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MINI REVIEW

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

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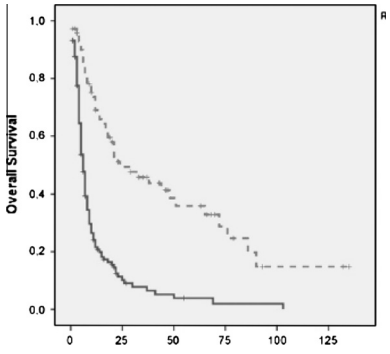
GRAPHICAL ABSTRACT



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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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chemotherapy having usually a dismal prognosis. Gene-profiling microarray diagnosis has a high diagnostic sensitivity, but its predictive or prognostic value remains uncertain.

Keywords:
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Prof. **Rabab Gaafar** 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