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Case Report

# Late distant recurrence of endometrial cancer in the lung after 5 years of radical surgery: a case report

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## Abstract

Most endometrial cancer recurrences are seen within 3 years of radical treatment and are associated with various prognostic factors (tumor size, stage, grading, histotype . . .). Late relapses are considered rare. In this report, we present a case of a patient who was treated for endometrial adenocarcinoma. She underwent total resection and received four cycles of first-line adjuvant chemoradiation therapy using a combination of platinum salts and taxane. A total of 58 months later, the patient presented with chronic cough, and hemoptysis. A computed tomography scan revealed the presence of lung nodules suggestive of metastases. Biopsies were performed, showed infiltration of the bronchial mucosa by a poorly differentiated carcinoma of an endometrial origin. Our patient received two cycles of palliative chemotherapy but was lost to follow-up and eventually died. Imaging after hemoptysis revealed disease progression. Endometrial carcinoma patients treated with radical surgery (R0) can relapse after years of free disease. Thus, recommended: closer follow-up, clinical examination, symptom-based imaging.

## INTRODUCTION

Endometrial cancer (EC) commonly metastasizes to the lungs, which is mainly attributed to hematogenous dissemination [1]. Its recurrence is prevalent within 3 years after primary treatment, with almost 80% in the early stages of all cases occurring during this period [2]. However, late relapse after 4 years is scarce in the medical literature. Past research reported a correlation between pulmonary recurrence and unfavorable prognosis [1]. The likelihood of recurrence is associated with various prognostic factors including tumor size, stage, grading, lymphovascular invasion, depth of myometrial invasion and high-risk histotypes including clear cell, serous and carcinosarcoma [3]. Notably, patients with relapsed EC have a poor prognosis and unfavorable outcomes. In this report, we describe a case of a 69-year-old female with a history of EC who was admitted with respiratory symptoms after 4 years of treatment and ultimately diagnosed with pulmonary metastasis from EC. To the best of our knowledge, this is the first case to be reported in Morocco on this rare clinical situation.

## CASE PRESENTATION

A 69-year-old female patient, postmenopausal for 24 years, was treated in January 2016 for an EC. EC was discovered after the patient presented with moderate postmenopausal uterine bleeding, endometrial thickening on ultrasound, and hypertrophy on hysteroscopy. The patient underwent total colpohysterectomy with bilateral adnexectomy and lymph node dissection and she was staged as FIGO stage II (pT2N0M0). The pathological examination of the surgical specimen revealed a high-grade clear cell EC infiltrating the entire uterine wall, the isthmus and the cervix. The lymph node dissection was free of any tumor infiltration. The patient received first-line adjuvant chemotherapy based on carboplatin AUC5 and paclitaxel at a dose of 175 mg/m$^2$ every 21 days, for four cycles. She also completed external radiotherapy on the tumor bed (46 Gray) after the completion of chemotherapy.

After 58 months, the patient presented with respiratory symptoms consisting of chronic cough and hemoptysis. The clinical examination of our patient showed no abnormalities.

A computed tomography (CT) scan (Fig. 1) revealed the presence of a bilateral metastatic right superior lobe hilar-pulmonary tumor process associated with enlarged mediastinal lymph nodes. Bronchoscopy was also performed, and it revealed a tumor-like growth at the entry of the right superior lobe with an inflammatory appearance of the mucosa (Fig. 2). Biopsies were consistent with infiltration of the bronchial mucosa by a poorly differentiated carcinoma with an immunohistochemical profile of an endometrial origin staged as T4N0M1a (Fig. 3). The histopathological analysis of a lung biopsy showed positive CK7, Vimentine and PAX8 with negative TTF1. After a multidisciplinary team meeting, she received two cycles of the previous regimen as a palliative option, and she was lost to follow-up. A total of 3 months after cancer recurrence, she died. Imaging obtained urgently after presenting with hemoptysis showed disease progression.

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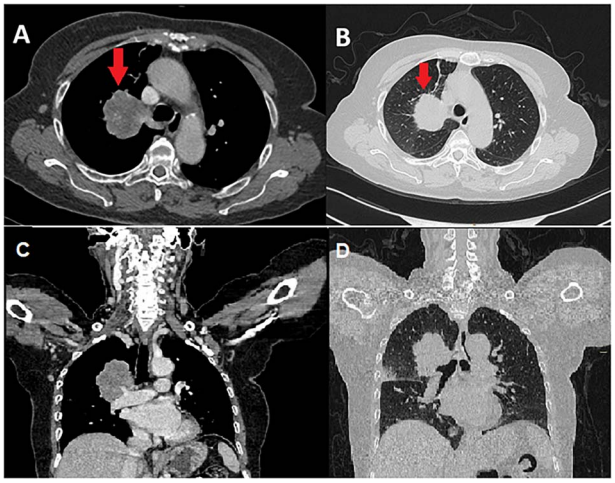


**Figure 1.** Thoracic CT scan with contrast enhancement in axial view, using mediastinal (**A**) and parenchymal (**B**) window settings, reveals a tissue-density lesion measuring 45 × 12 × 54 mm in the right hilar-pulmonary region. The lesion encompasses the upper lobe bronchus and the azygos vein and is associated with the presence of bilateral pulmonary nodules. (**C**) Thoracic CT scan with contrast enhancement in coronal view and (**D**) using mediastinal parenchymal window settings, reveals a tissue-density lesion measuring 45 × 12 × 54 mm in the right hilar-pulmonary region. The lesion encompasses the upper lobe bronchus and the azygos vein and is associated with the presence of bilateral pulmonary nodules.

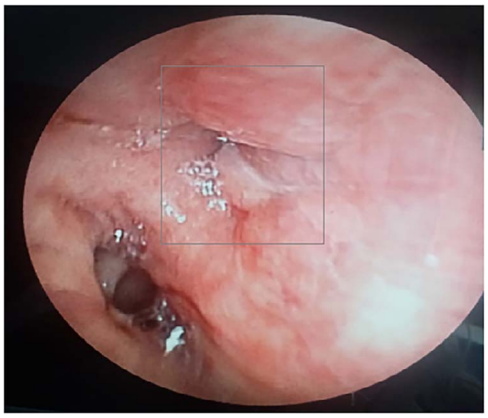

**Figure 2.** Photographed bronchoscopic image revealing a tumor-like growth at the entry of the LSD with an inflammatory appearance of the mucosa.

## DISCUSSION

The occurrence of pulmonary metastases in female genital tract tumors is relatively rare, with a reported prevalence ranging from 2.3% to 7% of cases [4, 5]. However, pulmonary metastases are the most common site of extrapelvic dissemination [6]. EC is also the most common gynecologic malignant tumor, with a recurrence rate of ∼13% [7]. It is essential to highlight that late relapses of early stage EC are rare after 4 years of follow-up. Of the cases with pulmonary metastases, 80% are metachronous lesions [2]. The risk of recurrence appears to be higher in women with certain clinical factors such as stage III or IV EC but rarely in early stages [2]. Interestingly, a long interval between the initial gynecological surgery and diagnosis of pulmonary metastases has been reported in the literature, with the longest interval being 17 and 22 years in two reported cases [8, 9]. Similarly, Ito *et al.* [5] reported an isolated pulmonary metastasis 17 years after the initial diagnosis of EC. Therefore, even though the incidence of

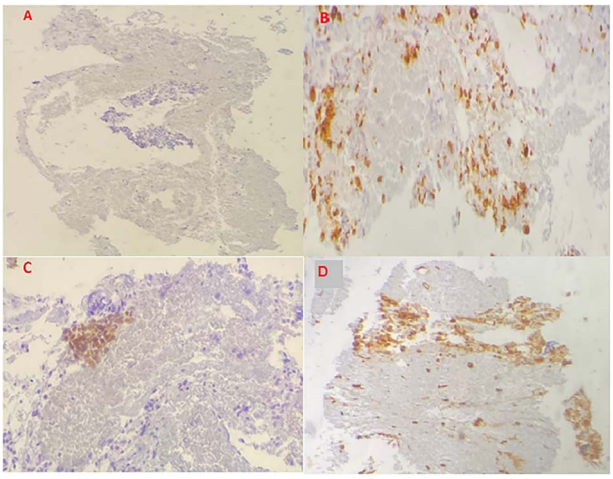


**Figure 3.** Invasion of the bronchial mucosa by an infiltrating poorly differentiated carcinoma, whose immunohistochemical profile is consistent with an endometrial origin. The suspicious flattened cells express cytokeratin 7, PAX 8 and vimentin, and do not express cytokeratin 20, and TTF1.

pulmonary metastases in tumors of the female genital tract is relatively low, it's important to keep in mind the possibility of late-onset pulmonary metastases, which can occur years after the initial diagnosis and surgery, particularly for early stages treated with radical surgery as in our patient.

In general, nearly 80% of all EC recurrences occur within 3 years following initial treatment [2]. Despite the use of chemotherapy, EC can sometimes metastasize, because not all cancer cells are equally sensitive to treatment. Twelve months is the reported median interval for diagnosing pulmonary metastases after initial surgery for EC [10]. The patient we described herein presented with metastasis even after radical resection and adjuvant chemoradiation. Indeed, lung metastasis of EC are usually characterized by multiple bilateral lesions [10] similar to our patient's presentation at the time of relapse. Several authors have suggested various favorable prognostic factors including disease-free interval >1 year, histology of grade 1–2, estrogen receptor positivity, myometrial invasion <50%, unilateral lung lesions, lesion size <2 cm and <5 nodular lesions in a single lung [11, 12]. In our case, the patient had a grade 3 tumor, negative estrogen receptors, myometrial invasion superior to 50%, tumor size of 56 mm and more than five nodular bilateral lesions. Once metastatic disease is identified, cisplatin, doxorubicin and paclitaxel-based chemotherapy may be used as palliative treatment [7]. Patients are classified as having high-risk EC if they have: stage IB grade 3 endometrioid carcinoma, serous or clear cell adenocarcinoma of any stage, stage III and IV, lower uterine segment involvement, positive peritoneal cytology, lymphovascular space invasion, older age (>65 years old), race (black patients have a poorer outcome compared to whites, and Asian patients appear to have a better outcome) and molecular factors including POLE, p53 and Phosphatase and tensin homolog (PTEN) mutations, microsatellite instability and tumor expressing estrogen/progesterone receptors [13]. In our case, the patient had several poor prognostic factors; age superior to 65 years, clear cell adenocarcinoma, lymphovascular invasion, grade 3 and infiltrated cervix and isthmus.

For selected patients with limited and resectable disease in distant isolated recurrences, surgical resection is a feasible option [3]. In addition, Dowdy *et al.* (14) reported an overall survival (OS) of 98 months in patients diagnosed with pulmonary tumor

solely confined to the lung and with low-grade malignancy, not exceeding 2 cm (14). Conversely, Taner *et al.* [1] revealed a significantly lower OS in patients with synchronized pulmonary tumor in comparison to those with isolated pulmonary tumor (10 months vs. 54 months, respectively). Interestingly, the size and number of tumoral nodules in the lung were not found to have any correlation with OS in both studies [1].

Furthermore, the underlying processes become challenging when late recurrence happens, which takes place several years after the initial therapy. This phenomenon has been illuminated by recent research, revealing potential cellular mechanisms involved (15). For instance, studies have highlighted the role of residual cancer stem cells, acquired genetic mutations or dormant micrometastases as potential factors that may contribute to late recurrence in these patients, eventually leading to tumor reactivation and recurrence. These micrometastases, undetectable at the time of initial treatment, can remain in a dormant state for years before initiating angiogenesis and subsequent tumor growth. Further investigation into these cellular mechanisms is essential to advance our understanding of late recurrence in early stage EC and potentially identify novel therapeutic targets for improved management and prevention of late relapses.

## CONCLUSION

The occurrence of pulmonary metastases in female genital tract tumors is relatively uncommon for patients diagnosed with early stage EC. Generally, EC recurrences occur within 3 years following initial treatment. Improved survival rates are observed in cases where the recurrence of EC is limited to the lungs. After patients with early stage EC have completed treatment, regular monitoring for >5 years is crucial. Promisingly, liquid biopsy-based approaches may provide accurate diagnostic assessment of circulating tumor cells in patients declared disease-free and responsible for late recurrence.

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## CONFLICT OF INTEREST STATEMENT

The authors have no competing interests to declare.

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## AUTHOR CONTRIBUTIONS

HC wrote the manuscript. AD and AH participated in the clinical practice management of this case. Prof. AT and Prof. HK supervised the clinical practice and the writing process of this case report.

## DATA AVAILABILITY

All data generated or analyzed during this study are included in this article.

## HUMAN AND ANIMAL RIGHTS

This case report was conducted in accordance with the Declaration of Helsinki and now ethical committee approval was required for this case report.

## INFORMED CONSENT

The patient provided consent for this case report to be published.

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