Cancer of Unknown Primary

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INTRODUCTION

Cancer of unknown primary (CUP) is defined as metastatic disease without an identifiable primary site despite comprehensive clinical evaluation. The incidence of CUP has been reported to be 3% to 5% of all malignancies, representing 30,000 cases each year. This incidence is similar to that of pancreatic cancer, making CUP the eighth most common cancer diagnosed annually in the United States. International registries have reported a similar incidence (2.3%–7.8% of malignancies).

CUP is an unsettling diagnosis for both patients and oncologists. Patients desire certainty and are uncomfortable with the “unknown” nature of their disease. From an administrative standpoint, CUP is challenging because compensation from insurance companies for diagnostic studies and therapy is based on diagnostic codes. Furthermore, oncologists are better able to recommend therapy and prognostic information once a specific diagnosis is attained. Management of CUP, therefore, poses an emotional as well as scientific challenge.

The primary goal in evaluating patients with CUP is to define subgroups that are potentially curable or treatable malignancies. Diagnostic work-up should also attempt to evaluate for a primary tumor comprehensively without exposing patients to unnecessary invasive testing. This review outlines the clinical and pathologic features of CUP, proposes a systematic diagnostic evaluation, and reviews the treatments for CUP.

PATHOGENESIS

The central scientific question in CUP is why are metastatic foci of disease present when the primary tumor is not clinically evident? Several theories attempt to explain this atypical presentation in neoplasia. One theory involves regression of the primary lesion. Empiric evidence for this theory includes stage III metastatic melanoma in which nodal disease is present although no primary lesion can be identified. In some instances, there may be a remote history of a “spontaneously” regressing pigmented skin lesion. Additionally, anecdotal evidence of testicular scarring has been noted in patients with metastatic germ cell tumors without an obvious primary mass.

Another possible explanation for metastasis without a known primary may be that the primary site is present microscopically, evading clinical detection by standard imaging or biopsy (occult primary). For example, patients with advanced head and neck cancer may present with cervical lymphadenopathy and no evidence of a primary tumor. In this case, there is a disconnect between the bulk of the primary tumor and metastatic foci.

A third theory challenges the traditional belief that metastasis is a late development in tumor evolution. Supportive evidence for this theory exists through the use of gene expression profiling data. Microarray study of breast cancer cell lines identified 4 highly overexpressed genes that are associated with the ability to metastasize to bone as well as with a poor-prognosis signature. These genes are present in primary tumors, which suggests that metastatic potential may be present at the inception of oncogenesis and that the forces controlling the survival of the primary tumor and metastases operate independently.

Another proposed explanation for differential survival of the primary tumor and metastases is “angiogenic incompetence.” According to this theory, primary tumors are unable to induce neoangiogenesis adequately to survive and grow. Tumor cells undergo apoptosis and gene instability at a high rate because of angiogenic incompetence. Some cells may evade apoptosis, spreading to visceral organs or lymph nodes, and lie dormant. These metastatic cells either utilize local vasculature and nutrient supply to survive and grow or develop the ability to induce angiogenesis via clonal evolution.

Finally, a number of genetic mutations are commonly found in CUP, in particular, the 1p chromosomal deletion. One hypothesis is that a tumor suppressor gene for metastasis may be located on chromosome 1p, thus resulting in a high propensity for tumors to metastasize. Such a gene has not yet been identified, however.
A 64-year-old woman presents to her primary care physician with a 3-week history of productive cough. She denies fevers, chills, night sweats, weight loss, hemoptysis, or hoarseness. Her past medical history is notable for chronic obstructive pulmonary disease, hypertension, depression, hypothyroidism, former smoking (> 80 pack-years), lumpectomy for ductal carcinoma in situ, and benign colonic polyps. Her family history is notable for her mother dying of stomach cancer in her sixties, her brother dying of colon cancer in his sixties, and her sister dying of lung cancer in her forties. Her remaining 4 siblings and her 2 children are healthy.

Physical examination reveals a mildly obese woman in no acute distress with hyperinflated lungs and no other focal findings (ie, normal breast examination, no evidence of lymphadenopathy, and a negative stool guaiac test). Laboratory studies reveal a normal complete blood count (hematocrit, 42%), serum chemistries, and liver function tests. Results for serum tumor markers reveal carcinoembryonic antigen (CEA) is minimally elevated at 3.7 ng/mL (normal, < 3.0 ng/mL), but cancer antigen (CA)-125 level is normal.

Chest radiography demonstrates right hilar prominence. Chest CT reveals a 1.8 x 1.4-cm right hilar lymph node and subcentimeter mediastinal nodes (Figure 1). There are no associated pulmonary nodules or parenchymal opacities, and there is no pleural effusion. PET reveals fluorodeoxyglucose (FDG) uptake in the right hilar lymph node only. Mammography is negative for a breast lesion.

Figure 1. Imaging results for the case patient. Chest computed tomography (A), standing positron emission tomography (PET) (B), cross-sectional PET (C), and composite PET images (D) reveal enlarged right hilar lymph node (arrowheads) and mediastinal nodes (arrows); fluorodeoxyglucose uptake is seen in C and D.

• What is the typical clinical presentation of CUP?

Most patients with CUP come to medical attention due to symptoms of metastatic disease, which can
manifest either as local symptoms from metastases, (eg, pain) or as generalized constitutional symptoms (eg, anorexia, weight loss, fatigue, fever). Patients usually present in the sixth decade. There is a slight male predominance. Approximately 60% of CUP patients present with more than 1 site of involvement. The most common sites are lymph node (37%), liver (30%), lung/pleura (12%–39%), and bone (10%–28%). At presentation, 24% of patients have disseminated disease.

The patient presented here is typical in that she is age 64 years. However, atypical features of her presentation are the sole involvement of a hilar lymph node and the paucity of symptoms, making this an almost incidental finding.

- **What is the appropriate evaluation for patients with CUP?**

Patients who present initially with metastatic disease should have a clinical evaluation aimed at identifying a primary site as well as defining the extent of disease. Standard evaluation for CUP includes history and physical examination, laboratory studies, imaging, and biopsy with pathologic testing. Approximately 20% to 25% of patients will have a primary site identified during their course. At necroscopy, 50% to 70% of patients will have a primary identified, usually lung, pancreas, kidney, or bowel. For the remaining 30%, no primary site is ever identified.

### Table 1. Serum Tumor Markers That May Indicate the Primary Site

<table>
<thead>
<tr>
<th>Marker</th>
<th>Primary Tumor(s)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>Prostate cancer</td>
<td>Specific and sensitive for prostate cancer in cases of CUP if confirmed by immunohistochemical markers</td>
</tr>
<tr>
<td>AFP</td>
<td>Nonseminomatous germ cell tumor, hepatoma</td>
<td>Especially useful in the diagnosis of extragonadal germ cell cancer (male patients with midline lymph node involvement); elevated in many other cancers as well</td>
</tr>
<tr>
<td>β-HCG</td>
<td>Nonseminomatous germ cell tumor, gestational trophoblastic disease</td>
<td>As above</td>
</tr>
<tr>
<td>CEA</td>
<td>Colorectal cancer</td>
<td>Elevated in many other tumors; not generally helpful in diagnosing the primary site unless the patient has isolated liver metastasis; helpful in following treatment response when elevated</td>
</tr>
<tr>
<td>CA-125</td>
<td>Ovarian cancer</td>
<td>Elevated in many benign conditions as well as other cancers (eg, lung); useful in women with peritoneal carcinomatosis</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>Pancreatic and biliary tract cancers</td>
<td>Elevated in 80%–90% of pancreatic cancers, 70% of biliary cancers; also elevated in other tumors</td>
</tr>
<tr>
<td>CA 27.29</td>
<td>Breast cancer</td>
<td>Elevated in two thirds of advanced breast cancer</td>
</tr>
</tbody>
</table>


AFP = α-fetoprotein; CA = cancer antigen; CEA = cancer embryonic antigen; β-HCG = β-human chorionic gonadotropin; PSA = prostate-specific antigen.

Laboratory Studies

Laboratory studies should include a complete blood count and chemistry panel including liver function tests. Assessing for serum tumor markers may be helpful in determining the primary site of involvement in some cases of CUP (Table 1). Prostate-specific antigen (PSA) levels should be assessed in men with CUP as elevated levels suggest occult prostate cancer. Male patients, especially young men with predominantly midline lymphadenopathy, should have germ cell tumor markers drawn at presentation, specifically β-human chorionic gonadotropin (β-HCG) and α-fetoprotein (AFP). Useful markers in patients with predominantly liver metastasis include AFP to evaluate for hepatoma and CEA for metastatic colon cancer. Elevation of CA-125 in women with predominantly peritoneal disease raises suspicion for ovarian cancer.

Additional indications for the use of serum tumor markers include prognostic information and to monitor treatment response. Lactic dehydrogenase (LDH) is commonly ordered as part of the diagnostic evaluation. It is elevated in lymphoma as well as many other malignancies. LDH is a strong prognostic factor in CUP (see “Prognostic Factors”). The role of serum tumor markers have not been clearly established, and routine testing
of serum tumor markers outside of the special circumstances discussed here is not recommended.

**Imaging Studies**

Imaging in CUP routinely includes a chest radiograph and abdominal and pelvic CT. Chest CT has been examined in a retrospective study of patients with brain cancer who had a chest radiograph followed by CT scan. CT detected primary lung lesions in 38% of patients whose chest radiography results were negative. In addition, chest CT may be valuable in defining mediastinal metastatic disease burden and to facilitate biopsy, thereby changing management. In 1982, a retrospective review revealed that abdominal and pelvic CT detected primary tumors in 45% of patients studied. In general practice, chest, abdominal, and pelvic CT are all performed.

Mammography is recommended in women with CUP to evaluate for occult breast cancer. The routine use of PET scans has not been recommended routinely in CUP evaluation. PET findings have not translated to changes in clinical management with the exception of head and neck tumors. In patients with head and neck CUP, PET scans have identified a primary lesion in 20% to 30% of patients. One study of cost-effectiveness suggests a utility to PET only if it replaces all other conventional diagnostics. Further analysis of the benefit of PET in the setting of limited monetary resources are under investigation. The use of PET scan in the case patient represents an institutional bias and reflects changing clinical practice. It is uncertain whether the routine use of PET scan will be accepted and reimbursed in widespread clinical practice.

- **What is pathologic testing in CUP?**

  A tissue biopsy is required in most cases to characterize the pathology of CUP and is obtained by fine needle aspiration, core needle biopsy, or excisional biopsy. In cancers with primary sites, cancer-specific treatment is directed by a definitive pathologic diagnosis and staging work-up. In CUP, this information is notably absent. Thus, the pathology of the metastatic disease guides treatment decisions.

  The initial goal of pathologic testing should be aimed at classifying the light microscopic appearance of the tumor into 1 of the 4 following categories of CUP: 1) poorly differentiated malignant neoplasm (PDMN), 2) poorly differentiated carcinoma and/or adenocarcinoma (PDC/PDA), 3) well- or moderately differentiated adenocarcinoma, and 4) squamous cell carcinoma. Clinical studies have used this classification system in order to describe natural history, define appropriate pathologic testing, and to guide therapy. The goal of further pathologic testing is to identify potentially treatable or even curable disease, such as distinguishing between non-Hodgkin’s lymphoma and carcinoma, or identifying tumors with specific treatments, such as hormone manipulation in breast or prostate cancer. Additional available pathologic testing includes immunoperoxidase staining, electron microscopy, and genetic testing with chromosomal analysis. The utility of these additional tests should be discussed between the clinician and pathologist as not every patient should undergo all of these tests. Further pathologic work-up is most useful in PDMNs and PDC/PDA. Approximately 20% of CUP patients can be classified into a subtype with further pathologic testing.

  **Light Microscopy**

  Specific clinicopathologic features of the 4 major classes of light microscopy are discussed below.

  **Poorly differentiated malignant neoplasm.** Approximately 5% of CUP cases involve tumors that are identified as PDMNs, which lack the appearance of a definable histology. The differential diagnosis of PDMN includes carcinoma, lymphoma, melanoma, neuroendocrine tumor, and sarcoma. The pathologic evaluation should be aimed at distinguishing between these entities by using ancillary pathologic testing (discussed below). Between 35% and 65% of cases will ultimately determined to be lymphoma upon further testing. The clinical behavior of these tumors varies considerably from highly curable to unresponsive.

  **Poorly differentiated carcinoma/adenocarcinoma.** PDC/PDAs represent 30% of CUP. These tumors generally present in younger patients and are associated with a rapid progression of symptoms. Despite their poor differentiation, these tumors are considered to be chemosensitive and thus have a better prognosis than more well-differentiated tumors. Favorable pathologic subtypes of PDC/PDA include patients with extragonadal germ cell syndrome, predominantly lymph node involvement, primary peritoneal carcinomatosis, and neuroendocrine subtype (see “Favorable Clinical Subsets”).

  **Adenocarcinoma.** The most common subtype of CUP are adenocarcinomas, well- or moderately differentiated,
which are found in 60% of patients. Adenocarcinomas are associated with a poor response to therapy and a short median survival of 3 to 4 months. Specific pathologic subsets include papillary features associated with ovarian cancer, signet ring cells suggestive of gastric cancer, and staining for estrogen and progesterone receptors (ER/PR), human epidermal growth factor 2 (Her-2/neu), and gross cystic disease fluid protein (GCDFP) in breast cancer or prostate-specific antigen (PSA) in prostate cancer. Clinopathologic groups with specific treatments include women with peritoneal carcinomatosis, which is considered ovarian cancer, and women with isolated axillary lymphadenopathy, which is classified as stage II breast cancer.

Squamous cell cancer. On light microscopy, 5% of patients with CUP have squamous cell cancer. As with well-differentiated adenocarcinomas, these tumors have a poorer prognosis and response to chemotherapy than PDC/PDA tumors. Most squamous cell cancers are thought to be metastatic non–small cell lung cancer. Exceptions include squamous cell cancers involving the cervix or supraclavicular lymph nodes (treated as head and neck primary) and tumors in the inguinal lymph nodes (representing anorectal or genital primary). These 2 groups of squamous cell cancers have a better prognosis than squamous cell cancer at other sites.

Immunohistochemistry

Immunoperoxidase staining uses antibodies directed to specific cell components and products, labeled with peroxidase. Immunohistochemistry is limited by the lack of both sensitivity and specificity of any 1 stain as well as variability of technical skill in both preparation and interpretation of these results. In addition, tissue from a fine needle aspirate may be limited in quantity, posing a technical barrier to extensive testing. Finally, the cost of extensive immunoperoxidase staining precludes the exhaustive evaluation of immunohistochemical stains on every tumor. Pathologists help direct the rational use of immunoperoxidase testing.

Carcinomas or epithelial malignancies generally stain positive for cytokeratins. Pancytokeratin testing, also called AE1/AE3 staining, can establish the epithelial origin of the tumor. Further specific cytokeratin testing may suggest the location of the tumor on the basis of the anatomic distribution of that particular cytokeratin. By staining for several cytokeratins as well as other immunohistochemical markers, a tumor-specific pattern helps to limit the possible differential diagnosis. The 2 most common cytokeratins used initially are CK7 and CK20. CK7 is expressed in lung, breast, endometrium, urothelium, stomach, pancreatobiliary tract, and skin adnexal glands. CK20 is found in carcinomas of the gastrointestinal and pancreatobiliary tracts, urothelium, and mucinous ovarian tumors. Using these 2 cytokeratins, a particular CK7/20 phenotype is identified that suggests a differential diagnosis.

Once CK7/20 phenotype testing is performed, additional immunohistochemical staining may further define the tumor subtype. For example, lung cancer often stains positive for thyroid transcription factor 1 (TTF-1). The combination of CK7+, CK20+, and TTF-1 positive, therefore is highly suggestive of a lung primary. Breast cancer typically stains positive for ER/PR as well as GCDFP. Prostate cancer is suspected when PSA staining is positive.

Figure 2. Differential diagnosis based on cytokeratin CK7/CK20 immunophenotype. (Adapted from Varadhachary GR, Abbuzzese JL, Lenzi R. Diagnostic strategies for unknown primary cancer. Cancer 2004;100:1780. Copyright © 2004 American Cancer Society. Reprinted with permission from Wiley-Liss, Inc.)
Other tumor types stain positive for specific immunohistochemical markers. The diagnosis of lymphoma is suggested by CD45+ (also called leukocyte common antigen staining).29 Further stains for CD20, CD5, CD3, and CD10 can help to further categorize lymphomas. Neuroendocrine tumors stain for neuron specific enolase,31 chromogranin A,31 and synaptophysin.32 Melanomas are suspected by desmin, vimentin, and c-KIT staining. Germ cell tumors are suspected with β-HCG or AFP staining. Sarcomas stain for S-100, vimentin, and desmin.1 One resource which allows practitioners to compare the immunohistochemical data for a specific sample against the published data is www.immunoquery.com.

Electron Microscopy

Electron microscopy reveals specific ultrastructural components of cells, which may demonstrate pathognomonic features of certain cell types. Adenocarcinomas have prominent inter- and intracellular lumina as well as surface microvilli. Squamous cell cancers are suggested by prominent desmosomes and bundles of prekeratin filaments. Neuroendocrine cancers can be diagnosed by the presence of neurosecretory granules. Unfortunately, electron microscopy is not widely available and is also costly. Electron microscopy should be reserved for cases where results would clearly alter management.1,2,13

Genetic Testing

Genetic testing currently has a limited role in the evaluation of CUP.1,39 When lymphoma is suspected, specific genetic testing can be performed to identify immunoglobulin gene rearrangement or T-cell receptor clonality. Specific translocations associated with certain tumors may yield a diagnosis. Isochromosome 12p suggests a germ cell tumor, especially in a male with midline disease.39 Translocation of (11;22) is suggestive of primitive neuroendocrine tumor (PNET) or Ewing’s sarcoma.1,13 Many tumors have a deletion of 1p as was discussed earlier (see “Pathogenesis”). DNA microarrays have been used in research settings and may be available in the future in clinical settings.40–42 DNA microarrays may help predict tumor location by specific gene expression patterns. This information will only be useful, however, if clinical outcomes are impacted by site-specific treatment.

CASE CONTINUED

The patient undergoes transbrional biopsy of the lymph node, which is positive for metastatic carcinoma. Immunoperoxidase staining shows positive staining for CK7 and TTF-1 as well as negative staining for CK20, ER/PR, and GCDFP. Flexible bronchoscopy reveals no bronchogenic lesions, and cervical mediastinoscopy with lymph node sampling is negative for malignancy. The patient is referred to an oncologist for further evaluation and treatment.

- What is the treatment of CUP?

TREATMENT

Most patients with CUP progress extremely quickly and have an overall poor prognosis, with reported median survival rates ranging from 3 to 11 months and an average survival of 6 to 9 months.1,13,14,43 One-year and 5-year survival rates are 25% and 10%, respectively.14 The behavior of the disease is often aggressive with rapid development of disseminated disease. Although the treatment of CUP has been studied for over 40 years, most data are reported as single- or few-institution case series, and there are very few randomized phase trials. The heterogeneity of the inclusion criteria makes interpretation of results and generalization challenging. However, several favorable subsets of CUP have been identified. Treatment of CUP is therefore divided into treatment of favorable (Table 3)1,15,32 and unfavorable subsets (Table 4).1,15

TREATMENT OF FAVORABLE CLINICAL SUBSETS

Extragonadal Germ Cell Syndrome

Male patients with predominantly midline tumor are suspected of having a metastatic germ cell tumor.44,45 The clinical criteria are inclusion of 2 of the following 5 features: age younger than 50 years; midline disease...
involving the retroperitoneum, mediastinum, and pulmonary nodules; short symptom interval and rapid growth; elevated β-HCG and/or AFP; and response to chemotherapy/radiation. These patients should be treated with platinum-based therapy. Supportive genetic testing includes the presence of isochromosome 12p.

**Peritoneal Carcinomatosis in Females**

Female patients with adenocarcinoma and PDC/PDA predominantly involving the peritoneum are treated as having International Federation of Gynecology and Obstetrics stage III ovarian cancer. Additional suggestive pathologic features include papillary histology and the presence of psammoma bodies. This presentation is more common in patients with a family history of ovarian cancer as well as patients who carry *BRCA-1* mutations. Clinically, the patients have elevated CA-125. They may also present with pleural effusions. The recommended treatment for these patients is cytoreductive surgery via laparotomy and oophorectomy with adjuvant taxane/platinum-based chemotherapy. Median survival is 16 months (range, 11–24 months), with 16% of patients surviving beyond 2 years.

**Isolated Axillary Lymphadenopathy in Females**

Female patients with isolated axillary lymphadenopathy are treated as having stage II/III breast cancer as defined by the American Joint Committee on Cancer guidelines, depending on the number of nodes (NI versus N2/N3 disease). Patients are evaluated with mammography and breast MRI for occult primary. Modified radical mastectomy reveals a primary breast cancer in 44% to 80%. In patients with a negative breast MRI, the role of mastectomy can be questioned. Serum markers for breast cancer (CA 15-3, CA 27-29) may provide additional evidence for occult breast cancer. These patients should be treated with chemotherapy, radiation, and hormonal therapy depending on ER/PR status. The 5-year survival rate is 75% and 10-year survival rate is 60%.

**PSA-Positive Lesions**

Male patients with PSA staining or elevated PSA should be treated as metastatic prostate cancer with hormonal therapy. Patients with predominantly osteoblastic bone lesions have also been treated in this fashion.

**Squamous Cell Cancer with Cervical/Supraclavicular Lymphadenopathy**

Patients with cervical or supraclavicular lymphadenopathy with squamous cell histology are treated as head and neck primary tumors. PET has been demonstrated to locate occult lesions in up to 30% of these patients. Patients are treated with surgery and/or radiation primarily. Surgery with radical lymph node dissection yields a primary lesion in 20% to 40% of patients. Long-term disease-free survival with aggressive therapy is 10% to 15%. The role of concurrent or induction chemotherapy as well as the role of cetuximab is under investigation. The 5-year survival rate is 35% to 50%.

### Table 3. Chemotherapy Regimens for Favorable Subtypes of Cancer of Unknown Primary

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extragonadal germ cell syndrome</td>
<td>Advanced testicular cancer, platinum-based chemotherapy</td>
</tr>
<tr>
<td>Peritoneal carcinomatosis</td>
<td>FIGO stage III ovarian cancer</td>
</tr>
<tr>
<td>Isolated axillary lymphadenopathy (female)</td>
<td>Stage II breast cancer</td>
</tr>
<tr>
<td>PSA-positive lesion</td>
<td>Prostate cancer, hormonal therapy</td>
</tr>
<tr>
<td>Cervical lymphadenopathy (with squamous cell cancer)</td>
<td>Stage IV head and neck cancer</td>
</tr>
<tr>
<td>Inguinal lymphadenopathy (squamous cell cancer)</td>
<td>Anorectal or genitil primary, surgery ± radiation</td>
</tr>
<tr>
<td>Neuroendocrine features (small cell cancer)</td>
<td>Small cell cancer treatment (platinum/etoposide)</td>
</tr>
<tr>
<td>Single site of disease</td>
<td>Consider resection or radiation</td>
</tr>
</tbody>
</table>


### Table 4. Outcomes of Chemotherapy Regimens for Unfavorable Subtypes of Cancer of Unknown Primary

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Response Rate, %</th>
<th>Survival, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin/vinblastine/etoposide</td>
<td>40–57</td>
<td>5–16</td>
</tr>
<tr>
<td>Cisplatin or carboplatin/etoposide ± other agents</td>
<td>20–30</td>
<td>5–11</td>
</tr>
<tr>
<td>Cisplatin/gemcitabine</td>
<td>42</td>
<td>12 (22% of patients alive) at 1 yr</td>
</tr>
<tr>
<td>Cisplatin/irinotecan</td>
<td>25</td>
<td>12 (23% of patients alive)</td>
</tr>
<tr>
<td>Carboplatin/paclitaxel, ± other agents</td>
<td>20–48</td>
<td>8–13</td>
</tr>
<tr>
<td>Docetaxel/carboplatin or cisplatin</td>
<td>22–33</td>
<td>6–8</td>
</tr>
<tr>
<td>Docetaxel/gemcitabine</td>
<td>40</td>
<td>NA</td>
</tr>
</tbody>
</table>

Squamous Cell Cancer Involving the Inguinal Nodes

Patients with inguinal lymphadenopathy and squamous cell histology represent occult anorectal or genital primary lesions. Therapy includes lymphadenectomy and radiation. With surgical resection, up to 50% of patients enjoy long-term survival. The role of combined modality therapy is under study.

CUP with Neuroendocrine Features

Patients with neuroendocrine features have a favorable prognosis in general. Neuroendocrine histology can be divided into well-differentiated or low-grade histology, poorly differentiated carcinoma with neuroendocrine features, and high-grade or small cell subtype. Low-grade neuroendocrine tumors have an indolent behavior, akin to carcinoids or islet cell tumors. They generally involve the bones and liver and may be associated with paraneoplastic syndromes (e.g., carcinoid syndrome, VIPoma, glucagonoma, Zollinger-Ellison syndrome). Patients with low-grade neuroendocrine carcinoma are treated if symptoms or clinical progression, usually with somatostatin analogues. Poorly differentiated neuroendocrine carcinoma and small cell histology are treated with carboplatin, paclitaxel, and etoposide with a response rate as high as 50% to 75%. Median survival is 12 to 35 months with poorly differentiated features and relapse is common.

Single Site of Disease

Patients with single sites of involvement generally have a better prognosis. Treatment with local therapy, either surgery or radiation, should be entertained. The efficacy of therapy depends on both severity of the disease at presentation and the site of disease.

TREATMENT OF UNFAVORABLE CLINICAL SUBSETS

By default, patients who do not fall into one of the favorable clinical subsets fall into the unfavorable clinical subset category. Nearly every cytotoxic agent has been tried at some point to treat CUP. Pavlidis et al report the overall response rate to single-agent 5-fluorouracil, cyclophosphamide, mitomycin-C, nitrosoureas, and vincristine to be less than 10%. Doxorubicin increased the response rate to 20% to 25% but had no impact on survival (4–6 months).

Since the 1980s, Hainsworth and Greco have studied platinum-based chemotherapy for treating CUP. They reported their experience in 1986 in a study of 62 patients treated with cisplatin, vinblastine, and bleomycin. Fifteen patients (22%) had complete responses with 9 (13%) long-term responses remaining tumor-free at 8 years, and 23 (34%) had partial responses, making an overall response rate of 56%. Cumulative results of 220 patients (median age, 39 years) treated with cisplatin-based therapy resulted in a 63% overall response rate with 26% complete response and 16% long-term survivors, yielding a 10-year actuarial survival rate of 16%. These results were critiqued for an enriched population of CUP patients by including only patients with poorly differentiated histologies, younger patients, and a high proportion of patients with PDC of midline origin (suggestive of extragonadal germ cell syndrome). Subsequent studies of platinum-based therapies have shown more modest responses, generally a 20% to 40% overall response rate, with median survival of 5 to 11 months.

The addition of taxanes to platinum-based therapy in unfavorable patient subsets has improved responses and survival. Hainsworth et al reported the results of a phase II study of 53 patients treated with paclitaxel, carboplatin, and etoposide in 1997. Patients diagnosed with a favorable CUP subset were excluded from the trial. The overall response rate was 47% with 7 (13%) complete responses, resulting in a median survival of 13.4 months. The combination was deemed safe, with few grade IV toxic complications. This study also demonstrated an equivalent response rate for adenocarcinomas and poorly differentiated histologies (45% versus 48%; P = not significant), suggesting that the regimen was effective for traditionally unfavorable subsets of patients. Updated results in 2000 confirmed similar results: out of 71 patients, 48% had major responses and 15% had complete responses, with a median survival of 11 months and no difference in response or survival between histologic subtypes.

Briasoulis et al studied a regimen of carboplatin plus paclitaxel in a multicenter trial that included patients with peritoneal carcinomatosis. The overall response rate was 38.7% and median survival was 13 months. Response varied by clinical subtype. In patients with predominantly pleural/nodal disease, response rates were 47.8% and median survival was 13 months. In patients with peritoneal carcinomatosis, the overall response rate was 68.4% and median survival 15 months. Patients with visceral or disseminated disease had a 15.1% response rate and median survival of 10 months. The results confirmed that peritoneal carcinomatosis was a favorable subtype and that lymph node predominant as well as pleural disease connotes a better prognosis.

The addition of gemcitabine to taxane/platinum-based combination therapy has also been studied. The results of 120 patients treated with gemcitabine, carboplatin, and paclitaxel followed by weekly paclitaxel were reported in 2002. Patients with a favorable clinical presentation were excluded. Of the remaining patients,
25% had an objective response. Median survival was 9 months, with actuarial survival at 1 year of 42% and at 2 years of 23%. The addition of maintenance paclitaxel did not improve response. This regimen was deemed to be safe with an acceptable response rate in an unfavorable group of patients.\(^\text{30}\)

Subsequent studies of gemcitabine-containing regimens have been reported. Balana et al\(^\text{31}\) studied the combination of cisplatin, etoposide, and gemcitabine in 2003. Overall response was seen in 11 of 30 patients (36.6%), with 13.3% complete responses. Median survival was 7.2 months. In 2004, gemcitabine and docetaxel (platinum-sparing combination) were evaluated in a study that included 35 patients. The overall response rate was 40% with 1 complete response, a rate that was achieved despite a 16% rate of withdrawal due to toxicity.\(^\text{32}\) Whether this combination is safe and active is debatable.

In 2003, Culine et al\(^\text{33}\) reported the results of a randomized phase II trial of 78 patients who received either gemcitabine with cisplatin (GC) or irinotecan with cisplatin (IC). Objective responses were observed in 21 patients (55%) in the GC arm versus 15 patients (38%) in the IC arm. Withdrawal due to toxicity was experienced in 7 patients in the GC arm and 8 patients in the IC arm (total withdrawal due to toxicity, 25%). Median survival was 8 months in the GC arm and 6 months in the IC arm. The authors concluded that both regimens are active, though with toxicity. Neither arm was deemed superior despite the apparent efficacy of GC. The next randomized study planned by the French National group is a trial of GC versus cisplatin alone.

**Summary**

The optimal regimen for patients with CUP is not known. Patients receiving platinum-based chemotherapy have improved response rates and survival compared with historical controls. It is unknown whether chemotherapy truly benefits patients as compared with supportive care or other treatments. Randomized clinical trials are needed to demonstrate the true benefit of chemotherapy as well as the optimal regimen.

**CASE CONTINUED**

The patient was treated with chemoradiation on the presumption that her disease represented locally-advanced non–small cell lung cancer. She was treated with weekly carboplatin/paclitaxel concurrent with 6 weeks of radiation. In addition, she received 3 cycles of carboplatin and paclitaxel at standard doses. She has achieved a partial remission by imaging at over 8 months’ follow-up (Figure 3).

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**PROGNOSTIC FACTORS**

Despite the advances in treatment of CUP, the overall response to chemotherapy and survival remains grim. Several studies have looked at identifying clinical features that provide prognostic information. In 1997, Lenzi et al\(^\text{34}\) reviewed data obtained from 977 patients with CUP to determine prognostic variables. Survival rates were highest in patients with predominantly lymph node involvement and limited sites of involvement (1–2 metastatic sites). Patients with the worst survival rates included male patients without lymph node involvement and women over age 64 years.

In 2002, Culine et al\(^\text{35}\) examined prognostic variables in 150 patients treated for CUP. Patients in favorable clinical subsets were eliminated. The clinical features that predicted for overall survival included good performance status (Eastern Cooperative Oncology Group Stage 0–1) and the absence of liver metastases. Biochemical predictors of poor outcome in a univariate analysis included elevated alkaline phosphatase, LDH, CEA, and CA-125. A multivariate analysis of clinical and biochemical parameters identified performance status and LDH as the strongest predictors of outcome. The median survival for patients with good performance status and normal LDH was 12 months versus 7 months in patients with poor performance status and elevated LDH. The 1-year survival was 53% and 23%, respectively.\(^\text{35}\)

Finally, Seve et al\(^\text{36}\) examined the Northern Alberta Cancer Registry of patients treated for CUP from 2000 to 2003, with the goal of studying patients treated at both tertiary cancer centers as well as in the community setting. Patients who were not evaluated at a cancer center were older (~10 years), had more comorbidities as well as poorer performance status, were less frequently treated with chemotherapy, and had a worse prognosis. Clinical variables that predicted for overall survival included good performance status and absence of liver metastasis. In addition, the researchers looked at the correlation of performance status and comorbidities in predicting survival. Patients who had more comorbidities had a worse prognosis. It was unclear whether comorbidities posed a barrier to treatment or reflected more symptomatic disease and thus a poor performance status. Also, factors predicting treatment were examined. Patients with fewer comorbidities and with lymph node/pleural metastasis were more likely to receive chemotherapy. Variables associated with patients who were referred to a tertiary cancer center were younger age, few comorbidities,
good performance status, and limited sites of metastatic disease. It remains unclear whether the patients who are older, with multiple comorbidities, worse performance status, and more disseminated disease, were undertreated and thus had a worse prognosis.

**Summary**

After identification of favorable clinical subsets, the strongest prognostic factors appear to be age, performance status, extent of disease (number of metastatic sites), presence of liver metastasis, and certain biochemical serum markers, such as LDH. In addition, patients who have never smoked have a favorable prognosis as opposed to smoking patients.²⁸

**CASE CONCLUSION**

The case patient had a good performance status at the outset and limited number of metastatic sites with lymph node predominance. However, she did have multiple comorbidities and was a former smoker. Her response to therapy and good prognosis thus far have been encouraging.

**REFERENCES**

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