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Misdiagnosed in double primary tumors: a case report

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ABSTRACT

Multiple primary malignancies (MPM) refer to the presence of two or more malignant tumors that are unrelated to each other in the same individual. Double primary malignancies that occurred in the lungs and extremities were relatively rare. We present a case of lung adenocarcinoma as pseudo-lung metastasis and pleomorphic liposarcoma on the extremity. A 62 yo male chronic smoker came with a referral from another hospital with a growing mass on his thigh and some imaging that showed pulmonary metastasis. The patient underwent a transbronchial lung biopsy and wide excision for a tumor on his thigh. However, histopathological examination revealed that both malignancies originated from different cells or as primary malignant. At 8 wk post-surgery, positron emission tomography (PET) scan was performed to rule out residual pleomorphic liposarcoma or any metastasis and the result showed no residual or metastasis. We suggest that the management of MPM be more careful and disciplined, as an error in choosing a diagnosis method might harm or worsen the patient's condition. In the case of multiple malignancies, particularly in organs with frequent metastasis sites, it is important to consider the possibility of MPM. The diagnosis and management strategy of double primary tumors was expected to provide important information for clinicians.

ABSTRAK

Tumor ganas primer jamak (TGPJ) merujuk pada keberadaan dua atau lebih tumor ganas yang tidak berhubungan satu sama lain pada individu yang sama. Tumor ganas primer jamak yang terjadi di paru-paru dan ekstremitas relatif jarang. Kami menyajikan kasus adenokarsinoma paru sebagai metastasis paru palsu dan liposarkoma pleomorfik pada ekstremitas. Seorang pria berusia 62 tahun, perokok kronis, datang dengan rujukan dari rumah sakit lain dengan pertumbuhan massa di pahanya dan beberapa hasil pencitraan yang menunjukkan metastasis paru. Pasien menjalani biopsi paru transbronkial dan eksisi luas untuk tumor di pahanya. Namun, pemeriksaan histopatologis mengungkapkan bahwa kedua tumor ganas berasal dari sel yang berbeda atau sebagai tumor ganas primer. Delapan minggu setelah operasi, dilakukan Positron emission tomography (PET) scan untuk menyingkirkan kemungkinan sisa-sisa liposarkoma pleomorfik atau adanya metastasis dan hasilnya tidak ditemukan sisa tumor ataupun metastasis. Kami menyarankan bahwa pengelolaan TGPJ harus lebih hati-hati dan disiplin, kesalahan dalam memilih metode diagnosis dapat merugikan atau memperburuk kondisi pasien. Dalam kasus TGPJ, terutama pada organ yang sering menjadi situs metastasis, penting untuk mempertimbangkan kemungkinan TGPJ. Strategi diagnosis dan pengelolaan dari tumor ganda primer diharapkan dapat memberikan informasi penting bagi para klinisi.

Keywords:
pseudo metastasis;
double primary malignancies;
liposarcoma;
adenocarcinoma

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INTRODUCTION

Liposarcoma is one of the most common soft tissue sarcomas with 50% retroperitoneal and 25% extremity.[1] Liposarcoma is divided into five different subtypes: well differentiated, myxoid, round cell, dedifferentiated, and pleomorphic. Pleomorphic liposarcoma accounts for only about 5% and is considered the highest malignancy grade, high invasion, propensity to metastasis, and recurrence.[2] Local recurrence rates range from 30-50%, while metastatic rates are around 50%. The five-year survival rate is 57%, which is significantly worse than for other types of liposarcomas.[3] The primary treatments for pleomorphic liposarcoma (PLS) include with and without radiotherapy and surgical resection, which can be either a wide local excision or amputation.[3,4] Predictors of a particularly poor outcome include tumor size greater than 10.0 cm, a high number of mitoses (more than 10 per 10 high-power fields), and a non-extremity location. On the other hand, superficially located tumors are a predictor of a better outcome due to their potential for complete excision.[3] Diagnosis of pleomorphic liposarcoma is challenging due to the significant risk of sampling error when only small samples are obtained from FNA biopsies. The diagnostic hallmark of pleomorphic liposarcoma in both tissue sections and cytologic smears relies solely on identifying classic Pleomorphic lipoblasts.[3,5] Lung tissue is the most common metastatic site for patients in this population.[6] Differentiating between primary lung cancer and lung metastasis can be challenging due to their similar characteristic presentations. However, making this distinction is crucial for clinicians to formulate treatment methods and predict prognosis more accurately. Pathologic evaluation combined with molecular or genetic examination remains the gold standard for distinguishing between primary lung cancer and pulmonary metastasis.[7-9]

Lung adenocarcinoma is the most prevalent type of primary lung cancer, strongly linked to smoking. It falls under the subtype of non-small cell lung cancer (NSCLC), with adenocarcinoma cases making up about 38.5% of all lung cancer diagnoses.[10] This tumor is recognized as advanced malignant with a poor prognosis, more than 80% of patients do not survive beyond 5 yr.[11,12] Diagnosing lung adenocarcinoma can be challenging because its clinical symptoms and radiological findings may overlap with viral pneumonia or miliary pulmonary TB.[13,14] The primary treatment modality for non-small cell lung cancer (NSCLC) is surgery. However, many patients are diagnosed late with advanced stages (III and IV) at diagnosis. Therefore, systemic treatment modalities become crucial, including concomitant chemo- and radiotherapy for the majority of stage III patients, and targeted therapy, chemotherapy, immunotherapy, or chemo-immunotherapy for stage IV patients and some stage III NSCLC patients.[15]

Multiple primary malignancies (MPM) are two or more unrelated primary malignant tumors that occur in the body. Multiple primary malignancies divided into synchronous, second malignancies have been occurring either simultaneously, or within 6 mo after the first malignancy occurred; while metachronous malignancies are secondary neoplasms that occur after 6

mo from the first malignancy.[16]

In multiple malignancies involving the lung tissue, the differential diagnosis typically focuses on distinguishing metastasis or other benign processes. However, distinguishing between pulmonary metastasis and a new primary cancer may be difficult due to pulmonary cancer as a second primary malignancy is less commonly considered in the differential diagnosis. We reported rare double primary malignancies pleomorphic liposarcoma and pulmonary adenocarcinoma as pseudo lung metastasis.

CASE

A 62 yo chronic smoker male came with a referral from other hospital to our orthopedic clinic with a growing mass on his right thigh for 4 m. The patient often feels fever and chills. However, pain, weight loss, or any lung symptoms were absent. Physical examination of the right thigh revealed an immobilized solid mass about 8cm in diameter, with unclear margin and tenderness. The motion of the right hip was unaffected.

Some imaging studies were already performed before came to our orthopedic clinic, such as an X-ray thorax, and computed tomography (CT) scan of the thorax and right thigh. The X-ray and CT scan of the thorax revealed a solid mass in the lower lobe of the left lung and the superior lobe of the right lung suspected as metastasis. The CT scan of the right thigh revealed a large solid mass without bone involvement. We performed A Magnetic resonance imaging (MRI) to show the details of the soft tissue tumor of his thigh and it revealed a large solid mass of the right thigh (64x70x152 mm) with an eccentric necrotic area, which showed a malignant features. The malignancy involved multiple muscles including the vastus lateralis, tensor fascia, rectus femoris, and vastus intermedius. Fortunately, the neoplasm had not infiltrated the femoral neurovascular bundle (FIGURE 1A and 1B). A transbronchial lung biopsy was performed and revealed a infiltrative nodule at right lower lobe (FIGURE 2A). The nodule specimens was brought to pathological anatomy and the result was confirmed with adenocarcinoma (FIGURE 2B).

The patient underwent surgery with spinal anesthesia, a patient positioned in the left lateral decubitus underwent a 10 cm long incision for radical excision of a vastus lateralis soft tissue tumor. The mass was examined, and a free tumor incision margin was marked with silk 1.0. The resected tumor was composed of soft tissue, measuring up to 20x10x7 cm and weighing 2000 g (FIGURE 1C and 1D). Some of the specimens were brought to the pathological anatomy and immunohistochemistry examination, and the results were positivity of p16, CD34, and low proliferation rate of 25% by Ki67. The microscopic finding showed high-grade pleomorphic sarcoma (FIGURE 1E). All of these results concluded the diagnosis of PLS. Four weeks after surgery, there were no signs of recurrence or metastasis, and the patient outcome was satisfying. However, the patient only complained of pain at the operation site, and we administered a nonsteroidal anti-inflammatory drug (NSAID) to alleviate the pain. Seven weeks post-operative follow-up, the positron emission tomography-computed tomography scan (PET CT-scan) whole body examination showed no residual or any metastasis (FIGURE 3Aand 3D). However, the therapeutic decision for lung adenocarcinoma has not been decided yet.

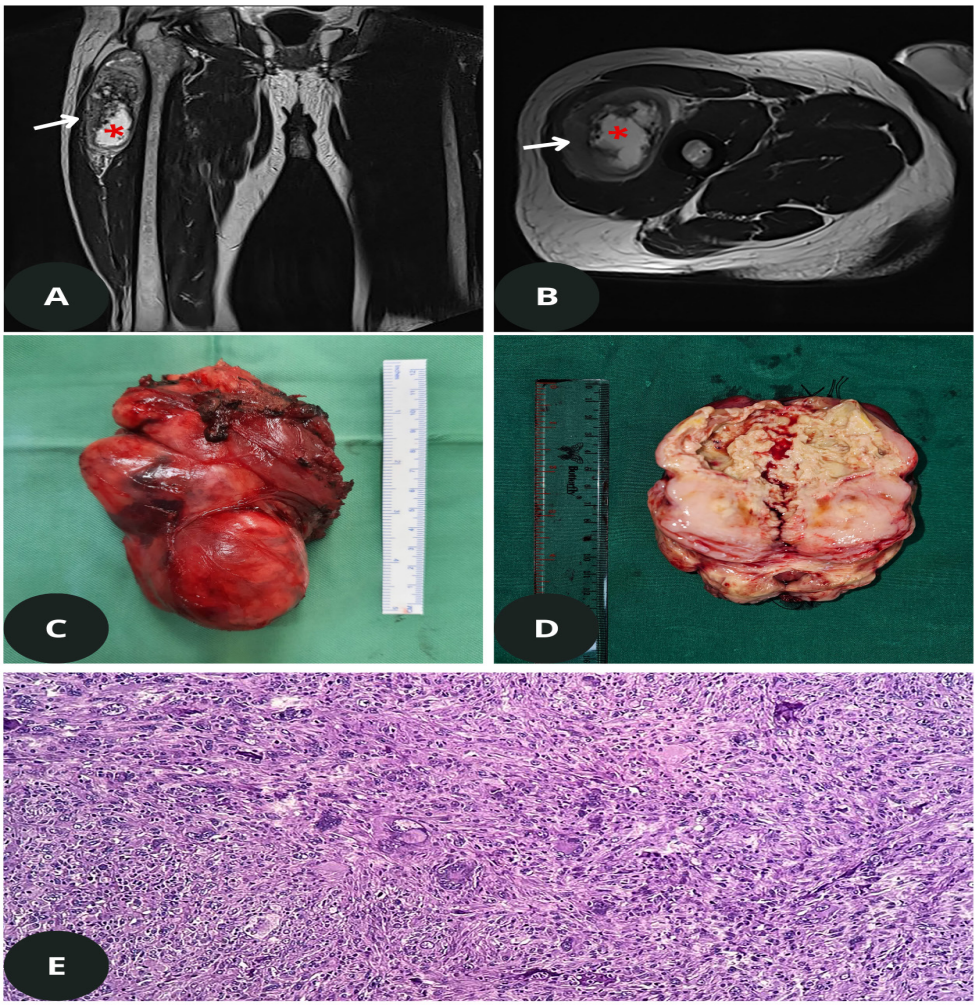

FIGURE 1. (A and B) The preoperative magnetic resonance imaging on T2-weighted images of the right thigh shows a large tumor (white arrow) with an eccentric necrotic area (asterisk). (C and D) The macroscopic appearance of the surgical specimen, and sectioning revealed a solid whitish fleshy area. (E) The microscopic examination of the resected specimen revealed a pleomorphic liposarcoma with a wide area of necrosis (hematoxylin and eosin staining, ×10).

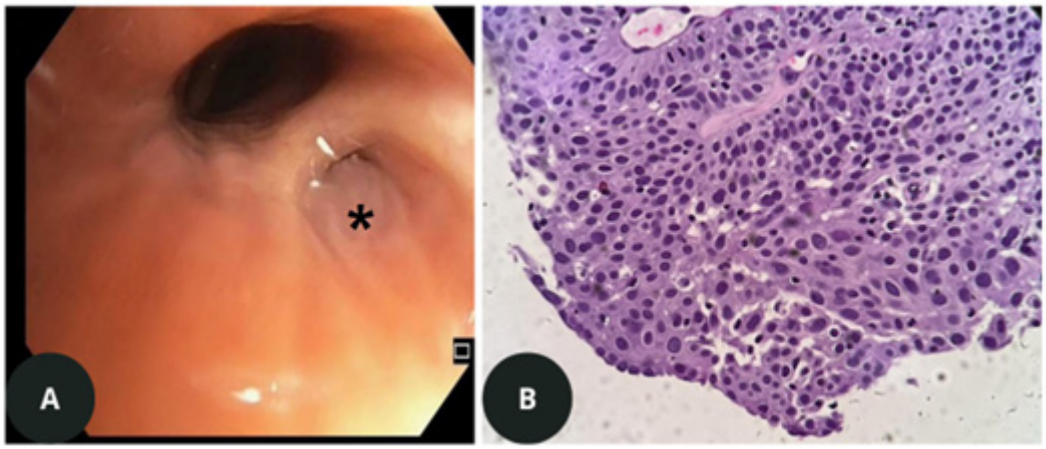

FIGURE 2. (A) Transbronchial lung biopsy showed an infiltrative nodule (asterisk) at the right lower lobe B7. (B) The microscopic of the resected specimen was pathologically diagnosed as pulmonary adenocarcinoma (hematoxylin and eosin staining, x40)

The patient underwent surgery with spinal anesthesia, a patient positioned in the left lateral decubitus underwent a 10 cm long incision for radical excision of a vastus lateralis soft tissue tumor. The mass was examined, and a free tumor incision margin was marked with silk 1.0. The resected tumor was composed of soft tissue, measuring up to 20x10x7 cm and weighing 2000 g (FIGURE 1C and 1D). Some of the specimens were brought to the pathological anatomy and immunohistochemistry examination, and the results were positivity of p16, CD34, and low proliferation rate of 25% by Ki67. The microscopic finding showed high-grade pleomorphic sarcoma (FIGURE 1E). All of these results concluded the diagnosis of PLS. Four weeks after surgery, there were no signs of recurrence or metastasis, and the patient outcome was satisfying. However, the patient only complained of pain at the operation site, and we administered a nonsteroidal anti-inflammatory drug (NSAID) to alleviate the pain. Seven weeks post-operative follow-up, the positron emission tomography-computed tomography scan (PET CT-scan) whole body examination showed no residual or any metastasis (FIGURE 3Aand 3D). However, the therapeutic decision for lung adenocarcinoma has not been decided yet.

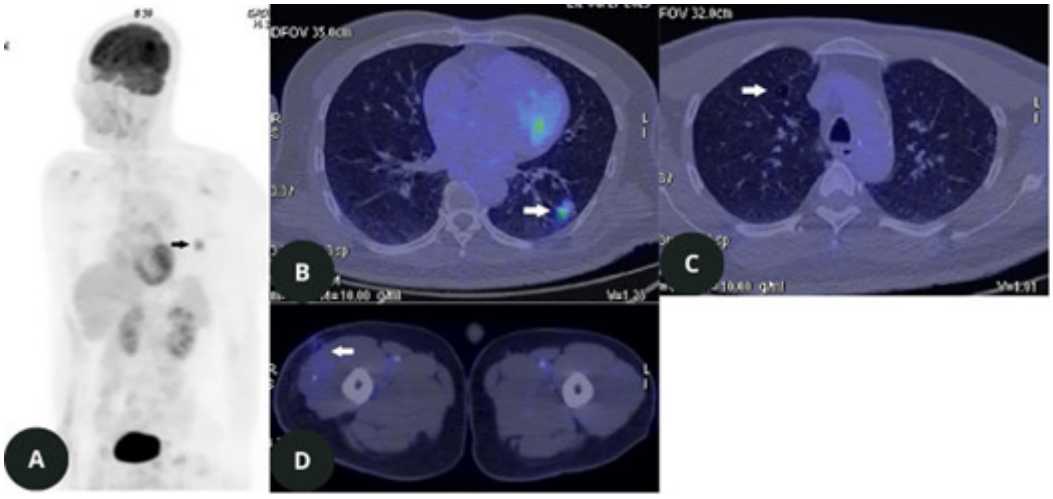

FIGURE 3. PET CT-scan whole body (A) small lacuner infark in the area of left corona radiata (black arrow). (B) enhancing spiculated nodule on the inferior lobe of the left lung (white arrow). (C) A tiny nodule non-metabolic on the superior lobe of the right lung is suspected of metastasis (white arrow). (D) no residual malignancy found in the right thigh, low metabolic activity as inflammatory post-surgery (white arrow)

DISCUSSION

Multiple primary malignancies were divided to synchronous if the interval between occurrences of primary malignant tumors was <6 mo and metachronous if the interval was >6 mo.[16] In this present case, the lung adenocarcinoma was discovered by a CT scan and initially thought to be metastatic from PLS. However, after pathological examination, the lung neoplasm was unrelated to the primary tumor in the thigh. The interval between the onset of these double primary malignancies could not be determined because the patient has no symptoms of lungs. Determining whether the second tumor is synchronous or metachronous is crucial as it can significantly impact the management and prognosis. However, based on our knowledge, there is no clear consensus in the literature regarding managing synchronous or metachronous for the second lung primary tumor. A study showed patients with early metachronous (< 2 yr) or synchronous lung cancer show lower survival rates when compared with those with late (≥ 2 yr) metachronous cancer.[17] The American College of Chest Physicians guidelines and recommendations indicate that survival outcomes after resection for either synchronous or metachronous presentations, especially when the interval between tumors is less than four years, are generally poor. This is because these patients might have had a pulmonary metastasis rather than a second primary lung cancer.[18] Double primary malignancies of extremity and lung are relatively rare to be reported. The pathogenesis of MPM is unclear until now. Some factors might be associated with MPM occurrences such as carcinogens, genetic susceptibility, immune system, and carcinogenic effects of radio/chemotherapy. Furthermore, smoking and family history might be the key risk factors of MPM.[16] The substances found in tobacco smoke, such as benzoapyrenes, polycyclic aromatic hydrocarbons, and nitrosamines, produce reactive oxygen species through their toxic effects on DNA. These reactive oxygen species can lead to mutations in genes like K-RAS and p53.[19] Similar study reported that nicotine plays an important role in angiogenesis, thereby promoting tumor growth.[20] A retrospective study reported common locations for MPM include the mouth/pharynx, esophagus, larynx, breast, uterus, ovary, stomach, esophagus, and colorectum.[21] However, there was no strong association between smoking and the development of PLS.

Pleomorphic liposarcoma is the rarest subtype of liposarcoma and it commonly occurs in older adults >50 yo. The extremities, especially lower limbs, are the most common sites of involvement. Pleomorphic liposarcoma was associated with a poor prognosis due to high mortality which occurred at more than 50%. It also has the highest malignancy grade, recurrence rate, and metastasis to the lungs in about 75% of cases.[6] The PLS usually presented with a growing mass without pain that has occurred for several months. In radiography, PLS would have appeared as a well-defined mass with a necrotic or hemorrhage area.[22] However, the histopathological findings of the PLS may resemble other sarcoma, thus requiring an immunohistochemical analysis to confirm a diagnosis.

Based on our knowledge, there are no available guidelines for MPM management at this time. The management of each patient has different multidisciplinary based on malignancy type, stage, and the health of the patient.[23] In this case, we did not perform needle core biopsy and direct wide excision to the soft tissue tumor of his thigh to confirm the histopathological diagnosis, because we thought that lung tumors were metastasis from soft tissue sarcoma in the thigh but in fact, these two

tumors were originating from different cells or as primary tumors. This mistake might trigger tumor seeding because tumor cells spread into nearby tissues or blood vessels. Core needle biopsy has more than 90% accuracy for bone and soft tissue malignancies and the incidence of tumor seeding is less than 1%.[24] Commonly, the diagnosis of soft tissue sarcoma had been done by core needle biopsy after imaging.[25] Lungs was one of the most common sites for tumor metastasis. However, there was a chance the lung tumor was a primary tumor as well as other malignancy sites. We suggest that the diagnosis and treatment of MPM must be more careful and disciplined, as an error in choosing a diagnosis method might harm or worsen the patient's condition.

CONCLUSION

Lung adenocarcinoma and PLS in this case are distinct entities that arise from different tissues. The pathomechanism of MPM is still unclear and we didn't discover the detailed mechanism of MPM from our patient. Smoking habits may be a key risk factor for multiple primary tumors. However, there was no strong association between smoking and the development of PLS. We suggest in cases of multiple tumors, especially in organs where metastasis frequently occurs, we need to consider the possibility of MPM until proven otherwise. Differentiating between primary tumors and metastasis is challenging when relying solely on radiographic imaging. Therefore, pathological and immunohistochemical analyses are crucial for distinguishing between metastasis and primary tumors. Molecular or genetic examinations may also offer valuable insights if needed. In this case, The diagnosis and management strategy of double primary tumors was expected to provide important information for clinicians.

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