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JCIMCR OPEN ACCESS Journal of Clinical Images and Medical Case Reports

ISSN 2766-7820

Case Report

Open Access, Volume 4

EGFR 19 deletion and FGFR2-FILIP1 rearrangement in lung adenocarcinoma with cervix and endometrium metastases: A case report and literature reviewcase report and literature review

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Received: Nov 12, 2023

Accepted: Dec 11, 2023

Published: Dec 18, 2023

Archived: www.jcimcr.org

DOI: www.doi.org/10.52768/2766-7820/2740

Abstract

Distant metastases of pulmonary adenocarcinoma are regularly observed in the bones, brain, and liver, rarely in the cervix or endometrium. We report a case of 53-year-old Chinese female with primary pulmonary adenocarcinoma which metastasized to the uterine cervix and endometrium with EGFR 19 deletion and FGFR2-FILIP1 rearrangement and had been taking osimertinib since then. To our knowledge, this is the first report of cervical and endometrium metastases from lung adenocarcinoma with EGFR 19 deletion and FGFR2-FILIP1 rearrangement which might be useful to clinicians. We reviewed the literature on cervical metastasis of lung cancer. This case suggests that women with lung cancer and abnormal pelvic fluid or abdominal pain should consider the possibility of distant metastasis. Furthermore, the relationship between EGFR gene mutations and metastasis is outlined. Identification and understanding of these rare mutations can help doctors develop personalized treatment plans and improve treatment effectiveness.

Keywords: EGFR 19 deletion; FGFR2-FILIP1 rearrangement; Cervix metastasis; Endometrium metastasis; Lung carcinoma

Introduction

Lung cancer is the primary cause of cancer-related deaths in individuals aged 50 years and up, for both males and females, resulting in more fatalities than breast and prostate cancers combined. In 2023, an estimated 384 individuals will succumb to lung cancer daily [1]. Recent studies indicate that advanced lung cancer patients suffer from distant metastases, affecting up to 47.3% of cases [2]. These metastases frequently impact organs such as the liver, adrenal gland, bone, brain, kidney, spleen, and abdominal lymph nodes [3]. According to the literature review, primary lung adenocarcinoma in the female repro-

ductive system is more likely to metastasize to the ovaries than the cervix [4-6]. Notably, most of the cervical metastases were adenocarcinomas originating from primary malignant lymphoma [7,8], breast cancer [9,10] and ovary cancer [11,12].

For patients diagnosed with non-small-cell lung cancer (NSCLC) and having somatic mutations in the epidermal growth factor receptor (EGFR), EGFR tyrosine kinase inhibitors (TKIs) can be administered. However, it is essential to note that resistance may develop within one year. In such cases, Osimertinib, a third-generation EGFR-TKI variant, is favored for sensitizing mutations, including L858R, T790M, or exon 19 deletion. We present the initial case of cervical and endometrial metastases with EGFR 19 deletion and FGFR2-FILIP1 rearrangement from lung adenocarcinoma after drug resistance. Furthermore, we reviewed the current literature on cervical metastasis diagnosed with lung cancer.

Case report

A 57-year-old Chinese woman was admitted to the hospital in 2018 with cough and sputum production associated with generalized fatigue. She had no family history of cancer. She was a nonsmoker. Computed tomography (CT) scan of the chest showed a large mass in both lobes and many nodules in her liver. Ultrasound bronchoscopy-guided puncture biopsy of enlarged lymph nodes near the right lower trachea was performed. Cytopathologic and immunohistochemical diagnosis: glandular epithelial cells with mild atypical changes, P40 (-), CK5/6 (+), TTF-1 (+), Naspin A (+), SP-B (+), Ki67 (15%), Cg A (-), Syn (-), CD56 (-). Genetic testing revealed an EGFR 19 deletion and no ALK, EML4 fusion or ROS-1 mutations. Since then, she had been taking gefetinib 0.25 g po pd, with a partial response (PR) according to RECIST 1.1 criteria and limited side effects. Four months later, a review of the CT scan revealed enlarged pulmonary nodules and an enlargement in the left neck lymph nodes, while the nodules in the liver were smaller than in the previous scans. The patient has completed two cycles of GP chemotherapy treatment, consisting of Gemcitabine at a dose of 1400 mg on day 1 and Cisplatin at a dose of 100 mg on day 1. The patient was admitted to our hospital complaining of virginal bleeding and discharge. A Papanicolaou smear at the time of initial evaluation was read as adenocarcinoma and signet ring cells. The levels of tumor markers including CA125, CA19-9, AFP and ThCG were within normal limits, and CEA is 8.8 ng/ml. The colposcopically sampled tissue showed cytologic features similar to the metastatic carcinoma present in the smear. Immunohistochemical staining showed reactivity for TTF-1, Napsin-A, HNF1-B, CK7, EMA, CEA, EGFR, and PAS and absence of Pax-8, ER, PR, CK5/6, P63, CK20, CDX-2, Her-2, P16, Muc-2, Muc-5, CA125, CA-199, SATB-2, and AB, supporting the diagnosis of metastatic adenocarcinoma from a primary lung cancer or digestive system. The patient's positron emission tomography showed lung, bone, and uterine metastases, but no gastrointestinal invasion. Given her history, this metastatic adenocarcinoma originated from a primary lung cancer. The genetic test results of the specimens indicated the EGFR 19 exon E746-A750del, the FGFR2-FILP1 gene rearrangement, the CDKN2A gene, and the CDKN2B gene. The patient switched to osimertinib 80 mg po qd, which showed a partial response (PR) according to RECIST 1.1 criteria with limited side effects. After six months, the patient presented with symptoms such as headaches, vomiting, occasional loss of consciousness, upward rolling of both eyes, and limb convulsions. These episodes are accompanied by profuse sweating and can self-resolve in a short time. Secondary epilepsy caused by brain metastasis is being considered. The patient is receiving a daily oral dose of 160 mg of Osimertinib, in addition to undergoing local radiotherapy and receiving relevant symptomatic treatment.

Discussion

Studies show that up to 93% of patients with advanced lung cancer suffer distant metastases. Common sites include the liver, bone, brain. Metastasis of extragenital carcinoma to the cervix uteri is rare. In our case, it is important to find out the origin of the adenocarcinoma in the polyp. Since no carcinoma in situ was identified, it is highly unlikely that the adenocarcinoma in the polyp is of endocervical origin. The neoplastic cells showed hyperchromasia and pleomorphism with mucin production similar to the metastatic carcinoma in the pleural fluid. This diagnosis was further supported by immunohistochemical staining showing reactivity for cytokeratin 7 and TTF-1 and absence of cytokeratin 20. Metastatic adenocarcinoma with signet ring features could originate from other organs, such as the gastrointestinal tract or breast. However, the presence of a pulmonary mass, malignant cells in the pleural fluid, and the lack of evidence of gastrointestinal or breast cancer in the 3 years since her diagnosis strongly support metastatic adenocarcinoma from a lung primary.

To note, differential diagnosis is a rigorous and thorough procedure that tasks a physician with utilizing all accessible data to ascertain the most probable source of a patient's illness.

Our table includes 11 cases of lung cancer with cervical metastasis. The patients' ages ranged from 41 to 76 years, with a median age of 62 years. Five patients were initially diagnosed with cervical or endometrial metastasis, and their time to progression (TTP) was 8-12 months, indicating cervical metastasis as a manifestation of the end-stage tumor with a poor prognosis. For other patients who develop cervical metastasis, their symptoms may include vaginal bleeding, vaginal discharge, and metastasis to the brain or bones. These cases suggest that clinicians should not overlook metastasis to rare sites in lung cancer. When female patients with lung cancer experience vaginal bleeding or abnormal secretions, the possibility of a secondary malignant tumor cannot be excluded. Due to the poor prognosis, early diagnosis is crucial, and immediate pathological diagnosis should be pursued, with appropriate treatment measures considered to control the progression of the disease.

The cause of metastasis to these uncommon locations remains unclear. The infrequency of cervical metastases can be explained by several factors. Firstly, the high content of fibrous tissue in the cervix creates an unfavorable environment for metastatic growth. Secondly, the cervix is small and has limited blood flow. Finally, the pelvic lymphatic vessels drain away from the cervix. Last to note, there might be a relationship with genetic changes. Although primary lung adenocarcinoma seldom metastasizes to the cervix, it is crucial to ascertain whether and how frequently cervical cancer screening is conducted, taking into account the individual's overall health, cancer history, and specific risk factors.

Our patient's disease progressed accompanied with brain

metastasis and cevical metastasis with EGFR 19 deletion and FGFR2-FILIP1 rearrangement. FGFR2-FILP1 gene rearrangement has never been reported. FGFR2 protein expression with female gender, younger age, histological subtype (AC) and lower tumor stage, and FGFR3 protein was significantly overexpressed in tumors of older patients and SCC histology. Mutational activation of FGFR2 resulting in aberrant FGFR2 signaling activation is known from both hereditary germ line alterations and somatic mutations in various malignancies (e.g. breast, gastric or ovarian cancer). FGFR2 mutations are mainly located within the hinge between Ig-like domains (exon 7), around the 3rd Ig-like domains and within the kinase domain [24]. FGFR2 signaling plays a substantial role in the cell growth and invasion [25]. Filamin-A-interacting protein 1 (FILIP1) is a structural protein that is involved in neuronal and muscle function and integrity and interacts with FLNa and FLNc [26]. FILIP1L is involved in cell proliferation and migration by inhibiting the WNT signaling pathway [27] was constructed and acted as a significant and independent prognostic signature for LUSC [28]. Limited by scientific means, we offer a conjecture regarding the potential involvement of the FGFR2-FILP1 gene in disease onset and progression, as well as its likely biological function and clinical significance for future investigation by researchers.

Our patient's disease progressed during treatment with TKI, accompanied with brain metastasis and cevical metastasis. To our knowledge, this is the first reported case of metastatic lung adenocarcinoma to a cervical polyp with EGFR 19 deletion and FGFR2-FILIP1 rearrangement.

Disclosure: No authors report any conflict of interest.

References

1. Siegel, R.L., et al., Cancer statistics, 2023. CA Cancer J Clin, 2023. 73(1): p. 17-48.
2. Tamura, T., et al., Specific organ metastases and survival in metastatic non-small-cell lung cancer. Mol Clin Oncol, 2015. 3(1): p. 217-221.
3. Zhu, T., et al., Mechanisms and Future of Non-Small Cell Lung Cancer Metastasis. Front Oncol, 2020. 10: p. 585284.
4. Niu, F.-Y., et al., Distribution and prognosis of uncommon metastases from non-small cell lung cancer. BMC Cancer, 2016. 16(1): p. 149.
5. Khan, A.M., et al., A rare case of primary lung adenocarcinoma detected by routine liquid-based cervical cytology. Lung Cancer, 2007. 58(2): p. 282-5.
6. Niu, F.Y., et al., Distribution and prognosis of uncommon metastases from non-small cell lung cancer. BMC Cancer, 2016. 16: p. 149.
7. Hanprasertpong, J., et al., Primary non-Hodgkin,s lymphoma of the uterine cervix. Asian Pac J Cancer Prev, 2008. 9(2): p. 363-6.
8. Hariprasad, R., et al., Primary uterine lymphoma: report of 2 cases and review of literature. Am J Obstet Gynecol, 2006. 195(1): p. 308-13.
9. Dessole, S., et al., Uterine metastases from breast cancer in a patient under tamoxifen therapy. Case report. Eur J Gynaecol Oncol, 1999. 20(5-6): p. 416-7.
10. Piura, B., et al., Abnormal uterine bleeding as a presenting sign of metastases to the uterine corpus, cervix and vagina in a breast cancer patient on tamoxifen therapy. Eur J Obstet Gynecol Reprod Biol, 1999. 83(1): p. 57-61.
11. Malpica, A. and M.T. Deavers, Ovarian low-grade serous carcinoma involving the cervix mimicking a cervical primary. Int J Gynecol Pathol, 2011. 30(6): p. 613-9.
12. Mazur, M.T., S. Hsueh, and D.J. Gersell, Metastases to the female genital tract. Analysis of 325 cases. Cancer, 1984. 53(9): p. 1978-84.
13. Liu N. A case of pulmonary solid adenocarcinoma with cervical metastasis [J]. Chinese Journal of Clinical Oncology,1997; 763
14. Omrani, A., Schnatz, P.F., Qi, J., Greene, J., & Curry, S.L. (2004). Lung cancer metastatic to a cervical polyp. Gynecologic oncology, 92 1, 22-4 .
15. Guo A, Chen X. A case of senile lung cancer with cervical metastasis[J]. Chinese Clinical Oncology, 2008, 13(9): 864
16. Kai K, Takai N, Nasu K, et al. Metastatic uterine cervical cancer originating in the lung: a case report[J]. Gynecol Obstet Invest, 2009, 68(4):269-271. DOI: 10.1159/000241297.
17. Tiseo M, Bersanelli M, Corradi D, et al. Endometrial metastasis of lung adenocarcinoma: a case report. Tumori. 2011;97(3):411–14.
18. Zhang J Yu P Cervical and endometrial metastasis after complete remission of lung cancer in an elderly woman [J]. China Medicine 2013 vol.8 no.2. doi: 10.3760/cma.j.issn.1673-4777.2013.02.056
19. Ahmad Z, Raza A, Patel MR. Endometrial metastasis of lung adenocarcinoma: a report of two cases. Am J Case Rep. 2015 May 18;16:296-9. doi: 10.12659/AJCR.892495.
20. Chuang X, Chen Y et al . ALK rearrangement in lung adenocarcinoma with concurrent cervix and breast metastases: a case[J] . Thorac Cancer 2018.9(11): 1513-1518.
21. Zhai Y, Wang Y. A case of non-small cell lung cancer with cervical metastasis [J] . journal of international oncology, 2019, 46(3) : 191-192. DOI: 10.3760/cma.j.issn.1673-422X.2019.03.013.
22. Wang, Y., et al., Lung adenocarcinoma with EGFR gene mutation metastatic to the uterine cervix: A case report. 2020. 99(42): p. e22636.
23. Yan, R.L., et al., Female genital tract metastasis of lung adenocarcinoma with EGFR mutations: Report of two cases. World J Clin Cases, 2019. 7(12): p. 1515-1521.
24. Spiegelberg, C., et al., Frequency of activating mutations in FGFR2 exon 7 in bladder tumors from patients with early-onset and regular-onset disease. Int J Clin Exp Pathol, 2014. 7(4): p. 1708-13.
25. Zhao, Y., et al., Downregulated ESRP1/2 promotes lung metastasis of bladder carcinoma through altering FGFR2 splicing and macrophage polarization. Front Immunol, 2023. 14: p. 1161273.
26. Roos, A., et al., Bi-allelic variants of FILIP1 cause congenital myopathy, dysmorphism and neurological defects. Brain, 2023
27. Kwon, M., et al., Filamin A interacting protein 1-like inhibits WNT signaling and MMP expression to suppress cancer cell invasion and metastasis. Int J Cancer, 2014. 135(1): p. 48-60.
28. Ma, X., et al., Identification of key genes associated with progression and prognosis for lung squamous cell carcinoma. PeerJ, 2020. 8: p. e9086.