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Case Study and Literature Review on Diagnosis and Treatment of Advanced Metastasis of Tumor with Unknown Primary Origin

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Abstract: Primary of Unknown Origin Cancer (CUP) is a metastatic tumor whose origin remains undetermined. The reason for this ambiguity in identifying the primary site remains unclear, possibly due to the tumor being too small or growing too slowly, or because the immune system has destroyed the tiny primary lesion. Most CUP patients receive only localized treatment or empirical systemic chemotherapy, leading to poor prognosis and shorter average overall survival. There is currently insufficient evidence-based medical support for the diagnosis and treatment of CUP. This study retrospectively analyzed clinical characteristics, diagnostic methods, treatment approaches, and prognostic outcomes of newly diagnosed CUP patients treated in our department. The findings aim to provide clinical guidance for diagnosis and treatment of CUP, with the goal of reducing diagnostic delays and improving patient outcomes.

Keywords: Primary of Unknown Origin Cancer; Case report; Literature analysis; diagnosis; Cervical lymph nodes

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1. Introduction

Primary of unknown origin tumors refer to metastatic lesions confirmed as malignant through pathological examination, where no anatomical primary site can be identified through detailed medical history review, physical examinations, and diagnostic tests prior to treatment. These tumors account for approximately 1–2% of all malignancies and rank fourth in mortality rates. Most patients with cutaneous upstitched carcinoma (CUP) receive only localized treatment or empirical systemic chemotherapy, resulting in poor prognosis with an average overall survival of 6-9 months. Therefore, early and effective diagnosis combined with targeted therapy holds significant value for improving survival rates among these patients.

2. Case report patient information

A 71-year-old female patient was admitted to the hospital with left supraclavicular lymph node metastatic adenocarcinoma detected 2 years prior and left lower limb pain for 3 months. Two years ago, she developed left supraclavicular lymphadenopathy without apparent cause, measuring approximately 3 × 2 cm. She was initially evaluated at a county hospital where a left supraclavicular lymph node biopsy was performed. Postoperative pathology (October 25, 2022) revealed: (Left supraclavicular mass) malignant epithelial tumor with carcinomatous features and metastatic potential. For further treatment, she was transferred to a municipal hospital. PET-CT scans indicated:

(1) Thickened gastric wall in the cardia and fundus with contrast filling defects and heterogeneous hypermetabolism, recommending gastroscopy;

(2) Multiple hypermetabolic enlarged lymph nodes in the right internal mammary region, left cardiac-diaphragmatic angle, and retroperitoneal area, suggesting metastasis.

Subsequent gastroscopies (December 18, 2022) showed gastric body posterior wall bulging and hiatal hernia. Pathology from gastroscopy (December 20, 2022) demonstrated gastric fundus polyps with chronic inflammation, focal mucosal erosion, and dilated small vessels in the lamina propria; HP (-). Endoscopic ultrasound (December 23, 2022) revealed no significant abnormalities in the cardia and fundus. Review of county hospital pathology slides at municipal hospital (December 26, 2022) confirmed metastatic carcinoma with possible adenocarcinoma, immunohistochemistry showing Her-2 (1+). The patient did not receive additional treatment. Three months ago, the patient developed left lower limb pain that progressively worsened. She sought treatment at a local county hospital. A CT scan (October 3, 2024) revealed a space-occupying lesion adjacent to the left psoas major muscle at L4-L5 levels and multiple retroperitoneal lymph nodes with suspected left iliac vein thrombosis. Subsequent procedures included a left psoas mass biopsy (October 4, 2024) and a left neck mass biopsy. The pathological report from the psoas biopsy (October 6, 2024) indicated metastatic carcinoma. Biopsy specimens from the left lymph node mass (October 6, 2024) showed lymph node metastasis with poorly differentiated adenocarcinoma. The patient was referred to our department for further evaluation. Her weight had decreased by 3 kg over three months. The patient has a history of hypertension for over six years, with peak blood pressure reaching 160/90 mmHg. Metoprolol was intermittently used for control.

A history of type 2 diabetes mellitus (T2DM) for over ten years, with peak blood glucose levels at 9 mmol/L. Regular oral administration of dapagliflozin maintained blood glucose at 5.5–6.3 mmol/L. No history of hepatitis, malaria, tuberculosis, or vaccination. No known allergies, surgeries, blood transfusions, or trauma. Physical examination revealed: T: 36.8 ℃; P: 78 bpm; R: 19 bpm; BP: 128/78 mmHg. The abdomen was flat without visible gastrointestinal patterns, peristaltic waves, or abdominal wall varices. Soft abdomen with no tenderness, rebound tenderness, or muscle rigidity. No palpable masses, liver or spleen detected, and negative Murphy's sign. Full abdominal percussion showed tympanic sounds but no shifting dullness. Bowel sounds were 4/min, with no metallic or air-fluid sounds heard. Left lower limb pain presents as radiating pain in the thigh and calf, occasionally with stabbing sensations without burning. No numbness or muscle weakness is present in the left leg.

Imaging findings at admission (**Figure 1**): Contrast-enhanced CT (October 10, 2024): (1) Cerebral atrophy. (2) Multiple lymphadenopathy in the mediastinum, supraclavicular region, and cardiac diaphragmatic angle, with lymph node metastasis not excluded. (3) Esophageal hiatal hernia with localized wall thickening. (4) Irregular right partial ribs. (5) Multiple intra-abdominal and retroperitoneal lymphadenopathy with lymph node metastasis not excluded. (6) Malignant space-occupying lesion in the left psoas muscle area. Upper gastrointestinal radiography (October 10, 2024): No significant abnormalities observed.

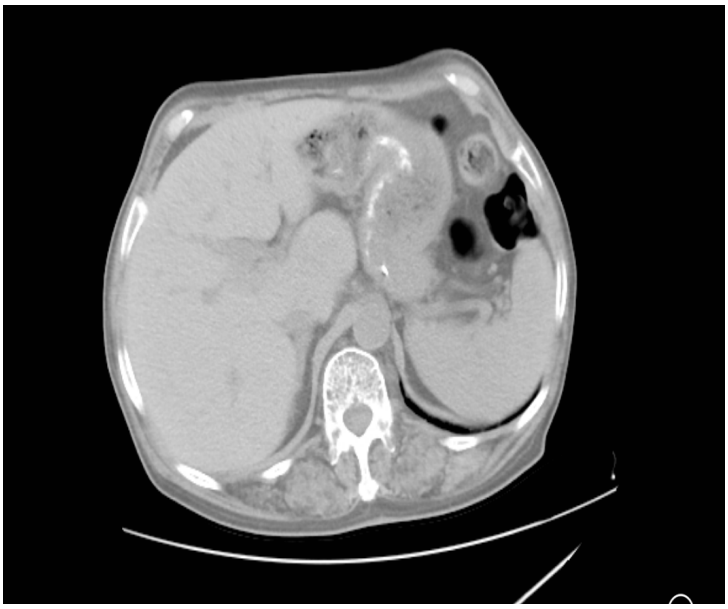

Figure 1: Enhanced CT before chemoradiotherapy.

Breast ultrasound (October 10, 2024): (1) Multiple nodules in the right breast (BI-RADS 3 grade); (2) Nodules in the left breast (BI-RADS 3 grade); (3) Multiple enlarged lymph nodes in the left neck, bilateral supraclavicular regions, and left subclavian area.

Superficial lymph node ultrasound (October 10, 2024): (1) Multiple hypoechoic lesions in the left neck and supraclavicular region, with a larger one measuring approximately 1.91 cm × 1.11 cm showing indistinct portal structure and visible blood flow signals on CDFI. (2) Multiple hypoechoic nodules in the right supraclavicular region, with a larger one measuring approximately 2.68 cm × 1.11 cm showing indistinct portal structure and visible blood flow signals on CDFI. (3) A hypoechoic lesion measuring approximately 5.48 cm × 5.18 cm × 2.57 cm with indistinct borders and irregular morphology in the deep layer of the left psoas muscle, showing unclear demarcation from the muscular layer and visible peripheral blood flow signals on CDFI. (4) Multiple hypoechoic nodules were observed beside the left iliac artery, with the largest measuring approximately 1.90 cm × 1.10 cm in size. The borders remained well-defined and the morphology regular. CDFI imaging revealed minimal blood flow signals.

Gastroscopy (October 11, 2024): Hiatal hernia. Colonoscopy (October 11, 2024): Multiple polyps in the colon. Whole-body bone imaging (**Figure 2**): Localized hypermetabolism of bone salts at L4 and L5. Laboratory tests upon admission: Complete blood count: Red blood cells 3.60×10^{12}/L; Hemoglobin 94 g/L. Biochemical profile: Glucose 6.84 mmol/L. Tumor marker panel: Glycoantigen 153:134.00 U/mL; Glycoantigen 125:133.10 U/mL; Glycoantigen 724:47.07 U/mL; Neuron-specific enolase: 33.45 ug/L.

Treatment: Our hospital's pathology department reviewed a 2-year-old pathological section from a local county hospital (**Figure 3**), which indicated metastatic adenocarcinoma. Immunohistochemistry will be performed if necessary for definitive diagnosis. BRS-6 pain score: (1) PS score: (2) Following multidisciplinary MDT consultation, we preliminarily considered primary gastric malignancy. The treatment plan includes SOX chemotherapy combined with radiotherapy. Radiotherapy targets include the right psoas major muscle and corresponding retroperitoneal lymph nodes (target areas) as shown by CT localization. Fractionated doses are 180 cGy/F per session, administered 5 times weekly for a total of 28 sessions, with a cumulative dose of 5040 cGy/F.

After completing synchronized chemoradiotherapy, the patient's pain significantly improved. A follow-up CT scan (**Figure 4**) revealed: (1) Multiple lymphadenomas in the mediastinum, supraclavicular region, and cardiac diaphragmatic angle, with partial reduction; (2) Esophageal hiatal hernia with localized wall thickening improvement; (3) Irregular right rib contour; (4) Multiple intra-abdominal and retroperitoneal lymph nodes showing partial shrinkage, with lymph node metastasis not excluded; (5) Reduced left psoas mass lesion, suspected malignancy. The patient experienced no significant gastrointestinal reactions during treatment and was discharged.

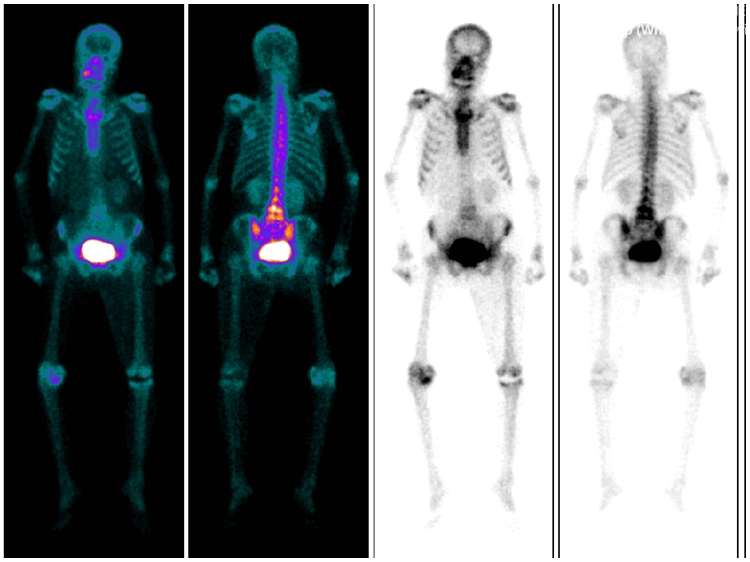

Figure 2: Bone imaging.

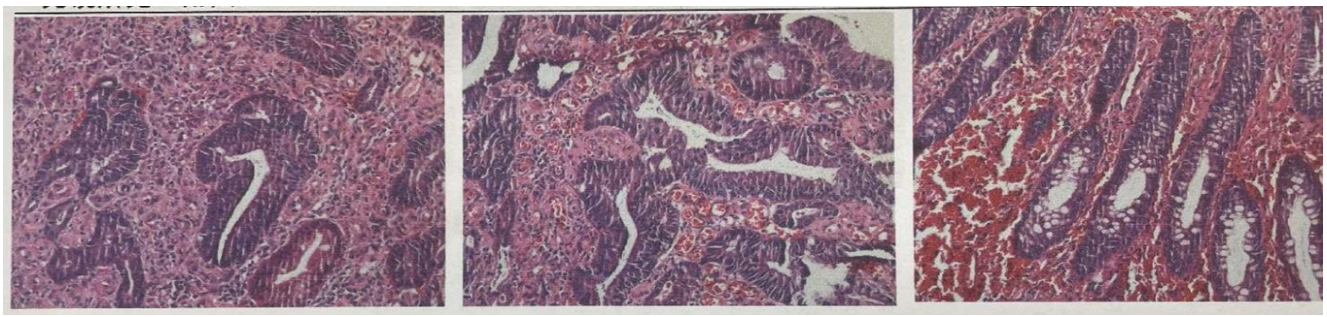

Figure 3: Re-read pathology.

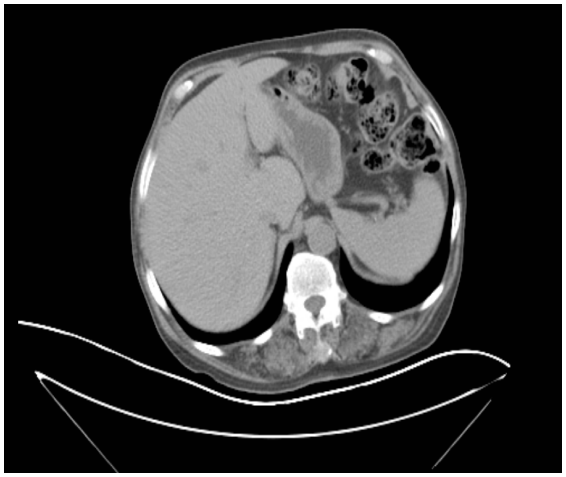

Figure 4: CT after chemoradiotherapy.

Final diagnosis: Primary adenocarcinoma of unknown origin, left cervical lymph node metastasis, left psoas metastasis, gastric primary carcinoma?

Follow-up instructions: Return for continued treatment after 3 weeks.

3. Discussion

Primary of Unknown Origin Cancer (Cancer of Unknown Primary, CUP), also termed cryptogenic carcinoma, refers to metastatic tumors confirmed as malignant through pathological examination, where no anatomical origin can be determined through detailed medical history review, physical examination, and diagnostic tests prior to treatment. Potential causes include: (1) Insufficient detection methods; (2) Inadequate tissue sampling; (3) Removal of the primary tumor; (4) Extensive metastasis obscuring the primary site; (5) Unique dissemination patterns; (6) Small primary tumor or spontaneous regression.

Even autopsy findings show 20–50% of cases lack identifiable primary sites. With an incidence rate of 1–2% among all malignancies [1], it ranks fourth in mortality rates [2]. Most CUP patients receive only localized therapy or empirical systemic chemotherapy, resulting in a poor prognosis with an average survival of 6–9 months. Early, effective diagnosis and targeted treatment are crucial for improving survival rates. Current diagnostic and therapeutic approaches lack robust evidence-based support [3]. Recent advancements in molecular biology and precision medicine have increased global research focus [4]. In CUP diagnosis, every clue suggesting a primary site should be carefully evaluated. Comprehensive medical history inquiries and thorough physical examinations are essential to identify potential diagnostic indicators. Imaging modalities include ultrasound, X-ray, computed tomography (CT), magnetic resonance imaging (MRI), emission computed tomography (ECT), and positron emission tomography-computed tomography (PET/CT). The selection of imaging studies should be based on the suspected primary site, with PET/CT being directly performed when indicated. During the diagnosis and treatment of cervical cancer with primary bone metastasis (CUP), endoscopic examination should be selected according to clinical indications to avoid unnecessary testing. In addition to imaging, other diagnostic methods include sentinel lymph node biopsy, evaluation of isolated or localized bone metastases via the prespinous venous plexus, 18F-FES PET/CT (estrogen receptor-targeted molecular imaging), and PET/CT scans using tumor-specific biomarkers.

Furthermore, tumor marker detection—particularly analysis of tumor marker panels—can provide valuable clues for identifying the primary tumor's location or system. Histopathological examination remains the gold standard for CUP diagnosis; if tissue samples are unavailable, immunohistochemical analysis of cellular aggregates may serve as diagnostic evidence. Clinical diagnosis of CUP follows two fundamental principles: first, consider common malignant tumors in China as potential primary carcinomas; second, avoid misdiagnosis or missed diagnosis of tumors with a favorable prognosis or curability. When developing personalized precision medicine treatment plans, it is recommended to conduct next-generation sequencing (NGS), liquid biopsy, and tumor origin gene testing. Additionally, participation in multidisciplinary team (MDT) consultations is advised to achieve comprehensive treatment strategies. Patients are strongly encouraged to enroll in clinical trials or receive targeted therapies based on NGS and tumor origin test results, or adopt empirical treatment. The tumor type should be determined through a comprehensive evaluation of medical history, symptoms, physical examination findings, imaging studies, endoscopic examinations, and pathological analyses. Treatment principles for primary-site unknown tumors:

(1) If a primary site is identified, follow specific disease guidelines.

(2) For localized tumors without identifiable origins (e.g., head/neck, supraclavicular, axillary, mediastinal, pulmonary, pleural/peritoneal effusions, abdominal, retroperitoneal, inguinal, bone, brain, or liver tumors), refer to specialized treatment protocols.

(3) For metastatic tumors without identifiable origins, prioritize symptom management with clinical trial enrollment as the first option, supplemented by empirical chemotherapy and targeted therapy [1].

MDT for primary-site unknown tumors: If expert consensus confirms tumor origin, recommend corresponding treatment plans according to current guidelines. If only preliminary suspicion exists, request additional immunohistochemical testing from pathology departments and consider genetic testing to identify tumor origin. It is hoped that such expressions will be clearer and accurate [1]. Due to the unique biological characteristics and heterogeneity of childhood upper respiratory tract infections (CUP), conducting clinical trials is challenging, with an overall poor prognosis: median survival duration is less than one year, and the 5-year survival rate is merely 14% [5]. To date, no specific treatment protocol has been established as a standard of care. Most CUP patients require empirical chemotherapy, such as taxane or platinum-based regimens [6]. Both symptomatic patients with invasive lesions (Eastern United States Clinical Oncology Group [ECOG] PS 1-2) and asymptomatic patients (ECOG PS 0) may consider chemotherapy. Different chemotherapy regimens should be selected based on histological types, and radiotherapy, immunotherapy, and targeted therapy may be added when necessary [1]. The cervical lymph nodes not only drain lymph from head and neck organs but also receive drainage from the chest, abdomen, pelvis, and limbs. Therefore, malignant tumors presenting with cervical lymphadenopathy as their initial symptom often have complex primary lesions, making misdiagnosis common [7,8].

Common clinical misdiagnosis scenarios include:

(1) Due to anatomical complexities of small tumors in specific areas like the tonsillar fossa or tongue root, combined with inherent limitations in diagnostic techniques, these conditions are frequently overlooked during physical exams and radiological examinations;

(2) Primary lesions grow slowly and remain dormant for extended periods, making them difficult to detect, while cervical metastases tend to be larger and appear earlier;

(3) Primary tumors may undergo immune suppression, causing micro or small diffuse primary cancers to regress while metastatic cancer continues to grow;

(4) Primary tumor cells may have undergone infarction;

(5) During metastatic cancer treatment, extensive radiotherapy or chemotherapy may suppress or eliminate sensitive primary tumors, or when primary tumors are small and adjacent to metastases, they might be removed during metastatic lesion surgery [9–11].

4. Conclusion

The emergence of novel diagnostic methods such as gene expression profiling, epigenetic analysis, and liquid biopsy, along with technological advancements, has provided new approaches for identifying primary lesions in Cancer of Unknown Primary Site (CUP). These innovations have been validated in clinical trials. Therefore, immunohistochemistry (IHC) should complement these new technologies to enhance diagnostic accuracy for CUP patients. Furthermore, the promising clinical outcomes observed in targeted therapy and immunotherapy trials strongly support the application of traditional chemotherapy regimens. However, further efforts are required to identify predictive biomarkers and establish effective patient classification systems to enable more personalized

treatment strategies. It is crucial to note that primary lesion identification is a prolonged process, with some lesions potentially remaining undetected for months or even years. When suspected new lesions are identified, repeat biopsies are necessary to confirm their status as primary lesions. Regular follow-up visits and close monitoring of disease progression are essential throughout the CUP management process.

Disclosure statement

The authors declare no conflict of interest.

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