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EGFR–TKI 治疗表皮生长因子受体野生型晚期肺腺癌 1 例并文献复习

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[摘　要]　报告1例表皮生长因子受体(epidermal growth factor receptor，EGFR)野生型晚期肺腺癌患者的相关临床资料，复习相关文献。患者，女，64岁，不吸烟，因反复头痛1个月于当地医院就诊。胸部CT提示右上肺占位。头颅MR提示脑内多发病灶，考虑转移。肺穿刺病理提示肺腺癌，血浆表皮生长因子受体野生型。因该患者拒绝放化疗，予埃克替尼靶向治疗，无进展生存期14个月。继发耐药后，组织二代测序示exon20.pT790M突变，予以奥希替尼二线治疗，疗效佳。对于无法获得组织标本或者血浆EGFR检测阴性的不吸烟亚洲女性肺腺癌患者，在放化疗失败或不适宜放化疗的患者中，可尝试EGFR-TKIs靶向治疗，部分患者可从中获益。

[关键词]　靶向治疗；肺腺癌；表皮生长因子受体；野生型

Tyrosine kinase inhibitor in the treatment of advanced lung adenocarcinoma with EGFR wild-type: A case report and literature review

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Abstract　We report a case of epidermal growth factor receptor (EGFR) wild-type advanced lung adenocarcinoma and review relevant literature. A 64-year-old female non-smoker was treated in a local hospital for no obvious cause of headache for 1 month. Chest CT showed a tumor in the right upper lung. Brain MR suggested multiple lesions in the brain, considering metastasis. Lung biopsy in our hospital indicated lung adenocarcinoma, plasma EGFR mutation test is negative. Because the patient refused to receive radiotherapy and chemotherapy, she was started on icotinib, progressive-free survival 14 months. After the front-line treatment failed, tumor tissue exon 20.pT790M mutation appeared. Third-denervation TKI Osimertinib was started and effective. For non-smoking Asian women with lung adenocarcinoma who cannot obtain tissue specimens or have negative EGFR mutation in plasma, targeted EGFR-TKIs therapy can be tried in patients who fail or are unsuitable for radiotherapy and chemotherapy, and some patients of those can benefit from it.

Keywords　targeted therapy; adenocarcinoma of lung; epidermal growth factor receptor; wildtype

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肺癌是临床上最常见的恶性肿瘤，其中又以肺腺癌最为常见[1]。对存在EGFR敏感突变的晚期患者，首选EGFR-TKIs的治疗，可明显延长患者的生存期。然而对于EFFR野生型患者，其缓解率只有1.0%~13.9%[2]。对于野生型患者，在没有最佳的治疗的方案时，虽缓解率低，但也可尝试EGFR-TKIs治疗。台州市立医院(以下简称“我院”)收治了1例EGFR野生型晚期肺腺癌的患者，予以EGFR-TKI治疗，且治疗有效，现报告如下。

1 临床资料

患者，女，64岁，因无明显诱因出现头痛1个月于当地医院治疗，查胸部CT提示右上肺占位，头颅MR提示脑内多发病灶，考虑转移，血癌胚抗原：116.46 ng/mL，诊断为“肺癌脑转移”，建议明确病理性质后放化疗，但患者家属拒绝放化疗。遂于2017年7月入我院治疗。入院后查胸部增强CT提示右肺上叶尖段占位，肺癌可能(图1)，头颅增强磁共振提示右侧小脑半球、右侧颞顶叶及左侧额枕叶多发占位，考虑转移瘤。在CT引导下肺穿刺活检病理提示腺癌(图2)，免疫组织化学染色：TTF-1(弱+)，Napsin-A(+)，CK7(+)，CK20(−)，p63(−)，Villin(少区弱+)，EGFR(+)，ALK(−)。骨扫描示：右第6侧肋局灶骨代谢增强，腹部B超(−)。诊断：右肺腺癌IVB期cT2bN0M1(脑多发转移)，体力状况(physical status，PS)评分为1。血浆表皮生长因子受体野生型。于2017年8月开始行一线治疗：酪氨酸激酶抑制剂(tyrosine kinase inhibitor，TKI)埃克替尼125 mg口服，3次/d。患者觉头痛明显好转，2017年9月12日评估复查胸部CT提示右肺上叶尖段病灶较前明显缩小，头颅MR提示颅内转移病灶较前明显缩小。评估为疾病缓解(partial response，PR)，2017年11月21日胸部CT提示肿块进一步缩小(图1B)，头颅MR示未见明显病灶，局部完全缓解。2018年11月复查胸部CT提示右肺尖段病灶增大(图1C)，颅内转移灶稳定，疗程评估为疾病进展(progressive disease，PD)，2018年11月再次CT引导下肺穿刺活检病理提示腺癌，组织送二代测序基因检测提示：exon19 del，exon20.PT790M点突变，2018年12月行二线治疗：奥希替尼80 mg口服，1次/d，2019年2月复查胸部CT提示右肺上叶尖段肿块缩小(图1D)，评估为PR，现患者继续口服奥希替尼治疗，目前仍在随访中。

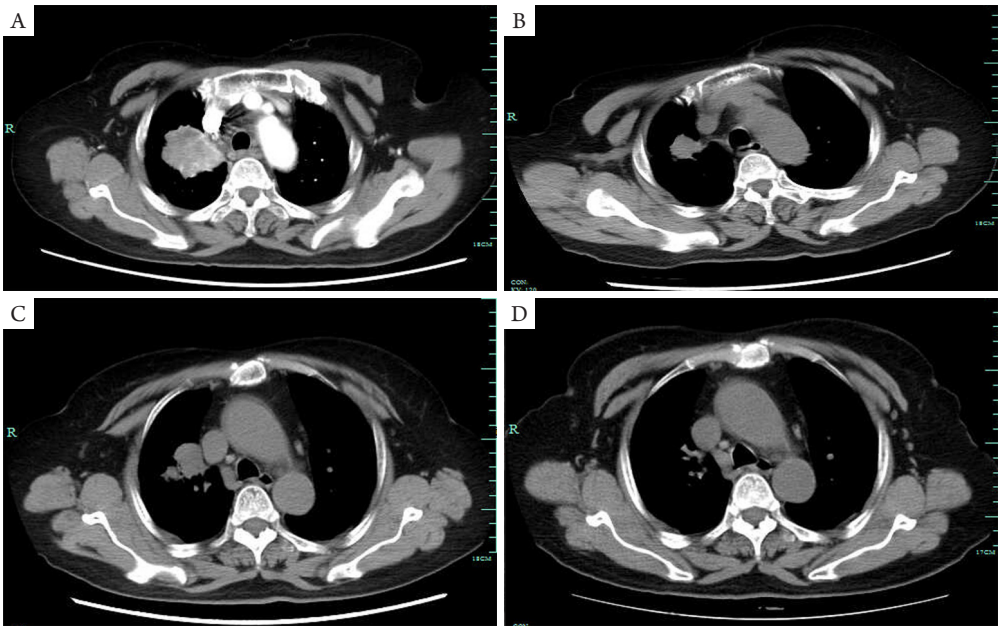

图1 治疗前后患者胸部CT表现

Figure 1 Chest CT scan before and after treatment

(A)埃克替尼治疗前的胸部CT表现；(B)埃克替尼治疗4个月后复查胸部CT；(C)埃克替尼治疗14个月后复查胸部CT；(D)奥希替尼治疗治疗3个月后复查胸部CT。

(A) Chest CT scan before taking icotinib; (B) Chest CT scan after 4 months of treatment with icotinib; (C) Chest CT scan after 14 months of treatment with icotinib; (D) Chest CT scan after 3 months of treatment with Osimertinib.

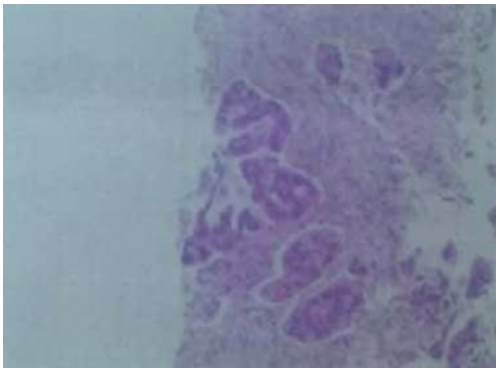

图2 肺穿刺活检病理显示腺癌(HE，×10)

Figure 2 Pathology of the tumor shows adenocarcinoma (HE, ×10)

2 讨论

肺癌是我国最常见的恶性肿瘤，脑转移是肺癌最常见的远处转移部位之一，肺癌脑转移人群，据报道[3]，其平均自然生存期不到2个月。随着医学技术迅速的发展，对肿瘤的深入研究，目前治疗手段也逐渐增多，尤其是分子靶向药物的问世，很大程度上改善了晚期肺癌患者生存状态。然而，对于基因检测阴性的晚期非小细胞肺癌脑转移患者，目前主要的手段依然是局部的放疗、手术、全身的化疗以及鞘内化疗，此外也可考虑联合应用免疫抑制剂或抗血管生成药物[4]。有研究[5]报道：肺癌伴脑转移瘤化疗的整体疗效差，联合化疗客观缓解率约30%，中位总生存期只有4~8个月，单药化疗客观缓解率不到10%，中位总生存期为4.5~7.7个月，疗效不佳的的原因为颅脑存在特有的血脑屏障，绝大部分的化疗药物在脑脊液中达不到有效的药物浓度，另外肿瘤细胞可通过外流泵将化疗药物泵出等。对于驱动基因阳性的非小细胞肺癌脑转移患者，目前虽然没有批准专门用于非小细胞肺癌(non-small cell lung cancer，NSCLC)脑转移的靶向治疗药物，但是近年来大规模临床研究[3,6]显示：EGFR-TKIs在NSCLC在脑转移患者中可以获益，在EGFR基因阳性的相关人群中，客观缓解率在32%~89%，无进展生存期为6.6~23.2个月，中位总生存期为12.9~21.9个月，原因可能为EGFR-TKIs脂溶性好、分子量小，相比于传统的化疗药物，更易透过血脑屏障等。

血浆EGFR基因检测相较肿瘤组织检测，具有高度的特异性(97.2%~100%)，敏感度不尽相同(50.0%~81.8%)[7-10]，说明血浆EGFR检测存在假阴性可能。研究[11-12]显示：血浆EGFR野生型患者EGFR-TKI靶向治疗1年内有效率为10.71%~19.49%。姚晓燕等[13]研究显示：在758例非小细胞肺癌患者中，EGFR突变率为49.7%，其中女性患者突变率为62.7%，肺腺癌患者突变率为54.4%，吸烟患者为36.4%，不吸烟患者为55.1%，因此EGFR在无吸烟史的腺癌女性患者中突变率相对更高。本例患者为不吸烟、腺癌晚期伴多发脑转移的女性患者，初始血浆基因检测阴性，血浆EGFR检测存在假阴性可能，由于该患者拒绝放化疗，故选择尝试EGFR-TKI治疗，且治疗有效，最终患者在1年后出现耐药，EGFR-TKI耐药后，T790M突变占据主导地位，比例达到50%甚至以上[14-16]。故再次予以肺穿活检组织送检二代测序，出现exon20.pT790M突变，予以奥希替尼二线治疗，疗效佳。无论是一代还是三代EGFR-TKI均无发生明显的不良反应，基本不需进行特殊的药物治疗处理，明显的提高了患者的生活质量。

综上，对于无法获得组织标本或者血浆EGFR检测阴性的不吸烟女性肺腺癌患者，在放化疗失败或不适宜放化疗的患者中，可尝试EGFR-TKIs靶向治疗，部分患者可从中获益。

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