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WHEN METASTATIC CERVICAL CANCER PRESENTS AS MILIARY LUNG NODULES

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ABSTRACT

Miliary lung nodules are usually associated with tuberculosis, sarcoidosis, or malignancy. Here we present a case of primary cervical cancer with metastasis to the lungs. The patient presented a short history of shortness of breath which worsened rapidly after admission and required extracorporeal membrane oxygenation. She died 25 days after initial presentation. Postmortem diagnosis was primary cervical squamous cell carcinoma with metastasis to the lungs. This case report emphasizes the need to work with a broad range of differentials including uncommon presentations for miliary lung nodules.

KEYWORDS

Miliary lung nodules, metastasis, cervical cancer

LEARNING POINTS

- Cervical cancer can present as metastasis to the lungs manifesting radiologically as miliary lung nodules.
- A miliary pattern of lung nodules is highly non-specific, and a wide range of differentials need to be considered including infection, inflammation and malignancy.

INTRODUCTION

Miliary nodules refers to the appearance of innumerable, rounded pulmonary opacities which are ≤3 mm on chest radiographs and computed tomography (CT) scans of the lung[1]. Causes of miliary lung nodules range from infections to inflammatory processes and malignancy. Tuberculosis is a common cause of miliary lung nodules especially in endemic areas[2,3]. A miliary appearance of the lung can additionally be seen in conditions such as pulmonary sarcoidosis, silicosis, pneumoconiosis and hypersensitivity pneumonitis. Fungal infections can also cause miliary changes in the lungs. In cases where malignancy is considered, primary lung cancer rarely presents as a miliary pattern in the lungs and such a picture is commonly indicative of a metastatic process.

While the lung is the most common site of metastasis in cervical cancer (although less commonly in squamous cell carcinoma), other cancers are more commonly suspected when lung metastasis is encountered in clinical practice.

CASE DESCRIPTION

A 46-year-old woman presented to hospital with progressively worsening shortness of breath with a dry

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cough for 10 days. Cough was non-productive and there was no history of haemoptysis. She also complained of mild chest tightness associated with cough. The patient did not complain of fever, abdominal pain or change in urinary or bowel habits. She had a high body mass index, was previously independent in activities of daily living and was a smoker for 15 years.

The patient had a history of asthma. She also had history of type 2 diabetes mellitus a hypercholesterolemia. On further examination of her previous hospital attendances, it was noted that she had been investigated for excessive menstrual bleeding 2 years prior to presentation and had opted for hysteroscopy under general anaesthesia but was found unfit for anaesthesia due to neck stiffness. As she was virgo intacta the possibility of cervical cancer was thought to be low but further discussions were planned. However, the patient had subsequently failed to attend further gynaecological clinic appointments.

On initial presentation, the patient was found to be hypoxic, tachycardic and tachypnoeic. Coarse crepitations were heart bilaterally on auscultation of the chest. The breast examination did not yield any abnormalities.

She was escalated to the intensive care unit from the respiratory ward for high flow nasal oxygen (HFNO)/ continuous positive airway pressure (CPAP) on day 8 and was intubated on day 9. The patient was transferred on day 10 to a tertiary centre for extracorporeal membrane oxygenation (ECMO).

On admission, inflammatory markers were elevated *(Table 1)*. The patient was also found to be hyponatraemic and had normal kidney function but mildly deranged liver function. D-dimer was elevated. Chest X-ray on admission showed widespread nodular opacities in both lung fields. CT pulmonary angiogram (CTPA) was negative for pulmonary embolism *(Fig.1)*. Also reported in CTPA were miliary nodules in both lungs with prominent mediastinal and right hilar lymphadenopathy. Subsequent CT-abdomen and pelvis showed an enlarged uterus *(Fig. 2)*. A transvaginal ultrasound was then planned. Bronchoalveolar lavage (BAL) was also strongly advised but could not be done due to patient's unstable condition and high oxygen requirement. Tuberculosis (TB) enzyme-linked immunospot (ELISPOT) assay and multiple blood cultures were done, all of which were negative *(Table 2)*. Some yeasts were isolated on sputum culture and sensitivity.

The initial impression at the time of admission was atypical pneumonia or an infective exacerbation of asthma. The patient's case was presented in the respiratory multidisciplinary team meeting to discuss possible diagnoses based on her history and the appearance of miliary nodules in the lung. The patient was also discussed with the interstitial lung disease team in a tertiary centre, which felt that the most likely diagnosis was TB. Sarcoidosis was also a differential diagnosis, but there were no obviously enlarged lymph nodes, and the degree of hypoxia was unusual for sarcoidosis. Malignancy was also considered as one of the differentials although there was no obvious primary noted but transvaginal ultrasounds and thyroid ultrasound were awaited. Obtaining a transbronchial biopsy sample ideally via bronchoscopy given the amount of disease burden in the chest was felt to be the investigation of choice. However, as mentioned earlier, this was felt to be high risk due to considerable oxygen requirements and pneumothorax risk. BAL and endobronchial ultrasound guided biopsy were alternative investigations considered.

The patient was initially treated with co-amoxiclav and clarithromycin for possible atypical pneumonia. She was also treated with oral prednisolone given her background of asthma. Antibiotics were escalated due to worsening inflammatory markers. TB was felt to be a likely cause of her illness given radiological appearance of miliary nodules despite the negative ELISPOT (which does not completely rule out TB). TB treatment was started on advice of the microbiology consultant on call on day 5 of admission. Treatment with steroids (originally to cover for possible exacerbation of asthma) was continued for possible sarcoidosis, although this was felt to be less likely than TB. The patient was intubated on day 9 of admission due to ongoing high oxygen requirements and worsening respiratory failure.

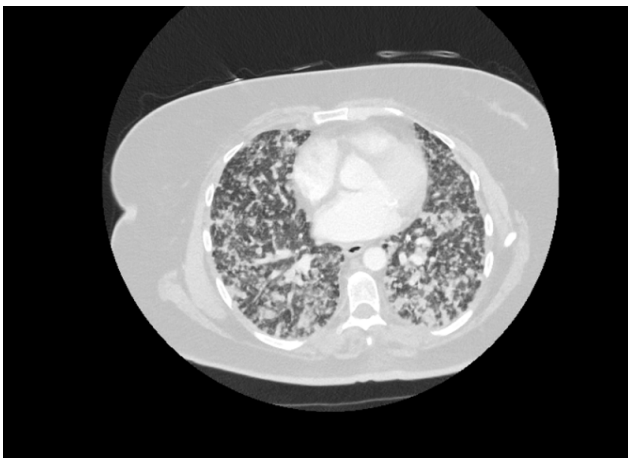


Figure 1. Computed tomography pulmonary angiogram – axial images of the chest showing numerous miliary nodules.



Figure 2. Coronal section of computed tomography scan of the-abdomen and pelvis showing enlarged uterus.

	Day 1	Day 3	Day 5	Day 9	Day 11
Haemoglobin (g/l)	101	96	92	92	76
White blood cells (g/l)	12.2	13.4	16.6	26.7	23.3
Platelets (g/l)	670	661	676	806	604
Neutrophils (g/l)	9.3	11.3	14.8	23.5	20.3
Prothrombin time (s)	13.1			12.4	15.3
Sodium (mmol/l)	126	126	126	132	139
Urea (mmol/l)	4	3.7	4	9	8.6
Creatinine (mmol/l)	49	45	42	51	62
Estimated glomerular filtration rate (ml/m)	>90	>90	>90	>90	90
Adjusted calcium (mmol/l)		2.65	2.65	2.78	
Phosphate (mmol/l)		0.4	0.6	0.6	
Lactate dehydrogenase (IU/l)					1833
Alkaline phosphatase (IU/l)	202	276	244	275	221
C-reactive protein (mg/l)	206	123	237	122	242
Procalcitonin (ng/ml)		0.18			
Random cortisol (nmol/l)					1075
Parathyroid hormone (pmol/l)			0.5 (day 4)		
Blood film					
Day 1		Hypochromic microcytic red cells Pencil cells Crenated red cells Rouleaux Thrombocytosis			
Day 8		Neutrophilia Thrombocytosis Red cell Anisopoikilocytosis			

Table 1. Blood results.

The patient was transferred to a tertiary centre for ECMO where she passed away 15 days after being transferred. A post-mortem revealed the primary cause of death to be metastatic cervical carcinoma to the lungs (primary -poorly differentiated squamous cell carcinoma of the cervix). Histology of the uterus showed benign adenomyosis.

DISCUSSION

A wide variety of pathologies, including inflammation, infection and malignancy, can give rise to miliary lung nodules[4]. When malignancy is considered, miliary appearance of the lungs is rarely seen as a primary lung cancer and its presence is almost universally indicative of a metastatic process[5]. The lungs are a commonly observed site for metastasis from other primary sites (including the lung itself) and frequently herald a guarded prognosis[4,6]. Extra pulmonary primary cancer sites include the colon, head and neck cancers, urologic and gynaecological cancers, breast cancer, melanoma and other organ primaries such as the thyroid and kidney[4,7].

According to the World Health Organisation, cervical cancer is the fourth most common cancer in women globally[8]. In the United Kingdom, cervical cancer accounts for 2% of all new cancer cases in women and is the 14th most common cancer in females[9].

Public education, routine screening programs as well as vaccination against human papilloma virus (HPV) have all contributed to a significant reduction incidence and prevalence of cervical cancer especially in the developed countries. Screening programs have also contributed to

	Positive	Negative	Comments
Blood cultures		Day 1	
RSV + Flu PCR		Day 1	
COVID 19 PCR		Day 1	
HIV- 1 + HIV-2		Day 2	
TB ELISPOT assay		Day 2	
TB blood culture		Day 2	
Urinary legionella		Day 2	
Urinary pneumococcus		Day 2	
Sputum MCS	Day 4		Blood-stained purulent. Yeasts isolated
TB culture (sputum)		Day 4	*Mycobacterium* sp. not isolated after 8 weeks
Serum beta d-glucan		Day 7	
EBV		Day 7	Equivocal
Parvovirus B19 IgM		Day 7	Equivocal (IgM detected)
Complement C3		Day 8	1.40 (g/l)
Complement C4		Day 8	0.27 (g/l)
Rheumatoid factor		Day 8	<0.15 (g/l)
Anti-DNA Abs		Day 8	0.6 IU/ml (reference range 0-15)
ANA	Day 8		Weak positive homogenous
Hepatitis B		Day 8	Not detected
Aspergillus		Day 8	*A. fumigatus* IgG: 6.2 mgA/l *A. fumigatus* IgG normal range: 0-79 mgA/l
Hepatitis C		Day 8	
High vaginal culture (London)	Day 12		Yeasts ++

Table 2. Specialised investigations and culture results.

cervical cancers being diagnosed at an earlier stage and therefore less metastatic disease being seen in conjunction with cervical cancer[10]. It is unlikely that our patient had been vaccinated against HPV (given her age) and pelvic examination had been limited by physical factors before she was lost to follow-up as mentioned in the case presentation. It is also important to note that patients with cervical cancer can remain relatively asymptomatic till the disease is detected at an advanced stage.

Our patient had a background of asthma and gave a history of being relatively well till approximately 2 weeks before presentation. Initial differentials included cancer, but on admission an infectious cause was felt to be more probable due to a short clinical history and raised inflammatory markers. Definitive diagnosis of lung nodules is histological[4]. A lung tissue biopsy was limited due to high oxygen requirements requiring intubation and ventilation within 10 days of admission and eventually ECMO. Only a postmortem definitive diagnosis of poorly differentiated squamous cell carcinoma of the cervix with metastasis to the lungs was ultimately possible.

Squamous cell carcinoma, adenocarcinoma and adenosquamous carcinoma are the three most common histological subtypes of cervical cancer[10]. Population based studies have demonstrated that the lungs followed by bone is the commonest site of distant metastasis in cervical cancer and the presence of metastatic disease (most often by haematogenous spread) carries a significantly poorer prognosis. Previously published case reports alluding to lung metastasis from primary cervical cancer have shown different presentations including consolidation, multifocal parenchymal nodules and hilar masses[11-15]. We did not find a

primary presentation of cervical cancer with lung metastasis appearing as miliary lung nodules as was seen in our patient in our search of the published literature.

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