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The Role of the Pathologist in the Diagnosis of Metastasis of Unknown Primary Origin

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Review Article

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Abstract: Metastasis of unknown primary origin (MUPO) account for 2–3 % of all malignancies in Western countries and represent a heterogeneous, often aggressive, and clinically challenging group of tumors with early metastatic dissemination for which a standardized diagnostic workup initially fails to identify the site of origin at the time of diagnosis. In the following chapter, we review the possibilities and challenges of tissue-based conventional as well as immunohistochimical procedures to categorize this heterogeneous group of neoplasms. We describe the role of pathology in MUPO diagnosis as part of a multidisciplinary effort primarily involving oncologists, surgeons, radiologists, and pathologists with the ultimate goal to aid in clinical reasoning and decision making.

Keywords: mestastasis of unknwon primary, Surgical pathology, immunohistochemistry.

INTRODUCTION

In oncology, 10 to 15% of patients present with metastatic disease. Often the primitive site is not obvious and in more than a third of cases, so 3-4%, the primitive tumor is not found.

To consider the metastasis of unknown primitive site leads in practice to the situation of unknown primitive carcinoma, in other words a metastatic malignant epithelial tumor [1,2].

Lymph nodes are the most common site, followed by the liver, bones, lungs and brain. The carcinoma of primitive unknown is a heterogeneous entity by the variety of its histopathological types and its sites.

The prognosis is poor with a median survival of a few months. However, faced with the therapeutic challenge of carcinoma of primitive unknown, the diagnosis histopathology with immunohistochemistry is of major importance [3,4]. So the differential diagnosis with primary carcinoma and other tumor types (lymphoma, germ cell tumor, melanoma, sarcoma ..) is crucial [5].

Specific strategies according to particular histopathological types are proposed in the form of two algorithms for an undifferentiated malignant tumor, a carcinoma or adenocarcinoma (the latter represents more than half of carcinomas primitive unknown) and squamous cell carcinoma.

The goal of this work is to redo a point on the antibody panels and determine immunohistochemical profiles diagnostic guidance (recommendations of FNCLCC) to attach a metastasis to its primitive origin.

Undifferentiated malignant tumor

Immunohistochemistry must be able to resolve more than 90% of undifferentiated malignancies using three antibodies directed against epithelial antigens, respectively (pancytokeratin), lymphoid (CD45) and melanic (protein S100).

When these entities like lymphomas, but also germ cell tumors very chemosensitive were discarded, the diagnosis of undifferentiated carcinoma is retained. An algorithm is then proposed to identify the exact histopathological type. However, despite clinical and immunohistochemical data, tumor diagnosis malignant undifferentiated will be retained in 10% of cases without any reference to an origin tumor [6].

Undifferentiated carcinoma or adenocarcinoma (pancytokeratin +, CD45-, protein S100-)

For the diagnosis of adenocarcinoma or carcinoma undifferentiated, despite their usually different morphology, the same algorithm can be used. First, neuro-endocrine markers must be employees for

the diagnosis of neuroendocrine tumor because these tumors of better prognosis require treatment specific [7].

In practice, the best choice is to evaluate the phenotype of a CAPI with two antibodies respectively directed against cytokeratin 7 and cytokeratin 20. But it is necessary to also use other antibodies that are more or less specific to different types of tumors. Four sites of primary tumor (prostate, breast, ovary and thyroid) are not to be missed for proper treatment with a best prognosis [8]:

- first situation: carcinoma cytokeratin 7- /cytokeratin 20-. Hepatocellular carcinoma (AFP not very sensitive) has a cytoplasmic expression of HepPar1 and a canalicular expression of CD10 and of carcinoembryonic antigen (polyclonal antibody). The majority of renal cell carcinomas express CD10 and vimentin. PSA is highly specific carcinoma of the prostate;

- second situation: carcinoma cytokeratin 7- / cytokeratin 20+. The main tumor with this phenotype is colorectal carcinoma usually carcinoembryonic antigen + (nonspecific). The Merkel cell carcinoma can be differentiated cutaneous metastasis with other antibodies (Chromogranin ...);

- third situation: carcinoma cytokeratin 7 + / cytokeratin 20-. About 90% of adenocarcinomas lungs exhibit this phenotype. 70% more Non-mucinous lung adenocarcinomas express TTF1 (nuclear marking). Breast cancers express EMA, estrogen and progesterone receptors, although undifferentiated carcinomas may be do not express any of these markers [9]. The situation is the same with the discriminative expression of the CD10 of the Endometrial and non-mucinous carcinomas of the ovary. Thyroid carcinomas express in general very strongly thyroglobulin and TTF1 but are weakly positive when they are poorly differentiated. The cholangiocellular carcinomas express antigen carcino-embryonic and cytokeratin 19, but the differential diagnosis with liver metastasis mucinous adenocarcinoma can be difficult

- fourth situation: carcinoma cytokeratin 7 + / cytokeratin 20-. Pancreatic carcinomas, gastric and bile ducts strongly express antigen carcinoembryonic. Mucinous carcinoma of the ovary (estrogen and progesterone receptors +) such as urothelial carcinoma (uroplakin +, specific but not very sensitive) has the same phenotype.

Squamous cell carcinoma

Standard staining (hemalun-eosin) allows the diagnosis of most cases but sometimes a squamous cell carcinoma poorly differentiated can benefit from immunohistochemistry (cytokeratin 5/6, cytokeratin 14). Strategies also depend on the location anatomical. In addition, the progress of immunohistochemistry lies in many new antibodies available especially for targeted treatments [10].

Certainly new techniques, such as molecular biology, bring interesting information but still in evaluation, as will be shown by following presentations of the symposium [11]. This implies a particular attention to the pre-analytical phase (quality and sample volume ...) to combine the techniques.

In conclusion, immunohistochemistry remains the most useful and economical tool for the diagnosis of unknown primitive carcinoma among site metastases unknown primitive [12,13].

Conflict of interest

The author declares to have no conflict of interest.

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