

# Pulmonary lymphangitic carcinomatosis from squamous cell carcinoma of the cervix: A retrospective study with review of literature

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## ABSTRACT

**Background:** Pulmonary lymphangitic carcinomatosis (LC) secondary to cervical squamous cell carcinoma (SCC) is an uncommon cause of diffuse infiltrative lung disease. Its reported incidence is quite low. **Materials and Methods:** Fifty cases of cervical carcinoma were studied from 2005 to 2014. There was only one case of squamous cell carcinoma cervix that developed pulmonary lymphangitic carcinomatosis subsequently. Clinical manifestations of LC such as dyspnea and non-productive cough can mimic with clinical picture of pneumonia, pneumonitis, pulmonary embolism, congestive heart failure, asthma, and sarcoidosis and thus can be a diagnostic dilemma for treating physician. A review of world literature was also done to examine all the reported cases of cervical carcinoma which presented as pulmonary lymphangitic carcinomatosis. A few cases have been reported so far. **Conclusion:** Pulmonary lymphangitic carcinomatosis is a rare manifestation of metastatic Squamous Cell Carcinoma (SCC) of the cervix and is associated with a poor prognosis. Increased clinical alertness of such patterns of metastases in cervical cancer along with accurate pathological diagnosis is compulsory to guide proper therapy in these patients.

**Key words:** Diffuse infiltrative lung disease, pulmonary lymphangitic carcinomatosis, squamous cell carcinoma of cervix

## INTRODUCTION

Cervical cancer is the second most common cancer in women despite extensive screening and vaccinations against different human papilloma viruses. Early lymphatic metastasis from carcinoma cervix often occurs in the parametrium and the pelvic lymph nodes. Distant spread through hematogenous route tends to occur relatively late and commonly involves the liver, lungs, and skeleton.<sup>[1,2]</sup> The incidence of pulmonary metastasis from all cervical carcinoma is about 2.2–9.1%. Adenocarcinoma and undifferentiated carcinoma of the

cervix have higher chances of pulmonary metastases as compared to squamous carcinoma.<sup>[3]</sup> Pulmonary lymphangitic carcinomatosis (LC) secondary to squamous cell carcinoma of the cervix is exceptionally rare. It has got very poor prognosis with limited survival period (17 days to 24 months).<sup>[4]</sup> LC of lungs is more common from carcinomas breast, larynx, prostate, thyroid, gallbladder, stomach, and pancreas rather than cervical carcinoma.<sup>[4-6]</sup> To the best of our knowledge, a few cases have been reported in world literature and the last one has been reported in the year 2010 by Kanthan *et al.*<sup>[7]</sup> We report a case of pulmonary LC metastatic from cervical squamous cancer (SCC) of the cervix which was treated in past with radical hysterectomy with salpingo-oophorectomy followed by external beam radiotherapy.

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## MATERIALS AND METHODS

A retrospective study was carried out in our institution from the year 2005 to 2014, and a total of 50 cases of squamous cell carcinomas were encountered. Age group ranged from 50 to 70 years. All patients were from poor socioeconomic status and were multipara. Only one case presented with pulmonary symptoms.

A search of the MEDLINE, PubMed, and Cochrane databases was conducted to identify reports. Manual cross-referencing was performed, and relevant references from selected papers were reviewed.

## CASE REPORT

A 52-year-old woman presented with abnormal vaginal bleeding and abnormal Pap smears. The ultrasound of abdomen revealed cervical growth with infiltration of right parametrium. There was no pelvic or paraaortic lymphadenopathy and was staged as 2B squamous cell carcinoma of uterine cervix. X-ray chest was normal. Wertheim's hysterectomy was carried out in January 2003 and histopathology showed moderately differentiated large cell nonkeratinizing type of squamous carcinoma of cervix [Figure 1]. Adjacent epithelium showed changes of *in-situ* carcinoma. Lymphovascular emboli were seen in cervix adjacent to tumor. Both parametria showed tumor deposits, so postoperatively tumor was staged as 2B. After 2 weeks of surgery, the patient was referred to a cancer institute for further management. At the time of referral, she was asymptomatic. Ultrasound examination of her abdominal revealed normal liver and there was no lump or ascites. On per vaginal examination, small 0.5 cm × 0.5 cm indurated area was felt over the sutured line and there were no signs of residual disease. No supraclavicular lymph nodes were palpable. Chest X-ray was normal. Hematological

investigations were within normal limits. She was treated with 5000 cGy of the external pelvic radiation in March 2003. During the treatment, she complained of weakness, loss of appetite, nonproductive cough associated with chest pain, and mild dyspnea. On physical examination, there was mild dyspnea but no fever. Her chest examination revealed few scattered wheezes. On examination, no locoregional recurrence was found. There were three supraclavicular lymph nodes on right side, measuring 1 cm × 1 cm hard and fixed. Her hematological investigations showed Hb - 10 g%, white blood cell - 8200/cumm, and platelets - 67,100/cumm. Chest X-ray was suggestive of bilateral diffuse interstitial infiltrate-pulmonary LC [Figure 2]. Sputum stain for acid-fast *Bacillus* was negative. Ultrasound abdomen revealed no pelvic or paraaortic lymphadenopathy but showed hydronephrosis and hydroureter on the right side. Fine needle aspiration cytology from supraclavicular node was consistent with metastatic squamous carcinoma. She was diagnosed to have pulmonary LC with positive supraclavicular lymph nodes. Her general conditions were deteriorated. She was offered steroids along with symptomatic treatment. However, she succumbed to the disease and died 64 days after establishing the diagnosis of pulmonary LC.

## DISCUSSION

Mostly cervical cancer spreads to adjacent structure such as the vagina, uterus, and pelvic cavity and usually diagnosed quiet late after initial treatment.<sup>[8,9]</sup> In advance stage, cervical cancer can spread to distant organs such as the lungs and bones.<sup>[3,10]</sup> Lung metastasis depends on the stage of disease. Three percent of cervical cancer treatment failures in Stage IA, 15% in Stage IB, 20–25% in Stage IIB, and 40% in Stage IIIB spread to lungs.<sup>[9]</sup> Adenocarcinoma, anaplastic cancer, and small cell neuroendocrine tumors of cervix spread more frequently to the lungs as compared to squamous carcinoma of cervix (<5%).

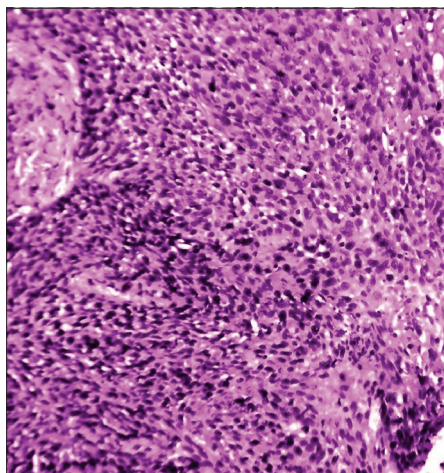


Figure 1: Slide showing SCC cervix



Figure 2: X-ray showing B/L infiltration with pulmonary carcinomatosis

LC of the lungs is defined as the diffuse infiltration and obstruction of the parenchymal lymphatic channels by a tumor. Its incidence is about 6–8% of all metastatic diseases of thorax. This type of cancerous spread generally infiltrates bilaterally in both subpleural and interstitial lymphatics.<sup>[11]</sup>

Squamous cervical cancer (SCC) presenting as LC of the lung is a very uncommon clinical entity, and only a few cases have been reported so far.<sup>[12]</sup> In a review of 245 cases of thoracic metastases from cervical carcinoma by Sostman and Matthey, lymphangitic pattern of metastasis was not observed.<sup>[13]</sup> Such metastases to the lung may take many forms: Solitary and multiple parenchymal nodules, LC, tumor emboli, endobronchial metastasis, and pleural effusion.<sup>[14]</sup> However, it is important to confirm that this SCC is indeed a metastatic lesion to the lung and not a primary pulmonary SCC. In this context, p16 is a useful marker for the discrimination between cervical and pulmonary SCC as overexpression of p16 has been consistently observed in HPV-related cervical cancer.<sup>[15]</sup> A search in PubMed revealed following cases until date [Table 1].

The exact mechanism by which cervical carcinoma metastasizes to the pulmonary lymphatic is unclear.<sup>[16-18]</sup> It has been suggested that tumor cells in the thoracic duct may reach the mediastinal and hilar nodes.

Due to the blockage of the normal lymphatic channels of the lungs, dilatation of lymph vessels occurs and spread of tumor is then possible either by retrograde embolization or proliferation of malignant cells within the lymph vessels. Second, intraperitoneal disease may lead to transdiaphragmatic seeding with subsequent involvement of mediastinal and hilar lymph nodes. Kojima *et al.*<sup>[19]</sup> proposed vascular dispersion of malignant cells throughout the lung, with subsequent accumulation in the neighboring lymphatic. It has been argued that radiation therapy may promote pulmonary metastasis by disrupting the physical barrier function and immunologic surveillance mechanism by lymph nodes.<sup>[16]</sup>

Clinical manifestations of LC such as dyspnea and nonproductive cough often lead to the incorrect diagnosis of pneumonia, pneumonitis, pulmonary embolism, congestive heart failure, asthma, and sarcoidosis.<sup>[4]</sup> Lymphangitic

**Table 1: Reported cases of pulmonary lymphangitic carcinomatosis due to cervical cancer**

Author	Year of publication	Age (years)	FIGO stage or extent of disease	Duration of pulmonary symptoms (days)	Initial diagnosis of pulmonary symptoms	Interval from diagnosis of cancer to diagnosis of LC (weeks)	Investigation of LC	Treatment	Survival from time of diagnosis of LC (days)	Patient status
Buchsbaum <sup>[16]</sup>	1970	41	Pelvic side wall, positive paraaortic nodes	1	Pneumonia, CHF	13	Chest X-ray	Chemotherapy	17	DOD
Buchsbaum <sup>[16]</sup>	1970	41	Unknown	27	LC	180	Sputum cytology	Prednisone	60	DOD
Buchsbaum <sup>[16]</sup>	1970	50	Positive pelvic and paraaortic nodes	Unknown	Pneumonia	103	Sputum and pleural fluid cytology	Supportive care	5	DOD
Maulitz and Sahn <sup>[17]</sup>	1979	58	Unknown	30	Pulmonary embolus	51	Transbronchial biopsy	Supportive care	7	DOD
Kennedy <i>et al.</i> <sup>[11]</sup>	1989	44	3B	1	Pulmonary embolus	26	Autopsy	Supportive care	8	DOD
Lipmann <i>et al.</i> <sup>[18]</sup>	1992	41	2	Unknown	LC	51	Transbronchial biopsy	Bleomycin, oncovin, mitomycin, and cisplatin	720	Unknown
Perez-Lasala <i>et al.</i> <sup>[5]</sup>	1992	31	2B	60	Pneumonia	3	Transbronchial biopsy	Taxol	60	DOD
Sawin <i>et al.</i> <sup>[8]</sup>	1995	48	3B	14	Pneumonia	39	Bronchoscopy washings	Prednisone	90	DOD
Storck <i>et al.</i> <sup>[4]</sup>	2004	24	Pelvic sidewall, paraaortic nodes	4	Asthma	1	Transbronchial biopsy	Supportive care	4	DOD
Kanthan <i>et al.</i> <sup>[7]</sup>	2010	48	Positive pelvic lymph nodes and parametrium	3	Pneumonia	104	Wedge biopsy	Taxol and corticosteroids	13	DOD
Our case	2015	52	2B	90	Diffuse interstitial infiltrate	100	Chest X-ray	Steroids	64	DOD

\*DOD: Died of disease, LC: Lymphangitic carcinomatosis

spread of cervical cancer represents a state of advanced metastatic disease with a grave prognosis and shortened survival.<sup>[7]</sup>

The diagnosis is often delayed as it is difficult to make unless one is aware. In two of the reported cases, the correct diagnosis was made at the autopsy<sup>[10,16]</sup> and in other two reports, the diagnosis was missed initially.<sup>[4,5,8,10,17]</sup> The dramatic and progressive pulmonary symptoms can mimic with various infections and malignancies such as millary tuberculosis, histoplasmosis, cryptococcosis, brucellosis, sarcoidosis, pneumonitis, vasculitic disorder and metastatic carcinoma, lymphoma, and leukemia. Medical conditions such as congestive heart failure and pulmonary embolism can also resemble pulmonary LC.<sup>[5,10,16,20]</sup>

The chest X-ray is highly characteristic and consists of bilateral diffuse interstitial infiltrates with most dense infiltrate in the lower and middle lung fields. Pulmonary LC is generally bilateral with tumor involving both subpleural and interstitial lymphatics. In three cases, diagnosis was made on chest X-ray (as in our case).<sup>[16]</sup> The pathological diagnosis was made only in 6 cases. Out of six cases, four cases were diagnosed by transbronchial biopsy,<sup>[4,5,17,18]</sup> fifth case by percutaneous lung biopsy and sixth case by open wedge biopsy of lung.<sup>[6]</sup> Lung biopsy is the definitive diagnostic procedure, but most clinicians hesitate to perform this procedure in a patient with border line pulmonary functions as in our case.

A computed tomography scan may support the diagnosis by detecting the “beaded chain” appearance due to uneven thickening in the septa of the lung secondary to lymphatic vessels, demonstrating cell infiltration.<sup>[4,5]</sup> Bronchoscopy with washings and sputum cytology is both unreliable in accurately confirming the diagnosis of LC.<sup>[4]</sup> A transbronchial or an open lung biopsy is often required for a definitive pathological diagnosis of pulmonary LC due to the proximity of lymphatics to the peribronchial space.<sup>[14]</sup>

Pulmonary metastasectomy for solitary metastasis to the lung is a safe and acceptable treatment to improve survival in cases where there is adequate control of the primary tumor without extrapulmonary metastasis.<sup>[21]</sup>

LC has a poor prognosis as it indicates advanced metastatic disease.<sup>[6]</sup> Often, extensive involvement of the hilar, mesenteric, and paraaortic nodes, diaphragmatic, liver, and abdominal metastases can also coexist in these patients.<sup>[10]</sup> The use of radiation treatment is a point of dispute as it has been argued that it may disrupt the immunologic surveillance mechanisms and physical barrier created by the nodes, thereby promoting metastases to the lungs.<sup>[6]</sup> Complete response to chemotherapy is

rare; however, patients who receive platinum-based chemotherapy with corticosteroids do show some degree of improvement.<sup>[4]</sup> Combination chemotherapy such as cisplatin + paclitaxel or topotecan has demonstrated improvement in response rates, progression-free survival, and sustained quality of life assessments.<sup>[22,23]</sup>

Barter *et al.* reviewed 2116 patients treated for cervical malignancy from 1969 to 1984 at the University of Alabama at Birmingham; 88 (4.16%) had pulmonary lesions consistent with metastatic cervical cancer. Platinum-type chemotherapy has a 67.7% response rate on chest X-ray, with one-third of the responses were completed. The prognosis is poor with a median survival of 0.69 year (8.3 months); only 2 of these 88 patients were long-term survivors. Although the survival is poor, a few statistically significant factors could be identified as prognostic.<sup>[2]</sup> Regardless of treatment, however, survival of patients with LC is short. Nevertheless, accurate diagnosis of metastatic SCC to the lung and LC is important in avoiding any unnecessary and potentially harmful treatments.<sup>[6]</sup>

## CONCLUSIONS

Pulmonary LC is a rare manifestation of metastatic SCC of the cervix and is associated with a poor prognosis. Clinical presentations of LC including radiographic imaging mimic other pulmonary diseases as diagnostic pitfalls. Despite the lack of recognized predisposing risk factors and the difficulty in accurate diagnosis, recognition of metastatic SCC to the lung is very important as it has a grave prognosis. Increased clinical alertness of such patterns of metastases in cervical cancer along with accurate pathological diagnosis is compulsory to guide proper therapy in these patients.

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### Conflicts of interest

There are no conflicts of interest.

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