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Review article

Diagnosis and management of metastatic neoplasms with unknown primary

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ABSTRACT

In cancer of unknown primary (CUP), metastases are clinically and histologically confirmed, but the primary tumor site remains elusive after extensive work-up. CUPs make up for 2–3% of all epithelial malignancies. The two prevailing histologies are adenocarcinomas and undifferentiated carcinomas, whereas squamous cell carcinomas, neuroendocrine carcinomas and rare histologies account for the remaining 10%.

The diagnostic work-up in CUP relies strongly on a detailed immunohistological (IHC) analysis in order to characterize the tumor type, nowadays aided by molecular techniques. Diagnostics also include a thorough clinical examination, a basic lab draw with the most relevant tumor markers, and cross sectional imaging. Additional PET-CT is recommended in cervical lymph nodes suggestive of head and neck cancer and in limited metastases potentially treatable in curative intent.

As for treatment, it is paramount to identify patients who fall into one of the six well defined "favorable" subset categories, namely extragonadal germ cell tumors, adenocarcinoma with isolated unilateral axillary lymph nodes in female patients, squamous cell carcinoma with neck lymph nodes, squamous cell carcinoma with inguinal lymph nodes, serous papillary peritoneal carcinomatosis in females and blastic bone metastasis in males with elevated PSA. These subsets are distinct both regarding the required treatment and the comparably favorable prognosis. Within the remaining "unfavorable" group, patients of colon and renal cancer type should be identified based on IHC and clinical picture, since the prognosis of these patients seems to improve with the use of therapy tailored to the presumed primary as well. For the few patients with limited metastases it should be assessed whether they are candidates for surgery, radiotherapy or surgery followed by irradiation in curative intent. The remaining majority of patients are treated with empiric palliative chemotherapy, typically a platinum – paclitaxel combination, though the level of evidence for this therapy recommendation is low. Gemcitabine alone or in combination can be used as an alternative.

Decoding of the molecular profiles in CUP offers the prospect of targeted therapy with novel agents. However, there appears to be no uniform molecular pattern for CUP, and the observed molecular diversity thus poses a challenge to respective clinical trials.

Introduction

Cancer of unknown primary (CUP) refers to malignancies, where metastases have been confirmed histologically, but where no primary site can be identified in spite of a comprehensive diagnostic work-up[1–3]. CUP accounts for 2–3% of all epithelial malignancies. From a biological point of view, they are characterized by an early dissemination and metastatic spread, whereas the primary tumor has receded or is too small to be detected[4,5]. The most common primaries identified at autopsy or unmasked during the clinical course of the disease include the lung, the pancreas, gastrointestinal tract (colon, stomach, bile duct and liver) – and the urogenital tract. The prevailing histologies are adenocarcinomas and poorly differentiated carcinomas.[6] Squamous cell carcinoma (SCC), neuroendocrine carcinomas and rare histologies account for about 10% of CUP cases[1,7]. From a clinical point of view, the prognosis of CUP patients is dismal with – favorable subsets let aside – median overall survival times reported in the up to one year range only.

The refinement of immunohistochemistry, the establishment of molecular tests, the even more sophisticated techniques of imaging and an increasing understanding of sub-entities offer the perspective to

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improve the currently still rather dismal prognosis of CUP patients.[8] In this review, we will address the clinician´s approach to CUP in the light of these new developments.

Diagnostic work-up in CUP tumors

Histological, immunohistochemical and molecular testing of the biopsy specimen

Clinical decisions in CUP heavily rely on a thorough histological and immunohistochemical (IHC) assessment of the biopsy specimen by the pathologist[8–10]. In the first place, the biopsy has to establish the main entity of the malignancy: carcinoma versus melanoma, lymphoma or sarcoma.[4] CUPs overwhelmingly fall in the carcinoma category. In a second step, the type of carcinoma needs to be established. About 80% of CUP cases belong into the undifferentiated or adenocarcinoma entities, with adenocarcinomas being further subdivided into moderately differentiated and poorly differentiated adenocarcinomas. Squamous cell carcinoma (SCC), undifferentiated neoplasms and neuroendocrine tumors are main further subtypes.[4]

In undifferentiated and adenocarcinomas – the most frequent types of CUP tumors - the specific type and the likely tissue of origin should be sought out. For this purpose, pathologists follow a stepwise algorithm of immunostainings with panels of selected IHC markers.[6] The allotment to subtypes is based on the pattern of cytokeratin expression. For example, the profile CDX2+, CK20+ and CK7- is characteristic of colon cancer[11–13], whereas the profile CK7+, WT1+, PAX8+ and CK20- is typical for ovarian cancer[4,5]. Chromogranin A and synaptophysin indicate neuroendocrine differentiation. Markedly, IHC techniques have been further refined over the past years.

Recent studies have demonstrated that the sensitivity of IHC to predict the likely site of tumor origin is further enhanced by gene expression profiling[14–16]. These molecular techniques have been shown to have a high concordance with IHC, and in case the IHC is not conclusive they add additional information.[8] When molecular tests are used complementary to IHC and the clinical presentation, a specific diagnosis seems possible in 95% of CUP patients with an accuracy of almost 80%.[8]

Patient history and physical examination

The ESMO guidelines require taking a thorough patient history and performing a detailed physical examination.[5] The performance status (ECOG status) should be sought out, given that it has been consistently identified as a strong and statistically independent prognostic factor[7,17,18]. Pain has also been described as a prognostically relevant parameter.[19]

Patient history should also include asking a family history. Recent data from the Swedish Cancer Registry have observed a familial cancer predisposition in CUP patients[20]. Interestingly, the metastatic location of CUP tumors displays a familial clustering pattern. So for example, abdominal metastatic CUP was associated with ovarian and stomach cancers among relatives, and liver metastasis was associated with liver cancers. It is a matter of speculation, whether this association is due to shared risk factors, a common genetic cancer predisposition or tumor development in genetically favored tissue[20]. The predisposition to CUP within families is also corroborated by a recent study by Samadder et al., who demonstrated that relatives from CUP patients are at an increased risk to develop CUP, lung cancer, pancreatic cancer or colon cancer themselves[21].

Imaging and endoscopy

The ESMO guidelines recommend a CT scan of thorax, abdomen and pelvis.[5] Obviously, CT is important in the search for a primary site of the malignancy, for staging and for remission assessment. The organs affected by metastatic lesions and their number also matter from a prognostic point of view: a higher number of involved organs as well as bone and visceral metastasis have been consistently shown to confer an inferior prognosis[7,17,19].

FDG-PET imaging, which displays tissue metabolism, is frequently additionally employed in CUP to identify malignant lesions. Typically, integrated PET-CT is used, which combines PET and CT and thus provides both metabolic and morphological information[22]. In clinical studies the sensitivity to detect a primary could be enhanced by PET-CT.[4] The most common primary sites detected by PET-CT are lung as well as head and neck cancers. PET-CT is regarded as particularly beneficial for the following two groups: firstly, it is recommended in patients with cervical CUP. In this group, an integrated PET-CT should be performed, since PET alone carries a high risk of false positivity due to the metabolism of the tonsillar lymphatic tissue[22]. Secondly, PET-CT is particularly helpful in patients with a single CUP metastasis who suffer from potentially resectable disease[4,5,23].

Mammography is obviously indicated in females with axillary lymph node CUP suspicious of breast cancer. If mammography fails to detect a primary site, an MRI of the breast is warranted next as method of choice[24]. However, apart from these female patients with axillary lymph nodes suggestive of breast cancer, mammography should not be routinely offered to CUP patients[25].

The role of endoscopy is also limited. The primary is identified by bronchoscopy or colonoscopy only rarely, and therefore these procedures should be performed only when IHC profile or clinical presentation is strongly suggestive of lung or colon cancer.

Laboratory tests

The initial diagnostic work-up should include basic blood analyses and relevant tumor markers.[5] LDH[18] and ALP[17,19] have been shown to confer prognostic relevance, likely as a surrogate marker for overall tumor burden in the case of LDH and as a marker for bone and liver metastasis in the case ALP. Relevant tumor markers should also be determined, including AFP, CA19-9, CEA and chromogranin A in addition to ß-HCG and PSA in male patients and CA15-3, CA125 in female patients. Elevated tumor marker levels have been demonstrated to be prognostically unfavorable, likely since they reflect a higher tumor load[17,19]

Identification of defined CUP sets with favorable prognosis

About 10–30% of CUP patients can be assigned to defined subsets. They are set apart by a distinct clinical pattern highly suggestive of a specific primary tumor. In this group, treatment should follow the guidelines for the equivalent primary tumor with metastatic spread[2,5,26]. The underlying biology, the clinical course and the response to treatment in these groups parallels that of the respective metastatic tumors with known primary site. The prognosis of these patients is also similar to that of the respective primary tumors, which is more favorable than the prognosis of the overall CUP group[4,17]. Therefore, these subsets are also referred to as “favorable subsets”. Typically, the following six subsets are regarded as distinct favorable subsets[27]: (i) carcinoma with midline distribution and poor differentiation in male patients reminiscent of extragonadal germ cell tumors, (ii) adenocarcinoma with isolated unilateral axillary lymph nodes in female patients suggestive of nodal positive breast cancer, (iii) squamous cell carcinoma (SCC) with neck lymph nodes suggestive of head and neck cancer, (iv) squamous cell carcinoma (SCC) with inguinal lymph nodes raising suspicion of anal, vulva, vagina, uterine, cervix, penis or scrotum carcinoma, (v) serous papillary peritoneal carcinomatosis in females indicative of an ovarian or peritoneal primary and (vi) blastic bone metastasis in male patients with high concentrations of PSA pointing to prostate cancer. Since it is paramount for the clinician to recognize these entities and to diagnose and treat the