Pulmonary microvascular metastases in cervical carcinoma: A case series

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ABSTRACT

Pulmonary microvascular tumor embolism (PMTE), pulmonary tumor thrombotic microangiopathy (PTTM), and lymphangitis carcinomatosis (LC) have an intricate pathophysiology and usually occur with cancers of breast, stomach, and lung. Microvascular pulmonary metastases attributable to cervical cancer are a rarity. Clinical presentation and autopsy findings of patients with microvascular pulmonary metastases in cervical cancers were studied with a review of literature. Four patients (mean age of 55.5 years) with carcinoma cervix showed microvascular metastases. Three of whom presented with respiratory symptoms, and the fourth case was unresponsive on presentation. Each patient succumbed to their illness shortly after admission. Autopsy examination performed on each patient depicted varying combination of PMTE, PTTM, and LC, all with squamous histology. This case series highlights the rare association of carcinoma cervix with the aforementioned microvascular phenomena. Besides, it underscores the sequential mechanism of occurrence of microvascular pulmonary metastasis and the associated guarded prognosis.

KEY WORDS: cervical carcinoma, lymphangitis carcinomatosis, pulmonary microvascular tumor embolism, pulmonary tumor thrombotic microangiopathy

Introduction

Despite availability of simple screening procedures, cancer of the uterine cervix continues to be a major cause of morbidity and mortality, particularly in developing countries. Cervical cancer frequently spreads by direct extension to surrounding tissues in the pelvis. Extrapelvic or distant metastases (lymphatic or hematogenous) occur in advanced stages and are seen commonly with adenocarcinoma or poorly differentiated subtypes. The lungs are the most common site of metastasis after lymph nodes. Pulmonary involvement is secondary to hematogenous dissemination and often manifests as well-defined subpleural or parenchymal nodules.

These pulmonary metastases are seen in about 2% to 9% of all cervical cancers. In this case series (the first to be reported), we describe rare microvascular patterns of metastatic lung disease in four patients with disseminated cervical cancers.

Case Reports

Case 1

A 66-year-old post-menopausal woman had been recently diagnosed on clinical assessment and biopsy as poorly differentiated Grade IIIB cervical adenocarcinoma (CK7/CEA

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positive and P63 negative) at a nearby cancer center; no treatment had been instituted. She was referred to our tertiary-care center with a 2-day history of increasing shortness of breath that rapidly progressed from grade 1 to grade 3. There was no history of chest pain, palpitation, or syncope. On examination, the pulse rate was 70 beats per minute, blood pressure 110/70 mmHg with tachypnea (37 breaths per minute) and a gallop rhythm. Hematological investigations showed anemia (Hb 8.9 g%) with normal WBC and differential counts. Routine biochemical investigations were within normal limits. Chest radiograph showed right atrial and ventricular dilatation, while ultrasonography showed bilateral pleural effusions. In view of progressive dyspnea, a venous Doppler was advised to rule out deep venous thrombosis, but no thrombi were seen. Presence of T-wave inversion in leads V_2 to V_4 suggested ischemic changes, but troponin T was in the normal range. She was started on low-molecular weight heparin and aspirin. However, the dyspnea progressed and the patient succumbed within 2 days of admission. A complete clinical autopsy was performed.

At autopsy, both lungs were of normal size and shape with a focally congested cut surfaces [Figure 1a]. On histology (8 of 11 sections), a large proportion of the small muscular arteries and the arterioles showed occlusive clusters of malignant squamous epithelial cells, some of which were surrounded or embedded in fresh fibrin thrombi [Figure 1b and c]. This histomorphology suggested pulmonary microvascular tumor embolism (PMTE); the cells were positive for cytokeratin 7 [Figure 1d]. The source of these tumor cells was a large firm gray-white mass in the posterior wall of the cervix, which revealed morphology of an adeno-squamous carcinoma. Metastases (all squamous) were present in the para-aortic and cervical lymph nodes; clusters infiltrating the hepatic sinusoids were also seen in the liver within thrombi present in the portal vein radicles; some cells were also present in the sinusoids [Figure 2c and d]. In this patient, a large cell nonkeratinizing squamous cell carcinoma (SqCC) of the cervix was seen as an endophytic lesion with thickening of the uterine walls due to numerous lymphovascular emboli; such emboli were also seen around the right adrenal gland.

Case 2
A 55-year-old post-menopausal and hypertensive woman was admitted in our tertiary-care center with severe progressive dyspnea progressed and the patient succumbed within 2 days of admission. A complete clinical autopsy was performed.

Autopsy examination revealed grossly visible red-brown to pale yellowish-white thrombi within the small pulmonary arteries on the cut surfaces of both lungs. The histology (9 of 10 sections) showed not only PMTE and fresh thrombi [Figure 2a] but also the presence of fibrocellular organization suggestive of pulmonary tumor thrombotic microangiopathy (PTTM, Figure 2b); at places, there were foci of lymphatic permeation (lymphangitis carcinomatosis LC) as well [Figure 2b]. Similar cell clusters were also seen in the liver within thrombi present in the portal vein radicles; some cells were also present in the sinusoids [Figure 2c and d]. In this patient, a large cell nonkeratinizing squamous cell carcinoma (SqCC) of the cervix was seen as an endophytic lesion with thickening of the uterine walls due to numerous lymphovascular emboli; such emboli were also seen around the right adrenal gland.

Case 3
A 50-year-old post-menopausal woman was brought to a surgical oncology outpatient department of a nearby cancer center in an unresponsive state. She had been recently diagnosed with hypertension and advanced cervical SqCC. She was declared dead on arrival and her body was referred to our center for a complete clinical autopsy was performed.

Figure 1: Case 1 - (a) Normal cut surface of the right lung; the histology revealed clusters of tumor cells without; (b) or with admixed fibrin; (c) Pulmonary microvascular tumor embolism (H&E x 400); (d) The tumor cells were positive for cytokeratin 7 (x400)

Figure 2: Case 2 - (a) Muscular pulmonary artery occluded by fresh thrombus with peripheral organization and strands of tumor (arrows); (b) Recanalized thrombus in a muscular pulmonary artery. The channels themselves are occluded by tumor clusters. Note the presence of lymphatic permeation; (c) Portal tract of the liver showing occlusive tumor embolus in the portal vein radicles V; (d) The sinusoids of the liver were focally dilated and some show the presence of tumor cells (H&E x 100)
Case 4
A 51-year-old postmenopausal, nondiabetic and nonhypertensive woman presented with abdominal pain, low backache, decreased urine output, progressive breathlessness, and cough for 4 days. There was a previous history of hospitalization for 16 days for fever and persistent dry cough, where she was diagnosed and treated as right lower lobe pneumonia. On examination, bilateral firm inguinal lymphadenopathy and right lower zone crepitations were noted. All biochemical and hematological investigations were within normal limits, except serum creatinine that was raised to 3.8 mg/dL. An abdominal CT revealed bilateral mild hydroureronephrosis with right urinoma [Figure 3a], thickening in the lower uterine segment with multiple enlarged celiac, retroperitoneal, pelvic, and inguinal lymph nodes [Figure 3b] and patchy subpleural parenchymal nodularity with a reticular pattern. This established a diagnosis of acute renal failure secondary to obstructive uropathy. The patient succumbed to her illness after 4 days of admission despite aggressive management of her acute renal failure.

At autopsy, both lungs had fine nodular sandy consistency with cob-web like gray-white and firm markings on pleural surfaces [Figure 3c] and accentuation of the lobular septa and bronchovascular bundles [Figure 4a]. These were produced by very prominent LC, seen in all the 12 sections taken [Figure 4b and c]. There were small partially organizing hemorrhagic infarcts in both lower lobes produced by fresh red-brown occlusive thrombi in intrapulmonary arterial branches [Figure 4a]. The mediastinal, para-tracheal, hilar, para-aortic, and pelvic lymph nodes showed metastases of keratinizing SqCC, secondary to retrograde lymphatic dissemination from a widely invasive moderately differentiated cervical SqCC. The right peri-renal urinoma was seen as hemorrhagic collection.

Discussion
We have reported unusual pulmonary microvascular involvement with fatality in four post-menopausal women with advanced cervical cancer (one clinically undetected). This was seen in the form of retrograde lymphatic metastases as well as hematogenous spread (as evidenced by even portal venous involvement). The insidious or acute respiratory distress had developed through PMTE, PTTM, LC, or their combinations, each of which has specific features [3].

PMTE, first described by Schmidt in 1897, [4] refers to occlusion of the small pulmonary arteries, arterioles and even capillaries by clumps of tumor cells, admixed with fibrin thrombi. [3,4] These are identified in 26% of patients (autopsy data) with solid tumors, but it becomes clinically apparent in about 8% of the patients when 30% of the small pulmonary vessels are involved. [3]

PTTM, on the other hand, appears to be a stage beyond PMTE and is seen in about 1% to 3% of patients with solid cancers. [3] The characteristic histopathological findings of PTTM, a term coined by von Herbay in 1990, [5] are widespread, nonocclusive tumor nests in the pulmonary microvasculature with secondary thrombosis and fibrocellular intimal proliferation. This remodeling of the pulmonary vasculature (including post-capillary vessels) leads to an increase in vascular resistance and consequent pulmonary hypertension (PH). [6] This complex phenomenon is triggered by endothelial injury due to entrapped tumor cells, followed by activation of the coagulation cascade and elaboration of growth factors and cytokines. [6] Hence,
PTTM is designated as a new para-neoplastic syndrome.[7] In about 7% of patients, the metastases produce an interstitial lung disease pattern due to tumor cell permeation and embolization of the pleural, interlobular septal, and peri-bronchovascular lymphatics, a process referred to as LC, a term introduced by Troisier in 1878.[8]

For reasons unknown, the most frequent primary sites of tumor for all the three types of microvascular involvement are the breast, stomach, and lung.[3,9,10] The association of microvascular metastases with cervical cancers is exceedingly rare, but is known to occur with highly invasive types secondary to retrograde lymphatic involvement as well as antegrade spread via the portal venous circulation (as seen in all four of our cases). Till date, there have been only 10 reported cases of PMTE in the setting of cervical carcinoma (adenocarcinoma histopathology in one of them), and all of them had intracardiac metastases as well.[11] None of our cases and in one other case reported by one of the authors of this series[12] (not included in the recent review[11]) had any lesion in the heart. In a recent review of 160 of PTTM cases, Godbole et al.[9] did not find a case related to cervical cancer. However, there have been two cases reported in 2018,[13,14] one of which is purported to be the first case.[13] However, a similar case has been reported as early as 1971, but had highlighted certain other characteristics.[11] All these cases were squamous cell carcinomas. In a recent extensive review spanning over 48 years of data, 12 cases of LC produced by squamous cell cervical carcinomas have been reported.[10] In all of our four reported cases, metastatic tumor was squamous in nature, though the primary tumor in one of the cases had adeno-squamous histomorphology.

The consequences of these three microvascular lesions[14,10] include subacute respiratory failure, PH, right-sided heart failure, and sudden death, which are predated by the development of cough and progressive dyspnea for varying durations (3 weeks to 6 months), seen in all our cases. It should be noted that they can also occur as the first manifestation of an occult cancer. Other features can be explained on the basis of the primary tumor and organ metastases. An interesting finding was urinoma (Case 4), which refers to an encapsulated collection of extravasated urine in the peri-renal or para-ureteral space. Urinomas do not exactly fall in the purview of pathologists and, hence, it is often overlooked or receives scant attention. Furthermore, only few cases of urinoma are caused by cervical cancers.[16]

Antemortem diagnoses of these conditions are challenging as changes seen on electrocardiogram and imaging techniques (including high-resolution computed and positron-emission tomography), and hematological parameters may be nonspecific.[1,5,6,10] Though cytological and/or histopathological examinations may offer a definitive diagnosis, it may not be feasible in all patients owing to respiratory distress and presence of pulmonary hypertension.[4,6,10] Nevertheless, there is a need for regular follow-up in patients with cancer, and to suspect and promptly diagnose this microvascular disease with appropriate imaging modalities. However, the overall prognosis is very poor despite combination therapy with anticoagulants, vasodilators, specific chemotherapeutic agents, and growth factor inhibitors.

Declaration of patient consent
The authors certify that appropriate patient consent was obtained.

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Conflicts of interest
There are no conflicts of interest.

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