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Trochlear nerve schwannoma with concomitant osimertinib-responsive stage IV lung adenocarcinoma: illustrative case

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BACKGROUND The prognosis for cancer patients has been improved because of the development of molecularly targeted drugs. Treatment of intracranial tumors must be personalized while prioritizing the treatment of comorbid cancers.

OBSERVATIONS A 38-year-old man presented with bloody sputum, bilateral multiple nodules, and a mass in the lower lobe of his right lung. Bronchoscopy revealed stage IV lung adenocarcinoma with an epidermal growth factor receptor (*EGFR*) mutation. Screening head magnetic resonance imaging revealed a 38-mm-diameter mass in the left petroclival area. Because the patient was neurologically intact, the treatment of lung adenocarcinoma was prioritized, and the third-generation EGFR–tyrosine kinase inhibitor osimertinib was used. Although nodules in the lung began to shrink, the intracranial lesion expanded and caused hydrocephalus, necessitating a ventriculoperitoneal shunt. The tumor also caused diplopia, dysarthria, and gait abnormalities. A left anterior transpetrosal approach was used to remove the tumor derived from the trochlear nerve. The pathological examination revealed schwannoma. Neurological symptoms improved following surgery. Osimertinib was continued during the perioperative period.

LESSONS Osimertinib was effective for lung adenocarcinoma but not for trochlear nerve schwannoma, which required surgical intervention. It is necessary to tailor the treatment of benign brain tumors in patients with concurrent malignant cancers.

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KEYWORDS trochlear nerve schwannoma; lung adenocarcinoma; osimertinib

Recently, the effects of molecularly targeted drugs on various cancers have been reported, and their therapeutic applications have increased.[1,2] Although this advancement has improved patient outcomes, neurosurgeons are encountering patients with benign intracranial tumors and comorbid cancers more frequently. It has become necessary to devise a strategy for treating benign intracranial tumors at the appropriate time while prioritizing the treatment of comorbid malignancies. In addition to surgical timing, the impact of molecularly targeted drugs on surgery and postoperative radiotherapy must also be considered. There are no established guidelines for the surgical treatment of patients during or after the administration of molecularly targeted drugs, and patients are currently treated on an individual basis.

We present the case of a trochlear nerve schwannoma complicated by stage IV lung adenocarcinoma. The adenocarcinoma was initially treated with the third-generation epidermal growth factor receptor (EGFR)–tyrosine kinase inhibitor (TKI) osimertinib. It was effective in treating the adenocarcinoma but not the schwannoma. We carefully planned the timing of surgical intervention for schwannoma so as not to interfere with the ongoing treatment of adenocarcinoma.

Illustrative Case

A 38-year-old man presented with bloody sputum and was found to have a mass in the lower lobe of the right lung as well as multiple nodules in the bilateral lungs (Fig. 1A). Chest computed tomography (CT) of the lung revealed a mass with a cavity in the right lower lobe, and a bronchoscopic biopsy revealed lung adenocarcinoma (*EGFR* exon 19 deletion positive). Stage IV adenocarcinoma was discovered. Although the patient was neurologically unaffected, screening head magnetic

ABBREVIATIONS CT = computed tomography; EGFR-TKI = epidermal growth factor receptor–tyrosine kinase inhibitor; FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography; MRI = magnetic resonance imaging; NF2 = neurofibromatosis type 2; NSCLC = non–small cell lung cancer.

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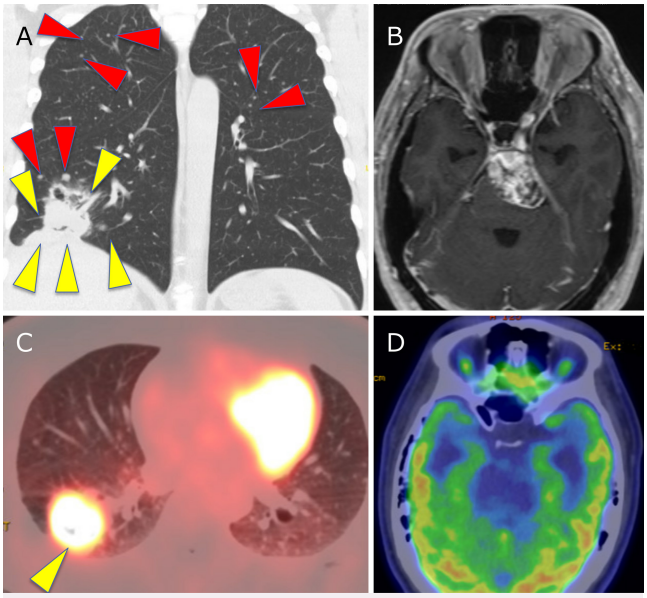

FIG. 1. Admission images. **A:** Coronal chest CT showed a mass (*yellow arrowheads*) in the lower lobe of the right lung and multiple nodules (*red arrowheads*) in the bilateral lungs. **B:** Axial MRI revealed a tumor in the left petroclival region. **C:** There was strong FDG-PET accumulation in the lung lesion (*yellow arrowhead*). **D:** There was no FDG-PET accumulation in the intracranial mass.

resonance imaging (MRI) revealed a large tumor in the left petroclival region (Fig. 1B). There was prominent ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) accumulation in the lung lesion (Fig. 1C), but no accumulation was found in the intracranial tumor (Fig. 1D). We were unsure about the diagnosis of the intracranial tumor, but given the prognosis of lung cancer, treatment of lung adenocarcinoma was prioritized. Radiotherapy for intracranial lesions was also considered, but it was not chosen due to the potential delay in lung cancer treatment caused by temporary tumor enlargement and possible hydrocephalus after radiotherapy. For lung adenocarcinoma, daily oral osimertinib administration (80 mg) was initiated, and the lung lesions had nearly disappeared after 6 months (Fig. 2A). In contrast, the intracranial lesion grew in size, resulting in obstructive hydrocephalus (Fig. 2B) necessitating a ventriculoperitoneal shunt (Fig. 2C). Headaches, diplopia, numbness in the right upper limb, difficulty swallowing, dysarthria, and gait imbalance appeared 11 months after the initial visit, and a CT scan revealed brainstem compression by the tumor (Fig. 2D–F). At this point, we decided to remove the tumor via the anterior transpetrosal approach (Video 1). Intraoperative findings revealed that the tumor was tightly attached to the trochlear nerve and tentorium but easily detached from the trigeminal and abducens nerves (Fig. 3). The slight adhesion to the basilar artery was also removed, and a gross-total resection was performed.

VIDEO 1. Clip showing the anterior transpetrosal approach for trochlear nerve schwannoma. Click here to view.

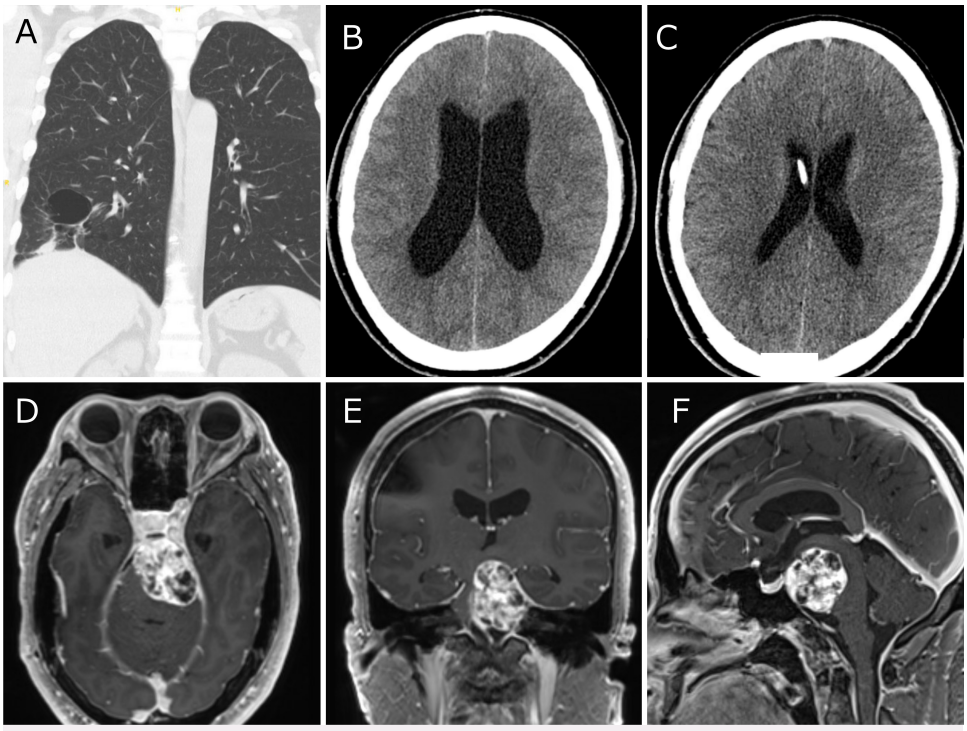

FIG. 2. Clinical course after oral osimertinib administration. **A:** The lung lesions shrank after 6 months of osimertinib, as shown on the coronal chest CT scan. **B:** The intracranial lesion increased in diameter and caused obstructive hydrocephalus. **C:** A ventriculoperitoneal shunt was placed for the treatment of hydrocephalus. **D–F:** The brain tumor continued to increase in size and compressed the brainstem.

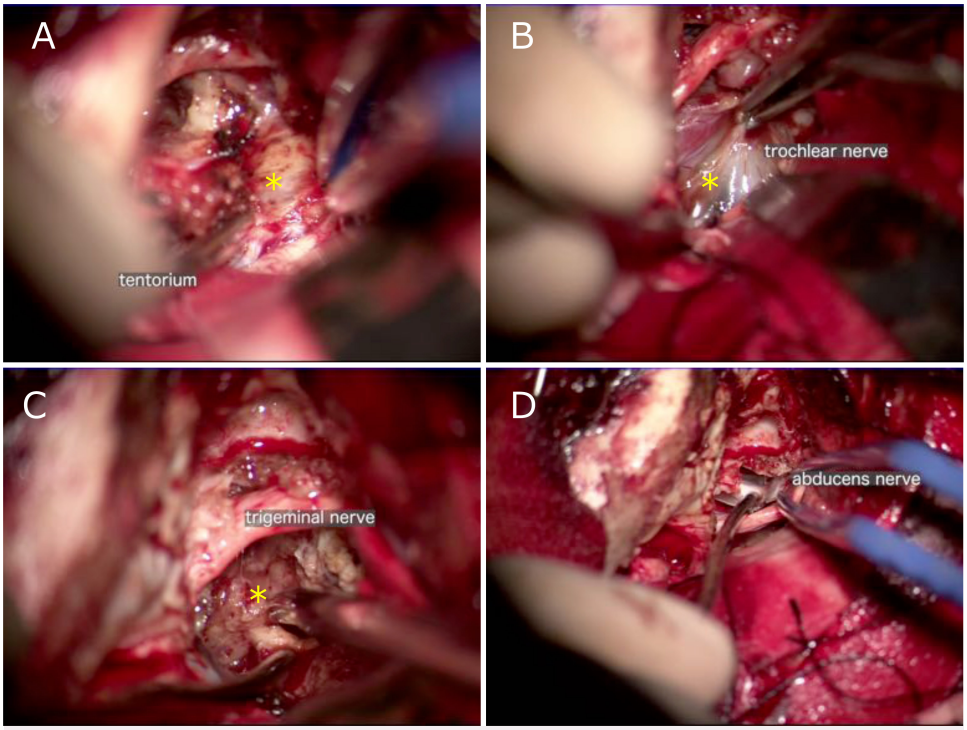

FIG. 3. The anterior transpetrosal approach was performed. The tumor (*asterisks*) adhered to the tentorium (**A**) and the trochlear nerve (**B**) but was easily detached from the trigeminal nerve (**C**) and abducens nerve (**D**).

Postoperatively, mild trochlear nerve palsy worsened. Osimertinib was continued throughout the perioperative period. Temporary postoperative pneumocephalus was discovered, and the ventriculoperitoneal shunt pressure was raised to the highest resistance. Since then, the intracranial air has decreased, and the size of the ventricles has shrunk gradually, even at maximum pressure, indicating that the shunt system is no longer needed. Postoperative MRI showed gross-total removal of the tumor (Fig. 4A).

Histopathological examination of the tumor tissue revealed the proliferation of tumor cells with oval, round, or spindle-shaped nuclei interspersed with collagen fibers. Various levels of degenerative changes, such as hemorrhage, cyst formation, and edema, were observed. Given these findings, the lesion was identified as a schwannoma (Fig. 4B and C). After combining intraoperative and pathological findings, the final diagnosis was trochlear nerve schwannoma. Eight months after the craniotomy, the trochlear nerve palsy had almost completely resolved. The patient had no neurological deficit.

Patient Informed Consent

The necessary patient informed consent was obtained in this study.

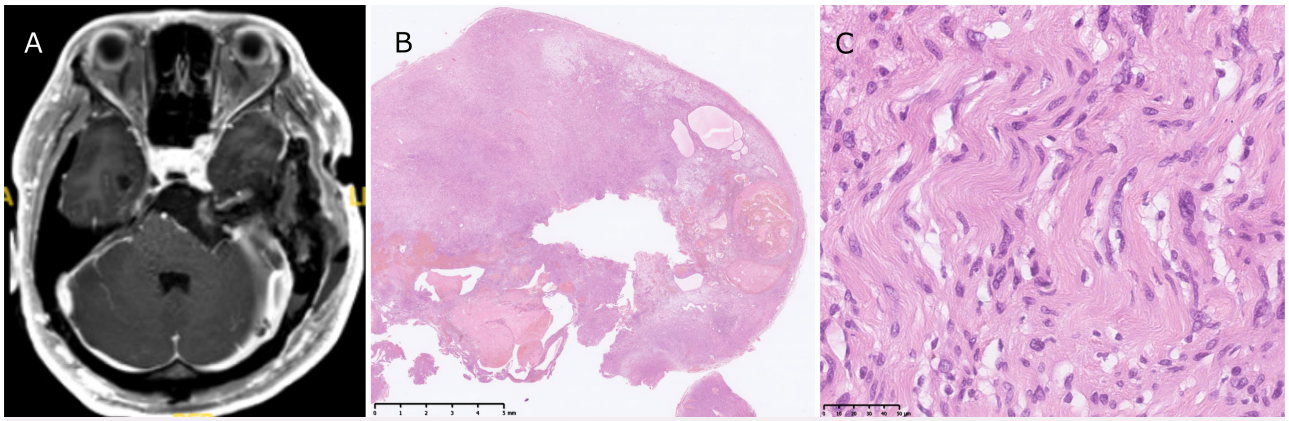

FIG. 4. A: Gross-total resection via the anterior transpetrosal approach was achieved. **B and C:** Pathological examination with hematoxylin and eosin staining revealed cystic, hemorrhagic, or edematous changes in the tumor tissue. The tumor cells harbored narrow, elongated, and wavy nuclei interspersed with collagen fibers.

Discussion

Observations

Here, we present a case of trochlear nerve schwannoma with concomitant stage IV lung adenocarcinoma treated with the EGFR-TKI osimertinib. The osimertinib was effective in treating adenocarcinoma but not the schwannoma, necessitating surgical intervention.

Recently, in addition to cytotoxic anticancer drugs, the indications for molecularly targeted drugs have expanded, and the range of cancer treatment options is growing rapidly.[1,2] Along with the improved patient prognosis, there is an increasing number of cases in which intracranial tumors are discovered in cancer patients. For such patients, neurosurgery is grappling with treatment strategies, such as how to balance primary cancer and intracranial tumor treatment.

Osimertinib is a third-generation irreversible EGFR-TKI that is commonly used to treat non–small cell lung cancer (NSCLC).[3,4] In contrast, the effect of TKI on schwannoma remains largely unknown. In an in vivo study, inhibition of the *ErbB* family of receptor tyrosine kinases reduced schwannoma cell proliferation.[5] Another study used brigatinib, an inhibitor of multiple tyrosine kinases, to treat neurofibromatosis type 2 (*NF2*)–related schwannomas in a genetically engineered murine model of spontaneous *NF2* schwannomas.[6] However, the network of tyrosine kinases in schwannoma cells is complex, and Carlstrom et al.[7] reported a case of vestibular schwannoma that progressed dramatically following TKI treatment, cautioning that TKI may cause unintended iatrogenic vestibular schwannoma progression. This mechanism is thought to be a conformational change in *MERLIN,* the *NF2* gene, caused by the inhibition of tyrosine kinases, which leads to the inactivation of growth control by the merlin protein via interaction with the actin cytoskeleton.

Perioperative treatment with osimertinib can also cause several possible postoperative adverse events, primarily by inhibiting normal cell tyrosine kinase activity. However, the optimal duration of preoperative and postoperative osimertinib interruption has not yet been determined. Our patient continued to receive osimertinib during the perioperative period. In fact, a third-generation EGFR-TKI has a lower toxicity profile, allowing for a shorter perioperative period interruption. In a clinical trial with neoadjuvant osimertinib for NSCLC,[8] surgery was recommended immediately following the completion of preoperative treatment, whereas another neoadjuvant trial requires 3–14 days of osimertinib cessation before surgery.[9] In general, it is critical to consider the preoperative interruption period for ongoing drugs that have been shown to delay wound healing. For example, bevacizumab, a vascular endothelial growth factor inhibitor used to treat rectal cancer[10,11] and other organ cancers,[12] requires a break of 4–6 weeks before surgery and 4 weeks after surgery. When there is no established guideline for a specific drug, the drug cessation period should be determined case by case. Future research will look into the safety of these drugs in surgery, as well as their interactions with surgery or postoperative radiation therapy.

The timing of surgical intervention for intracranial tumors is also critical. Torun et al.[13] proposed a treatment algorithm for trochlear schwannoma without other malignancy. If there are symptoms caused by brainstem compression, decompression or removal surgery is recommended; however, if the tumor is discovered without symptoms or with only minor symptoms such as diplopia, it is monitored or treated with radiation therapy. A similar algorithm was proposed by Lan et al.[14] Our patient was initially asymptomatic. Given that the treatment for lung adenocarcinoma had not yet begun, it was prudent to reserve direct surgery for the intracranial tumor and monitor the tumor first. Furthermore, because of its rarity, when the screening MRI revealed an intracranial mass, we were unsure of whether it was a trochlear nerve schwannoma. In light of the possibility of brain metastasis from lung cancer, FDG-PET scans were obtained. The lung adenocarcinoma was FDG-PET positive, but the brain lesion did not accumulate FDG, implying that it was likely a relatively benign tumor. We should also note that schwannoma cells occasionally exhibit unexpectedly densely accumulated lesions on PET scans, and PET alone cannot distinguish between schwannoma and adenocarcinoma.[15] In our case, because the brain lesion was asymptomatic, we prioritized confirmed stage IV lung cancer treatment, which was thought to be a prognostic factor. After the patient started taking osimertinib, the lung adenocarcinomas remarkably decreased, but the intracranial lesion grew slowly, indicating that it was not a metastatic tumor. Six months after receiving osimertinib, the patient developed hydrocephalus, which was caused by cerebral aqueduct compression. A ventriculoperitoneal shunt was selected because it appeared to be less invasive than radical resection. Later, the tumor grew steadily and caused brainstem compression symptoms. At that time, lung adenocarcinoma had responded well to osimertinib, and a longer prognosis was expected; thus, we ultimately decided to proceed with radical resection.

Concerning the surgical approach, there have only been about 38 reported cases of surgical treatment for trochlear schwannoma.[13] The most common method was the retrosigmoid approach. For our patient, we chose the anterior transpetrosal approach because the tumor diameter was large, primarily located in the petroclival area, and had spread to the anterior surface of the brainstem. The feeding vessels were discovered to form the tentorium during preoperative angiography. The anterior transpetrosal approach to trigeminal schwannoma has also been reported with excellent results.[16,17] To our knowledge, this is the third report of an anterior transpetrosal approach for trochlear nerve tumors.[18,19] The advantages of the anterior transpetrosal approach are 1) good exposure of the petroclival area and 2) early devascularization of the feeders from the tentorium, while the disadvantages are 1) temporal lobe retraction, 2) risk of venous infarction, and 3) a relatively small surgical field. Whichever approach is chosen, it is critical to choose one that has the least impact on the ongoing treatment of concomitant malignant tumors, and any complications that may deter the main treatment should be minimized to the greatest extent possible.

This study has limitations that need to be considered. Since we had continued osimertinib throughout the entire treatment course, we are not certain that the interruption of osimertinib will delay the observed growth of schwannoma. We are only certain that osimertinib was ineffective for schwannoma in our case and may have actually hastened progression. Another obvious limitation is its single-case nature. According to the classes of evidence in neurosurgery,[20] our study can be categorized as evidence level V.

Lessons

Here, we present a trochlear nerve schwannoma with concomitant stage IV adenocarcinoma. Osimertinib is not only ineffective for intracranial schwannomas but can actually hasten progression. The development of molecularly targeted drugs is expected to improve cancer outcomes even further, and neurosurgeons are increasingly encountering patients who have multiple malignancies. In the absence of neurological symptoms, priority should be given to systemic cancer in the case of concomitant diagnosis.

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Disclosures

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Author Contributions

Conception and design: Tanji, Kashiwagi, Natori, Arakawa. Acquisition of data: Tanji, Kashiwagi, Matsuoka, Sano, Ozasa, Natori, Takeuchi. Analysis and interpretation of data: Tanji, Kashiwagi, Sano, Natori, Mineharu. Drafting the article: Tanji, Kashiwagi, Sano, Natori. Critically revising the article: Kashiwagi, Sano, Makino, Hattori, Mineharu, Arakawa. Reviewed submitted version of manuscript: Tanji, Kashiwagi, Sano, Ozasa, Natori, Terada, Arakawa. Approved the final version of the manuscript on behalf of all authors: Tanji. Statistical analysis: Kashiwagi. Administrative/technical/material support: Matsuoka, Arakawa. Study supervision: Arakawa.

Supplemental Information

Videos

Video 1. https://vimeo.com/948351871.

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