Gefitinib-induced hemorrhagic cystitis and inflammatory contracted bladder in a patient with advanced lung adenocarcinoma harboring compound epidermal growth factor receptor G719S and S768I missense mutations: a case report

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Background: Numerous clinical studies have established the efficacy and safety of gefitinib for treating patients with epidermal growth factor receptor (*EGFR*)-mutant lung cancer. Gefitinib-induced urinary system-related adverse reactions are rare but may lead to discontinuation of gefitinib.

Case Description: In our report, we describe a patient with advanced lung adenocarcinoma harboring compound *EGFR* G719S and S768I who developed hemorrhagic cystitis and inflammatory contracted bladder during first-line gefitinib therapy. A 56-year-old male smoker, presented with chronic cough, sputum expectoration, and shortness of breath for 6 months that had worsened over the last 2 weeks, was diagnosed with T2N2M1A stage IV adenocarcinoma of the right lower lung with bilateral lung metastases. Upon detecting a compound *EGFR* G719S and S768I using a next-generation sequencing-based assay, the patient was administered with gefitinib (250 mg/day) as a first-line regimen. Despite achieving partial response (PR) within 6 weeks of gefitinib therapy, the patient developed several drug-related adverse reactions, including diarrhea, elevated liver enzymes, and inflammatory contracted bladder with hemorrhagic cystitis. Routine urinalysis indicated full high-power field (HPF) view of red blood cell (RBC) and 40–50 white blood cell (WBC) counts/HPF at 1.5 months of gefitinib therapy as compared with no RBC and WBC per HPF before gefitinib therapy (normal range: 0–1 RBC/HPF and 0–3 WBC/HPF). The urinary symptoms and hematuria were alleviated after discontinuation of gefitinib. Icotinib was administered without benefit and subsequently switched to afatinib as the third-line therapy. A PR was achieved; however, it only lasted for 3 months. Then the patient was lost to follow-up.

Conclusions: Our case shows that gefitinib can induce hemorrhagic cystitis and contracted bladder. Clinicians must be aware that these uncommon adverse reactions affecting the urinary system could occur in patients with *EGFR*-mutant lung adenocarcinoma. Monitor for urinary symptoms and hematuria in this cohort of patients is essential.

Keywords: Gefitinib; hemorrhagic cystitis; inflammatory contracted bladder; compound EGFR; case report

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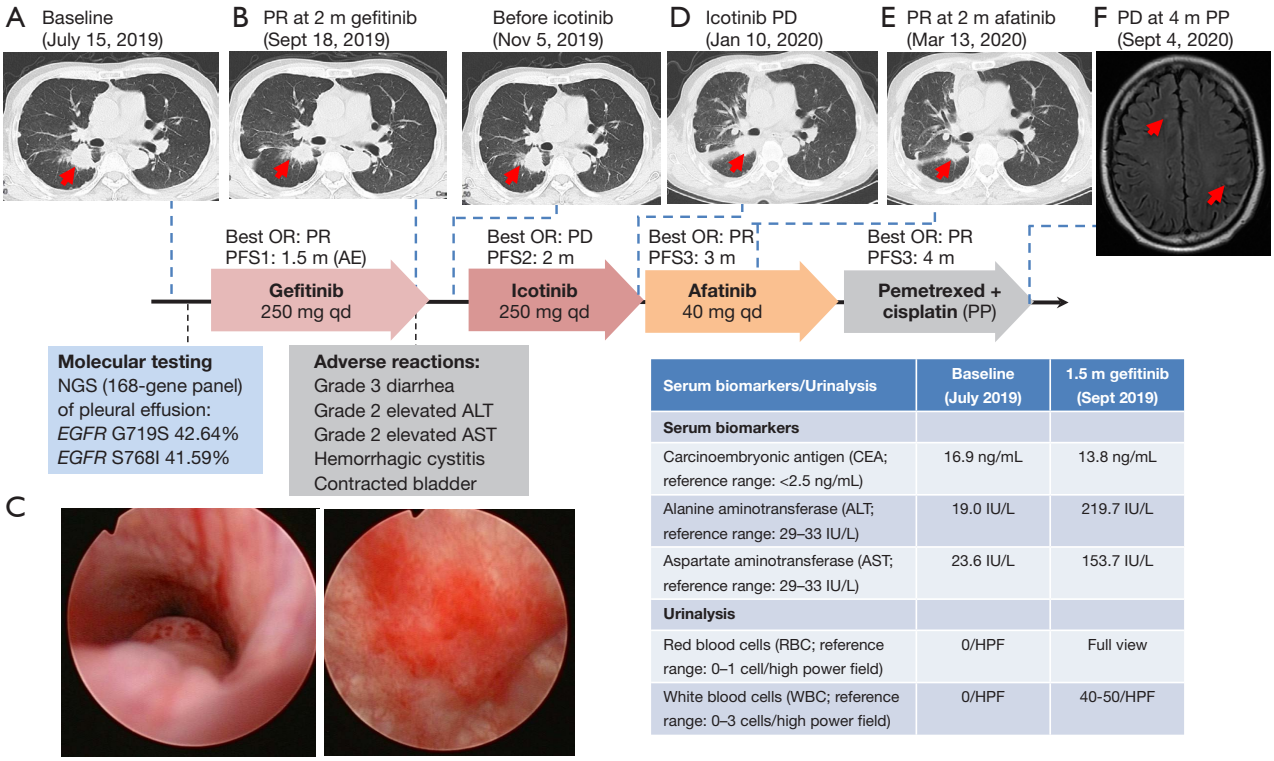
Introduction

Lung adenocarcinoma harboring sensitizing mutations in epidermal growth factor receptor (*EGFR*), including small in-frame deletions in exon 19, and missense mutation L858R, responds to gefitinib, a first-generation EGFR tyrosine kinase inhibitor (TKI) (1). Before its accelerated approval by the US Food and Drug Administration (FDA), the therapeutic efficacy and safety profile of gefitinib had been demonstrated in numerous clinical trials (2,3). At the standard recommended dose, gefitinib has a tolerable safety profile (4-6), with reported adverse reactions primarily involving the gastrointestinal system (i.e., diarrhea, nausea, vomiting), skin (i.e., rash, acne, dry skin), and liver [i.e., elevated alanine aminotransferase (ALT) and aspartate transaminase (AST)] (2,5,7). However, uncommon adverse reactions have been reported, including hematuria and hemorrhagic cystitis (8-14). Clinicians should pay more attention on monitoring for urinary symptoms and hematuria. Discontinuation of gefitinib is usually the main management approach of severe drug-related toxicities (2,9). This case report describes a patient with advanced lung adenocarcinoma who experienced gefitinib-induced hemorrhagic cystitis and inflammatory contracted bladder. With early detection and gefitinib discontinuation, the patient's symptom relived quickly. We present the following article in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3233/rc).

Case presentation

In July 2019, a 56-year-old male with a 60-pack year smoking history sought medical attention due to chronic cough, sputum expectoration, and shortness of breath for 6 months that had worsened over the last 2 weeks. He had no known comorbidity and reported no family history of cancer. A computed tomography (CT) scan showed a high-density shadow in the upper left lung, a 3.63 cm × 2.68 cm soft tissue mass in the lower lobe of the right lung, and the presence of pleural effusion in the right lung (*Figure 1A*). Multiple nodules were observed in both lung lobes and pleura. Right hilar lymph nodes were also enlarged. He was diagnosed with stage IV adenocarcinoma of the right lower lung with bilateral lung metastases. Molecular testing using the next-generation sequencing-based assay of pleural effusion samples identified a compound *EGFR* G719S and S768I with the allelic abundance of 42.64% and 41.59%, respectively. The patient was administered with gefitinib (250 mg/day) as a first-line regimen. His initial clinical symptoms improved within 4 weeks from starting gefitinib therapy; however, he subsequently experienced grade 3 diarrhea (7–8 times/day). After 40 days of gefitinib therapy, he also experienced dysuria, decreased urine output, and gross hematuria. No fever, urinary stones, or other symptoms were noted. Despite the adverse events, the primary lesion in the right lower lobe shrunk to 2.81 cm × 2.58 cm and was evaluated as a partial response (PR) based on the criteria of the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST; *Figure 1B*). Grade 2 elevation of liver enzymes, including AST and ALT, were detected (*Figure 1*). Routine urinalysis indicated full high-power field (HPF) view of red blood cell (RBC) and 40–50/HPF white blood cell (WBC) counts at 1.5 months of gefitinib therapy as compared with 0/HPF RBC and WBC before gefitinib therapy (normal range: 0–1 RBC/HPF and 0–3 WBC/HPF). Cystoscopy showed narrowing of the bladder neck, distension of the posterior bladder wall, hypertrophied trigone, and a sunken bladder base. No trauma or inflammation of the bladder was observed (*Figure 1C*). These findings suggested a contracted bladder with hemorrhagic cystitis. Gefitinib therapy was immediately discontinued, which resolved the urinary symptoms and hematuria as indicated by the marked reduction of RBC (5–10 RBC/HPF and 0 WBC/HPF). In November 2019, his treatment was switched to icotinib (125 mg orally thrice daily); however, the primary lesion was not responsive to icotinib therapy, as shown by the enlargement of lymph nodes, multiple lung and pleural metastases, and increased pleural effusion (*Figure 1D*). Afatinib (40 mg/day) was then initiated in January 2020 as a third-line therapy, and the patient achieved PR within 2 months of treatment (*Figure 1E*). Grade 2 rashes were observed. On 10 April 2020, his cough and shortness of breath worsened, which were suspected to be symptoms of disease progression. He received his first chemotherapy regimen comprised of pemetrexed and cisplatin on 4 May 2020, and achieved PR after three cycles of the regimen. At follow-up on 4 September 2020, enhanced cranial magnetic resonance imaging (MRI) revealed brain metastasis (*Figure 1F*). The patient refused to undergo craniocerebral radiotherapy and was lost to follow-up. 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 provided by the



Serum biomarkers/Urinalysis	Baseline (July 2019)	1.5 m gefitinib (Sept 2019)
Serum biomarkers		
Carcinoembryonic antigen (CEA; reference range: <2.5 ng/mL)	16.9 ng/mL	13.8 ng/mL
Alanine aminotransferase (ALT; reference range: 29–33 IU/L)	19.0 IU/L	219.7 IU/L
Aspartate aminotransferase (AST; reference range: 29–33 IU/L)	23.6 IU/L	153.7 IU/L
Urinalysis		
Red blood cells (RBC; reference range: 0–1 cell/high power field)	0/HPF	Full view
White blood cells (WBC; reference range: 0–3 cells/high power field)	0/HPF	40-50/HPF

Figure 1 Clinical summary of the patient. (A,B,D,E) Thoracic CT scans of primary lung lesions at various time points, including at (A) baseline (3.63 cm × 2.68 cm); (B) 2 months of gefitinib therapy evaluated as PR; (D) evaluation of PD at 2 months of icotinib therapy; (E) PR after 2 months of afatinib therapy. (F) Contrast-enhanced cranial magnetic resonance imaging of brain metastatic lesions at PD after three cycles of pemetrexed plus cisplatin regimen. Red arrows indicate the primary or metastatic lesions. An illustrated summary of the treatment received by the patient, including the best OR and PFS in each line of treatment. Compound *EGFR* mutations and their corresponding allelic fractions detected at baseline using targeted NGS of pleural effusion. (C) Cystoscopy images showing the contracted bladder. PR, partial response; PD, progressive disease; PP, pemetrexed and cisplatin combination chemotherapy; OR, objective response; PFS, progression-free survival; AE, adverse events; qd, once a day; NGS, next generation sequencing; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CEA, carcinoembryonic antigen; RBC, red blood cell; WBC, white blood cell; HPF, high power field; CT, computed tomography.

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

Gefitinib is effective in patients with advanced NSCLC harboring EGFR-activating mutations, and our patient achieved PR within 6 weeks of gefitinib therapy. Unfortunately, gefitinib was discontinued because of hemorrhagic cystitis and inflammatory contracted bladder. Gefitinib is primarily metabolized by the hepatic cytochrome P450 enzymes (15). Pharmacokinetic studies of gefitinib have demonstrated a urinary recovery of only <0.5%, indicating that the urinary system is only a minor route of excretion (4). Despite being generally well-tolerated, a small subset of patients have reported uncommon gefitinib-induced adverse reactions affecting the urinary system, including acute renal failure (10), hematuria (12), hemorrhagic cystitis (11,13), and inflammatory contracted bladder (11). *In vitro* studies have demonstrated that EGFR signaling is involved in the proliferation of urothelial cells, and gefitinib can inhibit the growth of normal urothelial cells and urothelial carcinoma cell lines (16). Hence, it is likely that gefitinib therapy might induce inflammatory changes

in the urinary system in a subset of patients (11,13). Additional studies are required to elucidate how gefitinib can induce urinary system-related adverse events.

To relieve the symptoms of severe drug-related toxicities, discontinuation of the medication is the standard management (2,9). In our patient, the termination of gefitinib treatment alleviated the symptoms of toxicity. Drug-related toxicity was not observed even after switching to another first-generation EGFR-TKI icotinib or the second-generation EGFR-TKI afatinib, which indicates that different EGFR-TKIs involve different drug metabolic pathways. This observation was also consistent with another gefitinib-induced hemorrhagic cystitis in an *EGFR* exon 19-mutant lung adenocarcinoma patient (13) and a cohort from a previous study demonstrating that the administration of a second EGFR-TKI after severe adverse reaction from the first EGFR-TKI is safe and affords substantial benefit to patients with *EGFR*-mutant non-small-cell lung cancer (17).

Some case reports of gefitinib-induced renal/urinary system-related adverse reactions have not specified the *EGFR* status of the patients (10-12); hence, we might not know the correlation between the specific *EGFR* mutation and the occurrence of gefitinib-related toxicities. Our patient harbored compound *EGFR* G719S and S768I mutations. Patients harboring compound *EGFR* G719X and S768I mutations have been reported to respond to erlotinib and afatinib therapy (18-21). Consistently, our patient benefited from afatinib therapy; however, the response was also not durable. Furthermore, our patient also achieved PR to chemotherapy until he developed brain metastasis.

Our case shows that gefitinib can induce hemorrhagic cystitis and contracted bladder and contributes to the awareness that these uncommon adverse reactions affecting the urinary system could occur in patients with *EGFR*-mutant lung adenocarcinoma.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3233/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3233/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 provided by 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.

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