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Case report

Case of lung carcinoma revealed by vulvar metastasis associated with systemic scleroderma and literature review

Cancer du poumon révélé par une métastase vulvaire associé à une sclérodermie systémique et revue de la litterature

*Safae Mansouri**, *Luis A. Glaria*, *Naim Asmae*, *Luis F. Flores*

Radiotherapy Oncology Center, Talavera, Grupo IMO, Spain

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ABSTRACT

Metastatic carcinoma to the vulva is rare, where the incidence is believed to be between 5% and 8%.

However, malignant tumors have been described in 3–11% of systemic scleroderma (SSc) cases.

We report the case of one patient, a 66-year-old postmenopausal woman, whose medical history was marked with rheumatic vascular disease (systemic scleroderma) since 1993 without muscular, renal, cardiac lesions or HTA (arterial hypertension) and without tobacco history.

The woman presented with a new vulvar mass of the right labia in December 2011 that had progressively enlarged in size.

CT scan of the abdominopelvic region demonstrated a lobular mass of the right labia with central necrosis, 7 cm on the wide axis, and the rectum and the vaginal wall were normal. No inguinal or iliac lymphadenopathy was noted.

An outpatient excisional biopsy revealed a poorly differentiated malignant tumor suggestive of carcinoma.

IHC: CK7+/CK20−, estrogen receptors−, AE 1 AE 3+, vimentine+, S100−, Desmina−, CD34−, KI 67: 20%.

The thoracic scan revealed a large mass of 4 cm × 3 cm in the right lung base with right paratracheal lymphadenopathy 3 cm × 2 cm.

A bronchoscopy revealed discrete stenosis of the mediastinal portion of the right bronchial tree.

The bronchial biopsy also revealed poorly differentiated lung carcinoma, non-small cell, which was identical with the vulvar tumor.

Conclusion: The presence of the single lung lesion with only one lymphadenopathy paratracheal with pathological and immunohistochemical (IHC) profile similar to the vulvar lesion,

* *Corresponding author*. Tel.: +21 2677479937.
E-mail address: m-safae@hotmail.fr (S. Mansouri).

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and a particular IHC profile with CK7+ and CK20− was detected – that is more specific to the primitive pulmonary cancer, and the presence of only one sarcoma marker vementine+, desmine and actine−. Also the presence of KI 67: 20%, predicted the proliferative and great metastatic power of the lung tumor was observed.
Additionally, lung cancer was the most frequent type and may develop in scleroderma as reported in most studies.
This allows to conclude for primitive lung carcinoma revealed with vulvar metastasis after elimination of the possibility of vulvar sarcoma.
The patient was treated by chemotherapy (Taxol/Platin) with partial response from the lung after 3 cycles and palliative radiotherapy in the vulva with a good response.
This case described primary lung carcinoma associated with scleroderma, revealed by a vulvar metastasis, which may be related to the aggressiveness of lung cancer when the lung fibrosis follow-up is not performed well to detect early the development of lung tumors in the patient with systemic scleroderma.

RESUMEN

Palabras clave:
Cancer du poumon
Metastases vulvaires
Sclerodermie systemique

Le carcinome métastatique de la vulve est rare, son incidence est estimé entre 5% et 8%.
D'autre part les tumeurs malignes ont été décrite dans 3-11% de la sclérodermie systémique (ScS) cas.
Nous rapportons le cas d'une patiente, 66 ans ménopausée, ses antécédents médicaux ont été marquée par une maladie vasculaire rhumatismale (sclérodermie systémique) depuis 1993 sans atteintes musculaires, rénales, cardiaques ou HTA (hypertension artérielle) et sans histoiretabagique.
La patiente a représenté une masse vulvaire de la lèvre droite de la vulve en Décembre 2011, qui avait progressivement augmenté de taille.
La tomodensitométrie abdomino-pelvienne a montré une masse lobulaire de la lèvre droite avec une nécrose centrale, 7 cm l'axe le plus large, le rectum et la paroi vaginale étaient normale. Aucune adénopathie inguinale ou iliaque a été noté.
Une biopsie-exérèse ambulatoire a révélé une tumeur maligne peu différenciée suggérant un cancer.
IHC: CK7+/CK20−, récepteurs des oestrogènes−, AE 1 AE 3+, vimentine+, S100−, Desmina−, CD34−, KI 67: 20%.
Le scanner thoracique a révélé une grosse masse de 4 × 3 cm au niveau de la base du poumon droit avec lymphadénopathie paratrachéaux droite de 3 × 2 cm.
Une bronchoscopie a révélé: une sténose de la partie médiastinale de l'arbre bronchique droit. Et la biopsie bronchique a révélé un carcinome du poumon peu différencié, non à petites cellules, ce qui était identique à la tumeur vulvaire.
Conclusion: La présence de la lésion pulmonaire unique avec un seul lymphadénopathie paratrachéal avec à l'anatomopathologie et immunohistochimie (IHC) un profil similaire à la lésion vulvaire, et le profil IHC particulier avec CK7+ et CK20− qui sont plus spécifiques au cancer primitif pulmonaire, et la présence d'un seul marqueur de sarcome vementine+, desmine et actine−. Aussi la présence de KI 67: 20%, qui prédit le grand pouvoir prolifératif et métastatique de la tumeur pulmonaire.
En plus le cancer du poumon est le type de cancer le plus fréquent qui peut se développer chez les patients sclérodermiques dans la plupart des études.
Ces arguments ont permis de conclure au carcinome primitif du poumon révélé par des métastases vulvaire après élimination de la possibilité de sarcome vulvaire.
Traités par chimiothérapie (Taxol/Platin) avec une réponse partielle au niveau du poumon après 3 cycles et radiothérapie palliative de la vulve avec une bonne réponse.
Ce cas décrit un carcinome primitif du poumon associé à une sclérodermie systémique, révélé par une métastase vulvaire, qui peut être lié à l'agressivité du cancer pulmonaire lorsque le bon suivi de la fibrose pulmonaire n'est pas effectué pour le dépistage précoce des tumeurs pulmonaires développées chez des patients suivis pour sclérodermie systémique.

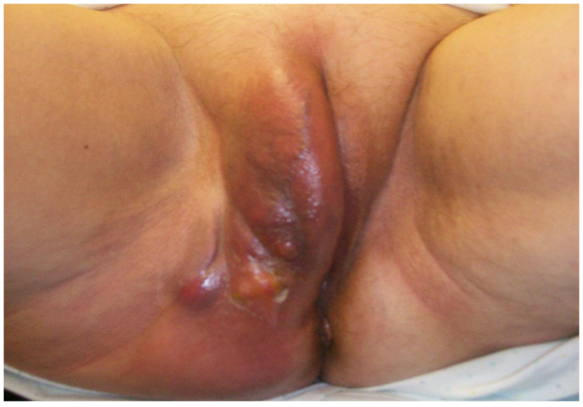

Fig. 1 – Inflammatory mass from the right vulva.

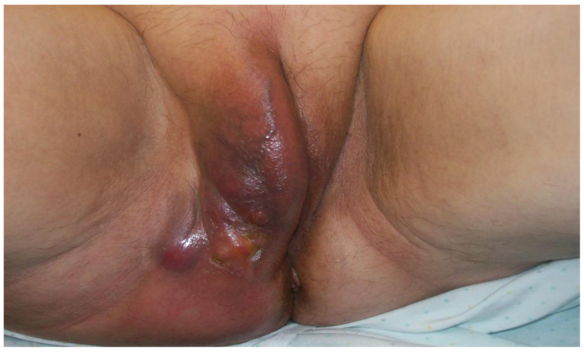

Fig. 2

1. Introduction

Scleroderma is a chronic, multisystem, autoimmune disease. Previous studies have shown an increased risk of malignancy in scleroderma; the most common cancers were lung cancer and breast cancer.

The lung cancer present at an advanced stage where palliative measures are utilized have a high propensity for distant metastases.

Metastatic carcinoma to the vulva is rare, the incidence is believed to be between 5% and 8% based on two large series from the Washington University School of Medicine. Lung cancer with metastasis to the vulva is very rare. One case has been reported in the literature as the presentation of lung carcinoma as a vulvar metastasis.

We reported one case of lung cancer developed by a nonsmoking woman with scleroderma in whom the mean disease duration was 18 years at the time of lung cancer diagnosis revealed at metastatic stage. This case revealed the interest for a good lung fibrosis follow up of the patient with scleroderma, especially that SSc patients have risk factors for the development of malignancy.

2. Case report

We report the case of one patient, a 66-year-old postmenopausal woman, whose medical history was marked with rheumatic vascular disease (systemic sclerodermy) with diffuse cutaneous (dcSSc) clinical subtype, overall decrease in number of capillaries, but without muscular, renal or cardiac lesions or HTA, and without tobacco history.

ANA (antinuclear antibodies) (+) and anti-scl70 (+), with disease duration of 18 years. With the vitamin D deficiency.

The last thoracic scan in 2008 revealed a minimal bilateral basal pulmonary and peripheral fibrosis without alveolitis.

The woman presented with a new vulvar mass of the right labia in December 2011 that had progressively enlarged in size.

The patient's exam found a 4 cm × 4 cm, firm, irregularly contoured and mobile inflammatory mass protruding from the right vulva just lateral to the perineal body (Figs. 1 and 2).

Bimanual and rectovaginal exam did not reveal vaginal or rectal involvement of the mass.

The remaining vulva, vagina, and vaginal cuff were without other notable lesions and there was no palpable inguinal lymphadenopathy.

CT scan of the abdominopelvic region demonstrated a lobular mass of the right labia with central necrosis measuring 7 cm in the wide axis, and the rectum and the vaginal wall was normal. The mass appeared to be contiguous with the obturator internus muscle and extended through the skin of the perineum. No inguinal or iliac lymphadenopathy was noted.

No other lesions in the abdomen were found. Metastasis of the vulva is shown in Figs. 3 and 4.

An outpatient excisional biopsy revealed a poorly differentiated malignant tumor suggestive of IHC: CK7+/CK20−, estrogen receptors−, AE 1 AE 3+, vimentine+, S100−, Desmina−, CD34−, KI 67: 20%.

The patient was referred for oncological consultation, and the new physical exam found crackles in the basal right lung.

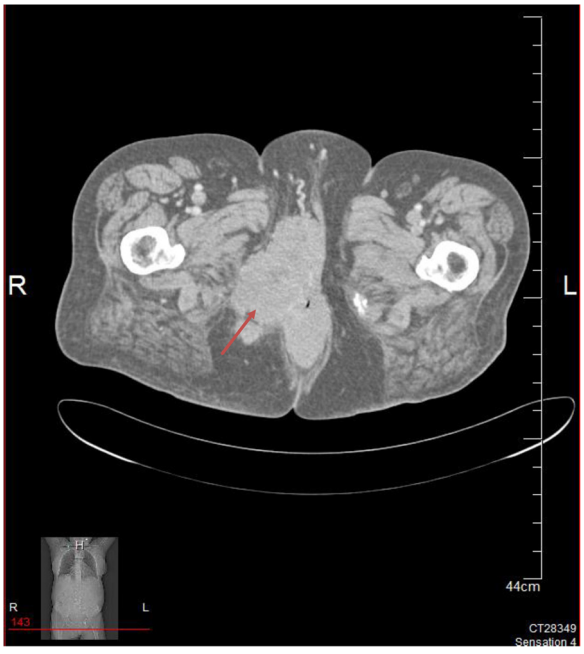

Fig. 3 – CT scan image for the tumor of the vulva.

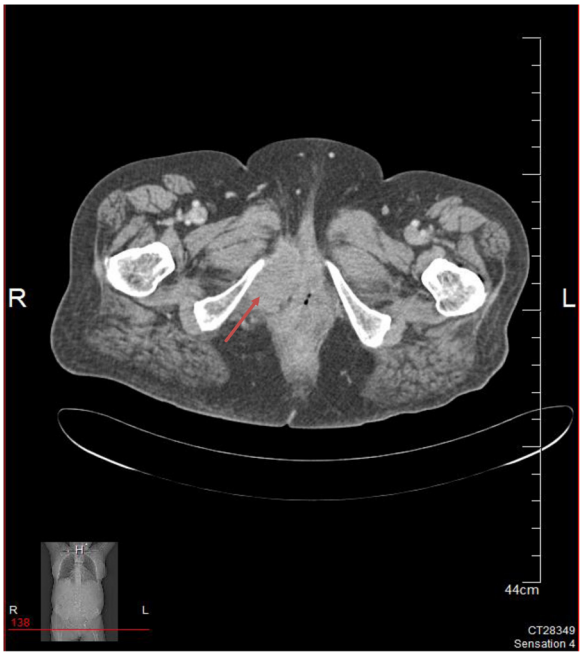

Fig. 4 – CT scan image for the tumor of the vulva.

The thoracic scan was performed and revealed a large mass of 4 cm × 3 cm in the right lung base with right paratracheal lymphadenopathy 3 cm × 2 cm (Figs. 5 and 6).

A bronchoscopy revealed: discrete stenosis of the mediastinal portion of the right bronchial tree.

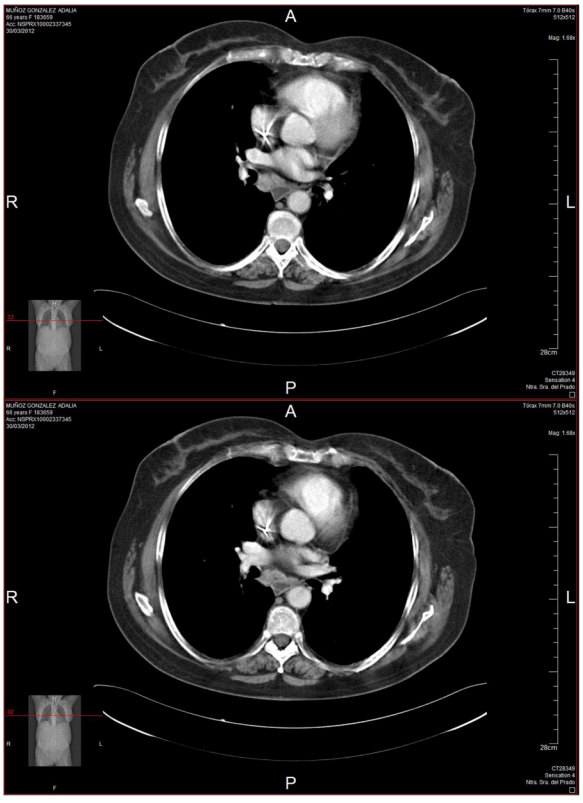

Fig. 5 – Scan image of paratracheal lymphadenopathy.

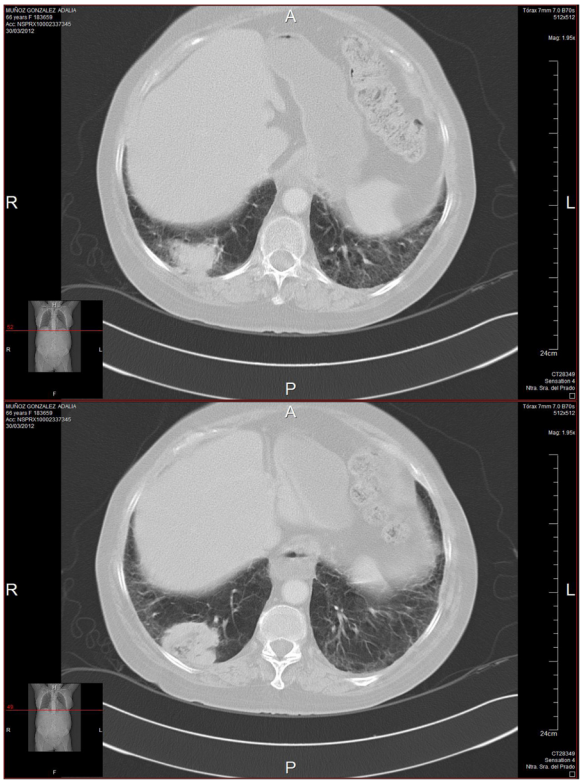

Fig. 6 – Scan image of tumor in the right lung base.

And the bronchial biopsy revealed poorly differentiated lung carcinoma, non-small cell, which was identical with the vulvar tumor.

3. Results

The history of scleroderma and the presence of risk factors for the development of malignancy, especially lung cancer, including female gender (older age at the time of diagnosis), and the diffuse cutaneous (dcSSc) clinical subtype, the presence of the single lung lesion with only one paratracheal lymphadenopathy with pathological and immunohistochemical (IHC) profile similar to the vulvar lesion, and the particular IHC profile with CK7+ and CK20− that are specific to the primitive pulmonary cancer and the presence of KI 67 20%, predicted the proliferative and great metastatic power of the lung tumor.

Also the presence of only one sarcoma marker vementine+, desmine and actine− was observed.

This allows to conclude for primitive lung carcinoma at the metastatic stage IV revealed with vulvar metastasis after elimination of the possibility of vulvar sarcoma.

The patient was treated by giving chemotherapy with partial response in the lung after 3 cycles CDDP/TAXOL but without improvement of sclerodermatous skin lesions, and palliative radiotherapy 30gry (10 × 3) in the vulva.

With good regression of tumor of the vulva (Fig. 7).

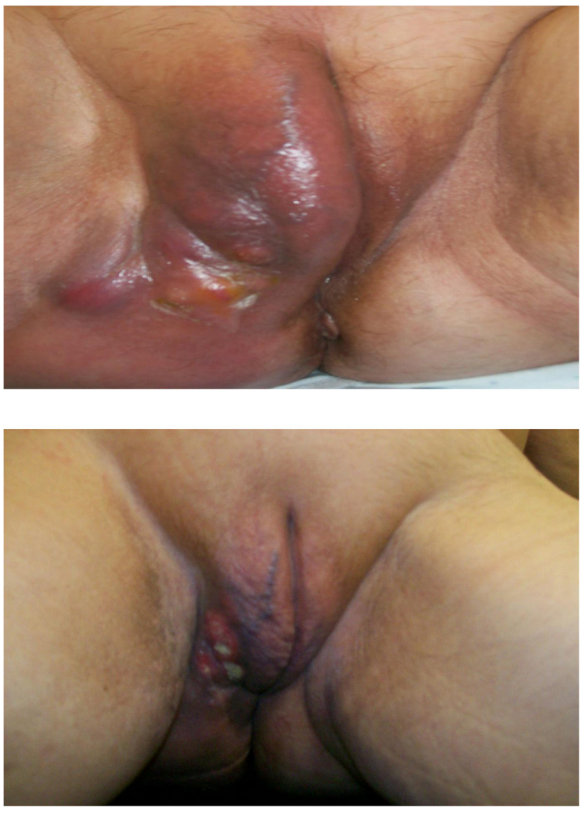

Fig. 7 – Vulvar masse before radiotherapy. Vulvar masse after palliative radiotherapy.

4. Discussion

In the large series from the Washington University School of Medicine, the most common sites of primary tumors of metastatic cancer to the vulva are the cervix, ovaries, and endometrium.

In our case the primary tumor was rare; it was the lung, and its histological type was carcinoma poorly differentiated malignant tumor. This type has a high propensity for distant metastases and it is often incurable, when metastases are present, the same as in our case, revealed by vulvar metastasis where palliative measures were used.

In our case the question was to determine whether the tumor is primary: vulvar sarcoma with lung metastasis or lung cancer with metastasis in vulva.

A biopsy of the chest lesion revealed poorly differentiated carcinoma, with histology identical to the vulvar biopsy.

In this case, considering the immunoprofiling played an important role in guiding the diagnosis: staining for TTF-1 was present and the pattern of differential cytokeratins, CK7 (positive) and CK20 (negative) could be seen with poorly differentiated primary carcinomas of the lung cancer.

However the sarcoma of the vulva was eliminated after IHC with desmin (–), actine liss muscle (–), and only vimentine (poorly+).

CD34(–), CD45(–), S100(–), RE(–), p63(–). KI67(+): 20%: predicted the proliferative and metastatic great power of the tumor.

The CT scan was used to help and confirm our diagnosis. It was demonstrated a single lesion in the right lung base with only a single right paratracheal lymphadenopathy, while the metastatic lesions were most often by multiples dropped ball.

4.1. *Vitamin D carence and lung cancer*

What is more, the patient had also the vitamin D deficiency, representing one of the factors promoting the development of certain types of cancer.

Calcitriol (1,25-dihydroxyvitamin D3), the hormonally active form of vitamin D, is involved in key regulatory processes such as proliferation, differentiation and apoptosis in a wide variety of cells, as it causes the suppression of inflammation and exerts growth inhibitory effects. Mechanisms for these actions have been proposed to be the interaction of active vitamin D derivatives with a specific nuclear receptor (VDR receptor) and/or with membrane targets. In vitro studies, performed with lung cancer cell lines, have shown an inhibitive effect of vitamin D derivatives on cell-growth and proliferation.

Furthermore, animal studies have demonstrated the capability of these compounds to suppress invasion, metastasis and angiogenesis in vivo, suggesting that administration of vitamin D derivatives may be used as an adjuvant therapy for lung cancer.

The institute for cancer research of Montbello, Norway presented the work that aimed at investigating the impact of season of diagnosis and residential region, both influencing the vitamin D level, on the risk of death from lung cancer in patients diagnosed in Norway.[1]

Data on all incident cases of lung cancer between 1964 and 2000 were collected. Risk estimates were calculated as relative risk (RR), with 95% confidence intervals using Cox regression model. The seasonal variation of 25-hydroxyvitamin D was proposed, as a high level of sun-induced 25-hydroxyvitamin D can be a prognostic advantage for certain groups of lung cancer patients, notably for young men.

Assessments were made from routine measurements of samples performed at the Hormone Laboratory of Aker University Hospital.[15,16]

These results indicate that season of diagnosis is of prognostic value for lung cancer patients, with a ≈15% lower case fatality for young male patients diagnosed during autumn versus winter (RR = 0.85; 95% CI, −0.73 to 0.99; $P = 0.04$). Residing in a high UV region resulted in a further lowering of the death risk than residing in a low UV region.

4.2. *Systemic scleroderma and lung cancer*

The strongest argument, however, was the history of the patient with scleroderma; it could be a paraneoplastic syndrome. Therefore, the history of scleroderma, with disease duration of 18 years and the lack of improvement of scleroderma lesion after lung chemotherapy suggested a probable absence of a paraneoplastic syndrome in our case.[2,3]

So, this lung cancer was probably a secondary tumor to patient's systemic scleroderma.

Indeed, among solid malignancies, lung cancer was the most frequent type of cancer in most studies, followed by breast, esophageal cancer and lymphomas.

In scleroderma, cancer may develop in organs affected by fibrosis, such as the lungs, esophagus or skin.

The higher incidence of lung cancer has been associated with pulmonary fibrosis.

Mechanisms for these actions have been proposed. If possible, a facilitator role of pulmonary fibrosis for cancer development. Chronic inflammatory processes inducing cell damage (cell atypia, metaplasia, dysplasia) via genetic abnormalities (P53 mutation, microsatellite unstable, heterozygous loss) and increased synthesis of growth factors and cytokines fibrosing (TGF–PDGF).

In the patients with scleroderma of the diffuse cutaneous (dcSSc) subtype, the same as in our case, the antibody: anti-topo-isomerase 1 distorted the function of this nuclear enzyme involved in genome repair thereby facilitating oncogenesis.

The aggressivity due to the high risk of apoptosis defect, genomic instability and surexpression of selectin, facilitates tumoral cells migration and metastatic dissemination.

The first example was reported by Zatuchni et al. in 1953.[4] His studies assessed and calculated the relative risk of cancer in patients followed for scleroderma at 1.5–2.1 (all backgrounds, all types and although in the absence of smoking) and demonstrated that the disease duration for SSc was 5–13 years at the time of cancer diagnosis with 22–39% of bronchogenic cancer.

It has been suggested that the risk of malignancy increases with age at the time of SSc diagnosis.

In the literature we found a large cohort of studies assessing malignancies that developed in scleroderma patients. Roumm and Medsger[5] reported 14 tumor cases in a cohort of 262 American SSc patients (5%).

Abu-Shakra et al.[6] reported a 7.3% prevalence of malignancies among 248 SSc patients. Lung cancer and breast cancer were the most common types.

Chatterjee et al.[7] reported 45 cases of malignancy in a cohort of 538 SSc patients (8.4%). Lung cancer was the most prevalent (10 cases).

According to a recent meta-analysis, the prevalence of malignancies in SSc is between 3.6% and 10.7%.

In a majority of the cohorts, lung cancer was associated with both smoking and pulmonary fibrosis and was the most prevalent malignancy in systemic scleroderma.

Risk factors for the development of malignancy in SSc patients, especially lung cancer, may include:

female gender
older age at the time of diagnosis
and the diffuse cutaneous (dcSSc) clinical subtype.

These factors were all present in our patient strengthening the diagnosis of primary pulmonary.

4.3. *E-cadherin–catenin adhesion complex in lung cancer*

E-cadherin, is a transmembrane glycoprotein that mediates calcium-dependent intercellular adhesion and is specifically involved in epithelial cell-to-cell adhesion molecule.[8,9] It plays a key role in the maintenance of tissue integrity. The function of this molecule is partly mediated by alpha-/beta-/gamma-catenin. Loss or dysfunction of E-cadherin is associated with an invasive phenotype, a more advanced tumor stage,[10] and has a role as a tumor suppressor gene.[6]

In the Feinberg School of Medicine, Northwestern University, Chicago, USA, Lam et al. reported that pulmonary fibrosis is a disease that results in the loss of normal lung architecture, but the signaling events that drive tissue destruction are incompletely understood. Wnt/beta-catenin signaling is important in normal lung development, but whether abnormal signaling occurs in lung fibrosis due to systemic sclerosis and the consequences of beta-catenin signaling toward the fibrogenic phenotype remain poorly defined. We can show nuclear beta-catenin accumulation in fibroblastic foci from lungs of patients with systemic sclerosis-associated with advanced pulmonary fibrosis.

In our case, pulmonary fibrosis secondary to scleroderma with reduced beta-catenin and E-cadherin expression is implicated in the progression and development of her lung cancer.[11]

In fact, Kase et al. analyzed the expression of E-cadherin and beta-catenin in human lung cancer to determine the relationship with clinicopathological factors and prognosis.

E-cadherin and beta-catenin expressions were evaluated in 331 lung cancer tissues in an immunohistochemical analysis.

Reduced E-cadherin expression was evident in 138 (42%), and reduced beta-catenin expression was noted in 122 (37%) patients. Reduced E-cadherin expression significantly correlated with lymph nodes metastasis ($P = 0.0199$). E-cadherin expression significantly correlated with an increasing histological differentiation ($P = 0.0403$). Although reduced E-cadherin did not correlate with the prognosis ($P = 0.0652$), reduced beta-catenin expression did significantly correlate with a poor prognosis ($P = 0.0001$). When both were reduced, prognosis was significantly unfavorable compared with either the reduced expression ($P = 0.0493$) or preserved expression ($P = 0.0003$). Multivariate analysis showed a significantly lower survival rate for patients with reduced beta-catenin ($P < 0.0001$).

Inactivation of the E-cadherin–catenin adhesion complex, induced by genetic and epigenetic events, plays a significant role in multistage carcinogenesis, and seems to be associated with dedifferentiation, local invasion, regional metastasis, and reduced survival in lung cancer.[12]

They interpreted these data to mean that dysfunction of the cell–cell adhesion molecule has a role in the progression of lung cancer and that analysis of E-cadherin and beta-catenin expression can provide clinically important evidence on which to base treatment.[13]

Also, scleroderma is an autoimmune disease with a characteristic vascular pathology, this vasculopathy was that scleroderma has true capillary rarefaction, the same as in our case, along with the loss of capillaries there was a dramatic change in endothelial phenotype in the residual vessels. The

molecules defining this phenotype are: vascular endothelial cadherin, a supposedly universal endothelial marker required for tube formation (lost in the scleroderma tissue) and a signaling molecule whose expression coincides with the end of branching morphogenesis during development and tumor angiogenesis.[14]

Immunosuppressive agents confer higher risk to develop malignancies in SSc (systemic scleroderma)[21].

In addition to the underlying disease, as described later, some immunosuppressive and antirheumatic agents, such as cyclophosphamide (CPH), azathioprine (AZA) or tumor necrosis factor α (TNF-α) inhibitors may further increase the risk of malignancies in various rheumatic diseases.[15–18]

Tumorigenicity of CPH has been correlated with duration of treatment, cumulative dose and concomitant smoking.[17,19,20]

Isik et al.[20] have recently reported 8 cases of malignancies in CPH treated SSc patients.

There have been much controversy regarding these immunosuppressants, as these agents, despite their possible carcinogenicity.

In clinical practice, CPH is usually administered for the treatment of severe manifestations of SSc including alveolitis, pulmonary fibrosis, and extended skin involvement. Thus, the expected benefit may override the direct carcinogenic risk conferred by CPH.[15]

In our case, patient does not have alveolitis and had localized lung fibrosis, so she did not receive immunosuppressants.

5. Conclusion

Increased risk of malignancies has been associated with SSc; the organs affected by extensive fibrosis include the lungs and esophagus and may be prone to cancer development. Cancer risk has been associated in most cases with dcSSc and older age, and diffuse cutaneous (dcSSc) clinical subtype like our case with metastasis in the vulva.

Therefore, performing a close follow-up in dedicated centers is essential in order to detect the development of tumors early.

Conflict of interest

None declared.

Financial disclosure

None declared.

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