistry (IHC) shows diffuse positivity for CK7 AND CD117 (C-Kit). IHC helps with the diagnosis and differentiating this tumour from renal oncocytoma as it has histological similarities with chromophobe renal cell carcinoma[3].

Related to the histological features of carcinoid tumour, they are classified into typical and atypical carcinoids based on the number of mitosis and the presence of necrosis. Typical carcinoid is diagnosed when less than two mitoses per 10 high power field without necrosis. When confirmed necrosis and two to ten mitoses per high power field are seen, atypical carcinoid is diagnosed which is more aggressive and presents with regional lymph node invasion[15]. Immunohistochemistry is necessary for diagnosis. Chromogranin A, synaptophysin, and CD56 antibody panels are recommended. Furthermore, some carcinoids have thyroid transcription factor 1 (TTF1) staining. In addition, neuron-specific enolase (NSE) is a highly specific marker for neuroendocrine cells and is expressed in lung carcinoids. Positive staining with carcinoembryonic antigen (CEA) and epithelial membrane antigen (EMA) have been reported in some cases of lung carcinoids[22]. Ki67 is recommended to differentiate carcinoid tumours from carcinomas particularly with small biopsies[23].

Treatment

Treatment of patients with multiple primary malignancies is challenging and need to be discussed in multidisciplinary team meetings. In patient with localized disease, surgery or chemoradiation therapy covering both types of tumours is the suggested strategy. In patients with advanced disease, treatment options in previous literature depend on individual decisions and they are not based on prospective trial evidence[21].

Surgery is the gold standard with localized chromophobe renal cell carcinoma patients. Partial or radical nephrectomy are the two available options bases on the expertise of the surgeon[3]. Furthermore, the condition of the extrarenal tumours should be considered which includes tumour stage, treatment complication and life expectancy[18]. It was reported that patients diagnosed with renal cell carcinoma as secondary tumours had a higher proportion of partial nephrectomy than patients diagnosed with primary renal cell carcinoma. This was attributed to the smaller tumour size in patients with secondary renal cell carcinoma[18].

For patients with localized bronchial carcinoid, surgical resection is the gold standard for treatment. The surgical approach is chosen according to the size and location of the tumour, patient preference, comorbid conditions. Lymph node dissection as the time of surgery is under debate and it differs depending on the histological type of carcinoid tumour. As previous studies showed that atypical carcinoid exhibits more aggressive behaviour with more nodal involvement and metastasis than typical carcinoid. There is no sufficient data for the role of adjuvant chemotherapy or radiotherapy in patients with localized carcinoid tumour[24].

The patient in our presented case has localized disease with concomitant chromophobe renal cell carcinoma and pulmonary carcinoid tumour. Radical nephrectomy was done for his localized renal cell carcinoma and surgical resection for his pulmonary carcinoid tumour.

Prognosis

The prognosis for renal cell carcinoma alone depends on the stage of the disease, histopathological factors and molecular markers[16]. Localized chromophobe renal cell carcinoma has a better prognosis than clear cell renal cell carcinoma. The 5-year cancer specific survival reaches 93%[3]. However, the coexistence of other cancer with renal cell carcinoma is an independent poor prognostic factor compared to localized renal cell carcinoma alone[25]. It depends also on multiple factors like the biological characteristics of the second primary malignancy. Poor prognosis was found when lung, liver and pancreatic cancer were diagnosed as the second primary malignancies. Conversely, a better prognosis for breast and penile cancer as second primary malignances was reported[16].

Because chromophobe renal cell carcinoma and carcinoid tumours have not been previously studied, this case report has certain limitations. This includes the treatment strategy we've reported which was personalized to our patient's conditions. Furthermore, there is a lack of knowledge regarding the prognosis of this uncommon combination.

Conclusion

Since the incidence of multiple primary malignancies increases in the past decade, further research into the relationship between their coexistence is warranted. In addition, multidisciplinary approach is necessary in diagnosing these cases due to difficulty in diagnosis and variety of treatment options. This case also emphasizes the importance of histopathologic confirmation in differentiating a second primary tumour from metastasis when clinical or diagnostic clues suggest the presence of a second primary malignancy rather than metastasis.

Ethical approval

Ethical approval for this study (Ethical Committee N° NAC 207) was provided by the Ethical Committee NAC of Alquds University, Palestine on 10 November 2023.

Consent

We obtained verbal and written informed consent from the patient for this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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The study did not receive any financial help.

Author contribution

Data collection: M.N. Study concept or design: M.N., A.Z., Z.M. M.Z., Y.M., M.A.M., B.A.A. Writing the manuscript: M.N., A.Z., Z.M.M.Z., Y.M., Review and editing the manuscript: M.N., A.Z., Z.M.M.Z. Histopathological interpretation: M.Q. and M.F.

Conflicts of interest disclosure

The authors have no conflict of interests to declare.

Guarantor

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Provenance and peer review

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