

World Journal of *Clinical Cases*

World J Clin Cases 2019 June 26; 7(12): 1367-1534



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World Journal of Clinical Cases (*World J Clin Cases*, *WJCC*, online ISSN 2307-8960, DOI: 10.12998) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The primary task of *WJCC* is to rapidly publish high-quality Case Report, Clinical Management, Editorial, Field of Vision, Frontier, Medical Ethics, Original Articles, Meta-Analysis, Minireviews, and Review, in the fields of allergy, anesthesiology, cardiac medicine, clinical genetics, clinical neurology, critical care, dentistry, dermatology, emergency medicine, endocrinology, family medicine, gastroenterology and hepatology, *etc.*

INDEXING/ABSTRACTING

The *WJCC* is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), and Journal Citation Reports/Science Edition. The 2018 Edition of Journal Citation Reports cites the 2017 impact factor for *WJCC* as 1.931 (5-year impact factor: N/A), ranking *WJCC* as 60 among 154 journals in Medicine, General and Internal (quartile in category Q2).

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Jie Wang*

Proofing Production Department Director: *Yun-Xiaojuan Wu*

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Semimonthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

EDITORIAL OFFICE

Jin-Lei Wang, Director

PUBLICATION DATE

June 26, 2019

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INSTRUCTIONS TO AUTHORS

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<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Female genital tract metastasis of lung adenocarcinoma with EGFR mutations: Report of two cases

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Author contributions: Zhou JY and Zhou JY designed the report; Wang J and Chen Z collected the patient's clinical data; Yan RL analyzed the data and wrote the paper.

Supported by the National Natural Science Foundation of China, No. 81670017.

Informed consent statement: Consent was obtained from the patient for publication of this report and any accompanying images and is available upon request.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Abstract

BACKGROUND

The female genital tract is an uncommon site of involvement for extra-genital malignancies. Ovarian metastases have been described as disseminations of lung adenocarcinoma; rare cases of secondary localizations in the cervix, adnexa, and vagina have also been reported in the literature. Here, we report two cases of advanced lung adenocarcinoma with female genital tract metastasis.

CASE SUMMARY

The first case was a 41-year-old woman with stage IV lung adenocarcinoma metastasizing to the cervix. Immunohistochemistry of the cervical biopsy specimen revealed thyroid transcription factor (TTF)-1(+), cytokeratin (CK)-7(+), and (CK)-20(-). Gene mutational analysis showed epidermal growth factor receptor (EGFR) L858R mutation in exon 21. She had a positive response to gefitinib, for both the pulmonary mass and cervical neoplasm. The second case was a 29-year-old woman who was diagnosed with stage IV lung adenocarcinoma with EGFR mutation. After 12 mo of treatment with icotinib, ovarian biopsy showed adenocarcinoma with CDX2(-), TTF-1(+++), PAX8(-), CK-7(+++), CK-20(++), and Ki67(15%+), accompanied with EGFR 19-del mutation and T790M mutation.

CONCLUSION

Immunohistochemistry and gene mutational testing have greatly helped in locating the initial tumor site when both pulmonary and female genital tract neoplasms exist.

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Manuscript source: Unsolicited manuscript

Received: January 29, 2019

Peer-review started: January 29, 2019

First decision: March 9, 2019

Revised: March 24, 2019

Accepted: April 18, 2019

Article in press: April 19, 2019

Published online: June 26, 2019

P-Reviewer: Sipahi EY

S-Editor: Ji FF

L-Editor: Wang TQ

E-Editor: Liu JH



Key words: Lung adenocarcinoma; Epidermal growth factor receptor; Metastasis; Ovary; Cervix; Case report

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Core tip: The female genital tract is an uncommon site of involvement for extra-genital malignancies. Ovarian metastases have been described as disseminations of lung adenocarcinoma; rare cases of secondary localizations in the cervix, adnexa, and vagina have also been reported in the literature. Here, we report two cases of advanced lung adenocarcinoma with female genital tract metastasis. The initial tumor site should be considered when both pulmonary and female genital tract neoplasms exist. Immunohistochemistry and gene mutational testing have greatly helped in locating the initial tumor site.

Citation: Yan RL, Wang J, Zhou JY, Chen Z, Zhou JY. Female genital tract metastasis of lung adenocarcinoma with EGFR mutations: Report of two cases. *World J Clin Cases* 2019; 7(12): 1515-1521

URL: <https://www.wjgnet.com/2307-8960/full/v7/i12/1515.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v7.i12.1515>

INTRODUCTION

Although metastases of lung adenocarcinoma may appear in any organ, they are more commonly observed in the bone, liver, adrenal gland, brain, and skin and seldom seen in the female genital tract, as metastasis in the female genital tract usually corresponds to small cell lung carcinomas^[1]. Ovarian metastases have been described as disseminations of lung adenocarcinoma; rare cases of secondary localizations in the cervix, adnexa, and vagina have also been reported in the literature^[2]. In these cases, immunohistochemistry and gene mutational analysis play an important role in determining the initial origin of tumor. In this article, we present two cases of advanced lung adenocarcinoma – the first case had cervical metastasis, and the other had metastasis to the ovary. The first case seemed to have cervical metastasis before targeted treatment; the other case developed ovarian metastasis accompanied by the newly presented T790M mutation in exon 20 during treatment with tyrosine kinase inhibitors (TKIs).

CASE PRESENTATION

Chief complaints

Case 1: A 41-year-old never-smoking woman came to our practice because of recurrent cough for 4 mo.

Case 2: A 29-year-old never-smoking woman was accepted because of complaints of cough and chest tightness.

History of present illness

There was no history of fever, weight loss, or sweating.

History of past illness

Case 1: History of past illness The patient's past medical history was a right lung nodule, which was observed 4 years ago.

Personal and family history

Case 1: She was a non-smoker and there was no history of drug abuse or recent travel. The family history was unremarkable.

Case 2: She was a non-smoker and there was no history of drug abuse or recent travel. The family history was unremarkable.

Physical examination upon admission

Case 1: The patient had no palpable lymph node.

Case 2: The patient had a low auscultation of breath and had no palpable lymph node.

Laboratory examinations

Case 1: The initial laboratory investigations including complete blood count and blood chemistry tests were normal. Carcinoembryonic antigen level was 1.5 ng/mL (0-5 ng/mL), which was negative.

Case 2: The initial laboratory investigations including complete blood count and blood chemistry tests were normal. Carcinoembryonic antigen level was 4.4 ng/mL (0-5 ng/mL) and tumor-associated carbohydrate antigen 125 level was 42.9 U/mL (0-35 U/mL).

Imaging examinations

Case 1: Computed tomography (CT) showed a right pulmonary mass characterized by a solid region with contiguous ground-glass areas, stellate borders, and pleural puckering (Figure 1C). The result of endotracheal biopsy was unsatisfactory, although cytology revealed adenocarcinoma cells; however, there was insufficient sample for pathological examination and epidermal growth factor receptor (EGFR) gene testing. A positron emission tomography-CT (PET-CT) scan was performed before lung biopsy and showed hyper-metabolic activity in pulmonary lesions and the cervix uteri (Figure 1A and B).

Lung biopsy was performed with CT guidance, after exclusion of relevant contraindications. Pathological examination showed adenocarcinoma with necrosis. Immunohistochemistry revealed thyroid transcription factor TTF-1(+) (Figure 2B), cytokeratin CK-7(+), and CK-20(-). EGFR mutational analysis could not be performed because we did not have sufficient biopsy specimen. Cervical biopsy was performed based on the hypermetabolic activity in the cervix uteri, and it showed poorly differentiated adenocarcinoma (Figure 2A). Immunohistochemistry showed TTF-1(+), CK-7(+), and CK-20(-). EGFR mutational analysis of the cervical biopsy specimen showed EGFR L858R mutation in exon 21. The patient displayed clinical symptoms including frequent micturition and hypogastralgia, and thus, pelvic magnetic resonance imaging (MRI) was performed, and it showed thickened cervical canal, without lymphadenectasis or pelvic effusion. Cervical cell cytology indicated negative results.

Case 2: Her initial CT scan showed lung lesions with cavity, as well as pleural effusion (Figure 3A). Ultrasound examination also showed pelvic effusion, although no ovarian masses were found. Pleural fluid cytology revealed adenocarcinoma, and immunohistochemistry revealed TTF-1(+) (Figure 4). EGFR mutational analysis of cell block showed EGFR 19-del mutation.

FINAL DIAGNOSIS

Case 1

Lung adenocarcinoma with cervical metastasis, stage IV (cT4N3M1b), with EGFR 21 L858R mutation.

Case 2

Lung adenocarcinoma with ovary metastasis, stage IV (cT2NxM1b), EGFR 19 deletion.

TREATMENT

Case 1

The patient received targeted therapy of gefitinib.

Case 2

The patient was started on icotinib, which is an EGFR TKI, with a plan of sequential antiangiogenic therapy.

OUTCOME AND FOLLOW-UP

Case 1

The patient had a positive response to gefitinib (Figure 1D and E), for both the

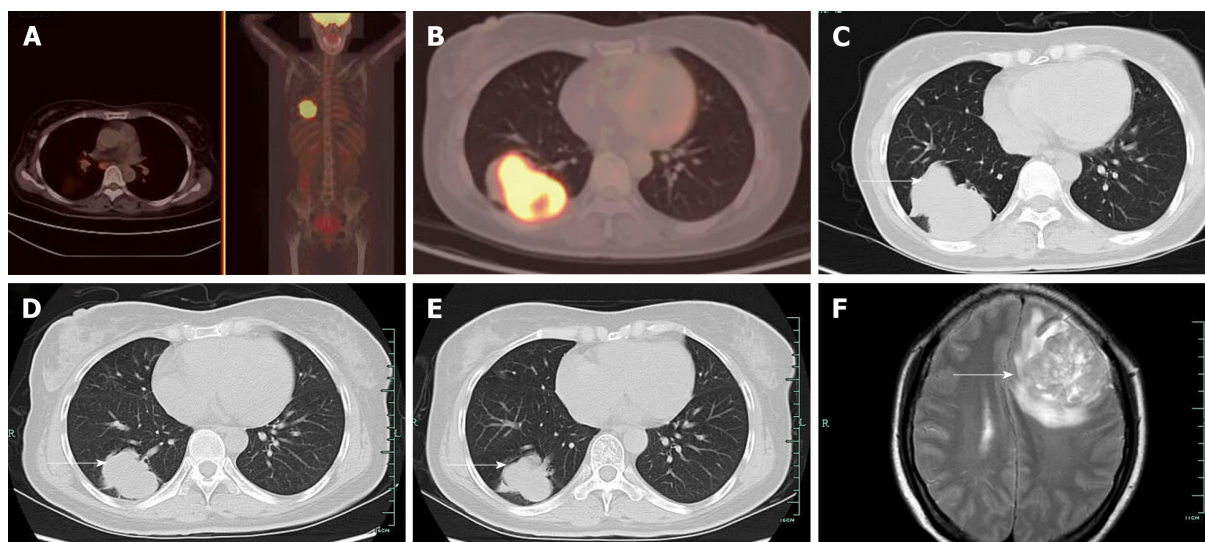


Figure 1 Case 1. A: Positron emission tomography-computed tomography (PET-CT) was performed before lung biopsy and showed hyper-metabolic activity in pulmonary lesions and the cervix uteri; B: PET-CT image showed hyper-metabolic activity in the inferior lobe of the right lung, where lung biopsy was performed; C: CT showed a right pulmonary mass characterized by a solid region with contiguous ground-glass areas, stellate borders, and pleural puckering before tyrosine kinase inhibitor treatment; D: CT showed a right pulmonary mass after 2 mo of gefitinib therapy, which indicated partial remission of tumor; E: CT image showed a right pulmonary mass after 4 mo of gefitinib therapy; F: Magnetic resonance imaging performed on April 12, 201 indicated brain metastasis.

pulmonary mass and cervical neoplasm. Routine examinations included chest CT scan and ultrasonography of the pelvic cavity and lymph nodes. Unfortunately, the patient was observed to have intracranial metastasis after 8 mo of gefitinib therapy (Figure 1F).

Case 2

Targeted therapy resulted in a partial response after 3 mo (Figure 3B). Since the patient complained of repeated pleural effusion, close drainage had to be done every two months. Since March 1, 2017, the patient has been treated with bevacizumab (Avastin) and icotinib to reduce pleural effusion. Routine CT scan examination showed pleural effusion without enlargement of the tumor (Figure 3C and D). Ultrasound examination of the pelvis showed ovarian mass, as well as pelvic effusion. Ovarian biopsy was performed on September 15, 2017, which revealed adenocarcinoma. Immunohistochemistry revealed CDX2(-), TTF-1(+++), PAX8(-), CK-7(+++), CK-20(++), and Ki67(15%+) (Figure 4B). EGFR mutational analysis of the ovarian biopsy specimen showed EGFR 19-del mutation and T790M mutation in exon 20. Lung biopsy could not be performed because of obstructive pneumonia and pleural effusion. Since the EGFR TKI resistance mutation (T790M) appeared in the ovarian biopsy sample, osimertinib (Tagrisso) therapy was started (September 26, 2017).

DISCUSSION

Although metastases of lung adenocarcinoma may appear in any organ, they are more frequently observed in the bone, liver, adrenal gland, brain, and skin and seldom seen in the female genital tract, as metastasis in the female genital tract usually corresponds to small cell carcinomas^[3,4]. We review the relevant studies both at home and abroad in recent years corresponding to patients with lung cancer metastasis to the female genital tract; ovarian metastases have been described in several articles^[1-3,5-8], while rare cases have been reported for cervical metastasis.

Metastases to the female genital tract of lung neoplasm have not received enough attention. According to the principles of precision medicine, the initial tumor site should be considered when both pulmonary and female genital tract neoplasms exist. Immunohistochemistry and gene mutational analysis have greatly helped in locating the initial tumor site. Between 74% and 92% of lung adenocarcinoma cases exhibit TTF-1 nuclear expression, and almost 90% of patients with lung adenocarcinoma are positive for CK-7 and negative for CK-20^[9]. Thus, a combination of TTF-1(+), CK-7(+), and CK-20(-) immunophenotypes is highly suggestive of primary adenocarcinoma of the lung (specificity, 100%)^[5,10]. The immunohistochemical profiles of the two cases described here are indicative of metastatic lung adenocarcinoma.

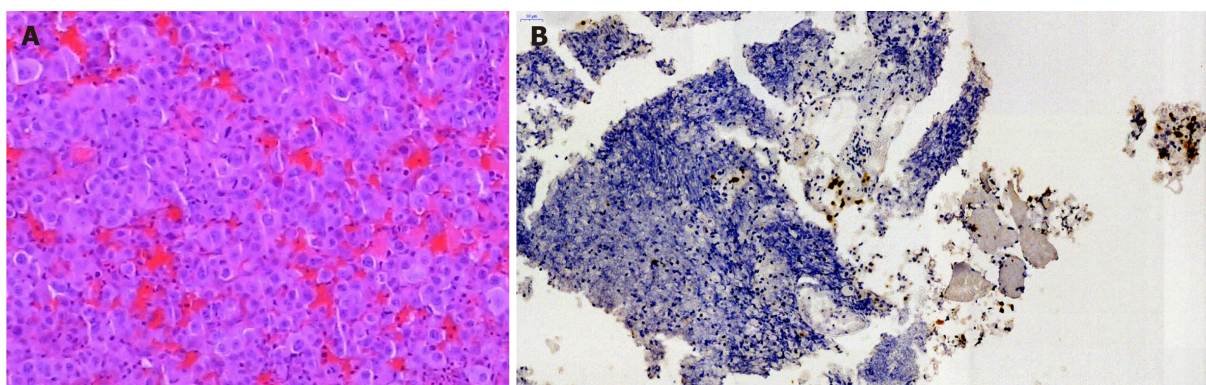


Figure 2 Case 1. A: Cervical biopsy showed poorly differentiated adenocarcinoma; B: Pathological examination of specimens obtained from lung biopsy showed adenocarcinoma with necrosis, and immunohistochemical staining for thyroid transcription factor-1 was positive.

In the first case, the patient did not have enough tissue sample in percutaneous lung puncture biopsy for gene mutational analysis; fortunately, cervical biopsy produced adequate tissue specimen on which we confirmed cervical metastasis by immunohistochemistry. PET-CT showed hypermetabolic activity in pulmonary lesions and the cervix uteri. According to clinical pathologists, the cervical neoplasm was a metastasis from lung cancer, which also confirmed by immunohistochemistry. Subsequent EGFR gene mutational analysis (using the Amplification Refractory Mutation System, ARMS) of the cervical tissue sample revealed EGFR L858R mutation in exon 21. The patient was then started on gefitinib and achieved partial remission after 4 mo of treatment.

In case 2, lung biopsy could not be performed because of obstructive pneumonia and pleural effusion. Pleural fluid cytology was performed on a cell block; thus, EGFR mutational analysis could be optimized. Although tissue biopsy still represents the gold standard for the diagnosis of lung cancer^[11,12], it is not always possible to obtain high-quality specimens from all patients. In certain situations, liquid biopsy could be an essential tool for clinicians, especially for patients who cannot undergo invasive diagnostic procedures^[11]. The patient's disease progressed during treatment with TKI, accompanied by ovarian metastasis and bone metastasis. Since repeated biopsy of the lung mass is not recommended, analysis of the ovarian biopsy showed EGFR 19-del mutation and T790M mutation in exon 20, which represents one of the two confirmed mechanisms of drug resistance. Approximately half of the cancers that acquire resistance to EGFR TKIs develop a secondary mutation in EGFR (T790M), which abrogates the inhibitory activity of the TKI^[13]. The patient was then started with osimertinib. As recently reported, osimertinib displays significantly greater efficacy than platinum therapy plus pemetrexed in patients with T790M-positive advanced non-small cell lung cancer (including cases with CNS metastases) in whom the disease has progressed during first-line EGFR TKI therapy^[12,14]. Timely biopsy of the ovarian metastasis provided reference for the patient's treatment, which greatly contributed to the patient's prognosis.

CONCLUSION

According to the principles of precision medicine, the initial tumor site should be considered when both pulmonary and female genital tract neoplasms exist. Immunohistochemistry and gene mutational testing have greatly helped in locating the initial tumor site.

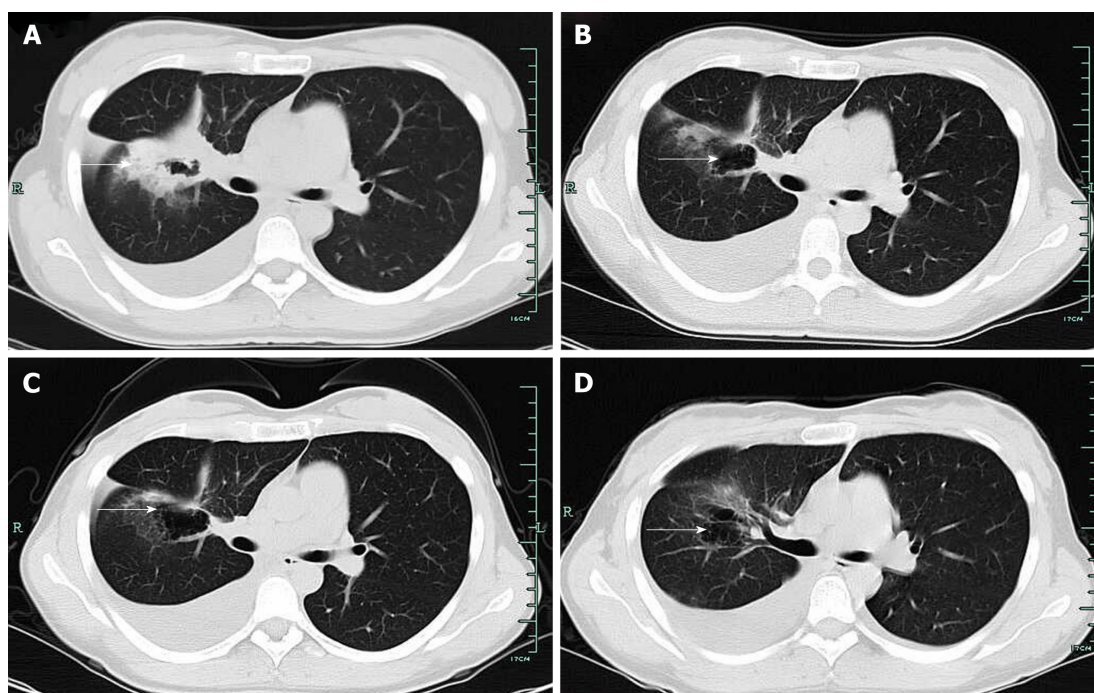


Figure 3 Case 2. A: Computed tomography (CT) scan showed lung lesions with cavity, as well as pleural effusion before tyrosine kinase inhibitor treatment; B: CT showed a right pulmonary mass after 3 mo of ecotinib therapy, which resulted in a partial response after 3 mo; C: CT scan showed pleural effusion after 1 mo of bevacizumab (Avastin) and icotinib therapy; D: CT scan showed pleural effusion after 4 mo of bevacizumab (Avastin) and icotinib therapy, without progression of initial tumor.

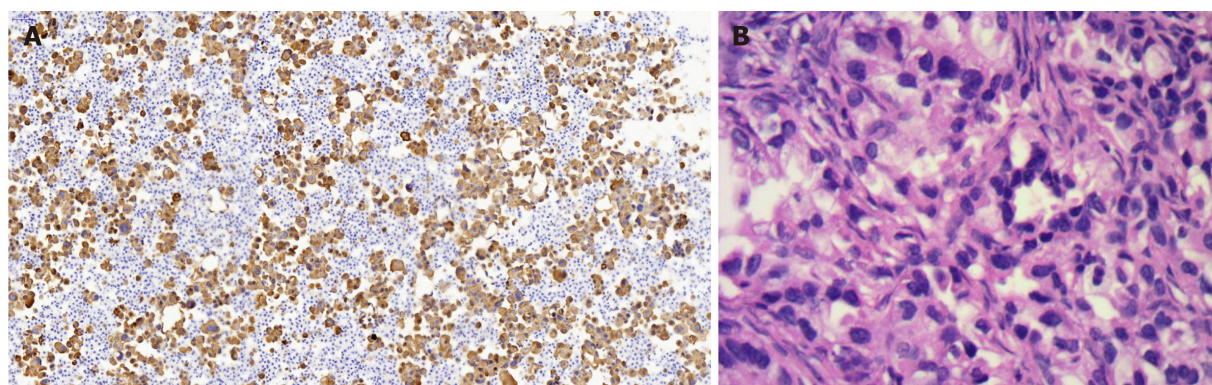


Figure 4 Case 2. A: Pathological examination of specimens obtained from lung biopsy showed adenocarcinoma, and immunohistochemical staining for thyroid transcription factor-1 (TTF-1) was positive; B: Ovarian biopsy revealed TTF-1 positive adenocarcinoma.

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