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Review article ■

Cancer of Unknown Primary Site Syndrome-CUP Syndrome - Diagnostic and Therapeutical Dillemas

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SUMMARY

Metastatic carcinomas of unknown primary origin (cancer of unknown primary-CUP) represent 3-5% of all cancers. This term includes all patients presented with metastatic disease in whom the primary site could not have been identified. Despite the use of modern and comprehensive diagnostic techniques and procedures, there is no improvement in efficacy (efficiency) of indentifying the primary site of disseminated disease. That is why a diagnostic procedure should be rational and should include the basic diagnostic examination (analyses) with the aim to define biological and clinical characteristics of diagnosed disease, as well as an optimal therapeutic approach. Although the overall prognosis of the majority of these patients is poor, it is possible, nowadays, to distinguish the subgroups of patients with favorable prognosis. Results of new basic research, better understanding of pathogenesis at the molecular level and introduction of new drugs through clinical trials suggest an advance in this disease treatment and outcome.

Key words: **malignant tumor, metastases, chemotherapy, CUP**

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INTRODUCTION

There are only a few clinical issues nowadays that represent as huge diagnostic and therapeutic challenge for a clinician as metastatic tumors of unknown primary origin. The common term for this group of diseases is "carcinoma of unknown primary" which underscores the fact that the patients present with metastatic disease in the absence of a discernible primary site. Heterogeneity of this disease, poor performance status of majority of these patients, inadequate therapy and poor prognosis are the main reasons why this problem, regardless of its high incidence (accounts for 3-5% of all malignancies) (1) and that it is a huge burden on the health system in every country, is not the focus of the scientific community.

Thus, CUP patients present with usually widespread metastatic disease for which no primary site can be detected after a good medical history, detailed clinical examination, and extensive investigations. The primary site may either have a slow growth or may possibly become involute and therefore unlikely to manifest itself (2).

Substantial improvements have been made in making reliable diagnosis and therefore in enhancing the capability of appropriate treatment, throughout technical training and introduction of new radiodiagnostic methods, improvement of histomorphological methods and using immunohistochemistry, electron microscopy and special molecular-genetic analyses, as well as introduction of new effective drugs.

Definition

The definition as well as the nomenclature itself of cancer of unknown primary site or origin have been varied over time and from one series to another under the influence of inclusion criteria and the evolution of diagnostic tools used. Historically, the simplest clinical definition has included all patients who presented with histologically confirmed metastatic carcinoma and in whom a complete medical history, careful physical examination, and chest radiography did not identify the primary site (3).

Epidemiology

Cancer of unknown primary origin represents 2-6% of all cancers diagnosed in the United States and accounts for 2-9% of cancers diagnosed worldwide. Median survival ranges from 11 weeks to 11 months. The five-year overall survival rate is about 11%. Most series reporting on or reviewing cancer of unknown primary origin patient groups give an approximate equal incidence for men and women. The median age on presentation for both men and women ranges from 59-66 years. Approximately, 10% of patients give a data on previous malignant disease in personal anamnesis (4). It is possible to reveal primary site of the tumor in 60-80% of cases by autopsy, and the most commonly affected organs are lungs and pancreas (5).

Biological features

Regardless of their heterogeneity, CUP tumors have common biological features. Their main characteristics are:

- Early dissemination in clinical absence of primary tumor;
- Unpredictability of metastatic pattern;
- Aggressive biology and clinical behavior.

Hypothetically, primary tumor remains of microscopic size and/or escapes clinical detection and/or disappears after the appearance of metastases.

Morphological features and histological classification

The initial light microscopic diagnosis usually identifies one of four histologies and should be used as the initial guideline for further evaluation of these patients. First and basic step in making CUP syndrome diagnosis is a histopathology assessment of a certain tissue specimen. According to routine light microscopy, cancers of unknown primary origin are divided into four (5) major subtypes (6, 7):

- Adenocarcinomas well to moderately differentiated;
- Poorly differentiated carcinomas and adenocarcinomas;
- Squamous cell carcinomas;
- Undifferentiated neoplasms;
- Carcinomas with neuroendocrine differentiation.

It is not always possible to identify a primary site of tumor origin by using light microscopy alone (8). For additional diagnostic accuracy, it is proposed to use also the immunohistochemistry staining, electron microscopy, molecular genetic and cytogenetic studies (PCR, FISH, DNA microarrays) (Table 1)(7).

There are 20 known subtypes of cytokeratin (CK) intermediate filaments, all of which have different molecular weights and levels of expression in different cell types and cancers. Monoclonal antibodies to specific CK subtypes have been used to help classify tumors according to their site of origin; the most commonly used CK stains in CUP adenocarcinoma cases are CK 7 and 20. CK 7 is expressed in the upper gastrointestinal tract tumors, cholangiocarcinoma, and pancreas, lung, ovary, endometrium, and breast cancers, whereas CK 20 is normally expressed in the lower gastrointestinal epithelium, urothelium, and Merkel cells. The CK 20+/CK 7- phenotype suggests a colon primary tumor; 75%–95% of colon tumors show this pattern of staining. CK 20−/CK 7+ is found in several cancer types, such as lung, breast, ovarian, and endometrial cancers. Cholangiocarci-

noma and pancreatic cancer can be CK 20−/CK 7+ or CK 7+ with focal positivity for CK 20. Eighty-five percent of lung cancers are positive for CK 7, and the use of thyroid transcription factor-1 (TTF-1) and surfactant apoprotein can further help distinguish lung primary tumors from other CK 7+ tumors. Approximately 68% of lung adenocarcinomas and 25% of squamous cell lung cancers stain positive for TTF-1 (9).

Electron microscopy is well-reputed diagnostic method for recognizing ultrastructural tumor features such are organeless, core granules, cell junctions. Since electron microscopy method is more expensive, time consuming and not widespread, using this method should be limited to selected cases of undifferentiated CUP not otherwise identified by light microscopy.

Whether CUP has a molecular genotype-phenotype that is distinct from metastases of known primary tumors remains to be elucidated. The identification of specific CUP-related molecular and biochemical targets may help us identify appropriate targeted agents for individual patients with this disease (9). In the near future, chromosomal and genetic aberrations identification will completely change tumor histological diagnosis. Molecular genetic and cytogenetic studies can offer today additional diagnostic information toward the identification of special tumor types that have specific genetic markers. Molecular tumor profiling is a promising diagnostic technique to determine the tissue of origin in patients with carcinoma of unknown primary site (CUP). However, the clinical value of these molecular predictions is unknown (Table 2).

Table 1. *Immunohistochemistry of CUP syndrome (7)*

Probable diagnosis	Antibody reactivity
Carcinoma	CK*, EMA*
Melanoma	S-100, vimentin, HMB-45*
Sarcoma	vimentin, desmin
Breast cancer	CK, EMA, ER*, PR*
Germ cell tumors	CK, EMA, beta-HCG*,AFP*, PLAP*
Neuroendocrine tumors	CK, EMA, NSE*, chromogranin, synaptophysin
Prostate cancer	CK, EMA, PSA*

**CK-Cytokeratins, EMA- Epithelial Membrane Antigen, HMB45-Human Melanoma Black 45, ER-Estrogen Receptor, PR-Progesterone Receptor, beta HCG-beta Human Chorionic Gonadotropin, AFP-Alpha FetoProtein, PLAP-PLacental Alkaline Phosphatase, NSE-Neuron specific enolase, PSA-Prostate-Specific Antigen*

Table 2. *Specific chromosomal rearrangements in CUP syndrome*

Tumor type	Specific chromosomal rearrangements
Lymphoma Anaplastic large cell lymphoma Burkitt lymphoma Mantle cell lymphoma	t (2;5) t (8;14) t (11;14)
Sarcoma Alveolar rhabdomyosarcoma Ewing sarcoma Synovial sarcoma	t (12;13) t (11;22) t (X;18)
Germ cell tumors	i (12p)
Retinoblastoma	Del (13)

Clinical presentation

The clinical presentation in cases of CUP depends on the predominant site of metastatic involvement. Regarding the organ sites affected, most patients (60%) have more than two sites affected at presentation (10) with lymph nodes being the most frequently involved. Liver, lung, bone, and pleura constitute common metastatic sites, whereas relatively high frequencies of odd localizations of metastases have been observed (11). General deterioration and weight loss are the most common symptoms, while digestive and respiratory symptoms, liver enlargement, ascites, skin nodules, and bone pains suggest the sites of predominant metastatic involvement.

Pattern of metastases in CUPs syndrome is quite different when compared with tumors with known primary site of origin. For example, bone metastases are rare from primary pancreatic cancer, but are very common in pancreatic cancer with clinical features of metastatic CUPs. Lung metastases are rare, but much more frequent than the same tumor where primary site of origin remained unrevealed.

Diagnostic standard

As a rule, a reasonable diagnostic approach to CUP patients is to avoid excessive diagnostic procedures without compromising clinically useful diagnostic efficacy. Based on the initial clinical presentation and pathology report, the diagnostic strategy for a probable CUP should be divided into the standard and optional diagnostic procedures. The reasonable diagnostic approach, nowadays, is to avoid superfluous procedures that have no results. However, attempts to detect primary tumor mainly remains futile, regardless of all available diagnostic procedures, and the primary site if origin is identified in only 13% of these patients (12).

Routine use of serum tumor markers (carcinoembryonic antigen (CEA), CA 19-9, CA 15-3, CA 125) does not offer any diagnostic assistance for patients with CUP. Their role could be as a prognostic markers and/or evaluation of therapy modalities. Males should have the high-specificity tumor markers beta-HCG, AFP and PSA tested to exclude treatable extragonadal germ cell tumors and prostate cancer. In patients with bone metastases higher thyreoglobulin level may suggest the existence of occult thyroid cancer. In children, testing for urinary catecholamines can produce valuable diagnostic clues, as high urine levels are diagnostic of neuroblastoma. In all other cases, routine evaluation of current, commonly used serum tumor markers have not been proven of any prognostic or diagnostic assistance, and a non-specific multiple overexpression in the majority of CUP patients has been observed (13).

Morphologic examination of a biopsy tumor specimen is a critical first step and provides a practical classification system on which to base subsequent investigations. All patients should have a complete history and physical examination and a full-body computed tomography scan at the onset in addition to complete blood counts, renal and liver function tests, and a urinalysis. Women should have mammography and men should have a serum prostate-specific antigen determination. These examinations may lead to finding the primary tumor site.

Most of the positron emission tomography (PET) scan literature in CUP patients is retrospective with a small sample size and it is unclear now if it impacts therapy and survival in the majority of patients (6). Most physicians agree that 18F-fluorodeoxyglucose (FDG)-PET is useful in this patient population, since it may help guide the biopsy, determine the extent of disease, facilitate the appropriate treatment (including radiation fields), and help with disease surveillance. In the near future, especially with the addition of intravenous contrast to PET-CT scanning, one can expect greater use of PET-CT scans in the CUP setting, and large well-designed studies of the cost-effectiveness of PET would be useful (9).

Prognosis

The overall prognosis in patients with CUP is poor, with a mean survival of five to ten months (14). Fewer than 25% of patients survive up to one year, but survival differs among clinicohistological subgroups. Significant prognostic factors recognized in CUP are: histopathology, organs involved, tumor burden, gender, and performance status. The prognostic significanceof histological type can be attributed to the chemo-sensitivity of the underlying occult primary in each category. In poorly differentiated carcinomas, several tumors chemo-sensitive in origin may be included, whereas adenocarcinomas usually represent chemotherapy-resistant primaries.

Regardless of the type of diagnostic technology utilized, the diagnosis of the possible primary tumor site must be interpreted with knowledge of the clinical context to enable optimal tumor characterization and thus potentially impact patient management. Communication between clinician and pathologist is therefore essential (6).

When the assay predicted tumor types that were clinically more responsive, the median survival was significantly improved when compared with predictions of more resistant tumors (13.4 v 7.6 months, respectively; P=.04) (15).

Treatment

Once the diagnosis of carcinoma is established, the main objective is to determine whether the patient belong to one of favorable subsets, for which there is a specific treatment. A reasonable treatment approach for CUP patients is to individualize the treatment, taking into consideration the most appropriate modality for each

case, whether locoregional, systemic, curative, palliative, or supportive (2).

Certain clinicopathological CUP entities are considered as favorable subsets responding to systemic platinum-based chemotherapy or managed by locoregional treatment. These subsets are: the poorly differentiated carcinomas involving the mediastinal-retroperitoneal nodes, peritoneal papillary serous adenocarcinomatosis in females, poorly differentiated neuroendocrine carcinomas, isolated axillary node adenocarcinomas in females or cervical nodal involvement by a squamous cell carcinoma. Patients who belong to the non-favorable subsets have a worse prognosis (16).

The management of carcinoma of unknown primary (CUP) has evolved over the past two decades from a wide-ranging work-up into a more algorithm-defined approach (17). Many subsets (approximately 20%) of CUP fall into recognizable syndromes; these include midline germ cell cancer in young men and isolated axillary lymph nodes in women. These better-prognosis subsets (these include papillary serous cancer in women, colorectal marker positive adenocarcinoma, and prostate-specific antigen [PSA]–expressing adenocarcinoma) can be treated with specific regimens, and their survival is much better than that of other CUPs. However, even after these subsets are excluded, a large category of CUP remains that cannot be further characterized on clinical and/or pathological grounds (18).

Although these cancers present as metastases and represent a spectrum of biological behavior, oncologists have stratified them into favorable (approximately 20%) and poor (approximately 80%) prognostic groups based on such factors as clinical presentation, host factors, tumor histology, number and location of metastatic sites, and their sensitivity to chemoradiation treatment. In general, patients with CUP have an overall survival of 6 to 9 months, although the favorable prognostic group may have a median survival of nearly 36 months (19) (Table 3) (20).

The unfavorable CUP group, which represents 80% of CUP patients, consists of: (I) adenocarcinoma metastatic to the liver or other organs; (II) non-papillary malignant ascites (adenocarcinoma); (III) multiple cerebral metastases; (IV) multiple lung/pleural metastases; and (V) multiple metastatic bone disease not expressing PSA in tumour/serum (16).

Patients with unfavorable CUP have dismal prognosis despite treatment with platinum- and/or taxane-based chemotherapy. Although chemotherapy can offer clinical benefit to some of these patients, overall survival remains poor. From mainly phase II studies as well as from some randomized trials the overall response rates range from 25% to 50%; however, median survival remains low at between 6 and 14 months (21). Moreover, a multiple treatment meta-analysis of 10 randomized trials (683 subjects) showed no significant survival benefit for any chemotherapeutic regimen over others (7, 22) (Table 4, 5).

Table 3. *Favorable prognostic subsets of patients with unknown primary cancer recognized by clinical and pathologic features in the last three decades (20)*

1. Extragonadal germ cell tumor
2. Poorly differentiated malignant neoplasms (60%=lymphoma)
3. Retroperitoneal, mediastinal and/or peripheral lymph node involvement
4. Squamous cell carcinoma (head/neck or inguinal area)
5. Isolated axillary carcinoma (women, rare in men)
6. Peritoneal carcinoma (women, rare in men)
7. Blastic bone METS or increased PSA in serum or tumor (men)
8. Neuroendocrine carcinoma (low-grade or well differentiated-carcinoid /islet cell type)
9. Neuroendocrine carcinoma (high-grade or poorly differentiated-small cell, large cell, others)
10. Single site of involvement (one lesion)

Table 4. *ESMO Clinical Practice Guidelines 2011(7)*

CUP type	Proposed treatment	Potential equivalent tumor
Poorly differentiated neuroendocrine carcinoma of an unknown primary	Platinum+etoposide combination chemotherapy	Poorly differentiated NET* with unknown primary
Well differentiated NET of unknown primary	Somatostatin analogs, streptozocin+5 FU*, sunitinibeverolimus	
Peritoneal adenocarcinomatosis of a serous papillary histological type in female	Optimal surgical debulking followed by platinum-taxane based chemotherapy	Ovarian cancer
Isolated axillary nodal metastases in female	Axillary nodal dissection, mastectomy or breast irradiation and adjuvant chemohormonotherapy	Breast cancer (found in 50-70% when breast MRI* is performed)
Squamous carcinoma involving non-supraclavicular cervical lymph nodes	Neck dissection and/or irradiation of bilateral neck and head-neck axis. For advanced stages induction chemotherapy with platinum-based combination or chemoradiation	Head and neck squamous cancer
Single metastatic deposit from unknown primary	Resection and/or RT*+/- systemic therapy	Single metastasis
Men with blastic bone metastases and IHC*/serum PSA expression	Androgen deprivation therapy +/- RT	Prostate cancer
Midline CUP	Platinum based chemotherapy	Extragonadal germ cell tumor

**NET-Neuroendocrine Tumor, 5 FU-fluorouracil, MRI-Magnetic Resonance Imaging, RT-RadioTherapy, ICH-ImmunoHistoChemistry*

Table 5. *Promising molecular targets in CUP (22)*

Promising molecular targets and targeting compounds in CUP		
Molecule	Therapeutic modulation	Developed agents
Ras *	Farnesyl-transferase inhibitors	Tipifarnib, lonafarnib
HER2*	Antibodies, tyrosine kinase inhibitors	Trastuzumab, lapatinib
EGFRP*	Antibodies, tyrosine kinase inhibitors	Cetuximab, gefitinib, erlotinib
C-KIT	Tyrosine kinase inhibitors	Imatinib, sunitinib
PDGFR *	Tyrosine kinase inhibitors	Imatinib, sunitinib
BCL2 *	Antisense oligonucleotides	Oblimersen G3139
P53	Gene therapy, degradation inhibitors	ONYX015, INGN201, MI63
VEGF*	Antibodies	Bevacizumab
VEGFR*	Tyrosine kinase inhibitors	ZD6474, sorafenib, sunitinib

**Ras-RAt Sarcoma, HER2-Human Epidermal growth factor Receptor 2, EGFR- Epidermal Growth Factor Receptor, PDGFR-Platelet Derived Growth Factor Receptor, BCL2-B Cell Lymphoma 2, VEGF-Vascular Endothelial Growth Factor, VEGFR- Vascular Endothelial Growth Factor Receptor.*

CONCLUSION

The recognition of treatable subsets within the large heterogeneous population of patients with carcinoma of unknown primary site represents a definite advance in the management and treatment of these patients. Regardless of the type of diagnostic technology utilized, the diagnosis of the possible primary tumor site must be interpreted with knowledge of the clinical context to enable optimal tumor characterization and thus potentially impact patient management. Treatable subsets can be defined with appropriate clinical and pathologic evaluation. For patients who do not fit into any defined subset but who are not debilitated, a trial of empiric chemotherapy is recommended. Other new drugs and regimens are currently being evaluated.

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SINDROM METASTATSKIH TUMORA NEPOZNATOG PRIMARNOG ISHODIŠTA - DIJAGNOSTIČKE I TERAPIJSKE DILEME

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Sažetak

Metastatski karcinomi nepoznatog porekla (cancer of unknown primary-"CUP") zastupljeni su sa 3-5% svih malignih tumora. Ova bolest se prezentuje kao metastatska sa nepoznatim ishodištem u trenutku dijagnoze. Moderne i sveobuhvatne dijagnostičke tehnike i procedure ne uspevaju da poboljšaju efikasnost u pronalaženju primarnog porekla diseminovane bolesti. Kao posledica navedenog, dijagnostički pristup bi trebalo da bude racionalan i da uključi bazična dijagnostička ispitivanja sa ciljem definisanja bioloških i kliničkih karakteristika ispitivanog procesa i definisanja optimalne terapije. Iako je prognoza bolesti loša, moguće je definisati podgrupe bolesnika sa dobrom prognozom. Rezultati novih bazičnih ispitivanja, bolje razumevanje patogeneze na molekularnom nivou i uvođenje novih medikamenata kroz kliničke studije ukazuju na pomak u lečenju i ishodu ove bolesti.

Ključne reči: **maligni tumor, metastaze, hemioterapija, CUPS**