

## LEARNING OBJECTIVES

- Describe the history and physical assessment of presumed carcinoma of unknown primary (CUP)
- Review the imaging studies and laboratory studies used to diagnose CUP
- Discuss how immunohistochemistry is used to determine tumor lineage
- Outline chemotherapy choices, especially for the favorable subset group

# Carcinoma of unknown primary: Searching for the origin of metastases

Identifying the potential, and often elusive, primary tumor is key to determining the most effective treatment. Diagnostic tests and select imaging studies can help in the search.

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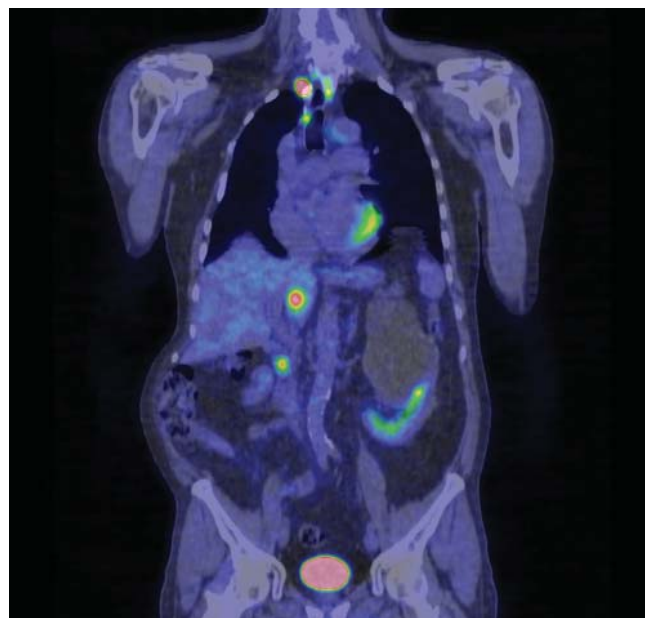
**C**arcinoma of unknown primary (CUP) is defined as metastatic carcinoma with no identifiable primary malignancy after a thorough diagnostic workup.<sup>1</sup> Approximately 3% to 5% of all diagnosed cancers are classified as CUP.<sup>2</sup> Adenocarcinoma, squamous cell carcinoma (SCC), poorly differentiated carcinoma, and neuroendocrine carcinoma are the primary histologies classified as CUP. Lymphoma, melanoma, and sarcoma have stage-specific therapies; therefore, these diseases are excluded from this group. A number of theories exist to explain CUP. One theory is that the primary lesion metastasized before necrosis occurred; therefore, the primary lesion is no longer identifiable when the metastatic tumor is detected. A second theory is that the primary cancer is microscopic; however, its metastasis is able to proliferate into a more significant tumor in different tissues. CUP presents a unique set of diagnostic and treatment circumstances for patients.

## THE DIAGNOSTIC PROCESS

A thorough history, physical examination, and selection of diagnostic tests are necessary to determine a differential diagnosis for the origin of disease. Symptoms, including hematuria, cough, hematochezia, and melena, can provide clues to the possible primary tumor. The patient's age, risk factors, and work or hobby exposures must also be considered. The most significant aspect of the patient's history is a family history of cancer, particularly any cancers in first-degree relatives. For example, Lynch syndrome should be considered in persons with a strong family history of early-onset colon cancer, or if the patient has a significant family history of malignancies that are associated with Lynch syndrome (such as endometrial, ureteral, ovarian, or small-bowel cancer).

A complete physical examination must be performed, even if the patient does not have any symptoms. All patients should have a rectal examination. Prostate and genitalia examinations should be performed on all men. If symptoms and test results in women suggest a gynecologic malignancy, pelvic examinations should be performed. A breast examination should be performed on all women with adenocarcinoma CUP.

**Imaging** A thorough search for the primary tumor via imaging studies should be undertaken in all patients, including a CT of the chest, abdomen, and pelvis. The role of



PET/CT of the thorax showing metastases.

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positron emission tomography combined with CT (PET-CT) imaging technology is controversial, and reimbursement can present a challenge. PET-CT is proven helpful in locating primary disease in the head and neck region in patients with a tissue diagnosis of SCC. In a retrospective review by Kothari and colleagues, <sup>18</sup>F-fluorodeoxyglucose activity seen on PET-CT identified ipsilateral tonsillar tumors as the primary source in three of five patients with CUP manifesting with cervical lymphadenopathy.<sup>3</sup> Based on these findings, tonsillectomy is recommended for patients who have cervical CUP because the potential primary may be small, undetectable tumors in the deep crypts of the tonsils.<sup>4</sup>

Women with CUP should have a recent mammogram. If mammogram results indicate that isolated axillary lymph nodes are involved, MRI and ultrasound of the breasts may be warranted to search for small or poorly visualized primary tumors in the breast.

**Laboratory tests and tumor markers** Laboratory studies, including liver and kidney function tests and a CBC, should be ordered to evaluate for underlying microcytic anemia. Serum tumor markers (carcinoembryonic antigen, carbohydrate antigen [CA] 19-9, CA 125, and CA 27.29) are nonspecific but can provide prognostic insight and indicate response to treatment (Table 1). However, these tests are rarely helpful with the diagnosis of the primary malignancy. Men should have prostate-specific antigen levels measured; if elevated, a prostate biopsy is warranted. An alpha-fetoprotein (AFP) level higher than 400 µg/L and presence of cirrhosis and a liver mass are suggestive of a hepatocellular carcinoma. AFP levels can be elevated along with beta-human chorionic gonadotropin (beta-hCG) in patients with testicular tumors when the pathology is undifferentiated or poorly differentiated carcinoma.

**Other studies** Patients should have a recent colonoscopy with verification that the endoscope reached the cecum. An upper endoscopy is warranted if pathology results, imaging studies, or symptoms are suspicious of an esophageal or gastric primary tumor. A triple endoscopy (laryngoscopy, esophagoscopy, bronchoscopy) may be indicated for patients with neck lymphadenopathy. Suspicious sites and common sites for malignancy should be biopsied.

## **PATHOLOGY AND IMMUNOHISTOCHEMISTRY**

Sixty percent of tumors in patients with CUP are adenocarcinomas. SCC constitutes about 5% of tumors and the remaining 35% are poorly differentiated carcinomas, poorly differentiated adenocarcinomas, and poorly differentiated neoplasms. A small percentage of tumors are neuroendocrine cancer, mixed lineage tumors (adenosquamous, sarcomatoid carcinomas), and undifferentiated neoplasms.

The pathologist makes the vital initial interpretation of the tissue, but valuable information can also be obtained with additional staining of tissue samples (Table 2). Tissue is usually acquired by fine needle aspiration or core needle biopsy. A core needle biopsy obtains a larger sample and is preferred in cases of CUP. If the initial sample contains a significant amount of necrotic tissue, a repeat biopsy is recommended. Immunohistochemistry is not 100% specific or sensitive but is helpful in determining tumor lineage.<sup>2</sup> More than 20 types of cytokeratin (CK) filaments with distinct molecular weights aid in identifying the origin of the disease. CK7 is present in patients with lung, endometrial, ovarian, or breast cancer; CK20 is present in the urothelium, Merkel cells, and the lower GI epithelium.<sup>5</sup> Some patterns of staining are highly suggestive of tumor origin. For example, CK7-/CK20+ suggests a colorectal cancer profile; in contrast, CK7+/CK20- is associated with lung, breast, upper GI, pancreas, and biliary tract cancer profiles.<sup>5</sup>

Estrogen receptor, progesterone receptor, and gross cystic disease fluid protein-15 (GCDFP-15) are markers for breast cancer, and 62% to 72% of breast carcinomas are GCDFP-15-positive. The expression of uroplakin III and thrombomodulin are consistent with a urothelial origin.<sup>6</sup> Thyroid transcription factor-I is positive in approximately 68% of adenocarcinomas and 25% of SCC in the lungs and is also a marker for thyroid cancer.<sup>7</sup> Lung cancers are also predominantly CK7+.

The future of pathologic diagnosis of CUP lies in building gene expression profiles determined by DNA microarray or reverse transcriptase polymerase chain reaction (PCR) into a database. CUP tumor analysis results would be compared to a database in an attempt to identify known gene features that suggest the origin of the tumor. Varadhachary and colleagues conducted a study on a molecular assay developed to detect

### **KEY POINTS**

- Approximately 3% to 5% of all diagnosed cancers are classified as carcinoma of unknown primary (CUP). Adenocarcinoma, squamous cell carcinoma, poorly differentiated carcinoma, and neuroendocrine carcinoma are the primary histologies classified as CUP. Lymphoma, melanoma, and sarcoma have stage-specific therapies; therefore, these diseases are excluded from this group.
- Symptoms, including hematuria, cough, hematochezia, and melena, can provide clues to the possible primary tumor. The patient's age, risk factors, and work or hobby exposures must also be considered. The most significant aspect of the patient's history is a family history of cancer, particularly any cancers in first-degree relatives.
- Laboratory studies, including liver and kidney function tests and a CBC, should be ordered to evaluate for underlying microcytic anemia. Serum tumor markers (carcinoembryonic antigen, carbohydrate antigen [CA] 19-9, CA 125, and CA 27.29) are nonspecific but can provide prognostic insight and indicate response to treatment.
- Patients with CUP experience a unique set of psychosocial issues. Clinicians must consider that patients are likely to be extremely anxious about having a disease with an elusive origin. Patients feel frustrated that no specific indications for screening exist for their children, and many of their family members have great difficulty understanding the diagnosis.

**TABLE 1. Common serum tumor markers**

Tumor marker	Primary disease
Alpha-fetoprotein	<ul style="list-style-type: none"> <li>• Germ cell cancer</li> <li>• Hepatocellular carcinoma</li> </ul>
Carbohydrate antigen 19-9 <sup>a</sup>	Carcinoma in the organs of the upper GI tract (ampulla of Vater, esophagus, pancreas, stomach)
Carbohydrate antigen 27.29	Breast cancer
Carbohydrate antigen 125	<ul style="list-style-type: none"> <li>• Ovarian cancer</li> <li>• Peritoneal disease</li> </ul>
Carcinoembryonic antigen serum <sup>a</sup>	<ul style="list-style-type: none"> <li>• Colorectal cancer</li> <li>• Lung cancer</li> </ul>
Chromogranin A	Neuroendocrine carcinoma
Prostate-specific antigen	Prostate cancer

<sup>a</sup> Marker levels can be falsely elevated in patients with hyperbilirubinemia.

**TABLE 2. Positive findings on immunohistochemistry and their associated primary**

Immunohistochemistry	Primary disease
Thyroid transcription factor-1	<ul style="list-style-type: none"> <li>• Lung cancer</li> <li>• Thyroid cancer</li> </ul>
Caudal type homeobox 2	<ul style="list-style-type: none"> <li>• Strongest positivity: Carcinoma in the colon, rectum, or small intestine</li> <li>• Less positivity: Carcinoma in the ampulla of Vater, esophagus, pancreas, or stomach</li> </ul>
Wilms' tumor gene	Ovarian cancer
Calretinin	Mesothelioma
<ul style="list-style-type: none"> <li>• Thrombomodulin</li> <li>• Uroplakin III</li> </ul>	Bladder cancer
Alpha-fetoprotein	<ul style="list-style-type: none"> <li>• Germ cell cancer</li> <li>• Hepatocellular carcinoma</li> </ul>
Human papillomavirus types 16 and 18	<ul style="list-style-type: none"> <li>• Anal cancer</li> <li>• Cervical cancer</li> </ul>
<ul style="list-style-type: none"> <li>• Chromogranin A</li> <li>• Synaptophysin</li> </ul>	Neuroendocrine carcinoma
<ul style="list-style-type: none"> <li>• Estrogen receptor</li> <li>• Gross cystic disease fluid protein-15</li> <li>• Mammoglobinulin</li> <li>• Progesterone receptor</li> </ul>	Breast cancer
Beta-human chorionic gonadotropin	Germ cell cancer
Prostate-specific antigen	Prostate

metastasis from lung, breast, colon, ovary, pancreas, or prostate origins. The assay determined a potential site of origin for 63 of 104 patients; the lung, colon, and pancreas were the most prevalent sites identified. Patients with a colon cancer profile were treated with colon cancer-specific regimens instead of the standard taxane and platinum-based CUP therapy. All patients in the prospective cohort with a colon cancer profile had a clinical benefit with standard colon cancer chemotherapy.<sup>8</sup> This group fared much better than those in the retrospective group with a colon cancer profile who were treated with taxane and platinum-based therapy. DNA microarray and PCR should enable us to better individualize therapy; and, prospective studies with larger study populations are warranted.

**TREATMENT**

Determining a treatment plan begins with a comprehensive review of all the known data—clinical, pathologic, and radiographic. A differential diagnosis based on possible primary profiles is established. Choice of therapy is guided by the burden of disease and the patient’s performance status. Given the heterogeneous presentations of patients with this disease, the number of possible treatment scenarios is extensive and thus will not be addressed entirely in this article. Some patients are amenable to surgical resection or radiation therapy, particularly those with a solitary metastasis; however, widespread disease requires palliative systemic treatment. The median survival for patients with disseminated CUP is 6 to 10 months, and the primary prognostic indicators are performance status, response to chemotherapy, serum lactate dehydrogenase levels, and the number of organs involved.<sup>9</sup>

For patients with disseminated disease and no strong indications of a primary site, first-line chemotherapy is often a platinum-based regimen. Briasoulis and colleagues saw a reduction in tumor size in 38.7% of 77 patients with CUP who were treated with a combination of paclitaxel and carboplatin.<sup>10</sup> Women with peritoneal carcinomatosis had the most favorable response, a greater amount of tumor shrinkage, and longest median survival; and patients with disseminated metastatic disease had the shortest median survival.<sup>10</sup> These findings were consistent with the results of a study by Greco and colleagues in which 55 patients with CUP were treated with paclitaxel, carboplatin, and oral etoposide.<sup>11</sup> The median overall survival in the Greco study was 13.4 months.

**CLINICALLY RELEVANT FAVORABLE SUBSETS**

**Peritoneal papillary serous carcinoma (PPSC)** is a syndrome that manifests with ascites, an elevated CA 125 level, and papillary serous pathology from peritoneal carcinomatosis, but no evidence of an ovarian mass is found on transvaginal ultrasonography or laparotomy. PPSC should be managed with the same protocol used for stage III ovarian cancer. Patients with PPSC may be candidates for cytoreductive surgery with adjuvant taxane and platinum-based chemotherapy.

**Neuroendocrine carcinomas** are classified as one of two distinct types: low-grade and high-grade. *High-grade neuro-*

endocrine carcinomas are distinguished by a high mitotic rate, as well as hemorrhage and necrosis on pathology. *Low-grade neuroendocrine carcinomas* (carcinoid type or neuroendocrine cancer not specified) often have an indolent natural history despite the absence of a primary lesion. Carcinoid symptoms, including flushing, diarrhea, and nausea, are often controlled with octreotide analogues, and systemic therapy is not necessary. The transition to systemic therapy is made when tumor growth causes the patient to become symptomatic or octreotide alone is no longer effective in controlling symptoms. Urinary 5-hydroxyindoleacetic acid and serum chromogranin A can be used as markers of neuroendocrine carcinoma. High-grade neuroendocrine carcinomas are chemosensitive and may respond well to cisplatin- and etoposide-based therapy.

**Isolated axillary adenopathy and an adenocarcinoma pathology** in women is an indication for mammography and ultrasonography; if these imaging studies are negative, bilateral MRI of the breasts should be obtained. Treatment should follow the protocol for stage II or III breast cancer. Radiation therapy, chemotherapy, and/or hormone therapy should be considered based on menopause status, amount of nodal disease, and hormone receptor status.

**Midline adenopathy and poorly differentiated carcinoma** in men suggests an extragonadal germ cell malignancy. AFP and beta-hCG levels should be measured. Platinum-based combination chemotherapy has a response rate of 50% or higher in select patients. A positive response was defined as shrinkage of tumor. Favorable prognostic factors include predominant tumor in the retroperitoneum or peripheral lymph node, low-volume disease, no history of cigarette use, and young age.<sup>12</sup>

**Solitary metastases** are potentially resectable; therefore, surgery should be considered for these patients. Surgical resection has the potential to result in cure. Given the heterogeneous nature of these cancers, some patients may be candidates for neoadjuvant chemotherapy and chemoradiation before surgery. Preoperative therapy may help gauge the aggressiveness of the cancer, treat micrometastases early, and predict chemotherapy responsiveness. Studies comparing surgery alone with preoperative therapy followed by surgery and the role of adjuvant therapy in this CUP population subset would be of interest, but recruitment of adequate numbers of study participants meeting enrollment criteria and tumor heterogeneity can be significant challenges.

## PSYCHOSOCIAL ISSUES

Patients with CUP experience a unique set of psychosocial issues. The unlikelihood of ever locating a primary source of the carcinoma must be expressed to patients at the initial office visit. Clinicians must consider that patients are likely to be extremely anxious about having a disease with an elusive origin. With many cancer diagnoses, patients are able to find a network of support. For example, breast cancer awareness in the community provides opportunities for raising money for research, family members understand the disease, and a pink ribbon symbolizes the disease. However, this type of commu-

nity support is not available for patients with CUP and their families. Patients feel frustrated that no specific indications for screening exist for their children, and many of their family members have great difficulty understanding the diagnosis.

Decisions regarding treatment options are an additional source of anxiety. Physician assistants need to reassure the patient with CUP that the disease is treatable, even if the primary tumor is not identified. They should explain that indications from pathology and imaging studies and the physical examination can help clinicians to develop a treatment plan. Empathetic and ongoing direct communication helps build a sense of confidence in the treatment recommendations. Patients with disseminated CUP must understand the palliative nature of disease management. The health care team should set realistic goals that enhance quality of life.

## CONCLUSION

Patients presenting with CUP should undergo an appropriate, directed search for a primary tumor. Clinicians must take into account clinical, diagnostic, and pathologic information when determining the most appropriate treatment plan. The cornerstone of treatment is double cytotoxic agents (platinum-based agents). Immunohistochemical stains and advancements in molecular profiling are allowing clinicians to tailor treatment plans to the patient's specific tumor biology, resulting in better outcomes. **JAAPA**

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## DRUGS MENTIONED

Carboplatin (Paraplatin, generics)	Octreotide (Sandostatina, generics)
Etoposide	Paclitaxel (Abraxane, Taxol, generics)

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