MINI REVIEW

A mini review on cancer of unknown primary site: A clinical puzzle for the oncologists

Nicholas Pavlidis a, Hussein Khaled b,*, Rabab Gaafar b

a Department of Medical Oncology, School of Medicine, University of Ioannina, Ioannina, Greece
b Department of Medical Oncology, National Cancer Institute, Cairo University, Cairo, Egypt

ABSTRACT

Cancer of unknown primary (CUP) is a well recognized clinical syndrome, accounting for 3–5% of all malignancies. It is characterized as a disease with an early dissemination of metastases without a primary detected site after extensive laboratory and clinical investigations. CUP is divided into the favorable and unfavorable groups based on histopathological and clinical manifestations. Adenocarcinoma of various differentiations is the commonest histopathological subtype. Favorable groups are treated with local or systemic treatment and some of them are enjoying long-term survival. On the contrary, unfavorable groups are treated with empirical...
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Nicholas Pavlidis is a Professor of Medical Oncology and Head of the Department at the University of Ioannina, Greece. Cancer of unknown primary is one of his research fields (more than 55 publications). He was the Chairman of the ESMO Guidelines Committee (2006–2011) and present Chairman of the ASCO/ESMO Core Curriculum of Medical Oncology since 2011. He is member of the Scientific Committee of the European School of Oncology (ESO) and Chairman of various educational activities. He is Editor-in-Chief of Cancer Treatment Reviews and Associate Editor of European Journal of Clinical Investigation.

Hussein Khaled is a Professor of Medical Oncology at the National Cancer Institute of Cairo University. He was the former minister of higher education of Egypt (2012), former vice president of Cairo University for post graduate studies and research (2008–2011), and the former dean of the Egyptian National Cancer Institute (2002–2008). He has many national, regional, and international activities. Some of his national activities include being the secretary general of the Egyptian Foundation for Cancer Research, the head of the council of the Egyptian medical oncology fellowship, the head of the committee of oncology university staff promotion, and the Editor-in-Chief of the Journal of advanced research, the official journal of Cairo University. Regionally he was the assistant secretary general of the Arab Medical Association Against Cancer for 4 years, the national representative for Egypt and North Africa for 6 years (2000–2006), and the current president of the South and East Mediterranean College of Oncology. On the International level, he is a member of many international societies including the ESMO, ASCO, INCTR, and a member of the lymphoma group in the EORTC. He was also a member of the editorial board of the Annals of Oncology, the ESMO official journal (2006–2012). His research activities are focused mainly on bladder cancer (both biologic and clinical aspects), breast cancer, and malignant lymphomas, with more than 150 national and international publications (total impact factor of 253.387, total citations of 1388, and h-index of 20).

Prof. Rabab Gaafer is former Chair Medical Oncology Department, National Cancer Institute, Cairo (NCI), Cairo University, Egypt, Board member of EORTC lung group, Board member of IMIG and ESMO regional representative for Egypt and North Africa and recently ESMO Panel committee member. She received her MD certification in Medical Oncology from the National Cancer Institute, Cairo University 1987. She is directing the Thoracic Oncology Program at NCI, Cairo. She is currently chairman of Quality Assurance in the Board of the European Organization for Research and Treatment of Cancer Lung Cancer Group (EORTC) and is also board member in IMIG. She is in the Editorial Board for the Journal Frontier in Thoracic Oncology and reviewer in many International journals such as Lung cancer, Eur Resp journal, Frontier in Thoracic oncology, journal Thoracic disease, journal of Clinical Practice, Journal of Advanced Research (JAR) and Egyptian National Cancer Institute Journal Cairo.

Introduction

CUP is a common disease with an incidence of 3–5% among other epithelial tumors. Worldwide the overall age-standardized incidence per 100,000 people per year is ranging between 4–19 cases. It is characterized as a metastatic cancer diagnosed without the primary site, despite histopathological and radiological laboratory investigations. The median age at diagnosis is 60 years with a male predilection [1].

Today, the definition of CUP includes patients who present with histologically-confirmed metastatic cancer in whom a detailed medical history, complete physical examination including pelvic and rectal examination, full blood count and biochemistry, urinalysis and stool occult blood testing, histopathological review of biopsy material with the use of immunohistochemistry, chest radiography, computed tomography (CT) of the abdomen and pelvis and, in certain cases, mammography and PET scan fail to identify the primary site [1].

Biology of CUP

CUP’s biology is poorly understood although several molecular or translational research studies are available. One hypothesis postulates that CUP does not undergo type 1 progression (from a premalignant lesion to malignant) but instead it follows a type 2 progression without forming a primary site. A second hypothesis supports that CUP follows the parallel progression model, where metastases can arise early in the development of a malignant process [2,3].

Several research data have shown that CUP rarely harbors activating point mutations in either oncogenes or tumor suppressor genes, has active angiogenesis in 50–80%, overexpress various oncogenes in 10–30%, hypoxia-related proteins in 25%, epithelial–mesenchymal transition markers in 16% and have activated intracellular signaling axes such as AKT or MAPK in 20–35% [4–6] (Table 1). Very recently global microRNA profiling showed no significant expression differences with metastases of matched known primary tumors failing to identify any specific “CUP signature” [7,8].

Clinicopathological subsets

CUP is associated with a short history of symptoms and signs, has an early dissemination with an aggressive behavior in most
### Table 1  Molecular events in CUP patients.

| N patients | Molecules | Method  | Results               | Prognostic/predictive value |
|------------|-----------|---------|-----------------------|-----------------------------|
| Oncogenes  |           |         |                       |                             |
| 420        | HER-2     | IHC     | Overexpression 10–35%  | None                        |
| 50         | HER-2     | PCR     | No mutations          | –                           |
| 201        | EGFR      | IHC     | Overexpression 12–61%  | Superior survival/correlated with response to cisplatin |
| 126        | c-Kit     | IHC     | Overexpression 3–13%   | None                        |
| 50         | c-Kit     | PCR     | No mutations          | –                           |
| 173        | PDGFR     | IHC     | Expression 3%          | None                        |
|            |           |         | Overexpression 10–25%  | None                        |
| Tumor suppressor genes | |         |                       |                             |
| 157        | p53       | IHC     | Overexpression 48–53%  | None                        |
| 46         | p53       | PCR     | Mutations 26%          | None                        |
| Angiogenesis/hypoxia | |         |                       |                             |
| 253        | VEGF      | IHC     | Overexpression 26–83%  | None                        |
| 197        | CD34      | IHC     | Density 56–59%         | None                        |
| 80         | TSP-1     | IHC     | Overexpression 20%     | None                        |
| 125        | HIF 1α    | IHC     | Expression 20%         | Adverse prognostic factor   |
| Tumor stroma |           |         |                       |                             |
| 76         | MMP-2     | IHC     | Overexpression 49%     | None                        |
| 76         | MMP-9     | IHC     | Overexpression 36%     | None                        |
| 76         | TIMP-1    | IHC     | Overexpression 44%     | Adverse prognostic factor   |
| 100        | E-Cadherin | IHC     | Expression 79%         | Adverse prognostic factor   |
| 100        | EMT-phenotype | IHC | Expression 8%         | Adverse prognostic factor   |
| Molecular pathways | |         |                       |                             |
| 100        | cMet      | IHC     | Expression 42%         | Adverse prognostic factor   |
| 100        | pMAPK     | IHC     | Expression 54%         | Predictive for chemotherapy |
| 100        | Notch 3   | IHC     | Expression 73%         | None                        |
| 100        | PTEN      | IHC     | Expression 50%         | None                        |
| 100        | pAKT      | IHC     | Expression 76%         | Prognostic for survival     |
| 100        | pRPS6     | IHC     | Expression 59%         | Prognostic for survival     |
| 100        | p21       | IHC     | Expression 60%         | Prognostic for survival     |

IHC: immunohistochemistry, MMP = metalloproteinase, TIMP-1: tissue inhibitor of metalloproteinase 1, EMT: epithelial mesenchymal transition, HIF: hypoxia – inducible factors.

### Table 2  Required investigations for searching the primary site.

**Clinicopathological data**
- Histologically confirmed metastatic cancer
- Detailed medical history
- Complete physical (including pelvic and rectal) examination
- Histopathology review with specific immunohistochemical study

**Work-up for all patients**
- Full blood count
- Biochemistry
- Urinalysis
- Testing for occult blood in stools
- Chest radiography
- CT scan of thorax, abdomen, and pelvis

**Work-up for selected patients only**
- Mammography (for all women)
- Breast MRI
- Testicular ultrasonography
- PET or CT scan
- Concentrations of serum α-fetoprotein and β human chorionic gonadotropin
- Concentrations of serum prostate-specific antigen (for all men)
- Concentrations of serum cancer antigen 125 and carcinoma antigen 15–3
- Endoscopy
of the times (three or more organs are involved) and often carries unpredictable metastatic patterns. Unpredictable metastatic pattern at diagnosis refers to the differences in the incidence of metastatic sites between known and unknown primary carcinomas i.e. pancreatic cancer presenting as CUP has 4-fold higher incidence to affect bones, and 30% incidence to appear with lung metastases in contrast to the known natural history of known primary pancreatic cancer.

To search the primary site a number of investigations are required including clinical data, immunohistochemistry studies, blood tests, radiological techniques and endoscopic procedures [1]. Table 2 indicates the necessary investigations that should be performed in suspected CUP cases.

Since 2003 CUP is divided into two separated groups the favorable (20%) and the unfavorable (80%) group [9]. Favorable subsets are those entities that respond to local and/or systemic treatments and have a longer survival. Table 3 demonstrates the classification of CUP patients into various clinicopathological subsets.

### Woman with adenocarcinoma involving axillary nodes

This is a CUP subset in which the primary site is most often hidden in the breasts. It has a presentation similar to breast cancer of stage II (N2 or N3 disease), and it affects exclusively women of a mean age of 52 years. The most frequent histology is ductal adenocarcinoma. Forty percent have positive estrogen receptors. After undergoing mastectomy, almost 70% of the patients have an occult breast primary identified [10].

### Women with papillary adenocarcinoma of peritoneal cavity

This entity has also been called primary peritoneal carcinoma. Clinical presentation includes pain, ascites, abdominal masses or intestinal obstruction. Median age is 60 years. Histopathology is always compatible with serous papillary adenocarcinoma with or without psammoma bodies. Immunohistochemical expression of MUC10, estrogen receptors, mesothelin, WT1 and KRT7 can be found. Serum CA 125 is very often raised.

In comparison with primary ovarian cancer, primary peritoneal carcinoma affects older women, has more bulky disease and has more overexpression of HER 2 oncogene and Ki67 [11].

### Squamous cell carcinoma involving cervical nodes

It is more frequent in men (80%) with a median age of 60 years and it constitutes 5% of all head and neck cancers. Clinical presentation includes a painless and unilateral cervical mass, most commonly affecting Level II lymph nodes (jugulodigastric or upper nodes). Fine needle aspiration has a diagnostic

### Table 3 CUP subsets.

| Favorable subsets | Unfavorable subsets |
|-------------------|---------------------|
| 1. Women with adenocarcinoma involving axillary lymph nodes | 1. Adenocarcinoma metastatic to the liver or other organs |
| 2. Women with papillary adenocarcinoma of peritoneal cavity | 2. Poorly differentiated carcinoma |
| 3. Squamous cell carcinoma involving cervical lymph nodes | 3. Non-papillary malignant ascites (adenocarcinoma) |
| 4. Poorly differentiated neuroendocrine carcinomas. Merkel cell carcinoma of unknown primary (localized disease) | 4. Multiple cerebral metastases (adeno or squamous Ca) |
| 5. Adenocarcinoma with a colon-profile (CK20**, CK7**, CDX2**) | 5. Multiple lung/pleural metastases (adenocarcinoma) |
| 6. Men with blastic bone metastases and elevated PSA (adenocarcinoma) | 6. Multiple metastatic bone disease (adenocarcinoma) |
| 7. Isolated inguinal adenopathy (squamous carcinoma) | 7. Squamous-cell carcinoma of the abdominal cavity |

### Table 4 Immunohistochemistry tests for investigating CUP.

| Step one | Diagnosis |
|----------|-----------|
| AE1 or AE3 pan-cytokeratin | Carcinoma |
| Common leukocyte antigen | Lymphoma |
| S100; HMB-45 | Melanoma |
| S100; vimentin | Sarcoma |

| Step two | Diagnosis |
|----------|-----------|
| CK7 or CK20;PSA | Adenocarcinoma |
| PLAP; OCT4; AFP; human chorionic gonadotropin | Germ-cell tumor |
| Hepatocyte paraffin 1; canalicual pCEA; CD10, or CD13 | Hepatocellular carcinoma |
| RCC; CD10 | Renal cell carcinoma |
| TTF1; thyroglobulin | Thyroid carcinoma |
| Chromogranin; synaptophysin; PGP9.5; CD56 | Neuroendocrine carcinoma |
| CK5 or CK6; p63 | Squamous cell carcinoma |

| Step three | Diagnosis |
|------------|-----------|
| PSA; PAP | Prostate |
| TTF1 | Lung |
| GCDFP-15; mammaglobin; ER | Breast |
| CDX2; CK20 | Colon |
| CDX2 (intestinal epithelium); CK20; CK7 | Pancreas or biliary |
| ER; CA-125; mesothelin, WT1 | Ovary |
comfort with a sensitivity of CT-scan accuracy of almost 95%. A panendoscopy with biopsy should follow. Radiology is very helpful with a sensitivity of CT-scan in 22%, MRI in 36% and PET-scan up to 60% [12].

Poorly differentiated neuroendocrine carcinoma

It represents the 90% of CUP neuroendocrine tumors, the rest being of well differentiated low grade histology. It affects males (65%) of a median age of 65 years. Retropertioneal, mediastinal or peripheral lymph nodes are the most common dominant sites (40%) following by liver (25%) and bones (10–15%) [13].

Recently, neuroendocrine Merkel cell nodal carcinoma of stage IIIIB has been recognized as having also a long-term survival [14].

Adenocarcinoma with a colon-profile (CK20+, CK7−, CDX2+)

Up to now less than 100 cases have been reported mostly in women, with a median age of 57 years. Disease is extended in the abdomen involving abdominal nodes in 51%, peritoneal surfaces in 50%, liver in 30% and ascites in 27% [15,16].

Unfavorable subsets metastatic visceral or skeletal CUP

These are the most frequent subsets of CUP. They have a poor prognosis with a short survival. The most common histological types are adenocarcinomas of moderate to poorly differentiated (64%), the rest been undifferentiated tumors. It involves mainly the liver in 40–50% of the cases, followed by lymph nodes (35%), lungs (31%), bones (28%) and the brain (15%) [1,9].

Searching for the primary

Pathology and immunohistochemistry

Histopathology is one the most important avenue in the elaboration of CUP diagnosis. Immunohistochemistry with a wide battery of staining (including cytokeratins), is of a great value since it could differentiate between: (a) carcinoma, sarcoma or lymphoma, (b) adenocarcinoma, germ-cell tumor, hepatocellular, renal, thyroid, neuroendocrine or squamous carcinomas as well as (c) the primary site of an adenocarcinoma (lung, breast, ovarian, prostate, colon, pancreas or biliary cancer) (Tables 4 and 5) [17].

Molecular diagnosis

During the last decade commercial tests of gene profiling microarrays became available for the diagnosis of CUP. Assays on cDNA or miRNA platforms gave accuracy rates up to 93% in detecting the primary site and could probably allow particular and specific therapeutic management in CUP patients [18,19]. Whether this promising technology will lead us to better patients’ outcome, it remains uncertain. A number of clinical trials are still ongoing.

Radiology

Over the past 30 years CT scan, MRI and PET-scan added substantially to the detection of primary site. CT scans provided a diagnostic accuracy of 55% (36–74%) mainly in pancreatic, colorectal and lung cancer, while MRI was found to be very sensitive in detecting primary breast cancers in 70% of cases [1].

Fluorodeoxyglucose (FDG) PET accuracy in CUP ranges between 25% and 43%. The most common primary sites detected by PET are lung cancer (33%), head and neck cancers (27%), followed by pancreatic, breast and colon cancers (4–5%). 68Ga-DOTA-NOC receptor PET/CT is also very accurate in identifying primary neuroendocrine tumors or their metastatic lesions [20,21].

Endoscopy

Endoscopies in general, carry low accuracy rates and low sensitivity and specificity. Endoscopies should not be used in all CUP patients for the detection of primary site, unless they are clinically presenting with relevant symptoms and signs or in patients with specific histopathological findings. A colonoscopy should be requested in CK7−, CK20− and CDX2− cases or bronchoscopy in CK7+ and TTF1+ patients [1].

Serum tumor markers

Elevated epithelial serum tumor markers can be overexpressed in CUP patients. In almost 70% of them two or three markers can be concomitantly increased in a non-specific way. CA-125, CA-15-3, CA19-9, CEA can be raised without any diagnostic, prognostic or predictive value. Therefore, routine request of these tumor markers is not recommended. However, in specific cases it might offer diagnostic aid such as serum prostate-specific antigen in men with osteoblastic bone metastases, CA125 in females with primary serous papillary peritoneal adenocarcinoma, or CA 15-3 in women with isolated axillary adenocarcinoma [22].

Molecular diagnosis

During the last ten years gene-expression profiling in the classification and detection of primary tumor sites has led to the development of commercially available tests. The accuracy
rates of these tests are up to 90% but its validity in daily practice remains uncertain. Randomized prospective studies are needed to establish whether patients’ outcomes are improved by its clinical use.

Therapeutic management (Table 6)

Women with adenocarcinoma involving axillary nodes

These patients should be treated with complete axillary dissection, ipsilateral breast radiotherapy followed by adjuvant chemotherapy and/or hormonotherapy depending on the risk factors. Patients without local treatment are associated with high locoregional relapse rates (40–55%). Survival is longer in patients who received primary breast radiotherapy as well as in patients with adjuvant systemic treatment [1,10].

Women with papillary adenocarcinoma of peritoneal cavity

Patients with primary peritoneal adenocarcinoma should be treated similarly to stage III and IV ovarian cancer. Surgical cytoreduction followed by platinum and paclitaxel chemotherapy is the treatment of choice. Median response rate is 80% with 30–40% complete responders and a median survival of 36 months. Some reports have demonstrated poorer survival of patients with primary peritoneal carcinoma as compared to primary ovarian cancer due to reasons depicted in the section of clinicopathological entities [1,11].

Table 6 Therapy of patients with CUP according to ESMO guidelines.

| CUP subsets                                      | Recommended treatment                                           |
|-------------------------------------------------|-----------------------------------------------------------------|
| Poorly differentiated neuroendocrine carcinoma  | Platinum + etoposide combination chemotherapy                  |
| Serous papillary peritoneal adenocarcinoma       | Optimal surgical debulking followed by platinum-taxane-based chemotherapy |
| Isolated axillary nodal metastases               | Axillary nodal dissection, mastectomy or breast irradiation and adjuvant chemohormonotherapy |
| Squamous carcinoma involving 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 |
| Adenocarcinoma with a colon-profile             | Chemotherapy regimens for colorectal cancer                     |
| Men with blastic bone metastases and IHC/serum  | Androgen deprivation therapy ± RT                                |
| PSA expression                                  | Resection and/or RT ± systemic therapy                          |
| Single metastatic deposit from unknown primary  | Platinum-based empirical chemotherapy                            |
| Unfavorable subsets                              |                                                                  |

Table 7 Prognosis of favorable CUP patients.

| CUP subset                                                 | Survival                                                   |
|------------------------------------------------------------|------------------------------------------------------------|
| Women with adenocarcinoma involving axillary nodes         | Mean 5-year overall survival: 72%                         |
| Women with papillary adenocarcinoma of peritoneal cavity   | Mean overall survival: 36 months (2–6 months less than primary ovarian cancer) 5-year survival: 60–65% |
| Squamous cell carcinoma involving cervical nodes           | Median survival: 15.5 months with 2-yr survival: 33–50%. Long-term survivors: 10–15% |
| Poorly differentiated neuroendocrine carcinoma              | Median overall survival: 20–36 months                      |
| Adenocarcinoma with a colon cancer profile                 |                                                            |
Squamous cell carcinoma involving cervical nodes

Patients with N1 or N2a disease without extra capsular extension could be treated with surgery alone including excisional biopsy, radical or modified radical neck dissection, and/or bilateral tonsillectomy. Locoregional control is around 80–90% and 5-year overall survival up to 65%. Postoperative radiotherapy is indicated in excisional or incisional biopsy, extracapsular extension, stage N2b or higher, in fixed nodes to the adjacent structure or in patients with low performance status and comorbidities. The irradiation fields include the involved nodal stations (65–70 Gy), the uninvolved sites (50 Gy) and the mucosal sites (50–60 Gy).

Chemoradiation could be indicated in N2 or N3 cases with cisplatin based chemotherapy. Chemoradiation could be associated with significant grade 3 toxicities [1,12].

Poorly differentiated neuroendocrine carcinomas

This group of patients should be treated with platinum-based or platinum–taxane combination chemotherapy. Response rates are up to 55% with 20% complete responders and overall survival of 15 months and almost 10–15% long-term survivors [1,13].

Adenocarcinoma with a colon-profile (CK20+, CK7+, CDX2+)

This subset of patients should be treated as advanced colorectal cancer cases. Overall response rate is 50% with 15% complete and 35% partial responses and median survival of 21–37 months [1,15,16].

Other favorable subsets

Patients with metastatic bone metastases and elevated serum PSA should be managed as advanced prostate cancer [1]. Patients with isolated inguinal nodal metastases or a single metastatic lesion should undergo local dissection with or without local radiotherapy [1].

Treatment of unfavorable subsets

Unfortunately, this group of CUP patients represents the 80% of the cases. They are usually treated with empirical chemotherapy mostly with platinum or taxane combinations. Response rates are around 20% and median survival of six months (Fig. 1). A recent meta-analysis has shown that no type of chemotherapy has demonstrated any survival benefit in these subsets [23,24]. Specific targeted treatment in CUP patients following gene profiling microarray tests has not yet been proven. Since there are no prospective randomized studies available, we have to wait until some already ongoing trials appear. Table 6 summarizes therapeutic options according to the ESMO guidelines [25] and Table 7 the prognostic features of favorable subsets. Finally, Table 8 provides an algorithm of searching the primary site and treating CUP patients accordingly.

Conclusions

CUP is a well recognized clinical syndrome and may be defined as a disease with early disease dissemination without a primary detected site. It could have a favorable or unfavorable out-
come. Adenocarcinoma is the commonest histopathological subtype. While favorable groups are treated with local or systemic treatment, unfavorable groups are treated with empirical chemotherapy having usually a dismal prognosis. The value of gene-profiling microarray diagnosis though sensitive, its predictive or prognostic impact remains elusive.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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