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以恶性胸腔积液为主要表现的 EGFR T790M 突变型肺腺癌 1 例及文献复习

王朋增[1]，朱辉[1]，高占杰[1]，尤杨[2]

(河北医科大学第四医院 1. 胸五科；2. CT室，石家庄 050011)

[摘　要]　报告1例64岁的晚期肺腺癌男性病例，患者主因咳嗽伴胸闷1个月于2017年4月22日第1次入院。CT显示左侧胸腔积液，正电子发射计算机断层显像(positiron emission tomography-computed tomography，PET-CT)示左侧胸膜稍增厚，局部胸膜见结节状异常葡萄糖高代谢，经胸腔镜胸膜活检术，胸膜病理：腺癌(考虑肺源性)。胸水细胞学回报：找到腺癌细胞，考虑肺来源。胸水脱落细胞基因检测EGFR 19del阳性，口服厄洛替尼治疗，胸水消失，多次肺部结节影像评估为部分缓解及稳定。2018年6月30日主因胸闷气短再次入院，考虑病情进展，胸部超声提示左侧胸腔大量胸腔积液。行胸腔闭式引流术，引流出约700 mL暗血性液体，细胞学诊断：找到癌细胞，胸水细胞*EGFR*基因检测结果：19DEL阳性，T790M阳性，更换三代表皮生长因子抑制剂(epidermal growth factor receptor-tyrosine kinase inhibitor，EGFR-TKI)后患者临床症状好转，胸水消失，肺部结节影像评估为部分缓解及稳定。

[关键词]　肺癌；EGFR TKI；奥西替尼

Malignant pleural effusion as main manifestation of EGFR T790M mutation lung adenocarcinoma: A case report and literature review

WANG Pengzeng[1], ZHU Hui[1], GAO Zhanjie[1], YOU Yang[2]

(1. Fifth Department of Thoracic Surgery; 2. Computed Tomography Room, Fourth Affiliated Hospital of Hebei Medical University, Shijiazhuang 050011, China)

Abstract　We reported a male, 64-year-old patient who suffered advanced lung adenocarcinoma admitted to The Fourth Hospital of Hebei Medical University. On April 22, 2017, he was sent to our department due to cough and chest tightness. His chest CT revealed plenty of left pleural effusion. The pleural effusion cells biopsy reported malignancy, possibility of lung adenocarcinoma. Positiron emission tomography-computed tomography (PET-CT) showed slightly thickening of the left pleura, local pleural nodular abnormal glucose high metabolism. After thoracoscopic

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通信作者 (Corresponding author)：朱辉，Email: zhdzuj@sina.com

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pleural biopsy, further diagnosis of cancer (considering pulmonary origin) was confirmed. The immune-cytology of pleural effusion also showed adenocarcinoma, considering the pulmonary origin. The gene analysis revealed EGFR 19del positive. So, he was given EGFR-TKI erlotinib regularly. After 14 months stable conditions, on June 30, 2018, this patient was admitted to our hospital again, due to chest tightness. The pulmonary ultrasound showed big liquid dark area (about 10.1 cm diameter) in his left thoracic cavity. Immediately, a thoracic drainage tube was placed in, then from which about 700 mL of dark blood pleural effusion was induced out. The cytology analysis found cancer cells. And the gene test results T790M positive. So, the third-generation EGFR-TKI Osimertinib was administrated to him on July 9, 2018. All patient's clinical symptoms were disappeared and his condition was stable until now.

Keywords　lung cancer; EGFR-TKI; osimertinib

肺癌是一种常见的恶性肿瘤，2018年全球新增肺癌210万人，尤其在男性中的发病比例呈上升趋势[1]。流行病学研究[2]表明：肺癌的发病率和病死率居中国恶性肿瘤的首位。对于晚期的肺癌患者，手术及放化疗效果较差，近几年随着分子生物学研究的深入，肿瘤的靶向治疗策略被提出，该治疗方法具有针对性强、不良反应少等优点，现将河北医科大学第四医院收治的1例以恶性胸腔积液为主要表现的EGFR T790M突变型肺腺癌病例报告如下。

1 临床资料

患者，男，64岁，于1个月前无明显诱因出现咳嗽、咳痰，为白色稀痰，痰量不多，并伴有胸闷气短，活动及劳动后加重，为行进一步诊治于河北医科大学第四医院，既往“甲状腺癌”病史，无吸烟史。正电子发射计算机断层显像(positiron emission tomography-computed tomography，PET-CT)示：左侧胸膜稍增厚，左侧胸腔积液，局部胸膜见结节状异常葡萄糖高代谢(图1)。血检癌胚抗原：22.99 ng/mL，可溶性细胞角蛋白组4.76 ng/mL。查体：左下肺野叩浊，呼吸音低。其余各项检查均未见明显异常。

1.1 诊疗过程

1.1.1 第 1 次入院情况

入院后行胸部CT：左侧胸膜局限性增厚，并可见左肺下叶结节影(图2)。为进一步明确病理性质，行胸腔镜胸膜活检：取右侧卧位，取左侧腋中线第5肋间为手术部位，常规消毒，铺无菌单后，用2%利多卡因10 mL局麻至胸膜切开，血管钝性分离至胸膜，插入戳卡进入胸腔镜，依次窥视胸膜腔，胸腔内可见淡血性积液，壁层胸膜可见散在结节，部分融合成片，质软，脏层胸膜未见明显异常，行壁层胸膜多点活检后操作结束，退出胸腔镜，置入胸腔闭式引流管(图3)。术后病理：腺癌(考虑肺源性)，免疫组织化学示：CK(+)，TTF-1(+)，Ki-67(50%阳性)，CK5/6(−)，D2-40(−)，NapsinA(+)，EGFR E746-A750de1(2+)，EGFR-L858R(−)，ALK阴性对照(−)，VENTANA ALK(D5F3)(−)(图4)。

胸水细胞学：找到腺癌细胞，考虑肺来源。免疫细胞化学：TTF-1(+)，CK7(+)，NapsinA(+)，TG(−)，CEA(+)，WT-1(−)，P40(−)，CD56(−)，M0C31(+)，SPA(±)，MC(-/+)，PAX-8(−)(图5)。

胸水细胞*EGFR*基因突变检测：18(G719X)阴性，19del阳性，T790M阴性，S768I阴性，20ins阴性，L858R阴性，L861Q阴性。

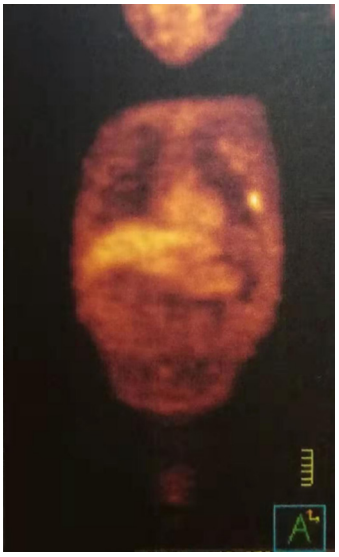

图1 PET-CT示左侧胸膜稍增厚，局部见结节状异常葡萄糖高代谢，其中临近左5前肋部位高代谢灶，大小约0.9 cm × 1.5 cm，最大SUV值3.6

Figure 1 PET-CT showed a slight thickening of the left pleura, localized nodular abnormal glucose high metabolism, which is about 0.9 cm × 1.5 cm, and the maximum SUV value is 3.6

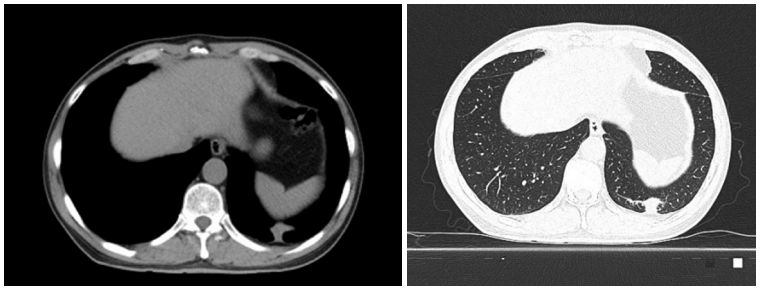

图2 2017年5月25日CT示左肺下叶基底段可见软组织结节，大小1.5 cm × 1.0 cm，形态欠规整，边缘可见毛刺及浅分叶，左侧胸膜局限性增厚

Figure 2 CT on May 25, 2017 showed soft tissue nodules in the basal segment of the lower lobe of the left lung, with a size of 1.5 cm × 1.0 cm and irregular shape; burrs and shallow lobules were visible at the edge, and the left pleura was localized thickened

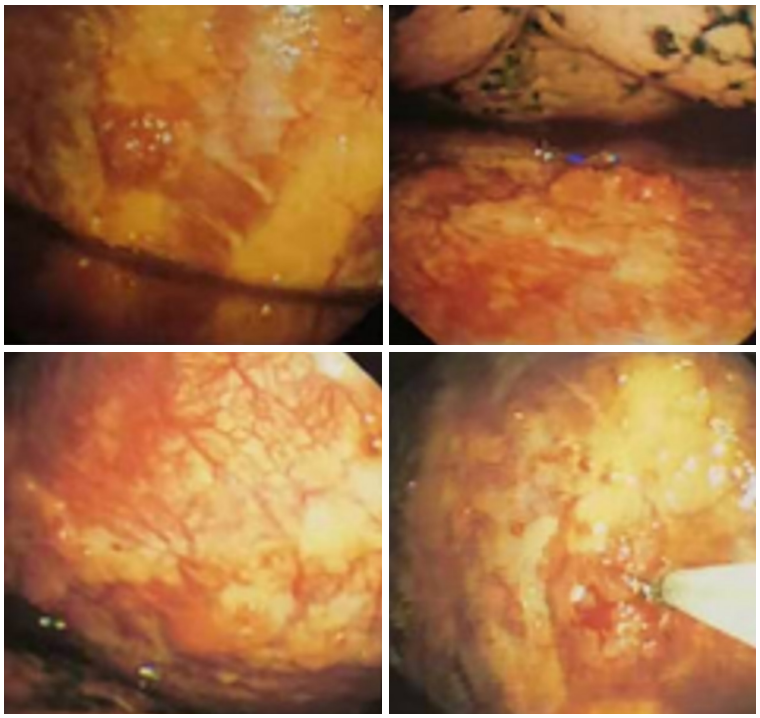

图3 胸腔内可见淡血性积液，壁层胸膜可见散在结节，部分融合成片，质软，脏层胸膜未见明显异常

Figure 3 Hemorrhagic effusion was seen in the pleural cavity, and scattered nodules were seen in the parietal pleura, which was partly fused into a soft film, and no obvious abnormality was found in the visceral pleura

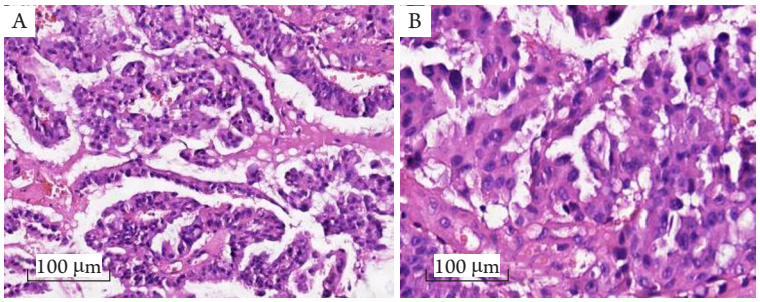

图4 肺泡上皮异性增生，形成腺管及筛状结构，细胞异性明显，可见核仁突出，深染(A：HE，×100；B：HE，×400)

Figure 4 Alveolar epithelial heterosexual hyperplasia, forming ductal and sieving structures, obvious cell heterogeneity, visible nucleoli prominent, deep staining (A: HE, × 100; B: HE, × 400)

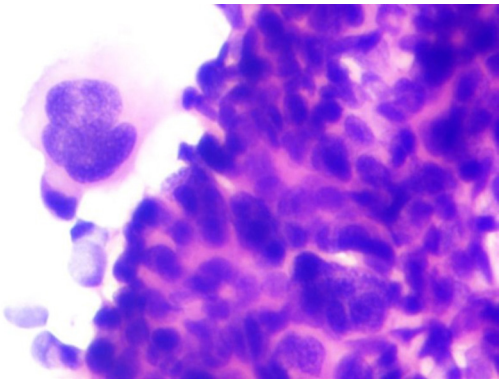

图5 细胞形态大小不一，细胞排列三维立体，排列呈桑葚状，细胞排列拥挤重叠，细胞增大，核浆比增大，细胞核呈圆形或椭圆形，染色质增粗(HE，×400)

Figure 5 The cell morphology is different, the cells are arranged in three-dimensional, arranged in a mulberry-like shape, the cells are arranged in a crowded overlap, the cells are enlarged, the nucleoplasm ratio is increased, the nucleus is round or elliptical, and the chromatin is thickened (HE, ×400)

给予一代表皮生长因子抑制剂(epidermal growth factor receptor-tyrosine kinase inhibitor，EGFR-TKI)盐酸厄洛替尼片150 mg口服，1次/d，患者临床症状明显好转。复查胸部CT影像胸水消失，肺部结节复查评估为PR及SD(图6~9)。

1.1.2 第 2 次入院情况

患者主因“胸闷气短10 d”于2018年6月30日再次入院。超声及胸部CT示：左侧大量胸腔积液(图10~11)。血检癌胚抗原：19.85 ng/mL，可溶性细胞角蛋白组3.35 ng/mL，鳞状上皮细胞癌抗原2.50 ng/mL。超声定位下行胸腔闭式引流术引流出约700 mL暗血性液体，送细胞学及胸水脱落细胞基因检测。细胞学：找到癌细胞。胸水*EGFR*基因：18(G719X)阴性，19DEL阳性，T790M阳性，S768I阴性，20INS阴性，L858R阴性，L861Q阴性。更换为三代EGFR-TKI奥西替尼80 mg，1次/d，临床症状较前明显好转，胸水消失，CT影像评估PR(图12~14)。

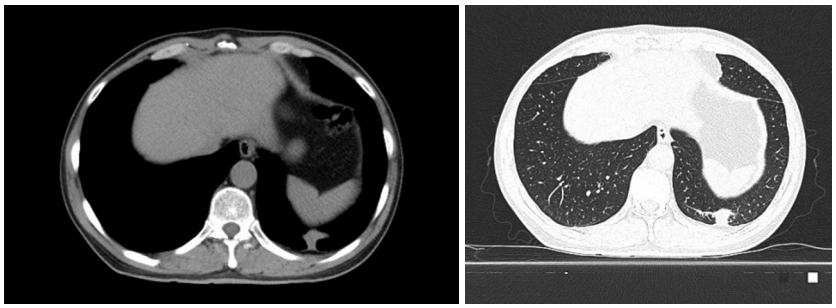

图6 2017年8月1日CT示左肺下叶基底段可见软组织结节，大小1.5 cm×0.9 cm，形态欠规整，边缘可见毛刺及浅分叶，左侧胸膜局限性增厚，纵隔未见明显肿大淋巴结，与2017年5月25日CT比较未见变化

Figure 6 CT on August 1, 2017 showed soft tissue nodules in the basal segment of the left lower lobe, 1.5 cm×0.9 cm in size, irregular shape, burrs and superficial lobes visible on the edges, localized thickening of the left pleura, no mediastinum significantly enlarged lymph nodes, no change compared with CT on May 25, 2017

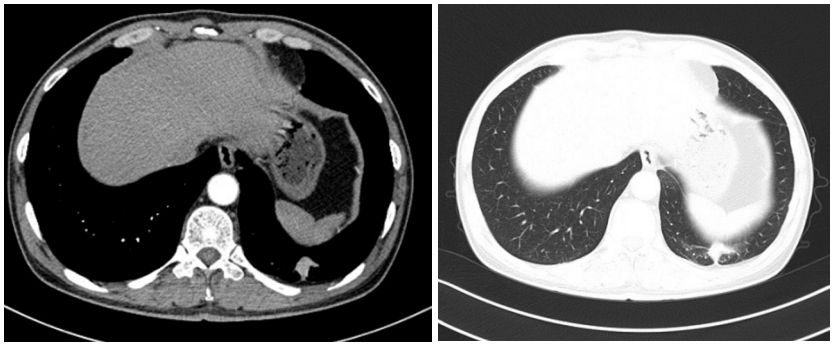

图7 2017年10月10日CT示左肺下叶基底段可见软组织结节，大小1.2 cm×0.8 cm，形态欠规整，边缘可见毛刺及浅分叶，纵隔未见明显肿大淋巴结，与2017年8月1日CT比较病变缩小

Figure 7 CT on October 10, 2017 showed soft tissue nodules in the basal segment of the left lung, 1.2 cm×0.8 cm in size, irregular shape, burrs and shallow lobes visible on the edges, and no obvious enlarged lymph nodes in the mediastinum. CT comparison of lesion reduction on August 1, 2017

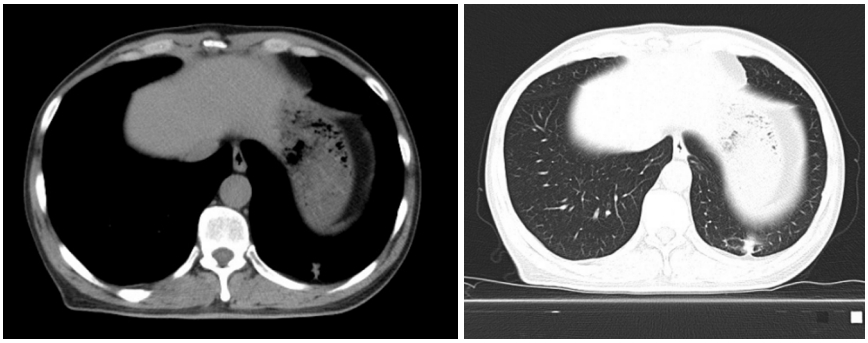

图8 2017年12月12日CT示左肺下叶基底段可见软组织结节，大小1.0 cm×0.7 cm，形态欠规整，边缘可见毛刺及浅分叶，纵隔未见明显肿大淋巴结，与2017年10月10日CT比较病变缩小

Figure 8 CT on December 12, 2017 showed soft tissue nodules in the lower basal segment of the left lung with a size of 1.0 cm × 0.7 cm, irregular shape, burrs and superficial lobes at the edges, and no obvious enlarged lymph nodes in the mediastinum. CT comparison of lesion reduction on October 10, 2017

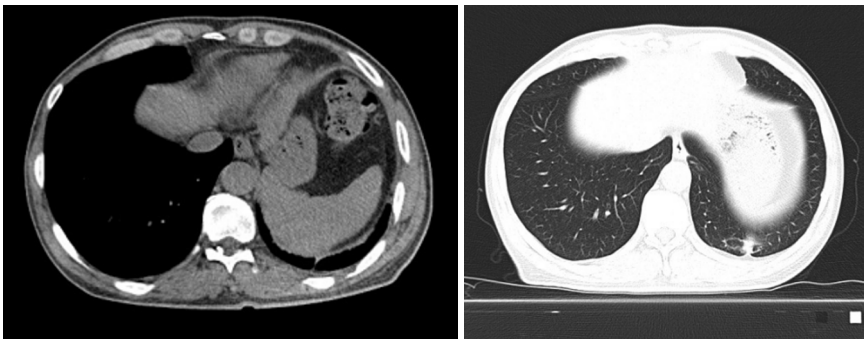

图9 2018年2月12日CT示左肺下叶基底段可见软组织结节，大小1.0 cm×0.8 cm，形态欠规整，边缘可见毛刺及浅分叶，纵隔未见明显肿大淋巴结，与2017年12月12日CT比较病变未见明显变化

Figure 9 CT on February 12, 2018 showed soft tissue nodules in the lower basal segment of the left lung, with a size of 1.0 cm × 0.8 cm, irregular shape, burrs and shallow lobes at the edges, and no enlarged lymph nodes in the mediastinum. CT comparison showed no significant changes on December 12, 2017

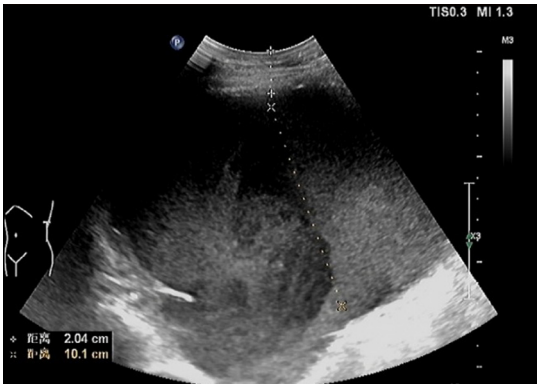

图10 超声示左侧胸腔自第三肋间至肋膈角可见片状液性暗区，内可见密集弱点状回声漂浮，暗区厚约10.1 cm

Figure 10 Ultrasound in the left thoracic cavity, a sheet-like liquid dark area can be seen from the third intercostal space to the rib angle; the dense and weak echoes can be seen floating inside, and the dark area is about 10.1 cm thick

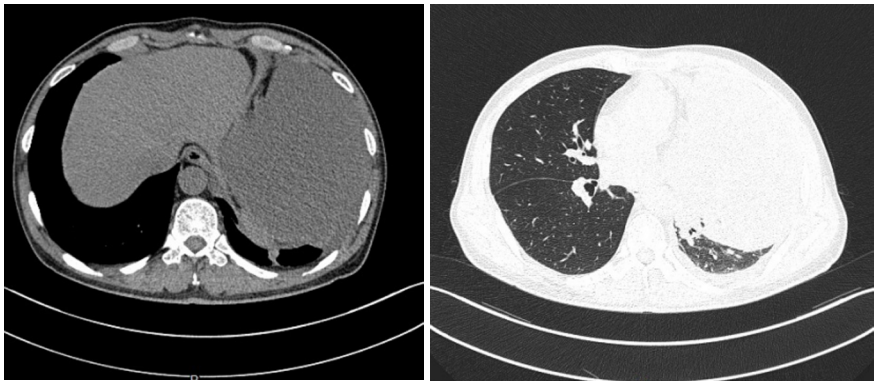

图11 2018年6月28日CT示左肺下叶基底段可见软组织结节，大小1.0 cm×0.8 cm，形态欠规整，边缘可见毛刺及浅分叶，病变大小与2018年2月12日CT比较病变未见明显变化，左侧胸腔积液伴局限性肺膨胀不全，左侧胸膜局限性增厚

Figure 11 CT on June 28, 2018 shows soft tissue nodules in the basal segment of the left lung, with a size of 1.0 cm × 0.8 cm, irregular shape, burrs and shallow lobes at the edges, and the size of the lesion compared with the CT of February 12, 2018, no obvious changes in the lesions, left pleural effusion with local atelectasis, and limited left pleural thickenin

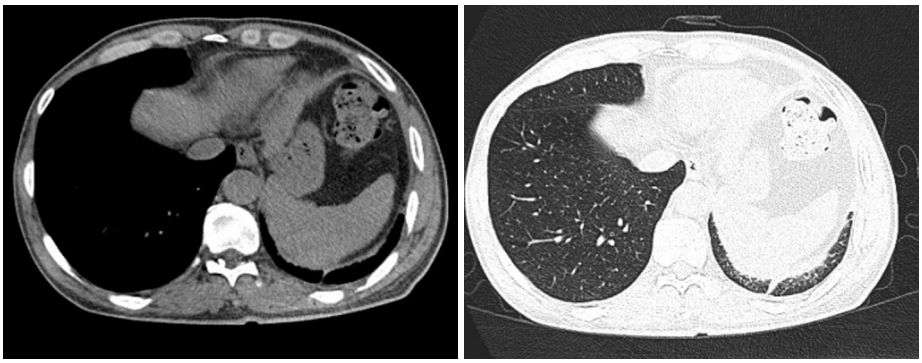

图12 2018年11月12日CT示左肺下叶基底段可见软组织结节，大小0.8 cm×0.5 cm，形态欠规整，病变大小与2018年6月28日CT比较病变缩小

Figure 12 CT on November 12, 2018 shows soft tissue nodules visible in the basal segment of the left lung, with a size of 0.8 cm × 0.5 cm, irregular shape, and the lesion size is smaller than that of CT on June 28, 2018

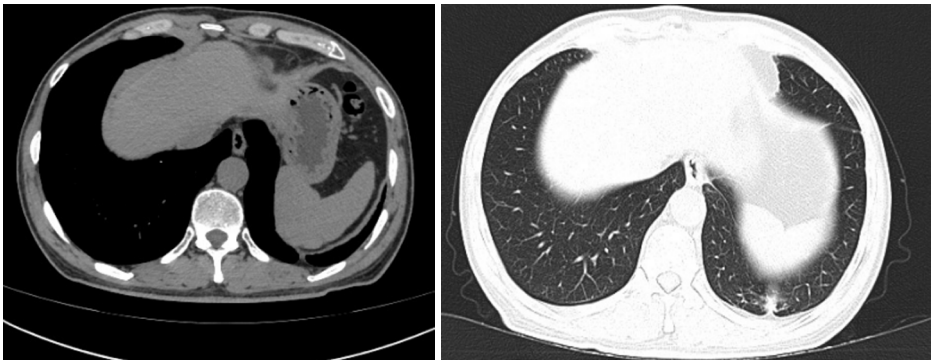

图13 2019年2月12日CT示左肺下叶基底段可见软组织结节，大小0.8 cm×0.5 cm，形态欠规整，边缘可见毛刺及浅分叶，病变大小与2018年11月12日CT比较病变大小未见变化

Figure 13 CT on February 12, 2019 shows soft tissue nodules in the basal segment of the left lung, with a size of 0.8 cm × 0.5 cm, irregular shape, burrs and shallow lobes on the edges, and the lesion size compared with the CT on November 12, 2018, no change in lesion size

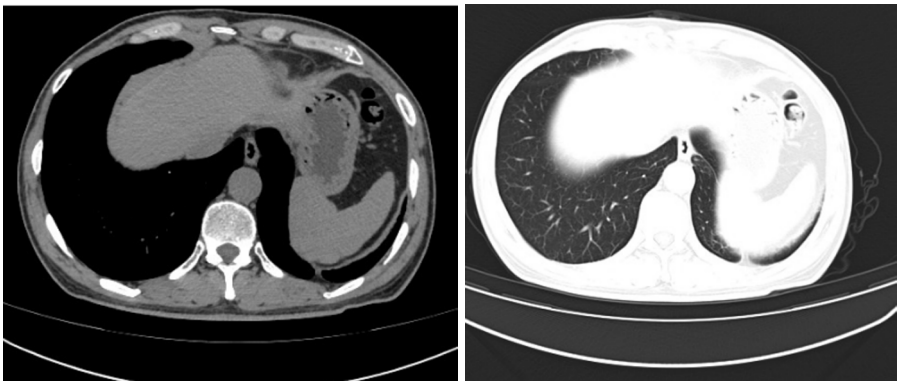

图14 2019年4月11日CT示左肺下叶基底段可见软组织结节，大小0.7 cm×0.5 cm，形态欠规整，边缘可见毛刺及浅分叶，病变大小与2019年2月12日CT比较病变大小未见变化，左侧胸膜局限性增厚

Figure 14 CT on April 11, 2019. Soft tissue nodules were visible in the basal segment of the left lower lobe, with a size of 0.7 * 0.5 cm. The shape was irregular, with burrs and shallow lobes at the edges. The size of the lesions was compared with the CT on February 12, 2019, no change in lesion size, localized thickening of the left pleura

2 讨论

研究[3]表明：使用一代或二代EGFR-TKI一线治疗EGFR驱动基因阳性肺腺癌的患者在8~14个月后将会不可避免地出现耐药。其中，T790M的突变是主要的耐药机制，约2/3的EGFR-TKI耐药进展的患者发生了T790M突变[4]。更进一步的临床研究[5]表明：对于一线EGFR-TKI治疗后出现T790M突变耐药的晚期非小细胞肺癌患者，奥希替尼与传统的培美曲塞联合铂类化疗相比，奥西替尼可以显著地延长患者的无病进展生存期(progression-free survival，PFS)，更显著地降低疾病进展风险，随之而来的药物不良反应发生率也更低。奥西替尼已然成为一代或二代EGFR-TKI耐药后的首选药物[6-7]。本例患者是以恶性胸腔积液为主要表现的EGFR突变型肺腺癌，一线的靶向治疗获得了近14个月的PFS，基本符合一代EGFR-TKI耐药的规律；在第2次入院治疗时，通过对患者胸水脱落细胞学的再次基因测序，明确了EGFR突变的状态，及时发现了T790M的耐药突变，随即将治疗方案给予相应的调整，无疑取得了较好的临床效果，患者生存有明显的获益。

需要引起注意的是，患者在出现胸闷气短等明显临床症状后才发现耐药，虽然及时更换了三代EGFR-TKI药物，但患者仍然承受了较大的身体和心理上的不适。对于更多的晚期肺癌患者，很有可能会因为临床症状的突然加重，而永远地失去了更换三代药物的机会。是否存在更敏感的检测方法，能够早期发现EGFR-TKI的耐药，从而使患者避免经历如上的痛苦历程？对于更换药物的时机，目前临床上更多的是依赖CT或者MRI等影像学检查[8]，在影像学出现进展之后，再做基因检测，看是否存在耐药的情况。但影像检查是否是最佳的评价标准？随着“液体活检”概念的兴起，有学者[9]通过动态检测发生耐药的EGFR突变型肺腺癌患者血浆中的循环肿瘤DNA(circulating tumor DNA，ctDNA)T790M突变状态，发现因T790M突变造成EGFR-TKI耐药的患者中，约45.7%(16/35)的患者在临床判定为疾病进展之前就已经能在血浆中检出T790M的突变。这部分患者从血中检出T790M突变的时间，可以比影像学的进展提前约2.2个月。因此，血浆中ctDNA的测定可能将探知病情进展提前到“分子耐药”阶段，早于影像学出现进展，当然更早于临床症状的出现。患者如果能在“分子耐药”阶段就及时地更换TKI药物，是否能有更高的生存获益呢？目前，国外学者已开始进行相应的多中心临床实验[10]，设立传统的以影像学为依据的实体瘤评价标准(Response Evaluation Criteria In Solid Tumors，RECIST)为进展标志，或以患者血浆ctDNA中检测到T790M的突变作为进展标志的不同临床实验组，通过比较采用不同标准进行一代和三代EGFR-TKI序贯治疗的患者的PFS，寻找更佳的更换三代EGFR-TKI药物时机。也许不久的将来，“液体活检”技术将作为更为灵敏的评价标准，从而使患者能够早期发现潜在的耐药突变，获得更多的临床生存获益。

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