INTRODUCTION

Cancer of unknown primary origin (CUP) is a heterogeneous group of malignant tumors identified by histological confirmation of one of the metastatic lesions when the primary lesion cannot be identified despite a standardized diagnostic approach. (1, 2) It is the eighth most common cancer in the world, (1) and it is a neoplasm with poor prognosis: average survival time after diagnosis is three months. (3) In 10% to 30% of cases, it is not possible to find the tumor from which metastasis originates even after an exhaustive search with the most advanced techniques such as the molecular profiling and even after an autopsy. (4) Due to the great difficulty of finding the primary site and offering specific treatment, new ways of acting against this tumor have recently been studied. They include molecular, imaging, immunohistochemical and genetic studies that improve patients’ abilities to survive these tumors. (2, 4-7)

Taking into account the importance of this topic in daily clinical practice, especially in gastroenterology, we decided to perform the following review to guide clinicians in their approach and management of patients with this type of oncological presentation.

METHODOLOGY

Search terms were based on combinations of “cancer of unknown primary”; “neoplasms” and “unknown primary” [MeSH] with each point of interest the terms “MeSH” and “not MeSH” in Spanish and English. The search strategies used were “neoplasms, unknown primary AND epigenetic”; “neoplasms, unknown primary AND immunohistochemical
This has been studied in depth and the evaluation includes performing the standard evaluation in order to define CUP. The result of the biopsy of a metastasis. Similarly, it is necessary to perform the standard evaluation including blood glucose, electrolytes, calcium, liver profile, creatinine, urea and lactic dehydrogenase, urine analysis, occult blood in fecal matter, and computed tomography (CT) with contrast of the thorax, abdomen and pelvis. (2, 14, 15) (16) The exception is CUP of the head and neck at nodal levels 1 to 3 for which it is suggested that the CT scan include the area from the base of the skull to the pelvis. (17)

Even after the initial steps supplemented with more advanced examinations, the original tumors that caused the metastasis of 20% to 50% cannot be found. (18) Under these circumstances, one is faced with a diagnosis of CUP by its strictest definition. (19, 20)

The biological events that allow a primary tumor to remain hidden after the development of metastases have yet to be defined. (16) Even after an autopsy, the primary tumor may not be detected. For these cases, various theories have been proposed including regression or involution of the primary tumor and development of the CUP in stem cells with capacity to differentiate into multiple cell lines to the liver, muscles, skin or even the cells of the gastrointestinal tract. They may be located in the connective tissue after birth. (7) There is no evidence that CUP is a different biological entity with exclusive genetic or phenotypic characteristics that differentiate it from other tumors. Various studies have shown chromosomal abnormalities, aneuploidies, and overexpression of several genes that are not specific to CUPs and which, to the contrary, occur in other malignancies. (10, 16, 20) The mutations and genetic alterations found have been divided into 6 groups (Table 1).
A review of metastatic cancer with unknown primary cancer

CLASSIFICATION

CUP is divided into two groups according to prognosis: favorable (20% of cases) and unfavorable (80% of cases). (2) Average survival time of patients in the favorable group is 12 to 36 months but is only 6 to 7 months for the unfavorable group. (19) Patients in the unfavorable group usually receive empirical chemotherapy with palliative intent, but they still have poor prognoses. Favorable subgroups are the most important, and all efforts are directed toward them. Identification of the subgroup is necessary for treatment specific to the type of cancer which improves prognosis. Some patients may survive for the long-term and even have the possibility of a cure. (25-33).

Favorable Subtypes

- NUT carcinoma (formerly NUT midline carcinoma) of germ cells predominantly affects men. In most cases it presents as mediastinal or retroperitoneal adenopathy. (25, 34)
- Serous peritoneal papillary adenocarcinoma predominates in women and may clinically present as pain, intestinal obstruction, a mass or ascites. (35)
- Single, small and potentially resectable metastasis. (1, 2)
- Metastatic squamous cell carcinoma of the neck that frequently manifests with cervical adenopathy that is unique and is not painful in most cases. (1) It is more frequent in men (80%). (25)
- Poorly differentiated neuroendocrine carcinomas which are usually located in the lymph nodes, liver or bones. (1, 2, 8, 25)
- Adenocarcinomas affecting the axillary lymph nodes in women which behave like breast cancer. (1, 8) Seventy percent of these hidden tumors are detected after mastectomies. (25)
- Isolated inguinal adenopathy whose pathology shows squamous cell carcinoma in which the primary tumor must be found in genital organs. (1, 2)
- Men who have blastic bone lesions with elevated prostate antigen and whose pathology reports shows adenocarcinoma. (25)
- Adenocarcinoma with colon differentiation may present as hepatic metastasis (30%), abdominal adenopathies (51%), peritoneal surface metastasis (50%) or ascites (27%). (25)

Unfavorable forecast subgroups

- Metastatic adenocarcinoma in the liver or other organs.
- Multiple brain metastases with adenocarcinoma or squamous cell differentiation.
- Multiple pleural or pulmonary metastases with differentiation of adenocarcinoma.
- Non-papillary serous adenocarcinoma. (1, 2)
- Poorly differentiated carcinoma.
- Squamous cell carcinoma of the abdominal cavity. (25)

Despite their poor prognoses, researchers have not lost interest in these types of CUPs. To the contrary, they are more enthusiastic every day and strive to investigate and develop multiple tests, including endoscopic studies, functional diagnostic imaging, immunohistochemistry tests, genetic profiles and epigenetic analysis. (6, 7, 36)

When the group of treating specialists has not made the correct assessment of the patient or when there is a possibility of additional investigation, the provisional diagnosis

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**Table 1. Genetic mutations found in the CUP**

<table>
<thead>
<tr>
<th>Chromosomal Alterations</th>
<th>Oncogenes</th>
<th>Tumor suppressor</th>
<th>Molecular Pathway</th>
<th>Suppressor of metastasis</th>
<th>Angiogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneuploidy 70% of patients (1)</td>
<td>HER2 (1, 2)</td>
<td>p53 (1, 8, 23)</td>
<td>c-Met (1, 24)</td>
<td>TIMP-1, (2, 10), MMP2, 9</td>
<td>VEGF (1, 2, 8, 10)</td>
</tr>
<tr>
<td>Chromosomes 1, 6, 7, 11 (2)</td>
<td>EGFR (2, 21)</td>
<td></td>
<td>pMAPK (25)</td>
<td>(1, 2, 10)</td>
<td>THBS1 (2)</td>
</tr>
<tr>
<td></td>
<td>C kit (1)</td>
<td></td>
<td>Notch 3 (25), PTEN (22, 25)</td>
<td>E-cadherina (25)</td>
<td>CD34 (2)</td>
</tr>
<tr>
<td></td>
<td>PDGFR (1)</td>
<td></td>
<td>pAKT, pRPS6 (25), p21 (25)</td>
<td>EMT (25)</td>
<td>HIF1α (25)</td>
</tr>
<tr>
<td></td>
<td>BCL2 (2, 8)</td>
<td></td>
<td></td>
<td>kisspeptin (2)</td>
<td></td>
</tr>
</tbody>
</table>
should be CUP. (13) If the patient has not been evaluated before, s/he must be referred to the oncology department. Indications for diagnostic studies are described below.

**TUMOR MARKERS**

Tumor markers have been studied extensively and are currently considered to have low sensitivity, low specificity, (13) and low positive predictive values (PPV). (25) They are not considered diagnostic and are not recommended, except in the following situations:

- Verification of germline differentiation for cases of NUT carcinoma through tests for human chorionic gonadotropin β subunit (BHCG) (2) and alpha fetoprotein (AFP). (1)
- Test for AFP when hepatocellular carcinoma is suspected. (2) At high titers, this test is specific for this type of tumor, although AFP does not occur in all cases. (9)
- Prostate-specific antigen (PSA) in men with predominantly metastatic bone disease with blastic lesions. (13, 16)
- Carbohydrate antigens (CA) 125 and 15-3 should be interpreted with caution given their limited specificity. (2, 13).

**DIAGNOSTIC PROCEDURES**

**Colonoscopy**

Colonoscopies are not routinely performed because they are not cost-effective while upper gastrointestinal endoscopy has low precision, sensitivity and specificity. (25, 37) Performance of either of these examinations is recommended only for patients with significant symptoms suggesting pathologies in those sites of the digestive tract, in patients who test positive for occult blood in fecal matter, and for patients whose findings from imaging or histopathology are suggestive of colon adenocarcinoma (Figures 1 and 2). (10, 14)

**Figure 1.** Diagnostic diagram of hepatic metastasis with colon adenocarcinoma profile. CDX2: caudal type homeobox 2; CK: cytokeratin.

![Diagram](image_url)
Bronchoscopy

A bronchoscopy is performed when a patient tests positive for thyroid transcription factor 1 and/or CK7 which indicate the possibility of pulmonary origin. (1, 15, 16, 25) For patients with cervical adenopathy whose histology shows squamous cells, panendoscopy consisting of indirect and direct laryngoscopy, bronchoscopy and upper digestive endoscopy should be performed. (17, 38)

Imaging Studies

CT scan of the chest, abdomen and pelvis

In the absence of contraindications, a contrast CT scan of the chest, abdomen and pelvis should be performed as the standard for all patients. (16)

Testicular ultrasound

Testicular ultrasound is indicated for patients with metastatic tumors who have either germinal differentiation or NUT carcinoma. (1, 13)

Mammography

It is a mistake to routinely perform mammographies. (13) They are only indicated when there are symptoms, positive findings from a physical examination, or positive findings from histopathology. They are especially important for patients with axillary adenopathy. (16)

Magnetic resonance imaging (MRI) of the breast

A breast MRI is indicated for CUP with axillary adenopathy when a mammography is normal. A breast MRI can detect up to 70% of hidden tumors. (39)
PET scan with 5-fluorodeoxyglucose

The use of PET scans with 5-fluorodeoxyglucoses is currently limited to patients who have CUP with squamous cells in the neck. (40, 41) For these patients, the scan can help guide the biopsy, determine the extent of the disease, facilitate planning of radiation therapy and help in follow-up. It has been found that PET scans can detect the primary tumor in 30% to 45% of cases even when other imaging studies have not been conclusive. Other studies favor PET scans over panendoscopy for this type of patients. (40, 42) Apart from this indication, the role of PET scans is not clear. (16)

PET scan with Gallium

Another scenario in which a PET scan is useful is a tumor of neuroendocrine differentiation. The best diagnostic image is made by PET/CT DOTA NOC (gallium (68) Ga-labeled [1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid] -1-Nal (3) -octreotide) which is more accurate than Octreoscan, CT scans, and MRI (1, 16, 43, 44). While Octreoscan has a detection rate of 39% for CUP with neuroendocrine differentiation, (45) PET/CT DOTA has sensitivity of 94%, specificity of 86%, PPV of 91%, negative predictive value (NVP) of 92% and accuracy of 91% NOC for CUP with neuroendocrine differentiation. (43)

IMMUNOHISTOCHEMISTRY

Immunohistochemistry is a procedure used by pathologists that is based on the use of antibodies directed against keratins (family of proteins that make up the intermediate filaments expressed in carcinomas), transcription factors, membrane markers, nuclear markers and cytoplasmic markers which are used to define cell differentiation. (46)

It is essential that the pathologist have an adequate sample of tissue and clinical information. Immunohistochemistry finds the primary tumor is found in 25% to 30% of cases, (16) but a recent metaanalysis found that it can detect the primary tumor in up to 65.6% of cases. (47) Despite being the most accepted algorithm, further studies are required to establish whether the identification of the primary tumor in groups without good prognoses or of certain types of tumor for which there are no specific treatments improves patient outcomes. (1, 2, 48)

Classically, it has been suggested that the pathologist follow a diagnostic algorithm for use of immunohistochemistry, and the Pavlidis algorithm is used most frequently. (1) This algorithm has three steps. The first step differentiates lymphoma, sarcoma and melanoma which are managed differently than are carcinomas. The second step differentiates among adenocarcinoma, squamous cell, neuroendocrine, thyroid, renal, hepatocellular and germinal carcinomas, and the third step differentiates among types of adenocarcinomas. This is very important, since adenocarcinomas account for 80% of metastatic CUPs. (49) In the first step (Table 2), lymphoma is differentiated by protein tyrosine phosphatase receptor type C (PTPRC) since lymphomas can be positive for cytokeratins. (2) If it is positive for carcinoma, continue with the second step. (2, 9, 25)

Table 2. First immunohistochemistry step

<table>
<thead>
<tr>
<th>Entity</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td>CD 45</td>
</tr>
<tr>
<td>Melanoma</td>
<td>S100, HMB-45</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>S100, vimentin</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>AE1-AE3 cytokeratin</td>
</tr>
</tbody>
</table>


The second and third steps for differentiation of carcinomas and adenocarcinomas (1, 25) are shown in Tables 3 and 4, respectively.

Table 3. Second immunohistochemistry step

<table>
<thead>
<tr>
<th>Entity</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germinal</td>
<td>Placental Alkaline Phosphatase, OCT4, AFP, BHCG</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>Chromogranin, synaptophysin, CD 56, PGP9.5</td>
</tr>
<tr>
<td>Renal</td>
<td>RCC, CD 10</td>
</tr>
<tr>
<td>Thyroid</td>
<td>TTF1, thyroglobulin</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>CK 5 or CK 6, p63</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>CK 7 or CK 20, PSA</td>
</tr>
<tr>
<td>Hepatic</td>
<td>HepPar1, pCEA canalicular, CD 10, CD 13</td>
</tr>
</tbody>
</table>


Tumors can also be classified according to CK 7 and 20. Four groups of tumors have been created which may suggest a tumor’s origin(Table 5). (9, 50) CKs are not completely specific, so they should not be used to invoke a primary site in the absence of morphological or immunohistochemical support. (46)
MOLECULAR PROFILING

Several gene expression studies available today have had their effectiveness validated through identification of primary tumors in patients with known primary tumors. Their precision range is 85% to 90%. In the case of patients with CUP, a probable primary is identified in 70% to 75% of cases (28) by real-time polymerase chain reaction (PCR) of messenger RNA (mRNA), micro-RNA (miRNA) or microarrays. (2, 9) Nevertheless, their impact on directing treatment according to the outcome of the possible primary remains questionable, and they have not yet been tested in randomized trials. (27, 28) A prospective non-randomized phase II study of 252 patients suggests that survival may be improved with these studies, particularly for patients with tumors sensitive to chemotherapy whose outcomes have been better than those of historical cohorts. Additional caution should be exercised since these studies are susceptible to biases and confounding variables given the great heterogeneity of unknown primaries. (16)

Currently, a phase III clinical trial is being conducted in Europe to compare the benefit of targeted therapy by molecular profile study against empirical treatment (NCT01540058). (27)

Molecular profiling may be indicated when immunohistochemistry and routine examinations have failed to establish a primary tumor even though these studies should not be performed routinely in all patients according to international guidelines. (28, 48, 51)

TREATMENT

The treatment of choice for patients in subgroups with unfavorable prognoses or whose primary tumor has not been established is palliative chemotherapy based on platinum and taxane. (2) Other chemotherapy schemes have been studied, but a review conducted in 2000 found no evidence of superiority of any chemotherapy regimen which includes platinum salts, taxanes or new generation cytotoxic agents (gemcitabine, vinca alkaloids or irinotecan). (27, 52, 53) Response rates are around 20% with average survival times of 6 to 7 months with or without chemotherapy. (1, 25) However, other therapeutic objectives are valued in oncology. These include quality of life related to health, control of symptoms, indirect results, safety and results perceived by patients. (54) Modest prolongation of survival and palliation of symptoms with preservation of quality of life is the real goal in these patients although remission has been reported in rare cases. (27)

On the other hand, favorable subgroups primarily receive regional treatment with surgery, radiation therapy and/or chemotherapy. (1) Survival is similar to that for patients with metastatic tumors of the same origin, (48) and treatments are also similar.

Poorly differentiated NUT carcinomas

NUT carcinomas receive platinum chemotherapy with schemes similar to those used in extra-gonadal germ cell tumors. Complete responses are achieved in 20% cases, partial responses are achieved in another 25%, of cases with average times survival of 12 months. Cure rates have been reported to be from 10% to 20%. (1, 8, 55)

Adenocarcinomas in women with axillary lymph node involvement

Patients with axillary adenopathy are treated as breast cancer patients and may require complete axillary lymph node dissection, breast mastectomy(ies), radiation therapy, adjuvant chemotherapy or hormone therapy. When indicated, the use of trastuzumab (HER2 antibodies) is appropriate. The five year survival rate is 72%, and the ten year survival rate is 60%, (1, 18) but relapses occur in up to 55% of the patients who do not receive local therapy. (25)
CONCLUSION

A metastatic tumor with an unknown primary tumor causes fear in the patient and in the doctor, but this review provides doctors with a guide for the initial approach, subsequent classification, and indications for complementary studies. In addition, it highlights recent scientific advances that focus on new methods of diagnosis and directed treatments.

REFERENCES


