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# Triple malignancy in a single patient including a squamous cell carcinoma of the cervix, a colloid adenocarcinoma of the colon and a lung adenocarcinoma: A case report and literature review

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## ABSTRACT

**INTRODUCTION:** The association of two cancers in the same patient is unusual but has been widely reported in the literature, while triple malignancy in the same patient is exceptional. Indeed, only very rare cases have been described.

**CASE PRESENTATION:** A 70-year-old woman treated in our institute in 2006 for a tumor of the cervix. She underwent extrafascial hysterectomy. Pathology revealed a well differentiated squamous cell carcinoma of the cervix (pT1N0M0). No external pelvic radiation or brachytherapy were done. The patient remained in good control until 2013 when she presented a tumor of the ascending colon. A right hemicolectomy was made. Pathology confirmed a colloid adenocarcinoma (pT3N0M0). No adjuvant chemotherapy was given. Three years later, a Computed tomography scan of the chest revealed a nodule of the lower lobe of the left lung. Biopsy was made. Histology with immunochemistry revealed the diagnosis of lung adenocarcinoma. Positron emission tomography scan showed abnormal fluorodeoxyglucose uptake in the lung nodule with no anomaly in mediastinal nodes and no metastasis. A left lower lobectomy was performed with lymph node dissection. Pathology confirmed the diagnosis of 2.5 cm lung adenocarcinoma without node invasion (pT1N0M0). No chemotherapy was given. After 14 months, the patient remained in good control. **CONCLUSIONS:** Triple malignancy in a single patient is exceptional. The management depend on stages. Surgery is the standard of care in localized cancers.

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## 1. Introduction

The improvement of diagnostic tools and the increasing effectiveness of cancer therapies have led to better prognosis with prolonged survival rates among cancer patients. This situation has made the problem of developing subsequent primary tumors more frequent. In the literature, the prevalence of multiple primary cancers is estimated between 0.73 and 11.7% and the incidence is increasing with age [1].

Cancers survivors had a 14% higher risk of developing a new malignancy than would have been expected in the general pop-

ulation according to the cancer registries in the National Cancer Institute. Woman had a slightly higher relative risk than men for multiple primary malignancy, and the most implicated sites were colon, breast, lung, and melanoma of the skin [2].

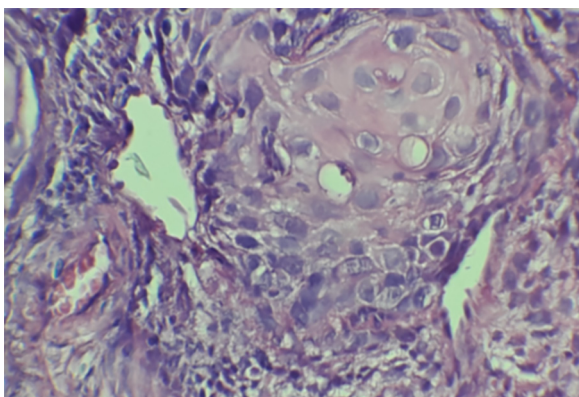
Despite its low incidence, the association of two malignancies in a single patient has been widely reported in the literature, while only very rare cases of triple malignancies have been described [3–5]. We report an exceptional case of a 70-year-old woman successfully treated by surgery in Mohamed V Military University Hospital of Rabat for a squamous cell carcinoma of the cervix, a colloid carcinoma of the colon and a lung adenocarcinoma while reviewing the appropriate literature. This work has been reported in line with the SCARE criteria [6].

## 2. Case presentation

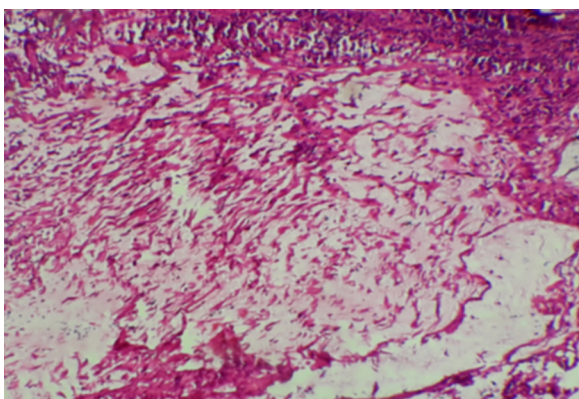
A 70-year-old non-smoking woman came to our institute in 2006 with a 2-month history of vaginal bleeding and malodor-

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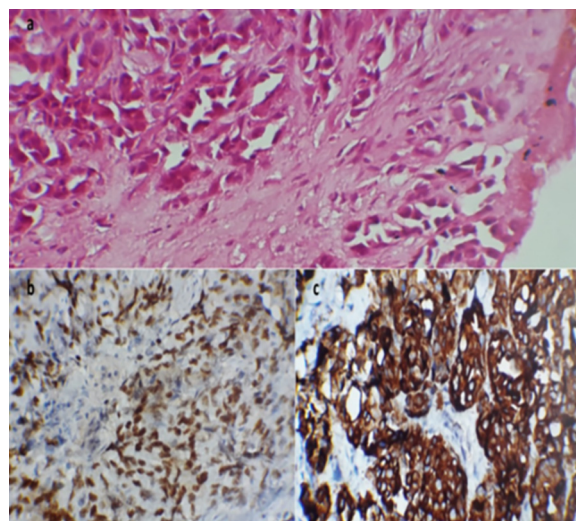


**Fig. 1.** Well differentiated squamous cell carcinoma of the cervix (HE x 40).

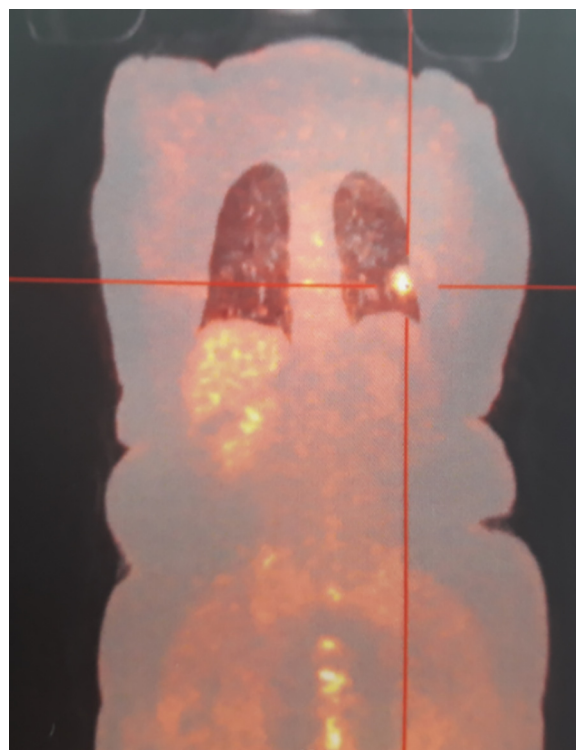


**Fig. 2.** Colloid adenocarcinoma of the colon (HE x 20).

ous discharge. Gynecologic examination found a 1 cm exophytic friable lesion arising from the cervix without parametrial or vaginal infiltration. Biopsy revealed the diagnosis of a well differentiated squamous cell carcinoma (Fig. 1). Imaging showed neither adenopathy nor distant metastases. The patient underwent extrafascial hysterectomy with lymph node dissection. Pathology confirmed the diagnosis of 1 cm squamous cell carcinoma without lymphovascular space invasion or node invasion (pT1N0M0). No external pelvic radiation or brachytherapy were done. The patient remained in good control until 2013 when she presented rectal bleeding. Colonoscopy showed an exophytic tumor of the ascending colon. Biopsy were performed and histological examination revealed a colloid adenocarcinoma (Fig. 2). Computed tomography scan did not find distant metastasis. A right hemicolectomy with lymph node dissection was made. Pathology confirmed a colloid adenocarcinoma without lymphovascular invasion or node invasion (pT3N0M0). No adjuvant chemotherapy was given. Three years later, the patient presented with 1-month history of cough and left chest pain. Physical examination was normal and the Karnofsky performance score was 90. A Computed tomography scan of the chest revealed a 2.5 cm nodule of the lower lobe of the left lung. Carcinoembryonic antigen and carbohydrate antigen 19-9 levels were normal. Biopsy was made. Histology with immunochemistry confirmed the diagnosis of lung adenocarcinoma; tumoral cells were positive for cytokeratin (CK) 7, Thyroid transcription factor-1 (TTF1), while there were negative for CK20, caudal-type homeobox transcription factor 2 (CDX2), synaptophysin and chromogranin (Fig. 3). Positron emission tomography scan revealed abnormal fluorodeoxyglucose uptake in the lung nodule (standardized uptake value = 4) with no anomaly in mediastinal nodes and no metastasis (Fig. 4). A left lower lobectomy was performed with lymph node dissection by a thoracic surgeon. There were no major complications,



**Fig. 3.** a- Lung adenocarcinoma (HE x 40); b- IHC: Positivity for TTF1; c- IHC: Positivity for CK7.



**Fig. 4.** Positron emission tomography scan showing abnormal fluorodeoxyglucose uptake in the left lower lung nodule (standardized uptake value = 4) with neither adenopathy nor distant metastases.

including bleeding, thrombosis, collapsed lung, respiratory failure or wound healing, and the patient left the hospital seven days after the operation. Histopathological examination of the surgical specimens confirmed the diagnosis of 2.5 cm lung adenocarcinoma without node invasion (pT1N0M0). No chemotherapy was given and the patient remained in good control without any recurrence at a 14-month follow up. Despite the interest that it could have, the study of the genetic panel of the patient could not be realized because of the lack of means.

### 3. Discussion

There are two categories of multiple primary cancers depending on the time of diagnosis of each primary site. Synchronous cancers occurs simultaneously or within an interval of six months, while metachronous cancers follow in sequence and more than six months apart [7].

Multiple malignancies are rare and most often involve two sites. The occurrence of the third malignancy is exceptional and occur in only 0.5% of malignant tumors [8]. Cervical cancer is the fourth most common cancer in woman in the world. Given the 67.2% ten-year relative survival rate for cervical cancer patients and the large number of women treated with radiotherapy, the development of subsequent primary cancers has become more frequent.

Data from 104760 one-year survivors of cervical cancer of 13 population-based cancer registries were analyzed. The risk of all second cancers was increased to a statistically significant extent (number = 12496; standardized incidence ratio [SIR] = 1.30; 95% confidence interval [CI] = 1.28 to 1.33). Cervical cancers patients treated with radiotherapy, were at increased risk for all second cancers and cancers at heavily irradiated sites (colon, urinary bladder, ovary, rectum, anus and genital sites) compared with general population [9].

Another study from the Taiwan's National Health Insurance database observed patients newly diagnosed with cervical cancer between 1997 and 2001. It has found 2004 cancers developed in 35175 patients with cervical cancer. The SIR for all cancers was 1.56 (95% CI, 1.50–1.63,  $p < 0.001$ ). SIR were significantly higher for cancers of the uterus (3.76), lung and mediastinum (2.28), bladder (2.26), bone and soft tissue (2.23) and colon (1.36) [10].

Recently, the occurrence of a second primary malignancy was analyzed in 12048 patients with cervical cancer reported to the Netherlands Cancer Registry between 1989 and 2008. During the study period, 676 (5.6%) patients were diagnosed with a second cancer. For women aged 50–69 years (the age of our patient when she presented cervical cancer), the SIR of second primary malignancies was 1.8 (95% CI: 1.6–2.0) for all cancers, 1.2 (95% CI: 0.8–1.8) for colorectal cancer and 3.5 (95% CI: 1.8–6.0) for lung adenocarcinoma. Cervical cancer survivors who underwent radiotherapy were at higher risk for a second tumor when compared to those without radiotherapy [11].

Our patient was 59-year-old at the moment of cervical cancer diagnosis for which she was successfully treated by surgery. Although she did not receive radiotherapy, she developed a second cancer in the right colon seven years later. A right hemicolectomy was performed with success. Three years later, she presented a 2.5 cm nodule of the lower lobe of the left lung. Biopsy reveled an adenocarcinoma. The problem was to differentiate between a third primary cancer located in the lung or a relapse of a colonic adenocarcinoma. Immunohistochemistry confirmed the diagnosis primary pulmonary adenocarcinoma. Indeed, tumoral cells were positive (+) for CK7, TTF1 and negative (–) for CK20, CDX2, synaptophysin and chromogranin; while in colonic adenocarcinoma, tumoral cells are typically CK20+, CK7+/- and CDX2+. The patient was treated successfully by a left lower lobectomy with lymph node dissection [12].

Only one similar case was reported in the literature; it was a patient with four primary tumors. These cancers were cervical carcinoma and lung carcinoma, which occurred synchronously, and basal cell carcinoma of the skin and rectal carcinoma which occurred metachronously. A successful resection of two synchronous and two metachronous cancers was performed successfully [13].

Although the mechanism of developing multiple primary cancers remains unclear, several factors have been suspected. Indeed, smoking, alcohol abuse, previous radiotherapy and/or chemother-

apy, hormonal factors, biological agents and genetic predisposition seem to be implicated.

Human Papilloma Virus (HPV) is the primary cause of invasive cervical cancer, and it plays a role in the etiology of cancers of the vulva, vagina, anus, and a subset of cancers in the oropharynx. The increased risk of HPV-related cancers among cervical cancer survivors may reflect transmission of HPV by sexual behavior to sites other than the cervix, a genetic susceptibility to oncogenic effects of HPV, or shared risk factors such as smoking. Indeed, it was observed increased risks for smoking-related cancers (pharynx, trachea/bronchus/lung, pancreas, and urinary bladder) in patients with cervical cancer treated with or without radiotherapy [9].

Among patients with colorectal cancer, 1–3% have a heritable cause. The most common is Lynch syndrome (LS). It is an autosomal dominantly inherited disorder of cancer susceptibility caused by germline mutations in DNA mismatch repair (MMR), including MLH1, MSH2, PMS1, and MSH6. MMR carriers have an excess risk for extracolonic cancers including the following sites: bladder, kidney, stomach, small intestine, hepatobiliary, endometrial, prostate, ovary, and breast. Multiple primary cancers are common in LS families. LS is characterized by microsatellite instability (MSI), but this condition is also found in sporadic colorectal cancer [14].

Others studies examining genetic factors found that phosphatase and tensin homolog (PTEN), loss of heterozygosity (LOH) and protein 53 (p53) mutations were more frequently observed in multiple primary cancer than in sporadic cancer [15]. In our case, molecular investigations were not considered because of absence of known familial genetic syndromes, but genetic analysis in patients with multiple primary cancers may provide information about the etiology of genetic changes that occur during carcinogenesis.

### 4. Conclusion

Triple malignancy in a single patient is exceptional. The management depend on stages. Surgery is the standard of care in localized cancers. The etiology remains controversial and a lot of cancer patients have to be followed for long periods to obtain adequate data about the development of subsequent malignancies.

### Conflicts of interest

The authors declare that they have no competing interests.

### Funding

None.

### Ethical approval

This case report was approved by the Military Hospital Mohamed V ethic committee.

### Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

### Author contribution

- Mahfoud T: Data collection, data analysis, design of the study, writing the paper.
- Tanz R: Data collection, data analysis, writing the paper.
- Khmamouche MR: Data collection, data analysis.

- EL Hammoumi MM: Surgeon performing the left lower lobectomy, data collection.
- Allaoui M: Data collection, writing the paper.
- Belbaraka R: Data analysis, design of the study, writing the paper.
- Ichou M: Data collection, data analysis, design of the study, writing the paper.

#### Guarantor

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