Editorial Commentary

Pleural diseases related to unknown primary carcinoma—a multidisciplinary approach in diagnosis and treatment

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Introduction

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 essudative 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).

Though the most of cases present at diagnosis in conjunction with primary tumor, 7–15% of all MPEs are caused by an unknown cancer (2). These cases fall into the group of metastatic cancer of unknown primary (CUP) site, a heterogenous group of tumors diagnosed at secondary site without a certain origin, despite histology of metastatic specimen and whole body extensive investigation. The absence of primary site may be explained by a very slow growth compared to metastatic foci or by its spontaneous involution (3).

CUPs are rare and cover 4–5% of all invasive cancer (4). They usually occur in adults (median age 60 years) with a minimal predominance in males. In children, they represent less than 1% of cases.

CUPs presenting with isolated pleural effusion are even more rare. However, MPEs from CUPs are an hot topic in clinical practice, as they pose many challenges to physicians. 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 very meaningful in providing adequate pleural specimen and alleviating symptoms by pleurodesis or fluid evacuation.

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References

1. Johnston WW. The malignant pleural effusion. A review of cytopathologic diagnoses of 584 specimens from 472 consecutive patients. Cancer 1985;56:905-9.
2. Awadallah SF, Bowling MR, Sharma N, et al. Malignant pleural effusion and cancer of unknown primary site: a review of literature. Ann Transl Med 2019;7:353.
3. Jordan WE 3rd, Shildt RA. Adenocarcinoma of unknown primary site. The Brooke Army Medical Center

experience. Cancer 1985;55:857-60.
4. Briasoulis E, Pavlidis N. Cancer of Unknown Primary Origin. Oncologist 1997;2:142-52.
5. Abbruzzese JL, Abbruzzese MC, Lenzi R, et al. Analysis of a diagnostic strategy for patients with suspected tumors of unknown origin. J Clin Oncol 1995;13:2094-103.
6. Hainsworth JD, Greco FA. Cancer of Unknown Primary Site: New Treatment Paradigms in the Era of Precision Medicine. Am Soc Clin Oncol Educ Book 2018;38:20-5.
7. Dixit R, Agarwal KC, Gokhroo A, et al. Diagnosis and management options in malignant pleural effusions. Lung India 2017;34:160-6.
8. Brock MV, Hooker CM, Yung R, et al. Can we improve the cytologic examination of malignant pleural effusions using molecular analysis? Ann Thorac Surg 2005;80:1241-7.
9. Milović M, Popov I, Jelić S. Tumor markers in metastatic disease from cancer of unknown primary origin. Med Sci Monit 2002;8:MT25-30.
10. Karsell PR, Sheedy PF, O'Connell MJ. Computed tomography in search of cancer of unknown origin. JAMA 1982;248:340-3.
11. Roh JL, Kim JS, Lee JH, et al. Utility of combined (18) F-fluorodeoxyglucose-positron emission tomography and computed tomography in patients with cervical metastases from unknown primary tumors. Oral Oncol 2009;45:218-24.
12. Nassenstein K, Veit-Haibach P, Stergar H, et al. Oral Cervical lymph node metastases of unknown origin: primary tumor detection with whole-body positron emission tomography/computed tomography. Acta Radiol 2007;48:1101-8.
13. Freudenberg LS, Fischer M, Antoch G, et al. Dual modality of 18F-fluorodeoxyglucose-positron emission tomography/computed tomography in patients with cervical carcinoma of unknown primary. Med Princ Pract 2005;14:155-60.
14. Pomjanski N, Grote HJ, Doganay P, et al. Immunocytochemical identification of carcinomas of unknown primary in serous effusions.. Diagn Cytopathol 2005;33:309-15.
15. Porcel JM. Biomarkers in the diagnosis of pleural diseases: a 2018 update. Ther Adv Respir Dis 2018;12:1753466618808660.
16. Greco FA, Rodriguez GI, Shaffer DW, et al. Carcinoma of unknown primary site: sequential treatment with paclitaxel/carboplatin/etoposide and gemcitabine/irinotecan: a Minnie Pearl Cancer Research Network phase II trial. Oncologist 2004;9:644-52.
17. Schliemann C, Neri D. Antibody-based vascular tumo targeting. Recent Results Cancer Res 2010;180:201-16.
18. Asakura H, Takashima H, Mitani M, et al. Unknown primary carcinoma, diagnosed as inflammatory breast cancer, and successfully treated with trastuzumab and vinorelbine. Int J Clin Oncol 2005;10:285-8.
19. Kato S, Krishnamurthy N, Banks KC, et al. Utility of Genomic Analysis In Circulating Tumor DNA from Patients with Carcinoma of Unknown Primary. Cancer Res 2017;77:4238-46.
20. Gröschel S, Bommer M, Hutter B, et al. Integration of genomics and histology revises diagnosis and enables effective therapy of refractory cancer of unknown primary with PDL1 amplification. Cold Spring Harb Mol Case Stud 2016;2:a001180.
21. Røe OD, Wahl SG. The undifferentiated carcinoma that became a melanoma: Re-biopsy of a cancer of an unknown primary site: a case report. J Med Case Rep 2017;11:82.
22. Stathopoulos GT, Kalomenidis I. Malignant pleural effusion: tumor-host interactions unleashed. Am J Respir Crit Care Med 2012;186:487-92.
23. Woolhouse I, Bishop L, Darlison L, et al. British Thoracic Society Guideline for the investigation and management of malignant pleural mesothelioma. Thorax 2018;73:i1-30.
24. Blanc FX, Atassi K, Bignon J, et al. Diagnostic value of medical thoracoscopy in pleural disease: a 6-year retrospective study. Chest 2002;121:1677-83.
25. Latham P, Dullye KK. Complications of thoracoscopy. Anesthesiol Clin North Am 2001;19:187-200.

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