Pleural effusions are caused by different underlying pathologies as infections, metabolic disorders, cardiovascular diseases and malignancies. In particular, 25% of all pleural effusions and about 70% of the effusive ones are due to metastatic cancer. They are called malignant pleural effusions (MPEs) and are defined by the presence of neoplastic cells in the fluid or at the pleural sheets. Therefore, definitive diagnosis is obtained by thoracentesis specimen cytology or by tissue biopsy histology. Many malignant tumors may involve the pleura, determining fluid collection; lung cancer is most common in men and breast cancer in women, with a percentage ranging between 50–65% of all cases. Lymphomas, urinary and gastro-enteric cancers follow with 25% (1).

In fact, it is known that CUPs are related to poor prognosis and survival time significantly improves in selected cases responsive to systemic therapy, but unfortunately no guidelines or consensus about their diagnosis and treatment are available.

Despite literature is poor, we focused on the following points: (I) advanced in the diagnostic phase with particular attention to prognostic factors that could influence therapies; (II) the role of surgery in the diagnosis and palliation of symptoms; (III) the role of systemic treatments. The aim is to contribute with an overview of a therapeutic diagnostic path as correct as possible.

Definition and clinical history

CUPs or unknown or occult primary tumors are metastatic histologically confirmed cancers in whom primary site has not been found despite a series of procedures including detailed medical history and complete physical examination (including pelvic and rectal examination), complete blood and urinary examination, occult blood testing, whole body CT scan, mammography, PET/CT scan and immunohistochemistry (IHC) of biopsy specimen (5).

CUPs are histologically classified in four subtypes at light microscopy: (I) adenocarcinoma well or moderately well differentiated, representing about 50% of cases; (II) adenocarcinoma poorly or undifferentiated (about 30% of cases); (III) squamous cell carcinoma (about 15%) and (IV) undifferentiated malignancy (5%) (6). The undifferentiated ones, after IHC, are usually included among differentiated carcinomas, neuroendocrine tumors, lymphomas, germ cell tumors, melanomas, sarcomas or embryonal malignancies.
CUPs behavior is characterized by type 2 progression, in fact they do not follow the histological path from premalignant to malignant lesion but already present with malignant morphology and behavior (5). Therefore, they tend to metastasize very quickly and in an unpredictable way with a completely different pattern from that of known primary tumors. That is way, patients affected by CUPs have different clinical history from others oncologic cases.

Clinical presentation is usually conditioned by metastatic locations whereas primary tumor is silent. The most frequent clinicopathological entities, based on organ involved, are liver, lymph-nodes, peritoneal cavity lungs, bones and brain. Lung and pleural involvement are less frequent.

Metastatic CUP to the lungs may include parenchyma metastasis or isolated MPE. Pleural effusions are note rare in CUPs, but only in few cases they present as the only site of disease. Differential diagnosis with most common mesothelioma, lung, breast and ovarian cancer is mandatory (4).

As every MPE entity, patients have dyspnea and cough correlated with effusion size. General symptoms are also frequent but never due to primary site (7). Care must be taken to not confuse with paraneoplastic effusions where there is not a pleural malignant involvement and pleural fluid collection is due to complications such as pulmonary embolism, thoracic duct obstruction, mediastinal syndrome, pericardial infiltration or pneumonia determined by primary cancer.

As regards chemical-physical characteristics, MPEs from CUP do not differ from the ones with know primary tumor. Both patterns are exudative with protein concentration about 4 mg/dL, increased lymphocytes with predominance of T-cell, glucose concentration <60 mg/dL and pH often <7.3. Glucose concentration and pH also correlate with prognosis that worsen with lower values. Hematic effusions are present in case of tumor with remarkable angiogenesis or vasoactive factors release.

Thoracentesis diagnostic yield in detecting malignant cells is about 60% independently by primary tumor and, since CUP are usually poor differentiated, even in cases where malignant cells are present diagnosis is difficult (8). Therefore also in MPEs from CUPs pleural biopsies are very often needed to confirm malignancy and to identify tumor origin.

In conclusion, we underline that definitive diagnosis of CUP is obtained from both the results of histological examination on one side and careful staging on the other.

### Diagnostic pathway

#### Serum markers

In case of suspected CUP, specific serum tumor markers could be useful in detecting primary tumor. However, their efficacy is limited to few malignant pattern. AFP, PSA and beta-HGC are always suggested to exclude malignancy amenable of hormonal treatment. CA 15-3 and CA 125 are useful in case of in peritoneal or nodal axillary adenocarcinoma, whereas thyroglobulin should be tested in patients with bone metastasis to exclude thyroid cancer. All other generic markers could present non specific elevation in CUPs (9).

#### Role of radiologist

Dealing with CUPs, tumor staging is very important, despite established advanced disease. In fact, prognosis is certainly influenced by both histology and number and location of metastasis. Moreover, a careful staging is critical in confirming CUP diagnosis, by excluding primary tumor. Indeed, the search for primary cancer is very important despite advanced stage, as it allows to optimize the treatment since usually its identification improves prognosis.

CT and MRI are two technologies widely adopted in detecting and stage malignant disease. It has been showed that CT detect about 30–50% of primary sites in suspected CUP (10).

However, they can detect just anatomical abnormalities or abnormal contrast enhancement therefore small lesions or non enhancing normal structures may be misunderstood. Moreover, the evaluation of the numerous images provided by CT or RMI is very demanding and time-consuming. On the contrary, PET/CT allows to detect functional or metabolic pathologic changes independently by any anatomical abnormality and its interpretation may be easier. Its main bias is space resolution, however modern available PET/CT can detect lesions since 4–7 mm and thanks to high lesion-to-background contrast, even smaller tumor could be found.

There are many papers in literature, showing that PET/CT is an excellent alternative to traditional imaging in patients with CUP showing a better capacity to find primary tumor. Roh et al. (11) published that FDG PET/CT sensitivity (87.5%) was higher (P=0.016) than that of CT scan (43.7%) in detecting primary tumors in 44 patients with cervical metastases and unknown primitive.
Nassenstein et al. (12) showed that CT alone revealed the primary tumor in only 5 patients (13%), while FDG PET/CT detected a primary tumor in 11 patients (28%) of 39 patients investigated for cervical metastases of unknown origin. Freudenberg et al. (13) found that CT showed only 5 primary tumors (23%), while FDG PET/CT 12 (57%), in their series of 21 patients with cervical metastases of unknown origin (P=0.03).

Summarizing, PET/CT scan should be adopted as first-line procedure in every patients with metastatic disease and unknown primary tumor independently by location and pattern, rather than using different procedure. Indeed, PET/CT is critical in detecting a possible primitive or, if CUP is confirmed, in staging completing.

**Role of pathologist**

The role of pathologist in CUPs management could be summarized in three points: type (carcinoma, lymphoma, melanoma or sarcoma) and sub-type cancer (adenocarcinoma, squamous cell carcinoma, etc.) identification, compatible primary tumor finding.

Diagnosis is obtained by the use of light microscopy and, above all, IHC and molecular diagnosis. IHC has a special role in targeting primary tumor. Pomjanski et al. showed a correct identification of primary tumor in 85% of 180 CUPs (118 with malignant effusion) by the use of an algorithm based on research of 6 monoclonal anybodies: cytokeratin 5/6, CK 7, CK 20, CA-125, TTF-1 (14). Molecular diagnosis, is used in identifying primary tumor as well, by searching tumor-specific chromosomal abnormalities.

However, its main role is in choosing targeted therapy by the identification of specific biomarkers needed for referring patients to gene therapy. Most common markers are EGFR, BRAF, KRAS, ALK and ROS1 (15). We would like to emphasize that an adequate specimen of tumor is mandatory to correctly perform all needed investigation. Fine-needle aspiration is quite a non invasive procedure but unfortunately provides insufficient tissue. Therefore, dealing with MPE, specimen from a thoracentesis may be not good for pathologist and pleural biopsies are strongly suggested.

**Role of endoscopist**

Endoscopy is recommended in patients with specific symptoms. Therefore, in case of MPE fiberoptic bronchoscopy should be performed as in patients with respiratory signs.

**Role of oncologist**

Systemic therapy for CUPs is conditioned by clinical presentation. Based on clinical pattern patients belong to favorable or unfavorable sub-set. Patients with pleural metastasis are in the unfavorable sub-set.

These patients were often unresponsive to therapy, but the introduction of platinum and platinum/taxane regimens in 1995 showed some clinical advantages with a median survival of 8–9 months. However a population of about 20% presented also better outcomes with a survival ranging between 1–2 years (16).

Better outcomes are expect with the introduction of new therapies. The presence in pleural fluid of one of the lung cancer biomarkers illustrated in the chapter above, should allow the use of monoclonal antibodies including immune checkpoint inhibitors (ICI). Few papers in literature described faired results in patients with CUP treated with monoclonal antibodies targeting EGFR, HER2 and VEGF antigens (17,18). The Authors were able to describe an arrest of disease progression. Moreover, at the moment there are two other ICIs targeting PD-1, and three targeting PD-L1. But, data on the use of these ICIs in patient with CUP are very limited and results controversial (19-21). Another new topic is the use of agents such as VEGF inhibitors, to improve traditional chemotherapy efficacy acting on pleural permeability (22). This could improve drugs bioavailability at the site of disease and at even potentially lower doses.

**The role of thoracic surgeon**

The role of thoracic surgeon in the management of MPE from CUP is twofold, diagnostic and therapeutic. Diagnostic step is mandatory since the evidence of malignant cell in pleural fluid may confirm clinical pattern but is not enough to obtain definitive diagnosis. Moreover, as reported above, pleural biopsies are needed to perform IHC and genetic studies in order to target therapy by defining an eventual primary tumor or CUP type an sub-type.

Unfortunately therapeutic step has the only aim to alleviate symptoms and improve quality of life, and is mainly based on pleural fluid evacuation. Therefore, palliative pleurodesis should be considered in the setting of...
recurrent symptomatic pleural effusions under controlled
with optimal tumor therapy or even at the moment of
diagnosis before systemic treatment.

According to the ongoing guidelines (23), thoracoscopy
is the gold standard in case of dubious pleural aspiration
when malignancy is suspected. Therefore, in patients with
MPE and unknown primary tumor, thoracoscopy is even
more suggested as the procedure is successful, safe and
pleurodesis is likely to be indicated.

Pleural biopsies may by performed by local anaesthetic
thoracoscopy or by VATS. Medical thoracoscopy is a
safe and well tolerated also by patients in poor general
conditions. It is successful since diagnostic sensitivity for
malignant pleural disease is about 92.0% (95% CI, 91.0%
to 93.9%) (24). Moreover it allows to perform talc poudrage
achieving pleurodesis in 80–90% of cases.

On the contrary VATS is not suitable for patients with
severe comorbidities or in poor general conditions but
has high diagnostic sensitivity rates of approximately 95%
for malignancy (25). The main VATS advantage is that, in
case of partial trapped lung or pleural cavity chambers, this
procedure allows adhesions debridement guaranteeing more
effective pleurodesis.

Our suggestion is to always perform frozen section
of pleural sheet biopsy during thoracoscopy. In case of
malignancy, we proceed immediately with talc poudrage,
providing at least palliative treatment. Definitive histology
will reveal if specimen was mesothelioma or metastatic
disease.

Indwelling pleural catheter is also an alternative to
pleurodesis. This can decreased hospital stay and improved
quality of life, in particular as concerning dyspnea.
Other procedures considered included decortication
and pleuroperitoneal shunts. For patients with very
compromised general conditions, repeated thoracentesis is
tolerable alternative for dyspnea relief.

Conclusions

CUPs presenting with MEP have bad prognosis despite
recent advancements in their management. Mean survival
is about 4–6 months, with one-year survival rate in patients
responsive to target therapy.

In order to improve quality of life and survival the
ESMO recommendations underline the relevance of correct
diagnosis and tumor sub-typing. In this context, the role
of surgery is vey meaningful in providing adequate pleural
specimen and alleviating symptoms by pleurodesis or fluid
evacuation.

Acknowledgment

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned
by the Guest Editors (Duilio Divisi, Roberto Crisci) for the
series “Malignant Pleural Effusion” published in Journal of
Xiangya Medicine. The article did not undergo external peer
review.

Conflict of Interest: All authors have completed the ICMJE
uniform disclosure form (available at http://dx.doi.
org/10.21037/jxym-2019-mpe-03). The series “Malignant
Pleural Effusion” was commissioned by the editorial office
without any funding or sponsorship. MC serves as an unpaid
ditorial board member of Journal of Xiangya Medicine from
Nov 2019 to Oct 2021. The authors have no other conflicts
of interest to declare.

Ethical statement: The authors are accountable for all
aspects of the work in ensuring that questions related
to the accuracy or integrity of any part of the work are
appropriately investigated and resolved.

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References

1. Johnston WW. The malignant pleural effusion. A review
of cytopathologic diagnoses of 584 specimens from 472
pleural effusion and cancer of unknown primary site: a
3. Jordan WE 3rd, Shildt RA. Adenocarcinoma of unknown
primary site. The Brooke Army Medical Center


doi: 10.21037/jxym-2019-mpe-03