



A case report of vesicovaginal fistula following Bevacizumab without pelvic disease and radiochemotherapy

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Background: Bevacizumab has gradually become an important adjuvant therapy for many advanced tumors including lung cancer. Although it can improve the survival of many cancer patients, it also brings many adverse reactions, including fistula formation. However, vesicovaginal fistula in the absence of pelvic lesions and radiation history has not been reported before.

Case Description: We diagnosed an advanced non-small cell lung cancer patient with left pleural, bone and liver metastases in February 2017. She then received Gefitinib-targeted therapy. Ten months later, liver metastases achieved complete remission and the remaining metastases partial response. Then she received whole brain radiotherapy (30 Gy/10 F) for new brain metastases, and Oxitinib was used to replace Gefitinib. In March 2018, the patient underwent TVT-O sling surgery for stress urinary incontinence, and recovered well after the operation. The patient was treated with Bevacizumab at 400 mg once every 3 weeks in March 2019 because of the poor efficacy of Oxitinib. After using bevacizumab for 3 months, the patient complained about frequent urination, urgency, dysuria, and vaginal leakage. The presence of vesicovaginal fistula was confirmed by color Doppler ultrasound and positron emission tomography/computed tomography (PET-CT). After discontinuation of Bevacizumab, urine leakage was disappeared.

Conclusions: Bevacizumab can also cause vesicovaginal fistula, even without pelvic lesions and radiotherapy. Previous pelvic surgery and foreign materials implantation may be factors that promote the formation of vesicovaginal fistula.

Keywords: Bevacizumab; case report; genitourinary fistula; lung cancer; radiochemotherapy

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Introduction

Lung cancer is a malignant tumor with high mobility and mortality. The non-small cell lung cancer is the most common type, accounting for over 80%, and is life-threatening (1,2). According to the results of ECOG4599, Bevacizumab is the first-line treatment for advanced lung cancer (3). Although it can improve the survival of many cancer patients, it also brings many adverse reactions, including fistula formation (4). Esophago tracheal fistula is a rare but fatal complication associated with bevacizumab in lung cancer (5). Vesicovaginal fistula is another not-gastrointestinal fistula which has been reported in cervical

cancer using bevacizumab (6). However, patients with vesicovaginal fistula always have a history of pelvic diseases or radiotherapy (7). Here, we present a patient with lung cancer who has not received pelvic radiotherapy and developed a vesicovaginal fistula after using Bevacizumab. We present the following case in accordance with the CARE reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-251/rc>).

Case presentation

A 58-year-old woman was diagnosed with left upper lobe lung adenocarcinoma with left pleural, bone and liver

metastases in February 2017. She then received Gefitinib-targeted therapy. Ten months later, liver metastases achieved complete remission and the remaining metastases partial response. Then in December 2017, she received whole brain radiotherapy (30 Gy/10 F) for new brain metastases, and Oxitinib was used to replace Gefitinib. In March 2018, the patient underwent TVT-O sling surgery for stress urinary incontinence, and recovered well after the operation. The patient was treated with Bevacizumab at 400 mg once every 3 weeks in March 2019 because of the poor efficacy of Oxitinib. After using bevacizumab for 3 months, the patient complained about frequent urination, urgency, dysuria, and vaginal leakage. Color Doppler ultrasound showed the absence of echo between the posterior wall of bladder neck and the anterior wall of vagina. The ultrasound found the tape of TVT-O was not related to the bladder wall. Further positron emission tomography/computed tomography (PET-CT) examination showed a passage from the bladder to the vagina and a large amount of radioactive urine accumulated in the vagina, indicating vesicovaginal fistula. A gynecological examination revealed a fistula leaking urine in the anterior vaginal wall. However, the patient refused further cystography or cystoscopy to confirm the vesicovaginal fistula. Considering that it may be the adverse reaction of Bevacizumab, drug was discontinued. One month after discontinuation of Bevacizumab, the symptoms of lower urinary tract and leakage of urine disappeared completely, and no abnormality was found by color Doppler ultrasound.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

This is the first report of vesicovaginal fistula in lung cancer after the use of Bevacizumab, while in the absence of pelvic diseases and history of pelvic radiotherapy. It is well known that Bevacizumab can cause fistula formation, among which gastrointestinal fistula is the most common one. Although lung cancer can also lead to gastrointestinal fistula, esophago tracheal fistula is more common, which is a life-threatening complication (5,8). Two phase II clinical trials

about lung cancer using bevacizumab were closed early due to tracheoesophageal fistulae development (9). In lung cancer, we found no reports of vesicovaginal fistula caused by bevacizumab from now on.

Vesicovaginal fistula is another not-gastrointestinal fistula associated with bevacizumab which have been reported in cervical cancer (6). In the GOG-024 study, the incidence vesicovaginal fistula was 1.8% and all cervical cancer patients developing vesicovaginal fistula had received pelvic radiotherapy in the past (6). Subsequently, in the Cecilia study, almost all patients with fistula after the treatment of Bevacizumab had a history of radiotherapy, except for one patient who had not received radiotherapy, but combined with pelvic tumors (7). In our study, vesicovaginal fistula occurred after Bevacizumab with no pelvic metastasis or radiotherapy, which is worth our attention.

From now on, the mechanism of fistula formation associated with bevacizumab is still unclear. Bevacizumab inhibits the activity of vascular endothelial growth factor and leads to local ischemia, which may be the main mechanism of fistula disease (10). The predisposing causes of fistula formation may be as follows (11). One possible factor is tumor location. In the case of Bevacizumab killing the tumor, tumor necrosis could lead to fistula formation. Another possible factor is that Bevacizumab can cause subepithelial vascular embolism, leading to ischemia and necrosis of normal tissues. Finally, Bevacizumab may cause poor healing of anastomotic stoma in patients undergoing tumor resection, promoting the formation of fistula. In addition, researchers also found that radiotherapy, combined with other chemotherapy drugs can promote the occurrence of fistula in patients under the treatment of Bevacizumab (12-14).

Although our patient had no history of pelvic radiotherapy and tumor, she underwent TVT-O for stress urinary incontinence, which may be related to the formation of fistula. The previous study has found that sling surgery can lead to vaginal necrosis and ulceration (15). The surgical approach of TVT-O is through the anterior wall of vagina, which may change the vascular environment around the urethra. In addition, the TVT-O sling is a foreign body, which can have a reject reaction. In Alessio's study, the patient with recurrent cervical cancer who was treated with Bevacizumab, double-J tube was ectopic into the colon due to fistula (16).

Treatment of vesicovaginal fistula caused by Bevacizumab has not been reported too much before. The patient stopped using Bevacizumab immediately after the discovery

of fistula and fistula healed one month later, which indicated that the conservative treatment was effective.

Although it is a case report which has some limitations, it provides some significant values for clinicians encountering Bevacizumab-related vesicovaginal fistula: (I) Bevacizumab could induce vesicovaginal fistula without pelvic lesions or radiation history; (II) local surgical trauma and foreign matters may lead to fistula formation; (III) conservative treatment can be the first choice for non-fatal fistula.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-251/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-251/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

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