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CASE REPORT

Uterine Leiomyoma with Lung Metastases Stump Tumour

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We present one clinical case of a 41-year-old, female Russian origin patient, with lung nodules suggestive of metastases, with no primary tumor found, referred for study and treatment in our Oncology Department.

After a deep analysis of the case, reviewed the literature and result of the pathology of biopsy from lung lesions, the final diagnosis reached was: Benign muscle tumors of Gynecological origin, with the capacity for produce distant metastasis compatible with STUMP Tumor (Metastatic leiomyoma).

Literature Review and States of the Art

This rare case has apparently been recognized for many years at different publication. It has specific features of a benign smooth muscle tumour, (leiomyoma), but with the capacity to produce distant metastasis whilst maintaining the same histology.

In 1912 this disease was first described by Deussing referring as multiple pulmonary metastasis with myomas histology.

In 1939, Steiner [1] described one case of a patient who had died due to pulmonary metastases from a primary uterine myoma.

Reviewing posterior data published until 1983, there were 54 cases and only 3 of them in Spain [2].

At that time Martin E, classified these tumours in 3 groups [3,4]:

- Leiomyomatosis in women, subdivided into benign metastasising leiomyomatosis, lymphangiomyomatosis, disseminated peritoneal leiomyomatosis and intravenous leiomyomatosis (which do not meet the criteria for the diagnosis of leiomyosarcoma, but which demonstrate unusual behaviour and have a location suggestive of malignancy).
- Metastatic leiomyoma in men and children.
- Multiple pulmonary fibro-leiomyomatous hamartomas.

The terminology or name of this type of tumour is not clearly established, there being many variations under the same name as:

- Benign metastasising leiomyoma [5].
- Atypical leiomyoma (controversially named).
- Smooth muscle tumours of uncertain malignant potential (STUMP).

The WHO defines as those uterine smooth muscle tumours which cannot be histologically classified as benign or malignant, but are of intermediate grade between benign leiomyomas and malignant sarcomas.

This type of tumour, there is no doubt that had uterine origin. The differential diagnosis must always include uterine or extrauterine leiomyosarcoma.

To reach such a diagnosis, there should also be reference to previous existence of uterine leiomyoma in the patient's history. In reality, on many occasions, this is not easy to confirm. In our case analysed here, the patient referred to previous resection of a uterine myoma, (myomectomy) having been performed in Russia many years ago.

Case Report

42-year-old female Russian patient in March 2015 was found on routine chest CT multiple pulmonary nodules, suggestive of metastases together with a 3

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cm mass adjacent and posterior bifurcation of the right bronchus suggestive of conglomerate hilar lymph nodes.

The abdominal CT was normal, but an enlarged myomatous uterus with a prominent cervix on the pelvic CT, the ovaries did not present significant abnormalities.

Mammography and breast ultrasound performed were normal (BI-RADS 2). The patient was completely asymptomatic and clinically well. Blood tests performed as part of the investigation were normal, including tumour markers (CEA, CA15.3, CA 19.9 y CA125).

Amongst the patient's background, 3 pregnancies with 3 caesareans noted. At 26 years age, had an important bleeding due to a uterine myoma treated with myomectomy, reported as a benign tissue.

PET-CT performed on April 2016, corroborated the presence of multiple lung nodules of differing sizes with normal metabolic activity. The 2.8 cm lesion at the bifurcation of the bronchus intermedius described on CT had an SUV of 1.4. No pathological images identified in the abdomen, describe a myomatous uterus and a 2 cm, hypodense, right adnexal lesion.

Bronchoscopy performed on April 2016 with attempt made to biopsy of the pulmonary lesions, were negative for tumour. Therefore EBUS guided needle aspiration or a percutaneous thoracic CNB recommended.

On May 2016 it was decided to perform percutaneous FNA which identified a tumour with rare malignancy, for which reason we decide to perform percutaneous lung biopsy. This identified the presence of tissue with fusocellular proliferation and mild pleomorphism suggestive of carcinoid tumour.

The histopathology was reported as mesenchymal proliferative lesion of smooth muscle fibres with uncertain malignant potential. The IHC was negative for TTF-1 and H-Cadherin. SALL4, PAX8, p53 and GATA3 were also negative with moderately weak staining for TLE1. Neuron-specific enolase was negative and the possibility of a glandular-carcinoid or neuroectodermal tumour was ruled out.

At follow-up on 17/5/16, trilaminar endometrium described with presence of other intramural myomas measuring 15, 14.6 and 4.6 mm. Study completed with serum and urine catecholamine determination which was negative and a body-Octreoscan (20/5/16) which was also normal.

The patient continued in excellent clinical condition, asymptomatic and leading a normal life, moved on to clinical monitoring.

Further PET performed in September 2016 demonstrated an increase in the number and activity of pulmonary nodules, (SUVmax 3.1). The right parahilar lesion next to the bronchus intermedius was still present with a craniocaudal length of 3.4 cm and increased metabolism (SUVmax 3.9).

The uterus was still increased in size and irregularly shaped, although with no metabolic abnormalities, findings suggestive of myomas. The right adnexal, hypodense lesion was similar in size with an area of increased metabolism in its lateral zone, possibly follicular cyst inflammatory focus.

As these findings suggested tumour progression, it was decided to perform further transthoracic percutaneous needle biopsy which was negative for tumour and quite painful for the patient. Therefore, as the patient was asymptomatic, it was decided not to take any further active measures.

The case was analyzed by Internal Medicine specialists who suggest sarcoidosis, but all relevant investigations performed on this sense were negative. The patient returned for reviewed with her gynecologist afterwards, who performed an ultrasound showing uterus of 8.33 × 6.82 × 4.7 cm with presence of stable myomas. Both ovaries seen, negative for any abnormal images. Blood tests demonstrated an increase in CA 125 to 54. As the situation was unclear, further biopsy of the lung nodes via thoracoscopy suggested to the patient.

On January 13th 2017, a VATS exploration was done, with resection of a lung segment measuring 15 × 5 × 1.5 cm delineated at the parenchymal margin with surgical staples. 3 nodular lesions was identified, macroscopically solid, whitish, fleshy, and fasciculate in appearance and very well circumscribed.

Pathology pattern corresponded microscopically to a proliferation made up of smooth muscle, fusiform cells with elongated, blunt-ended nuclei and eosinophilic cytoplasm, also elongated. No necrotic foci or mitotic figures observed.

The phenotypic profile of tumour cells expressed immune reactivity for actin and desmin, being negative for SS-100, HMB-45, CK and TTF-1. Low cell proliferation index (Ki67: < 5%). The IHC revealed strong nuclear positivity in both oestrogen (80%) and progesterone (95%) receptors.

The case was reviewed in its entirety, bibliography search revealed a pathology named STUMP (uterine smooth muscle tumours of uncertain malignant potential) which matched that of this patient. Treatment for this would be gynaecological surgery with the aim of identifying and removing the primary, given afterwards hormone therapy.

The patient had a further PET/CT on 22 February 2017 which continued to show multiple bilateral pulmonary nodules, with low metabolism and no radiological changes compared to previous study. Surgical changes noted in relation to resection of lung tissue in the lingula of the left upper lobe. The uterus continued to be increased in size due to presence of myomas.

On 23 May 2017, total hysterectomy performed with double adnexectomy. The histopathology results showed proliferative endometrium, a leiomyoma in the myometrium and no significant abnormalities of the adnexa.

PET-CT repeated after 6 months (13/9/17) still demonstrating multiple bilateral pulmonary nodules, however some were decreased in size on imaging with no metabolic activity, possibly suggesting loss of tumour activity. The patient continued to be monitored with no treatment at that time.

Further PET-CT performed on 2 February 2018 did not show any radiological change in size, appearance of any new lesions or any increased metabolism.

Blood analysis performed at that time showed FSH (53.4) and LH (28.31) in relation to post-menopausal state with level of 17 beta-estradiol still 31 pg/ml (menopause: < 21).

On March 13th, 2019 a new evaluation with PET-TAC was made showed decreased in size of the pulmonary nodules and no detection of metabolic activity. Blood analysis performed at time showed FSH (81,17) and LH (37,57) in relation to post-menopausal state. The level of 7 beta-Estradiol is falling down (24 pg/ml).

Discussion

Smooth muscle tumours of undetermined behaviour or uncertain malignant potential have macroscopic and microscopic features intermediate between those of leiomyoma and leiomyosarcoma [6,7]. There is a set of parameters for classification of different smooth muscle neoplasms. These features indicate the clinical behaviour of the tumour [8-12]. The term STUMP is used if there is uncertainty with respect to the classic criteria which we detail below [12-14]:

Benign criteria

- Low mitotic index (< 5 mitoses per 10 HPF)
- No cytological atypia
- No cell necrosis (except for ischaemic-type necrosis)
- No intravascular composition
- Well-circumscribed mass
- Fusiform cells, uniform in size and shape

Criteria of malignancy

- High mitosis count (> 10 mitoses per 10 HPF). Mitosis count of > 10 per 10 high-power fields known as the mitotic index.
- Predominance of cytological atypia (moderate to severely diffuse, degree of atypia to be determined)
- Presence of coagulative tumour cell necrosis or hyaline necrosis (geographical pattern)
- The subtype of standard smooth muscle differentiation (epithelioid or myxoid).

The border between benign and malignant has been established at more than 10 mitoses per 10 high-power fields [15]. For the fusocellular histological form (the usual type) it has been suggested that 2 of these 3 criteria (diffuse cytological atypia, tumour necrosis and > 10 mitoses per 10 high-power fields) can diagnose leiomyosarcoma.

Unlike leiomyosarcoma, leiomyoma is a tumour of soft appearance, which must be comprised of muscle cells (leiomyoma) of histologically benign features, without infiltrating margins, without tumour necrosis, without high mitotic count (< 4) per 10 high-power fields, and without significant cytological atypia.

Its variants include mitotically active leiomyoma (5-19 mitoses/10 high-power fields) and atypical leiomyoma with cytological atypia, but without necrosis and < 10 mitoses per 10 high-power fields. Tumours which do not meet these two definitions are classified as STUMP.

In principle there is no coagulative necrosis in STUMP, but there can be atypical mitotic figures, margin infiltration and a mitotic index of around 8-9 mitoses.

Uterine origin has been demonstrated on histopathology of resected myoma, with signs of architectural disruption in certain uterine veins and protrusion into the lumen by the myoma. In metastasis the presence of normal lung tissue trapped in the growth of the myomas located in the lung has been demonstrated. STUMP [3,8,16] continues to be a diagnostic challenge due to its rarity and due to incorrect diagnosis. One way to define it is by exclusion.

The immune-histological diagnosis [13,17,18] has shown to be effective in the diagnosis of benign versus malignant alongside histopathological diagnosis. Over expression of p16, p53 and MIB1 and low expression of hormone receptors are often observed.

Over expression of p16 [19] is frequently observed in leiomyosarcomas and not in leiomyomas (except as focal positivity) or normal myometrium. Over expression of p53 is typical in leiomyosarcomas but not in leiomyomas. If over expression of p53 is negative, weak or focal in the case of suspected STUMP, patients often have a benign clinical course. On the contrary if positivity is diffuse > 66% there is a high risk of malignant tumor behavior. Increased MIB1 is present in leiomyosarcomas.

It has been demonstrated with statistically significant differences, that there is greater expression of MIB1 in STUMP than in leiomyomas. STUMP presents diffuse positivity for progesterone receptors in 71% of cases as opposed to leiomyosarcomas which often show low

progesterone and estrogen receptor expression [20,21]. With respect to estrogen receptors the difference between leiomyosarcomas and STUMP is not significant [5].

Therefore, we can see that IHC has its limitations, but it has been observed that Ki-67, p53 and p16 expression is higher than in the benign subtypes and helps in the diagnosis of clinically more aggressive STUMP.

Pathogenesis

Uterine myoma (also known as leiomyoma, fibromyoma or fibroid) is a common gynecological tumor in women of reproductive age, it is a benign smooth muscle tumor situated in the myometrium. The etiology of benign metastasizing leiomyoma has still not been clarified, and there are various hypotheses in this regard [10,17,22].

The lung [9,18,23] is the organ most affected, which supports the theory of hematogenous spread, the theory is also supported by the location of this type of metastasis after endometrial curettage (which can drive cells into the bloodstream) [11,24] and cases described after myomectomy or hysterectomy.

The lesions being situated in the alveolar interstitium of the lungs, where smooth muscle cells are absent, also supports this type of spread. The time between the source and development of metastases can be years [25].

Benign metastasizing leiomyomas (BML) result from clonal proliferation of smooth muscle tissue. They should be considered hormone-dependent tumors.

There are studies performed by Rivera which reproduced the clinical symptoms and demonstrated the hormonal relationship monitoring the mid-cycle peaks of FSH-LH- estradiol which directly coincided with clinical deterioration of the disease.

There is no published case of BML originating from a uterine sarcoma, even of low grade, the majority of published cases have a history of primary uterine myomas.

The majority of uterine leiomyomas present in women of childbearing age and usually with multiple well-defined nodules.

A slow clinical course is always described in the literature, but in the case of developing pulmonary tumours, they may continue to grow and cause respiratory failure and death.

Therapeutic Recommendations [8,9]

There is no established treatment for this type of process due to the rarity of cases. The ideal treatment would be resection of all the lung nodules, which is often not possible. The presence of hormone receptors [26] in these tumors is a therapeutic target which should be considered. Spontaneous regression has been observed with pregnancy, oophorectomy, menopause and the use of progestogens (megestrol), selective estrogen receptor modulators, aromatase Inhibitors and GnRH agonists. On the contrary, oral contraceptive agents appear to cause an increase in the pulmonary symptoms and an increase in size of the leiomyomas.

As they are hormone-dependent neoplasms, stopping oral contraceptives or HRT is advisable. Despite good progress, cases of death attributable to the disease have been described, therefore bilateral oophorectomy, the administration of tamoxifen or progesterone proposed. The aim of treatment is to decrease estrogen levels.

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