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1 例 EGFR T790M 突变阳性晚期肺腺癌的治疗策略及文献复习

全玲丽，黄彭，刘双柏，梁彦超

(中南大学湘雅医学院附属株洲医院呼吸内一科，湖南 株洲 412007)

[摘　要]　回顾性分析中南大学湘雅医学院附属株洲医院1例晚期肺腺癌患者的临床资料，并进行相关文献复习。该患者经胸腔穿刺术及左侧淋巴结活检确诊为肺腺癌，头部MRI及上腹部增强CT示头、肝、脾、胰腺及左侧肾上腺多发转移，表皮生长因子受体扩增阻滞突变系统(epidermal growth factor receptor-amplification refractory mutation system，EGFR-ARMS)检测提示EGFR 21外显子突变(L858R)，给予第1代EGFR抑制剂(tyrosine kinase inhibitors，TKIs；吉非替尼)治疗11个月后，病情出现进展，再次基因检测EGFR T790M突变为阳性，二线给予第3代EGFR-TKIs(奥西替尼)治疗，病情得到缓解。说明初次EGFR-TKIs治疗后，部分晚期肺腺癌患者耐药后仍然可在EGFR-TKIs治疗中受益。以奥西替尼为代表的第3代EGFR-TKIs治疗耐药后出现T790M突变的患者疗效显著，给晚期肺癌患者带来更多的生存获益。

[关键词]　非小细胞肺癌；表皮生长因子受体抑制剂；T790M突变；吉非替尼；奥西替尼

Therapy strategy of advanced lung adenocarcinoma with EGFR T790M positive mutation: A case report and literature review

QUAN Lingli, HUANG Peng, LIU Shuangbo, LIANG Yanchao

(Department of Respiratory Medicine 1, The Affiliated Zhuzhou Hospital of Xiangya School of Medicine CSU, Zhuzhou Hunan 412007, China)

Abstract　The clinical data of a patient with advanced lung adenocarcinoma in Zhuzhou Central Hospital was retrospectively analyzed and the relevant literatures were reviewed. The patient in study was diagnosed with lung adenocarcinoma by thoracentesis and left lymph node biopsy, and the head MRI and epigastric enhancement CT of upper abdomen showed that the cancer cells had multiple metastasized in the head, liver, spleen, pancreas and left adrenal gland. The genetic testing of epidermal growth factor receptor-amplification refractory mutation system (EGFR-ARMS) was carried out for the patient, which indicated that the exon of EGFR 21 mutation (L858R). The patient's condition deteriorated after 11 months treatment with the first-generation of EGFR-TKIs, and the result of genetic testing of the patient showed that the EGFR T790M mutation was positive. The attending physician treated the patient with third-generation EGFR-TKIs (osimertinib) for second-line treatment, and the patient's condition was relieved. After primary EGFR-TKI treatment, patients with advanced adenocarcinoma of the lung are still able to

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通信作者 (Corresponding author)：全玲丽，Email: 350220574@qq.com

benefit from EGFR-TKI treatment after resistance. The third-generation EGFR-TKIs, represented by osimertinib, has been approved to overcome the EGFR T790M mutation in patients who are resistant to the first- or second-generation TKIs, which brings more survival benefits for patients with advanced NSCLC.

Keywords non-small cell lung cancer; epithelial growth factor receptor-tyrosine kinase inhibitors; T790M mutation; gefitinib; osimertinib

近年来，全球肺癌的发病率及病死率均呈上升趋势，每年新发病数达135万。2015年我国的肺癌新发病数达73.3万，死亡人数达61万，发病率及病死率均位居恶性肿瘤首位[1-3]。其中非小细胞肺癌(non-small cell lung cancer，NSCLC)占肺癌总发病率的85%，为肺癌最常见组织学亚型[4]。过去的10余年里，表皮生长因子受体(epithelial growth factor receptor，EGFR)突变状态的检测和EGFR酪氨酸激酶抑制剂(tyrosine kinase inhibitors，TKIs)的应用开创了晚期NSCLC治疗的新纪元[5-7]。EGRF突变[即外显子19缺失(19del)或外显子21突变(L858R)]的NSCLC患者对第1代(吉非替尼、埃克替尼、厄洛替尼)或第2代(阿法替尼)EGFR-TKIs治疗非常敏感，其作用机制在于阻断了细胞信号转导通路，从而抑制肿瘤细胞的生长、增殖和转移。令人沮丧的是，随着疾病进展，有超过50%的患者在服用第1代或第2代EGFR-TKIs 9~14个月后会发生继发性耐药，同时检测到EGFR T790M突变阳性[8-9]，否定了第1代和第2代的抑制活性，而第3代EGFR-TKIs(奥西替尼)的出现很好地解决了第1，2代药物耐药的问题[10]。本文通过1例EGFR T790M突变阳性晚期肺腺癌的临床实践来探讨EGFR-TKIs的使用疗效。

1 临床资料

患者，男，61岁，因“气促、咳嗽1周，胸痛2 d”于2017年12月3日入院。患者入院前1周无明显诱因出现活动后气促(仅可爬2楼)，休息后好转，伴咳嗽，以早晨为主，咳少量白色黏痰，在诊所口服感冒药，无明显效果。2 d前出现胸痛，为钝痛，吸气时明显，无畏寒发热，无咯血，门诊胸片疑右侧肺门占位性病变，为进一步治疗入院。吸烟30余年，20支/d，无肿瘤家族史。

入院后血常规、降钙素原、红细胞沉降率、C-反应蛋白等，肝肾功能、电解质、心肌酶、输血前检查、凝血四项均正常。癌胚抗原16.08 ng/mL，糖类抗原CA125 49.80 U/mL，糖类抗原CA199、甲胎蛋白正常。肺部增强CT：1)考虑右中肺癌(6 cm×6 cm)并右中肺癌性淋巴管炎，纵隔淋巴结转移？右中肺支气管及分支狭窄、闭塞。2)双肺多发粟粒状结节，转移？3)右侧胸腔积液(图1)。头部MRI：1)左顶叶占位，考虑转移瘤？2)双侧枕部蛛网膜囊肿(图2)。上腹部增强CT：1)肝、脾、胰腺及左侧肾上腺多发低密度结节影，考虑为转移瘤可能大。2)腹主动脉周边数个小淋巴结(图3)。完善胸腔穿刺置管引流术，胸水癌胚抗原732.99 ng/mL，胸水甲胎蛋白1.63 ng/mL，胸水病检：(胸水沉渣液基细胞学检查)查见核异质细胞团，考虑腺癌，(胸水)石蜡切片中见异型腺体，考虑腺癌(图4)。同时完善左侧颈部淋巴结活检，术后病理检查：(左锁骨上结节)淋巴结转移性腺癌，符合肺来源；免疫组织化学：Syn(−)，TTF-1(+)，CK7(+)，Ki-67(20%+)，p63(−)(图5)。根据美国癌症联盟委员会第八版TNM分期诊断为原发性支气管肺癌 右中肺 腺癌 cT3N3M1 IV期双肺、右侧胸膜、头部、肝、脾、胰腺、左侧肾上腺转移。患者左侧颈部淋巴结肿瘤组织行EGFR-ARMS检测，提示EGFR 21外显子突变(L858R)，2017年12月20日给予吉非替尼0.25 g/d。服药后主要不良反应是1级皮疹，无腹泻，患者咳嗽、气促、胸痛症状逐渐缓解。吉非替尼治疗1个月后复查肺部CT：1)右中肺肿块较前明显缩小；2)双肺多发粟粒状结节较前明显减少；3)右侧胸腔积液较前稍减少(图6)。之后患者每8周复查，最佳疗效为部分缓解(partial response，PR)。2018年11月患者出现胸闷、气促，快步行走时明显，肺部CT：1)右中肺肿块较前增大伴周边肺部感染；2)右肺小叶间隔网格状肥厚，考虑癌性淋巴管炎可能；3)右侧胸腔积液较前增多，右侧胸膜增厚(图7)。考虑疾病进展(progressive disease，PD)，抽血行基因检测EGFR T790M突变，结果呈阳性，提示对第1代EGFR-TKIs耐药，对第3代EGFR-TKI敏感，2018年12月13日给予奥西替尼80 mg/d，2019年1月11日肺部CT：右中肺肿块、右肺感染、右肺小节结间隔网状格增厚明显好转(图8)。随访情况：患者目前无胸闷气促，偶有右侧背部疼痛，对轻微体力活动无影响，临床症状稳定，PS评分1。

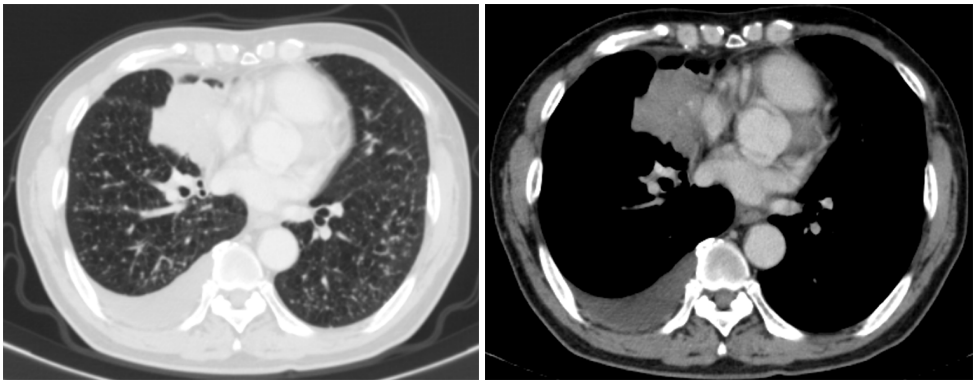

图1 肺部CT示右中肺近肺门区不规则软组织肿块影60 mm × 60 mm，边缘欠光整、分叶状

Figure 1 CT of the lung shows an irregular soft tissue mass shadow of 60 mm × 60 mm in the right middle lung near hilus pulmonis, with margins less polished and lobulated

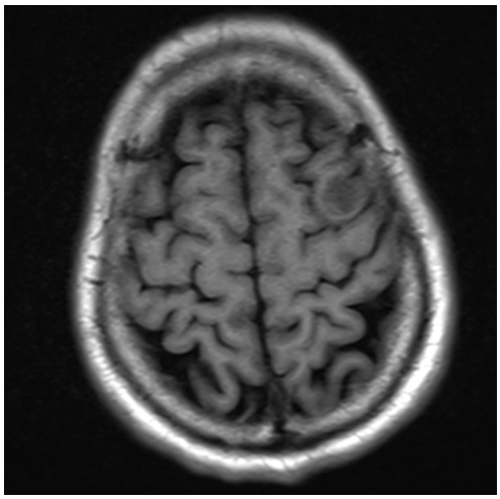

图2 头部MRI示左顶叶结节状稍长T1稍长T2信号影，约15 mm，边缘模糊

Figure 2 Head MRI shows a nodular, slightly longer T1 and slightly longer T2 signal shadow in the left parietal lobe, about 15 mm, with blurred edges

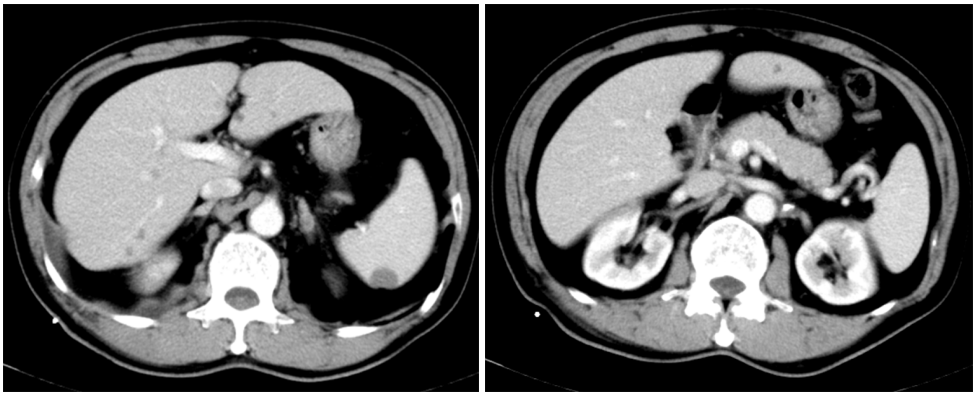

图3 上腹部CT示肝实质数个低密度结节影，边界不清，19 mm × 18 mm；胰腺斑片状低密度影，边界欠清晰；脾脏低密度影，10 mm × 16 mm；左侧肾上腺低密度结节影，10 mm × 16 mm

Figure 3 CT of the upper abdomen show several low-density nodules in liver parenchyma with unclear boundaries, 19 mm × 18 mm, low-density shadow of pancreas patchy with unclear boundary, low density shade of spleen, 10 mm × 16 mm, low density nodule shadow of left adrenal gland, 10 mm × 16 mm

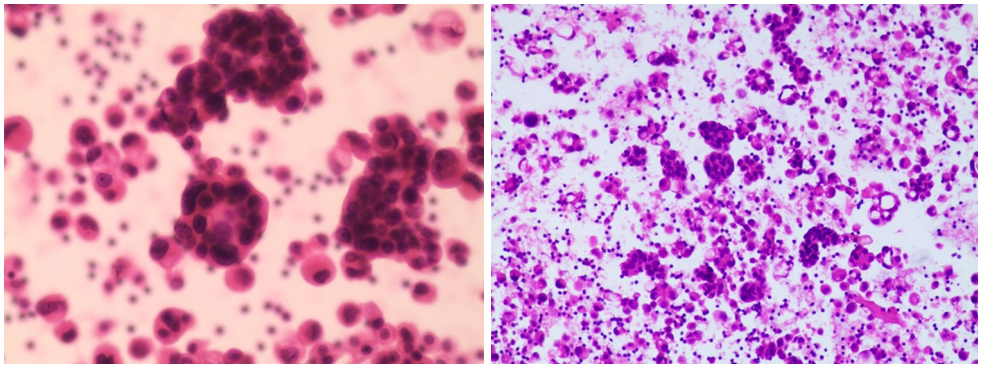

图4 (胸水)石蜡切片见异型腺体，考虑腺癌(HE，×100)

Figure 4 Paraffin section of hydrothorax shows heteromorphous gland, considering as adenocarcinoma (HE, × 100)

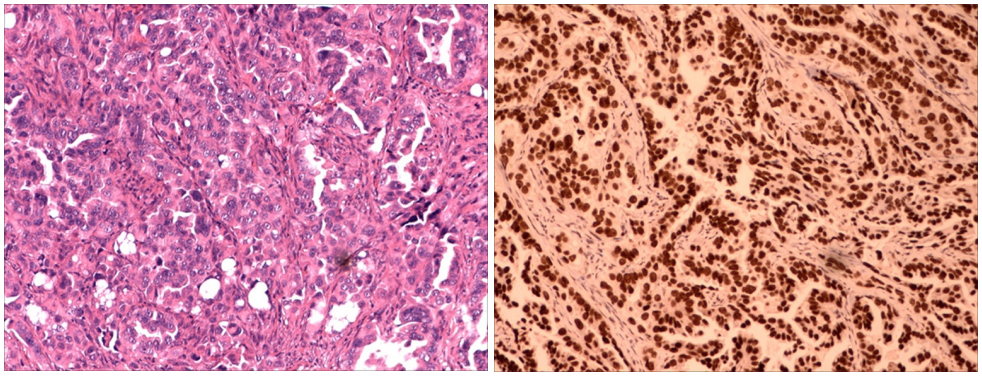

图5 (左锁骨上结节)淋巴结转移性腺癌，符合肺来源(HE，×100)

Figure 5 (Left supraclavicular nodule) Metastatic adenocarcinoma of lymph node, consistent with pulmonary origin (HE, × 100)

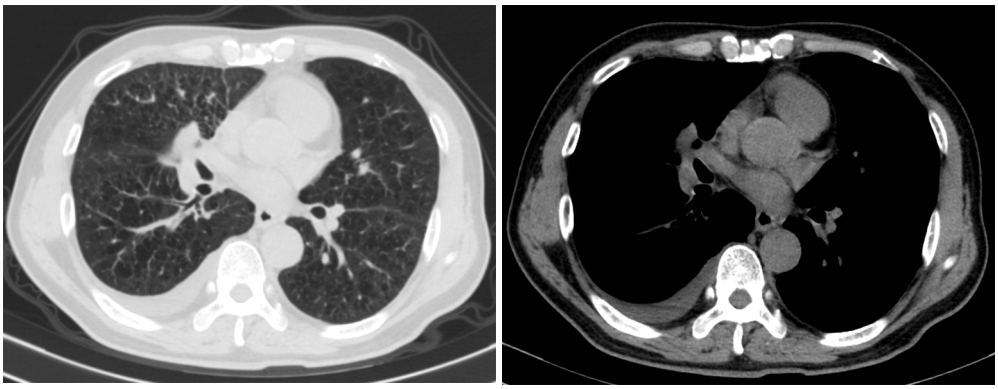

图6 肺部CT示右中肺肿块缩小，40 mm × 40 mm

Figure 6 CT of the lung show a reduction of the mass in the right middle lung, 40 mm × 40 mm

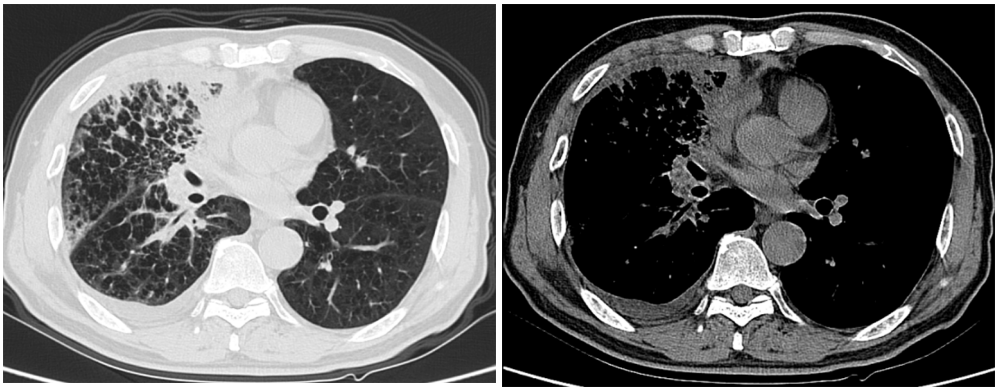

图7 肺部CT示右侧斑片状模糊增多，小叶间隔网格状增厚

Figure 7 CT of the lung shows the increase of patchy blurring on the right side of lung and the grid-like thickening of interlobular septum

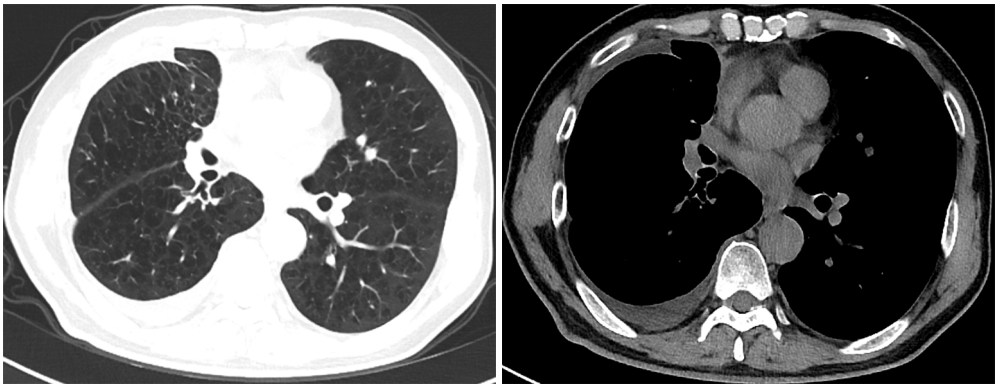

图8 肺部CT示右肺肿块缩小，斑片状模糊影、小叶间隔网格状增厚明显好转

Figure 8 CT of the lung shows the mass in the right middle lung has shrunk, the shadows of patchy blurring and the grid-like thickening of interlobular septum have improved significantly

2 讨论

目前研究[11-12]表明T790M突变是第1或2代EGFR-TKIs最为常见的耐药机制，作为选择性的作用于EGFR-TKIs敏感突变和继发性T790M耐药突变的第3代EGFR-TKIs，奥希替尼在早期临床试验(AURA1和AURA2)中已经发现具有良好的安全性和有效性。前瞻性、多中心、开放临床试验(AURA3)研究[13-14]表明奥希替尼二线治疗第1或2代EGFR-TKIs耐药后出现T790M突变阳性的晚期NSCLC患者的无进展生存期(progression-free survival，PFS)优于含铂双药化疗，中位PFS可延长5.7个月(10.1个月vs 4.4个月)，客观缓解率(objective response rate，ORR)可达71%，且透过血脑屏障的能力相对于其他各代TKIs更强，因此对肺癌脑转移患者的疗效尤为突出。Wu等[15]深入分析了奥希替尼治疗T790M突变阳性晚期NSCLC中枢神经系统(central nervous system，CNS)的疗效，奥希替尼的中位PFS较含铂双药组提高4.3个月(8.5个月vs 4.2个月)，不良反应降低。随着奥西替尼的应用，患者的PFS、总生存及耐受均有明显改善，那么接下来不可避免的就是对于第3代TKIs的耐药，现已经对耐药机制有广泛研究，针对性的药物也已进入试验阶段，同时耐药后治疗方式的选择也都还在摸索中。总之，肺癌的靶向道路是在跌宕起伏中抱有希望，还需要充分掌握EGFR-TKIs的耐药机制，寻找与EGFR激酶结合的最佳方式，综合应用靶向、化疗、放疗及免疫等多种治疗方式，寻找最佳结合模式，延长患者生存时间，为患者带去新的希望。

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