EGFR TKI Combined with PD1 Inhibitor for EGFR Mutated Lung Cancer with Breast Metastasis

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Case report

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Abstract

Background: Lung adenocarcinoma with breast metastasis is rare. In the present study, a case of an advanced patient with breast metastasis from lung adenocarcinoma with EGFR 21 exon p.L858R mutation who underwent EGFR TKI combined with PD1 inhibitor is reported.

Case presentation: A 62-year-old female patient diagnosed with lung adenocarcinoma who had undergone six times disease progress and breast metastasis in fifth-time disease progress.The patient underwent left breast puncture and axillary lymph node in ultrasound-guided and the postoperative pathological diagnosis of metastatic lung adenocarcinoma was confirmed. And then gene detection showed EGFR 21 exon p.L858R mutation. Breast metastasis from lung adenocarcinoma was diagnosed and the patient is being treated with Almonertinib combined with PD1 inhibitor.

Conclusion: Breast metastasis is rare and lung adenocarcinoma might be the primary disease. Gene indection is important. And for lung cancer patients with recurrent pleural effusion, visit of the breast should be included in the follow-up process. In addition, the treatment model of interspersed immunotherapy after EGFR resistance has brought new ideas for the treatment of lung cancer with breast metastasis.

Learning Points

Breast metastasis from lung cancer is rare. An accurate diagnosis is of great clinical importance. Distinguishing whether breast malignant tumors are primary or secondary is directly related to the principles of treatment and prognosis. For lung cancer patients with recurrent pleural effusion, visit of the breast should be included in the follow-up process. And it is not clear that patients with advanced lung cancer with breast metastases may be considered for EGFR TKI combined with PD1 inhibitor. At present, there are few clinical cases, and it is necessary to accumulate clinical time to specify the best treatment plan.

Background

Lung cancer is the most common malignant tumor and the leading cause of cancer-related death in China[1]. Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancers[2]. Despite the advanced progress made in the treatments of NSCLC, the prognosis is still not satisfactory and the 5-year survival rate is lower than 20%[3]. The most common sites of metastasis in patients with NSCLC are brain, bone, adrenal gland, and lungs[4].Breast cancer is not common in clinical settings.And breast metastasis from primary lung cancer is rather rare, about 0.41‰ of breast cancer[5]. In this case report, we illustrate a case of lung adenocarcinoma causing breast metastasis and report the clinicopathological features and therapeutics interventions, as well as the outcomes of this aggressive disease. We hope that this case report can provide a reference to avoid misdiagnosis and mistreatment and give patients more reasonable treatment.

Case Presentation

A 62-year-old Chinese female complained of coughing and chest tightness at the the first visit (in 2017). An enhanced chest computed tomography (CT) was performed and revealed a mass in the left lower lobe and massive pericardiac fluid. The patient underwent pericardiocentesis drainage together with pericardial effusion cytology, which revealed lung adenocarcinoma and EGFR 21 mutation, mutation abundance 10.83%. She then treated with Gefitinib (Iressa, 0.25g, q.d.) and cardiac perfusion with Cisplatin (10mg).

After nine months,the patient developed chest tightness again in March 2018. An enhanced chest CT showed massive pleural effusion, followed by pleural effusion cytology revealing lung adenocarcinoma cells. Then The patient received 5 cycles of systemic chemotherapy with Pemetrexed (Pemetrexed 500 mg/m^2, Cis-platinum 75 mg/m^2, q3w) and cis-platinum intrapleural infusion (20mg). However, the patient refused further chemotherapy and took 6 cycles of Anlotinib (12mg q.d., d1-d14, q3w) by herself. Unfortunately, an enhanced chest CT showed pulmonary masses became more larger compared with the former CT images in December 2018. EGFR 21 exon p.L858R mutation (1.15%) was detect in blood-based genetic test, so the patient took Gefitinib (Iressa, 0.25g, q.d.) instead of Anlotinib form January 2019 to April 2019.

The disease progressed with lager pulmonary masses and more pleural effusion in April 2019. The patient received 2 cycles of chemotherapy with albumin-bound Paclitaxel plus Carboplatin and Bevacizumab (albumin-bound Paclitaxel 200mg/m^2, Carboplatin 15mg/kg, Bevacizumab 440mg/kg, q3w). It came up with IV° myelosuppression. As a result, chemotherapy protocols was changed with albumin-bound Paclitaxel plus Cisplatin and Bevacizumab (albumin-bound Paclitaxel 135mg/m^2, Cisplatin 75mg/m^2, Bevacizumab 15mg/kg, q3w). The patient was received 4 cycles of above chemotherapy.

The patient’s condition progressed with brain metastases in December 2019, EGFR 21 exon p.L858R mutation (0.81%) was detect in blood-based genetic test, so the patient received 5 cycles of Erlotinib (Tarceva) with bevizumab (Erlotinib 150mg q.d., Bevizumab 450mg, q3w).

The patient found a mass in the left breast by herself-examination in June 2020. Mammograms revealed multiple mass in the left breast, BI-RADS 4B (Fig. 2). Therefore, breast and lymph node puncture in ultrasound-guided were performed and the postoperative pathological diagnosis of metastatic lung adenocarcinoma was confirmed (Fig. 3). The patient received pembrolizumab (Keytruda) (200mg, q3w). We recorded the results of the tumor biomarkers before the patient’s each treatment (Fig. 4).

Fig.2 Mammograms Multiple mass in the left breast, BI-RADS 4B

Immunohistopathological analysis demonstrated postive for TTF1(B),CK7(C),NapsinA(D) and negative stain for ER(E), PR(F),Gata-3(G), GCDFP-15(E) (orginial magnification×400).

However, disease progressed again with larger brain metastatic lesions in August 2020.The maximum diameter of the patient's breast mass did not change significantly before and after immunotherapy (Fig. 5). The patient underwent genetic testing again. The test results are the same as before. Gene detection of breast metastasis showed EGFR 21 exon p.L858R mutation. The patient received Almonertinib (110mg po q.d.). After the patient has used Almonertinibfor one month, we can clearly see from the head MRI that the patient’s lesions are smaller than before (Fig. 6). And the tumor biomarkers were significantly lower than before.The patient's breast lesions have been in a stable state. The patient's condition was partially relieved. After resistance to multiline therapy, the patient has been treated with Almonertinib combined with PDL1 inhibitor until now. The patient's condition is currently in a stable state.

Discussion

Primary malignant tumor of breast is one of the most common malignant tumors in adult women, but as the breast is rich in fibrous tissue, poor blood circulation, so secondary metastasis of breast is very rare. Metastatic breast tumors are very rare, accounting for only 0.4–1.3% of breast malignancies, and the most common are leukemia, lymphoma, melanoma, rhabdomyosarcoma, and lung cancer[6]. The ways of breast metastasis in patients with primary lung cancer are as follows: To the ipsilateral breast through intrathoracic lymphatic metastasis; Tumor cells along with the lymph circulation through the thoracic duct into the vein, through systemic circulation to the contralateral breast; Tumor cells enter the blood circulation and metastasize far away[7].Mirrielees et al. analyzed through a systematic retrospective analysis of 43 cases of lung cancer breast metastasis reported from 1989 to 2013; Among them, 10 cases were small cell lung cancer, 33 cases were non-small cell carcinoma, including 19 cases of adenocarcinoma, 3 cases of squamous cell carcinoma, 4 cases of large cell carcinoma, 4 cases of neuroendocrine carcinoma, 3 cases of undifferentiated carcinoma or others; The report involved 38 female and 5 male patients, with similar incidence in each age group. Among them, the average age of breast metastasis in NSCLC patients was 55 years old, SCLC patients were 58 years old, and patients were between 28 and 83 years old[8]. The correlation between the incidence of lung cancer and breast metastasis and pathological types remains to be studied with large samples.

There are big differences between primary breast cancer and secondary breast cancer in clinical features, imaging, pathology and immunohistochemistry. This patient started with pericardial effusion and pleural effusion. Breast masses are clues. Adenocarcinoma cells were found through puncture and drainage of pericardial effusion and exfoliated cytology. Combined with immunohistochemistry, tumorous lesions in the lung were further found. At the time of diagnosis, it was at an advanced stage. It is easy to be considered as primary breast cancer at the first diagnosis, or the coexistence of lung cancer and breast cancer. The role of histopathology as the gold standard in the diagnosis of diseases is beyond doubt. However, the morphological identification of small biopsy specimens with atypical morphology is limited, and immunohistochemical testing is indispensable for diagnosis at this time. At present, the commonly used immune markers in lung adenocarcinoma include NapsinA, TTF-1, CK7 and alveolar surface glycoprotein, etc[9]. Breast cancer mainly expresses ER/PR, GATA-3 and Mamma-globin, etc. The positive

rate of GATA-3 is 47%-100%, which is a specific marker of breast cancer[10]. Immunohistochemistry of the breast tumor in this patient showed positive TTF-1, NapsinA, and CK7, supporting the diagnosis of lung adenocarcinoma. The patient's immunohistochemical results showed TTF-1 positive and ER negative. Although a small number of breast cancers can also express TTF-1, they need to be distinguished from primary breast cancer[11,12]. Because of the more specific NapsinA positive and GATA-3 negative, the diagnosis of lung adenocarcinoma and breast metastasis is clear.

Our patient had metastasis to her right breast, which is the same side affected by the malignant pleural effusion, consistent with the hypothesis by Huang et al[13]. To this end, they considered a stepwise mechanism involving parietal pleural seeding, followed by invasion into chest wall lymphatic vessels draining to ipsilateral axillary lymph nodes and retrograde lymphatic spreading to the breast. This mechanism of breast metastasis could be supported by findings of enlarged homolateral axillary lymph nodes. Moreover, Barber et al[14] demonstrated lymphatic communication between the breast and mediastinal lymphatic channels. These hypotheses could be confirmed by the fact that almost 80% of the cases reported from 2000 to date had ipsilateral lesions. Another potential type of spread could be hematogenous. However, if lung cancer spreads through this route, both breasts should have the same probability of being affected. This is not reflected in the reviewed cases, where only 5.4% of patients had bilateral breast involvement. The last possible explanation could be direct tumor invasion through the chest wall to the breast, but chest CT scans did not reveal this alteration in the reported cases. Therefore, lymphatic spreading might be the most reasonable mechanism of lung cancer dissemination to the breast.

Judging from previous research evidence, EGFR TKI and immunotherapy are incompatible. Current research does not support the use of immunotherapy in patients with EGFR mutations, because of low efficacy, high toxicity, and prone to super progress. But a clinical study broke this conventional "consensus"[15].The use of PD-1 inhibitor after drug resistance in patients with EGFR mutations is not only safe but also makes patients susceptible to EGFR TKI again.This study retrospectively analyzed the efficacy of EGFR TKI (Afatinib, Erlotinib, or Gefitinib) after progressing.The study included 75 patients with advanced NSCLC with EGFR mutations (19Del or L858R or L851Q) who had previously received EGFR-targeted therapy and had disease progression.The study was divided into two groups according to whether or not to use immunotherapy in the future. The experimental group: received PD-1 treatment (pembrolizumab or nivolizumab), and then challenged EGFR-targeted drugs after progress (n = 13 cases) ; Control group: did not receive PD-1 treatment and was challenged with targeted drugs (n = 62 cases).The results found that after EGFR TKI resistance was interspersed with immunotherapy, EGFR TKI challenged again, with ORR reaching 46.1%; In the group that did not receive immunotherapy after EGFR resistance, the ORR was only 16.1%, and the difference was statistically significant (P = 0.026). In addition, the DCR of the experimental group reached 76.1%, and the PFS and OS were 5 months and 25 months, respectively.

Our case was advanced lung cancer, genetic testing revealed an EGFR mutation, and Almonertinib was treated. Almonertinibis the second third-generation EGFR TKI innovative drug in the world. It is mainly used for disease progression during or after treatment with EGFR TKI. The test confirmed the presence of EGFR T790M mutation-positive adult patients with locally advanced or metastatic non-small cell lung cancer. Almonertinibis easier to cross the blood-brain barrier than other EGFR TKI targeted drugs. We took into account the presence of brain metastases in our patient, so in the case of ineffective immunotherapy, we chose amitinib combined with EGFR TKI. As a result, the patient controlled the brain lesions and achieved stable disease control for 2 months. Treatment is currently underway. We will continue to track and record the patient's disease.

The above PD-1 inhibitor sequential EGFR TKI treatment model brings new ideas for the treatment of breast cancer lung metastasis. Remind us that the sequential/crossover schemes of immunization and targeted therapy can be flexible and changeable. Breaking the conventional thinking after multi-line resistance may be surprisingly successful. However, the number of clinical studies is currently limited, and it is expected that researchers will release more research data. EGFR TKI re-challenge treatment brings us many medicine inspirations.In summary, switching to another regimen for a period of time after the treatment of drug resistance may change the characteristics of tumor cells, and there may be a chance of being sensitive to the original regimen again.Of course, the beneficiaries of EGFR TKI challenges are also the focus of clinical exploration. It is expected that in the future, EGFR TKIs can be rationally selected and the order of medication can be arranged under precise guidance, so as to maximize the benefits of patients.

Abbreviations

CT: computed tomography, NSCLC: non-small cell lung cancer, EGFR: epidermal growth factor receptor, TKI: tyrosine kinase inhibitor, CK 7: cytokeratin 7; TTF1: thyroid transcription factor 1, MRI: Magnetic Resonance Imaging, PD:progressive disease, SD: stable disease.

Declarations

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Author's contributions

Chanchan Gao was responsible of the clinical management of the patient presented and acquisition of data, and helped to draft the manuscript. Xuyu Gu and Shiya Zheng were responsible of the clinical management, interpretation of the data, and drafting the manuscript. Longfei Wang collected and analyzed the pathologic data. All the authors read and approved the final manuscript.

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Ethics approval and consent to participate

The study was approved by Zhongda Hospital Southeast Universtiy. The patients consented to participate.

Consent for publication

Written informed consent for research and publication from the patients was obtained.

Competing interests

The authors declare that they have no competing interests.

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Figures

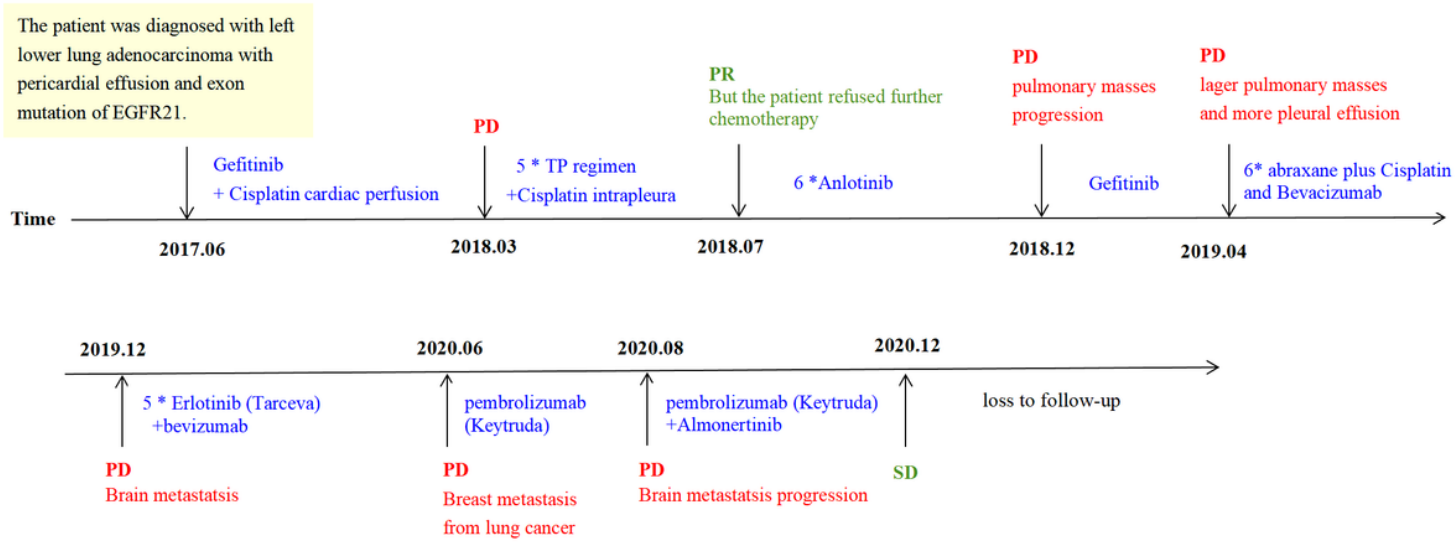

Figure 1

The timeline of this case report

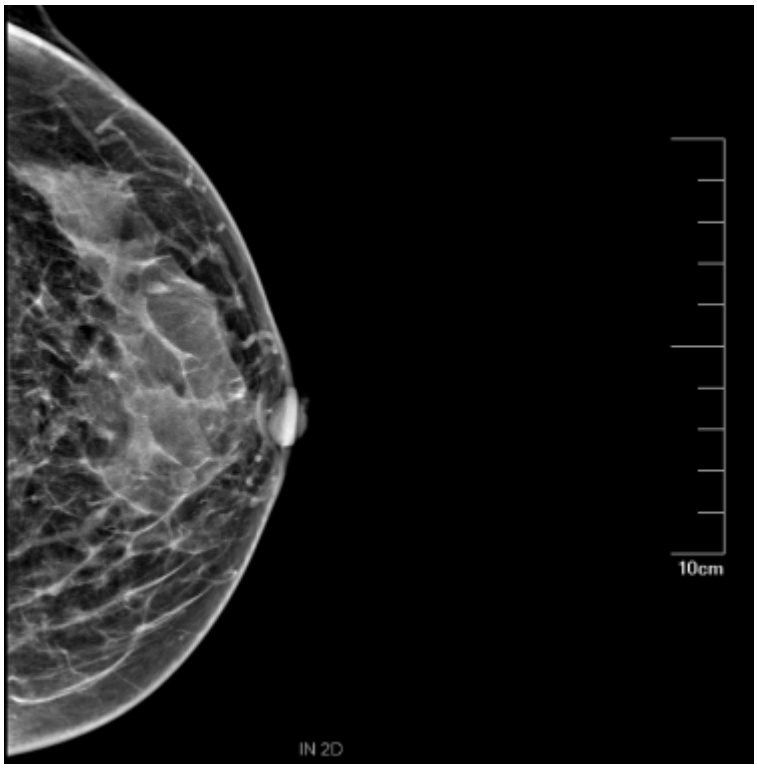

Figure 2

Mammograms Multiple mass in the left breast, BI-RADS 4B

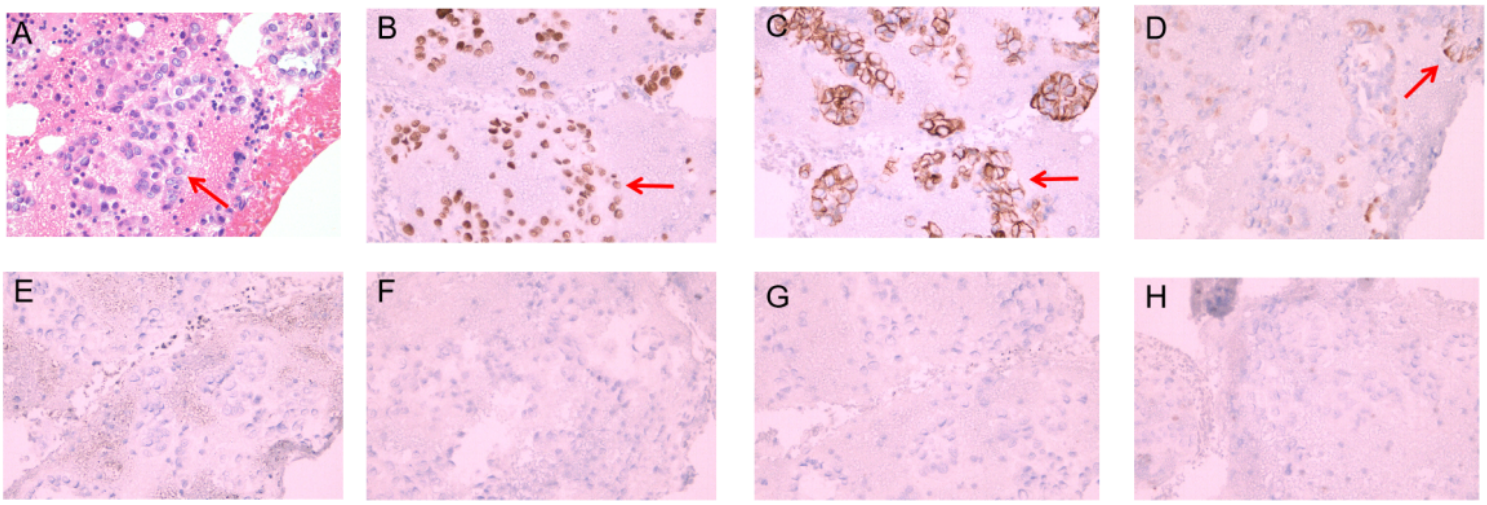

Figure 3

FNA cell block in left axillary lymph node showed adenocarcinoma cells:hematoxylin and eosin stain(A) (orginial magnification×400).

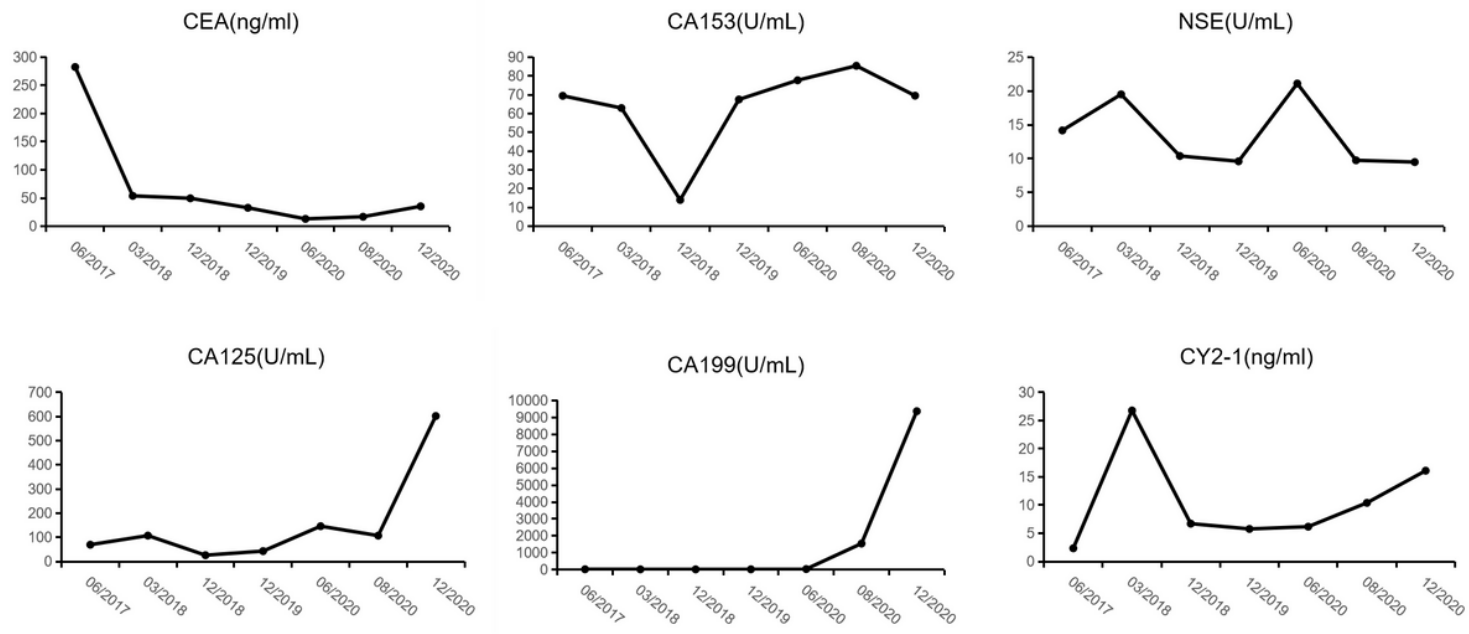

Figure 4

The results of the tumor biomarkers before the patient's each treatment

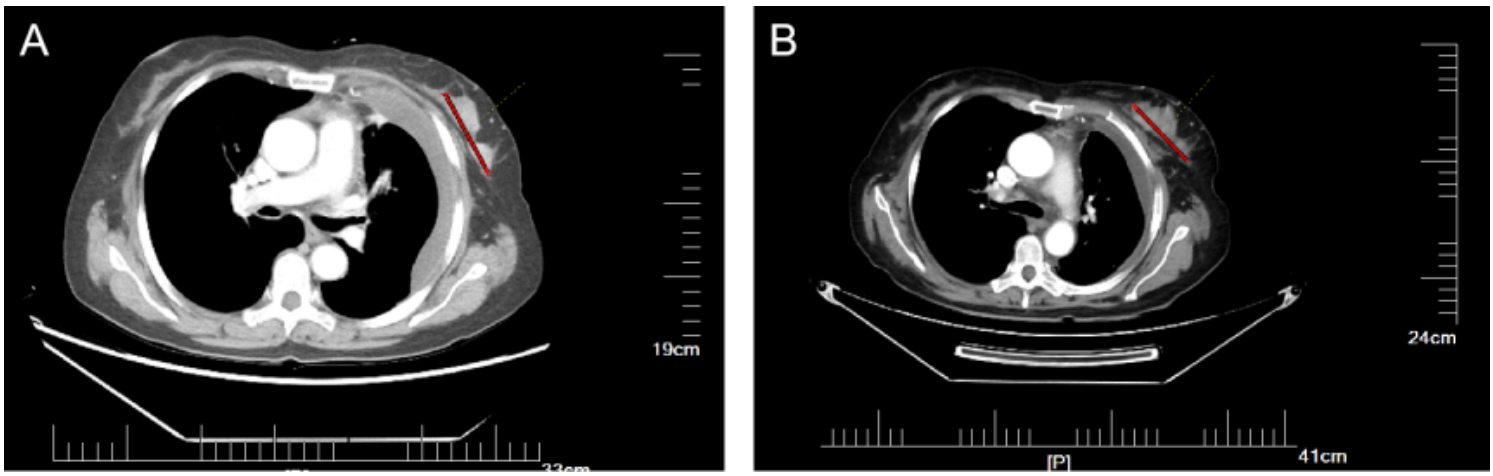

Figure 5

Chest computed tomography (CT) scans: (A) Before immunotherapy, (B)After immunotherapy.

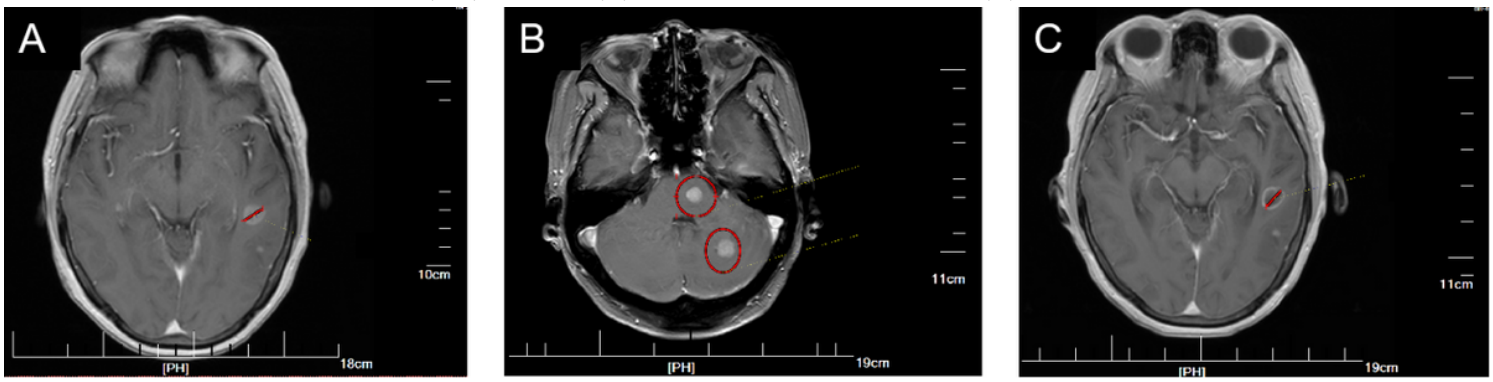

Figure 6

Head magnetic resonance imaging (MRI): (A)Before immunotherapy, (B) After immunotherapy, (C)After targeted therapy.