Learning From Errors: Response to Gefitinib in Kidney Urothelial Carcinoma With *EGFR* Mutations

The occurrence of *EGFR* mutations in urinary tract tumors is generally considered rare if not absent [1, 2]. Double mutations in the *EGFR* gene have been described only in lung tumors with variable clinical response [3].

In this letter, we describe the case of a 62-year-old woman with a strong smoking habit and a silent history of cancer who presented with hematuria and abdominal pain. A lesion of the left kidney and bilateral lung lesions, the main in the right upper lobe, were discovered at imaging. The transbronchial biopsy of the main lung nodule was histologically diagnosed as squamous cell carcinoma, leading to the suspicion of primary advanced lung cancer with kidney metastasis. This suspicion was confirmed by the finding in the lung biopsy of double mutations in exons 19 and 21 (p.L747_T751del and p.S768I) of the *EGFR* gene, with sensitization to EGFR tyrosine kinase inhibitors (Fig. 1A, 1B). A week later, radical nephrectomy was performed for urgent symptoms of the kidney mass and

revealed a high-grade urothelial cancer with adenosquamous features, stage pT4N1, associated with urothelial carcinoma in situ of the renal pelvis (Fig. 1C). A chemotherapy schedule with carboplatin plus gemcitabine was started and discontinued after 3 months (four cycles) due to disease progression. Poor response raised the suspicion of metastatic origin of the lung masses from the kidney tumor, which was confirmed by the finding in the kidney tumor tissue of the same *EGFR* double mutations found in the lung (Fig. 1D). The patient was switched to single therapy with gefitinib at a dose of 250 mg per day with good tolerance. The patient is now in good general clinical condition under continuous treatment with gefitinib, and the control computed tomography scans at 9 months showed good partial response (>50%) of all lung lesions (Fig. 1E, 1F).

To our knowledge, we describe the first demonstration of clinical response to the anti-EGFR inhibitor gefitinib in a case of urothelial carcinoma of the renal pelvis harboring a rare *EGFR* double mutation. In the era of personalized oncologic medicine, the therapeutic approach should not be based a priori on only the histological appearance and the frequency of the reported genetic alterations for that tumor type. New mutations and unexpected clinical responses should be always explored through wide-spectrum mutational analyses.

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Figure 1. Microscopic appearance and *EGFR* mutational status of the lung (A, B) and the kidney (C, D) tumors. Inset in (C) depicts in situ carcinoma of the renal pelvis. (E, F): Sequential scans of the main lung mass before (E) and after (F) monotherapy with gefitinib.

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