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1 例晚期肺鳞癌患者 EGFR 突变病例报道并文献复习

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[摘　要] 1例表皮生长因子受体(epidermal growth factor receptor，EGFR)突变阳性的晚期肺鳞癌患者，男，65岁，无明显诱因出现刺激性咳嗽10余天。胸部CT见右下肺实性肿块，隆突下肿大淋巴结。支气管镜取活检病理诊断为中低分化鳞状细胞癌。全身骨显像检查考虑骨转移。*EGFR*基因检测结果显示*EGFR*基因第19号外显子缺失。给予患者口服吉非替尼治疗。1周后症状即消失。胸部CT显示肺部肿物及纵隔淋巴结显著缩小。3个月后患者病情出现进展，复查*EGFR*基因检测显示T790M突变。遂开始口服奥希替尼治疗。胸部CT可见肿块影显著缩小。口服奥希替尼3个月后，肿瘤复发，再次行支气管镜活检，行基因检测可见C797S突变。之后患者未行任何治疗，3个月后因肿瘤进展死亡。

[关键词] 肺鳞癌；表皮生长因子受体；靶向治疗

EGFR mutations in patients with advanced lung squamous cell carcinoma: A case report and literature review

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Abstract A 65-year-old man with advanced lung squamous cell carcinoma of epidermal growth factor receptor (EGFR) mutation positive, was admitted to the hospital for no obvious cause of irritating cough for more than 10 days. A solid mass in the lower right lung and enlarged lymph nodes under carina were displayed by CT exam. Bronchoscopy biopsy was performed and the pathologic diagnosis was medium and low differentiated squamous cell carcinoma. Radionuclide bone imaging showed bone metastasis. The results of the gene test showed the deletion of exon 19 of *EGFR* gene. Patients were given gefitinib orally. The symptoms disappeared after 1 week. Chest CT showed a significant reduction of lung mass and mediastinal lymph nodes. After 3 months, the disease progressed, and a reexamination of *EGFR* gene showed T790M mutation. So, the patient was treated with orxitinib. CT scan of the chest shows a significantly reduced mass. Three months after oral administration of

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oxitinib, the tumor recurred and was biopsied again with bronchoscopy. Gene detection revealed C797S mutation. The patient received no treatment and died of tumor progression 3 months later.

Keywords lung squamous cell carcinoma; epidermal growth factor receptor; targeted therapy

鳞状细胞癌是肺癌常见的病理类型之一，在肺癌中发病率居第2位，仅次于腺癌[1]。近些年，靶向治疗迅猛发展，在表皮生长因子受体(epidermal growth factor receptor，EGFR)突变的晚期肺癌，特别是晚期肺腺癌的治疗中占据举足轻重的地位。相较于传统的化疗，靶向治疗能够明显提高患者的客观有效率(objective response rate，ORR)、疾病控制率(disease control rate，DCR)、无进展生存期(progression-free survival，PFS)[2]。中国临床肿瘤学会(Chinese Society of Clinical Oncology，CSCO)、美国国立综合癌症网络(National Comprehensive Cancer Network，NCCN)等发布的指南已将酪氨酸激酶抑制剂(tyrosine kinase inhibitor，TKI)列为EGFR突变的晚期肺腺癌的一线治疗。但对于晚期肺鳞癌的治疗，目前仍以传统的放化疗为主，这一方面是由于肺鳞癌的EGFR突变率低，仅3.3%~4.6%[3]。另一方面，即便是针对存在EGFR突变的肺鳞癌，TKI的疗效也远不及治疗肺腺癌。现报告1例EGFR突变阳性的晚期肺鳞癌患者，并复习相关文献，进一步探索TKI在晚期肺鳞癌患者中的应用价值。

1 临床资料

患者，男，65岁，因无明显诱因出现刺激性咳嗽10余天入院治疗。胸部CT见右下肺实性肿块，隆突下肿大淋巴结(图1)。支气管镜活检，病理诊断为中低分化鳞状细胞癌。全身骨显像示：胸骨、脊柱、骨盆骨等见多发、无规律分布的异常放射性浓聚灶，考虑骨转移癌可能性大。头部CT及腹部+双肾上腺超声未见异常。行*EGFR*基因检测，结果显示：*EGFR*基因第19号外显子缺失。既往冠心病病史10余年，否认吸烟史。

遂给予患者吉非替尼片治疗，1周后，患者刺激性咳嗽症状基本消失。口服吉非替尼3周左右时，患者出现皮疹，对症治疗后缓解。口服药物1个月后复查胸部CT可见肿瘤显著缩小，隆突下淋巴结显著缩小(图2)。

口服吉非替尼3个月后，患者再次出现刺激性咳嗽症状，并伴有咳痰带血。复查胸部CT可见右侧肺门肿物(图3)，行支气管镜检查，病理显示：(右肺中下叶)非小细胞癌。行EGFR检测，结果显示：*EGFR*基因第19号外显子缺失，*EGFR*基因第20号外显子突变(T790M)。遂给予患者口服奥希替尼治疗。服药2周后症状逐渐好转，并未出现明显的不良反应。服药1个月后查胸部CT可见右肺门肿块影显著缩小(图4)。

口服奥希替尼3个月后，患者再次出现咳嗽、咳痰带血。复查胸部CT可见右肺中下叶肿瘤局部复发。再次行支气管镜活检，行基因检测可见C797S突变。之后患者未行任何治疗，3个月后因肿瘤进展死亡。

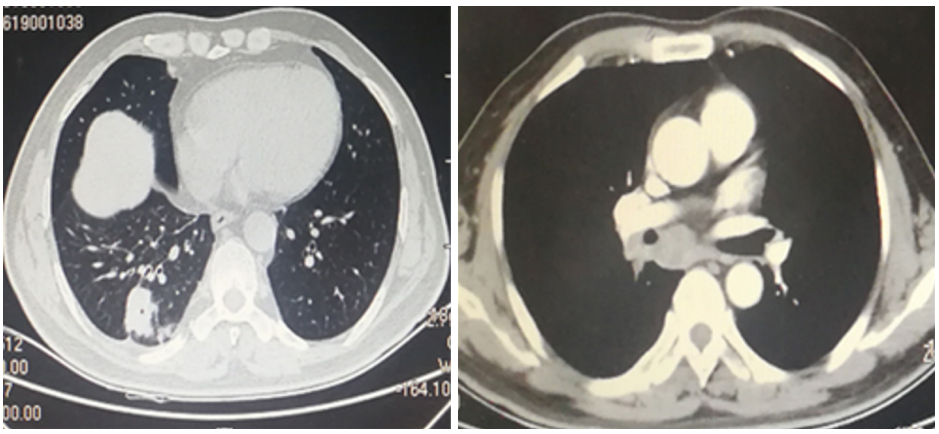

图1 治疗前胸部CT可见右肺下叶肿块，隆突下肿大淋巴结

Figure 1 Before treatment, chest CT shows a mass in the lower lobe of the right lung and enlarged lymph nodes under carina

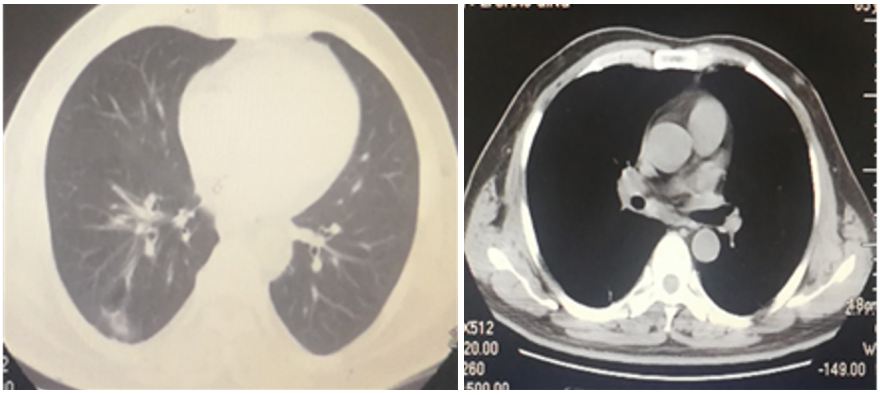

图2 服用吉非替尼1个月后，胸部CT可见肿瘤显著缩小，隆突下淋巴结显著缩小

Figure 2 After taking gefitinib for 1 month, the tumor was significantly reduced on chest CT, and the subcarinal lymph nodes were significantly reduced

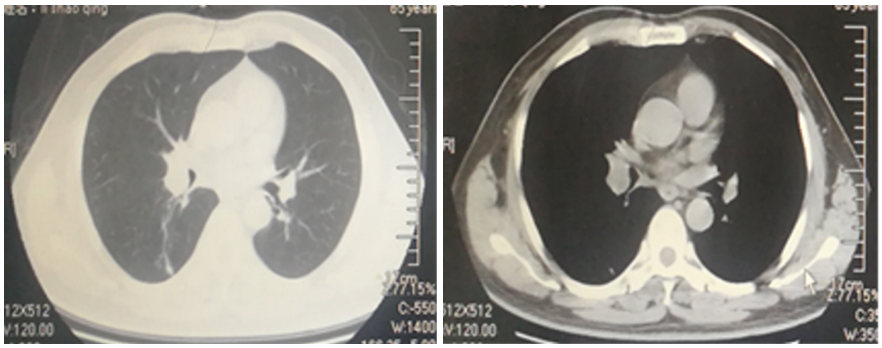

图3 服用吉非替尼3个月后，胸部CT可见右侧肺门肿物

Figure 3 After 3 months of gefitinib administration, a right hilar mass was seen on chest CT

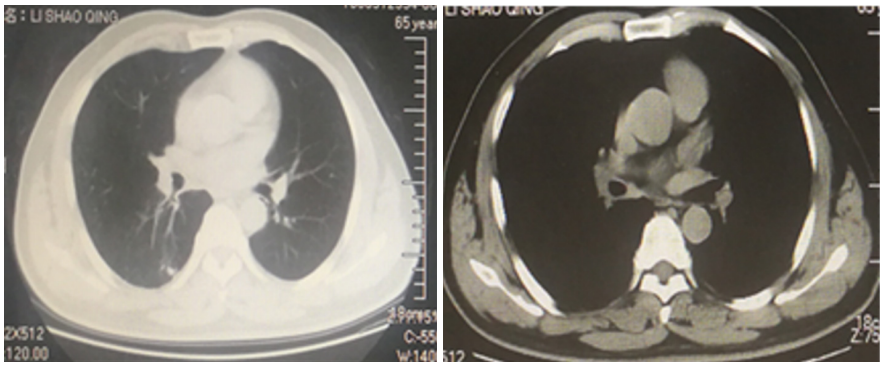

图4 口服奥希替尼1个月后，CT可见右肺门肿块影显著缩小

Figure 4 One month after the administration of oxitinib, CT showed a significantly reduced mass shadow in the right hilum

2 讨论

肺癌已居我国恶性肿瘤发病率和病死率首位。然而由于多种原因，多数肺癌患者初次就诊时已属晚期，无法进行手术切除。鳞癌是肺癌的常见病理类型之一。晚期肺鳞癌的治疗长期以来以含铂双药方案化疗为主，然其疗效却不尽如人意。

EGFR是一种跨膜糖蛋白，其基因突变可促进癌细胞增殖、分化等，在非小细胞肺癌(non-small cell lung cancer，NSCLC)的疾病演进中起重要作用[4]。近些年，晚期肺癌的治疗正在发生着突飞猛进的改变，相较于传统的化疗，靶向治疗由于其

疗效显著、不良反应小等优势，CSCO，NCCN等发布的指南已将TKI列为EGFR突变的晚期NSCLC的一线治疗。但鳞癌的EGFR突变率较低，Joshi等[5]检测了639例肺鳞癌患者*EGFR*基因，结果显示：29例检出突变，突变率为4.5%。于起涛等[6]回顾性分析了172例行*EGFR*基因检测的肺鳞癌患者，发现15例具有敏感突变的患者，突变率为8.7%。均显著低于腺癌的突变率。另一方面，TKI针对EGFR突变的肺鳞癌的疗效不及肺腺癌。有研究[7]表明：TKI治疗EGFR突变的肺鳞癌患者的ORR为27%，DCR为67%~70%，PFS为3个月，均远低于同期接受TKI治疗的EGFR突变肺腺癌患者。本例患者PFS约3个月，与该研究结果较为一致。临床研究[8-9]证实：针对肺鳞癌，TKI组对比安慰剂组，两者的总生存期无统计学差异。

与腺癌的靶向治疗相同，TKI的耐药同样是肺鳞癌患者难以逃避的问题。研究[10-11]显示：针对1代TKI的耐药，无论其是否有T790M突变，奥希替尼均有良好的疗效，但T790M突变阳性的患者效果要优于阴性者。本例患者口服吉非替尼，疾病进展后，T790M突变，口服奥希替尼后可见肺门肿物显著缩小，效果显著。

突变率低且疗效有限，这虽然限制了TKI在肺鳞癌的应用，但不能因此全面否定TKI在鳞癌治疗中的地位。由于其相对于传统含铂双药化疗具有更弱的不良反应，患者一般可耐受，且服药方便，患者治疗的依从性好。研究[6]表明：女性、不吸烟患者的*EGFR*基因突变率高于男性、吸烟患者。若在临床中针对女性或不吸烟患者常规行*EGFR*基因检测，使患者获得更好的疗效及个体化治疗，或是更值得考虑的方案。

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