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CUTANEOUS METASTASES REVEALING SMALL CELL LUNG CANCER: CASE REPORT AND REVIEW OF LITERATURE

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ABSTRACT Cutaneous metastases as a first presentation of internal malignancies occurs are very rare, and usually indicated a poor prognosis. We reported a case in which a 45 years old male patient initially presented with rapidly growing skin nodule on his back and left chest wall. Then, he developed dyspnea and loss of weight. Thoraco-abdomino-pelvic scan revealed a process in the upper lobe of lung with multiple mediastinal lymphadenopathies and distant localization in adrenal gland. Biopsy of the skin mass has shown a metastatic process of an adenocarcinoma consistent with lung primary. Palliative chemotherapy was administered but the outcomes were poor with rapid progression leading to death. This article highlights an atypical presentation of lung metastases to the skin and provides an overview of clinical, radiological, therapeutic and prognostic features of this entity.

KEYWORDS : skin, metastasis, chemotherapy, prognosis

Introduction:

The skin is an uncommon site of metastases from internal malignancies (Rolz-Cruz & Kim, 2008) (1). It generally occurs after initial diagnosis of the primary cancer and usually in a later stage of the disease (Liao, Wu, Karbowitz, Morgenstern, & Rose, 2014; MD, 2013).

Among the skin metastases, lung cancer is the most frequent primary site in men, and the fourth most common primary site in women (MD, 2013). Cutaneous metastases are usually accompanied by metastases to other organs such as liver, bone, adrenal glands and brain, which lead to poor outcomes (Mollet, Garcia, & Koester, 2009).

Case presentation:

We report the case of a 45 years old Moroccan male, treated in the department of Medical Oncology at Hassan II University of Fez. In his medical history, he had active smoking for 30 years. He presented 2 months before his admission 3 cutaneous nodules localized in the back and one in the left chest. The nodules were painless, fixe, with firm consistency and measured 5 to15 millimeters. The patient also presented weight loss, anorexia, deep fatigue and dyspnea.

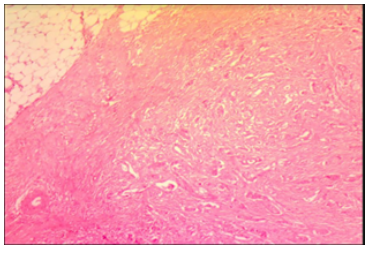

Figure 1: Hematoxylin and eosin stain of the skin lung cancer metastase with subepidermal adenocarcinom

A biopsy of the skin lesion was performed and revealed a metastatic process of an adenocarcinoma suggesting the lung origin, with diffuse strong nuclear staining for thyroid transcription factor 1 (TTF-1) and membranous staining for cytokeratin 7 (CK7) (figure 1). Staining was negative for cytokeratin 20 (CK20) and CDX2 eliminating lower gastro-intestinal cancers, and also negative for p63, for squamous carcinoma (figure 2). EGFR and ALK mutation testing were negative.

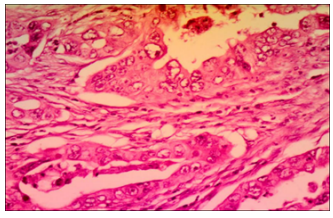

Figure 2: Ck 7 stain of the skin metastases of lung adenocarcinoma

Thoraco-abdomino-pelvic scan showed a process in the upper left lobe of the lung, measuring 36 * 74mm and mediastinal lymphadenopathy; with secondary lesions in the left adrenal gland (figure 3). Brain imaging did not show cerebral lesions.

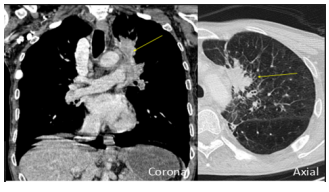

Figure 3: Heterodense process in the upper left lobe of the lung

Given the diagnosis of stage IV lung adenocarcinoma with distant metastases, without driver mutations, the patient received first line of chemotherapy based on carboplatin, paclitaxel and bevacizumab. The evolution was marked after 3 cycles by clinical and radiological progression by occurrence of new skin nodules in abdominal wall (Figure 4) and the progression of primitive process.

Figure 4: Subcutaneous metastasis nodule of lung cancer in abdominal wall

The patient passed away four months after the initial diagnosis due to pulmonary embolism.

Discussion:

Cutaneous metastases of lung cancer are extremely rare (Brownstein & Helwig, 1972; Hidaka, Ishii, & Kitamura, 1996). According to the data of the literature, they appear in around 1-12% (Dreizen, Dhingra, Chiuten, Umsawasdi, & Valdivieso, 1986). A large series of retrospective studies reported that the skin is the 13th common site of lung cancer metastasizing (D'Aniello, Brandi, & Grimaldi, 2001; Dreizen et al., 1986). Although lung cancer has the highest incidence of skin metastasizing in men (Bolognia et al., 2003; Pajaziti et al., 2015). In women it occur only in 2% of cases (Bolognia et al., 2003). Most skin metastases are developed in region close to the primary cancer (Bolognia et al., 2003). For lung cancer, metastases arise in supradiaphragmatic region mostly in chest. The most common metastatic sites of lung cancer are hilar nodes, liver, adrenal glands, bone and brain (Homler, Goetz, & Weisenburger, 1986; Kikuchi, Matsuyama, & Nomura, 2001).

The cutaneous metastases can take on different non-specific clinical aspects, which can explain the delay of the diagnostic (Estarriol & Goday, 2006; Marcoval, Moreno, & Peyrí, 2007). They can mimic many other benign dermatological lesions (Marcoval et al., 2007).They can be described as erysipelas-like lesion, infiltrating plaques that may be ulcerated, sclerous lesions or cutaneous or subcutaneous nodules, as for our case (Ambrogi, Nofroni, Tonini, & Mineo, 2001; Schoenlaub, Sarraux, Grosshans, Heid, & Cribier, 2001). It can be a single nodular lesion, or multiple skin nodules (MD, 2013). Their favorite localizations are the scalpe, head, neck and chest (Ambrogi et al., 2001). The most common histological diagnosis of primary lung cancer is adenocarcinoma (Bolognia et al., 2003; Liao et al., 2014). But all histological types of lung cancer may develop skin metastases.

The histology and immunohistochimy battery, which follows a biopsy, confirms the secondary nature of the cutaneous lesions. Useful markers include CK 7 and CK 20 and anti-thyroid transcription factor (TTF) are using for diagnosis (Ardavanis, Orphanos, Ioannidis, & Rigatos, 2006). CK 7 is very sensitive and is positive in virtually all cases of primary lung adenocarcinoma; however, it has lower specificity since it is also positive in may other types of lung carcinoma (70% of large cell neuroendocrine, 40% of large-cell, and 23% of squamous-cell) (Ardavanis et al., 2006; Lookingbill, Spangler, & Helm, 1993). Anti-TTF is a sensitive and specific marker that identifies pulmonary origin of an adenocarcinoma, broncho-alveolar carcinoma, and small-cell carcinoma if a thyroid origin is excluded (Ardavanis et al., 2006).After morphological diagnosis, the next consideration is therapy-predictive biomarker testing (Lookingbill et al., 1993). Testing for EGFR mutations and rearrangements involving the ALK and ROS1 genes have become indispensable, because of their therapeutic implication (Lindeman et al., 2013). They represent strong predictive biomarkers and are excellent therapeutic targets (Kovács, Kenessey, & Tímár, 2013; Lindeman et al., 2013). For our case, given the positive expression of CK7 and TTF1in addition to the negative staining of squamous cell carcinoma marker (p63), we confirmed the primary malignancy as lung adenocarcinoma. EGFR and ALK mutation testing were negative in this case.

The treatment of skin metastases of lung cancer is similar to that of other metastatic forms of malignant tumors of the lung by palliative treatment (Lindeman et al., 2013). The purpose is to delay the evolution of the tumor disease by maintaining a good quality of life (Kovács, Hegedus, Kenessey, & Tímár, 2013; Kovács, Kenessey, et al., 2013).

Chemotherapy by Cisplatin-based combinations with a third generation drug; are another therapeutic standard for metastatic NSCLC (Coslett & Katlic, 1990). Indeed, palliative chemotherapy offers a tumor response rate of up to 35%, but patient survival remains mediocre and not exceeds 10 months (Molina Garrido, Guillén Ponce, Soto Martínez, Martínez Y Sevila, & Carrato Mena, 2006; Wan, Pantel, & Kang, 2013).

Other treatment options are available to patients who cannot tolerate cisplatin, including carboplatin-based combinations, navelbine or gemcitabine in monotherapy (Terashima & Kanazawa, 1994). Radiotherapy to cutaneous metastases is indicated for severe pain or bleeding (De Argila, Bureo, Márquez, & Pimentel, 1999).

Targeted therapies have proven their efficacy comparing to chemotherapy (Liao et al., 2014). In fact anti EGFR therapies such as osimertinib, afatinib, erlotinib and gefetinib (Lindeman et al., 2018) or oral ALK inhibitors such as crizotinib, ceritinib, lorlatinib, brigatinb and alectinib (Gainor et al., 2016) can be used for patients with respectively EGFR mutation or ALK gene rearrangements with improving overall and free progressive survivals (Gainor et al., 2016; Lindeman et al., 2018).

The development of monoclonal antibodies against the checkpoint inhibitor programmed cell death protein 1 (PD-1) such as nivolumab and pembrolizumab and inhibitor of PD-1 ligand (PD-L1) like atezolizumab, haveled to high activity in cancer patients with long lasting responses (Tazdait et al., 2018). Indeed pembrolizumab and atezolizumab, an anti PD-1/ PD-L1 inhibitors respectively, have demonstrated in monotherapy or in association whit chemotherapy a very good tolerability, higher response rates and a survival benefit. They have also become the new standards of care in first and later lines (Tazdait et al., 2018).

The appearance of a cutaneous metastasis is the pejorative sign of tumor dissemination and therefore an indicator of poor prognosis with a mediocre survival not exceeding 06months (Perng, Chen, Lee, & Perng, 1996; Ussavarungsi, Kim, & Tijani, 2013).

In our case, the patient did not receive these targeted therapies due to a lack of molecular drivers (EGFR and ALK). He also did not respond to chemotherapy with carboplatine, paclitaxel and bevacizumab. He passed away four months after lung cancer diagnosis.

Conclusion:

The skin is an uncommon site of metastasis of internal cancers. The majority of cutaneous metastases are diagnosed after the primary cancer but they may be the initial presentation. Therefore, they should be raised in front of atypical skin lesions. In lung cancer, they are usually accompanied by metastases to other organs and are subsequently considered as a poor prognostic indicator.

Conflicts of interest:

There are no conflicts of interest.

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