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BRAF V600E-mutated combined large cell neuroendocrine carcinoma and adenocarcinoma responding to targeted therapy

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SUMMARY

We present a case of combined large cell neuroendocrine carcinoma (LCNEC), harbouring a *BRAF* V600E mutation, which significantly benefited from *BRAF*-targeted therapy. A 57-year-old woman was referred to our hospital for headache and vomiting. A head MRI showed a large tumour in her brain, and a whole-body CT revealed a tumour in the hilum of the right lung and mediastinal lymphadenopathies. Both the resected brain tumour and the mediastinal lymph node tissue contained LCNEC. Next-generation sequencing revealed a *BRAF* V600E mutation, and a combination therapy with dabrafenib and trametinib was initiated. The patient had a good response to treatment. Like non–small cell lung cancer patients, LCNEC patients should undergo multiplex somatic mutation testing.

BACKGROUND

Lung cancer is still the leading cause of cancer-related deaths worldwide. The treatment strategy in non–small cell lung cancer (NSCLC) is subdivided based on multiple driver oncogenes. However, the treatment for neuroendocrine lung carcinoma, particularly large cell neuroendocrine carcinoma (LCNEC), has not improved. Due to the low frequency of LCNEC, its genetic status and the significance of somatic mutation testing in daily practice are unclear.

In 2013, the nationwide Lung Cancer Genomic Screening Project for Individualized Medicine in Japan (LC-SCRUM Japan) was conducted to develop molecular-targeted therapies for NSCLC patients with rare genes. Since 2019, the Oncomine Dx Target test multi-CDx system has been used in daily practice for multiplex gene testing of advanced lung cancer in Japan. As such, lung carcinoma patients were likely to undergo somatic mutation testing.

We report a case of LCNEC, harbouring a *BRAF* V600E mutation, that responded to dabrafenib and trametinib (DT). The case demonstrated the importance of somatic mutation testing in LCNEC.

CASE PRESENTATION

A 57-year-old woman with a history of well-controlled bronchial asthma and smoking (25 pack-years) was referred to our hospital for headache and vomiting. One month prior to the consult, the patient noted the headache, but this was ignored. However, her symptoms did not improve spontaneously, and she was admitted to a nearby hospital after 2 weeks. A head MRI showed a large tumour in her brain, and she was referred to our neurosurgery department. On examination, she was afebrile and normotensive with normal oxygen saturation. She was noted to lose her balance occasionally while walking, but her neurological exam was unremarkable.

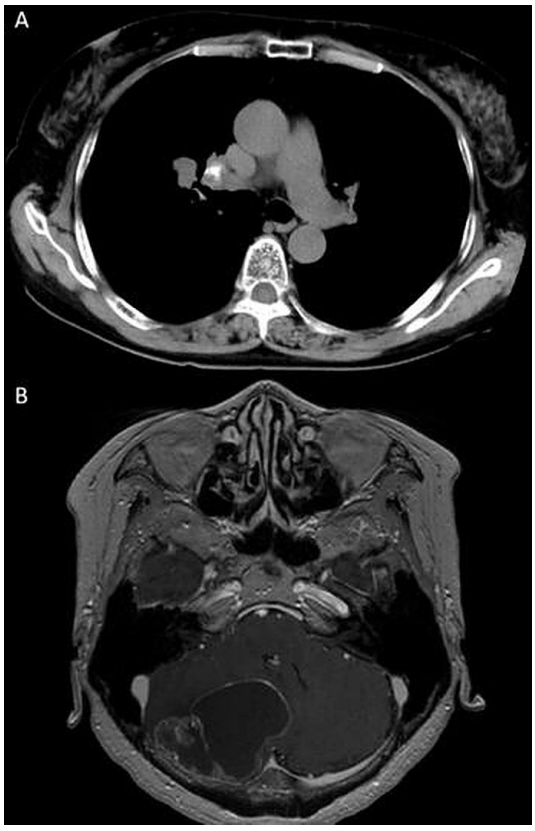

Figure 1 (A) A CT reveals a tumour in the hilum of the right lung, with mediastinal lymphadenopathies. (B) A head MRI reveals a 45 mm cystic mass in her right cerebellum.

INVESTIGATIONS

The whole-body CT revealed a tumour in the right pulmonary hilum and mediastinal lymphadenopathies (figure 1A). The head MRI revealed a 45 mm cystic mass in her right cerebellum (figure 1B). The tumour was resected to control the symptoms associated with the brain tumour. The postoperative course was uneventful.

The pathological specimens of the cerebral tumour contained a mixture of adenocarcinoma-like

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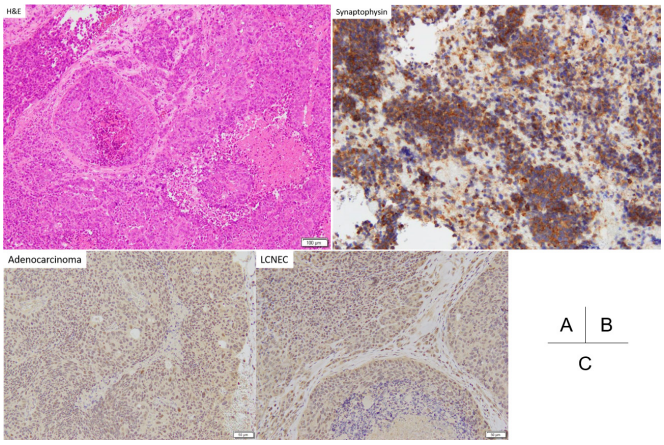

Figure 2 (A) The cerebral tumour is a mixture of adenocarcinoma-like cells that form and proliferate small ducts, and atypical cells with abundant acidophilic cytoplasm and distinct nucleoli. (B) Synaptophysin is diffusely positive in all regions. (C) Immunostaining of *BRAF* V600E with cerebellar tumours stain both adenocarcinoma and large cell neuroendocrine carcinoma. Both cells showing adenocarcinoma morphology and LCNEC cells stained for synaptophysin are stained with *BRAF* V600E antibody.

area with atypical cells forming small ducts and nests and an area with abundant eosinophilic cytoplasm and prominent nucleoli (figure 2A). On immunohistochemical analysis showed that CK AE1/3, CK7 and synaptophysin were diffusely positive in all regions (figure 2B). TTF-1 was diffusely positive in the former, but focal positive in the latter. Chromogranin A and CD56 were both focal positive, but the former showed stronger positive. In addition, p40, Napsin A and CK20 showed negative results. Based on the above findings, the pathologist diagnosed the lesion as a mixture of adenocarcinoma and LCNEC. In addition, we performed endobronchial ultrasound-guided transbronchial needle aspiration on the mediastinal lymph nodes. Adenocarcinoma-like atypical cells were not found, and they were occupied by atypical cells considered to be LCNEC. Gene analysis using this sample detected a *BRAF* V600E mutation. To decide the treatment strategy, it is necessary to clarify if the *BRAF* mutations are present in both LCNEC and lung adenocarcinoma, or lung adenocarcinoma only. In other words, if *BRAF* mutation-positive lung adenocarcinoma and non-*BRAF*-mutated LCNEC are mixed together, *BRAF*-targeted therapy will have limited therapeutic effect. Therefore, it was thought that immunostaining might be useful as a means of confirming that. Immunostaining of *BRAF* V600E (anti-*BRAF* V600E rabbit monoclonal antibody clones: RM8, RevMAb Biosciences) with cerebellar tumours tested positive in both adenocarcinoma and LCNEC (figure 2C). The results indicated that both the adenocarcinoma cells and LCNEC cells likely harboured *BRAF* V600E mutation. In addition, the next-generation sequencing (NGS) data also suggested that both adenocarcinoma and LCNEC cells had *BRAF* mutations. Based on the NGS results (Oncomine Comprehensive Assay, Thermo Fisher Scientific), the tumour had two major somatic mutations, *BRAF* V600E and TP53 H179Q mutation. TP53 H179 is known as a missense mutation that worsens prognosis.[1] The mutation allele frequency (MAF) of *BRAF* was 0.483 and that of TP53 was 0.916. The MAF values showed that this mutation in TP53 caused mutations in both alleles of DNA. On the other hand, *BRAF* V600E mutation is known to cause deletion of one allele, loss of heterozygosity, and the *BRAF* MAF value close to 0.5 indicated that most of the cells had the *BRAF* V600E mutation. Based on these, we concluded that most of the tumours were cells likely to be *BRAF*-dependent and that targeted therapy would be effective.

TREATMENT

DT combination therapy was started for *BRAF*-mutated NSCLC. Fever and rash appeared on the fourth day after treatment. Antihistamine and topical steroids were given, but the symptoms did not improve. Furthermore, DT was temporarily suspended because of hepatic dysfunction on the sixth day. On the ninth day after DT withdrawal, adverse events improved to grade 1 or lower, and dose-reduced DT administration was resumed. On the fifth day after the resumption of administration, fever and rash reappeared, so DT was discontinued and prednisolone (PSL) (20 mg/day) was given. After that, DT was resumed, and the patient did not develop a fever or rash. PSL was gradually reduced to 7.5 mg/day.

OUTCOME AND FOLLOW-UP

The CT results 10 weeks after the start of DT revealed a decrease in the size of the tumour in the right lung hilum. This corresponded to a partial response (figure 3A). The brain tumour was surgically removed. There was no recurrence for at least a year thereafter, including in the central nervous system (figure 3B). She continues to work while receiving DT.

DISCUSSION

LCNEC is a tumour with a poor prognosis comparable with that of small cell carcinoma, with a 5-year survival rate of 40.3% for all pathological stages.[2] According to Yamazaki *et al*, the response rate to cisplatin-based chemotherapy was 50%, and that of small cell carcinoma showed that the response rate to cisplatin-based chemotherapy was 50%, similar to that of small cell carcinoma.[3] Furthermore, Fujiwara *et al* reported a response rate of 55.6% for cisplatin plus irinotecan.[4] In general, lung cancer with more than one histological type has a high biological grade.[5] However, the prognosis of combined LCNEC is reported to be similar to that of LCNEC.[6]

The treatment strategy in NSCLC, especially in lung adenocarcinoma, was subdivided based on driver oncogenes, such as *EGFR*,[7] *ALK*,[8] *ROS1*,[9] *BRAF*,[10] *NTRK*,[11] *MET*[12] and *RET*.[13] Various clinical practice guidelines recommend multiple somatic mutation tests to select the initial treatment for NSCLC.[14 15] However, little is known about driver genes in LCNEC. Lou *et al* analysed 108 cases of pulmonary neuroendocrine tumours, including LCNEC, and reported that no *BRAF* mutations were found.[16] In contrast, Zakka *et al* analysed the cell-free tumor DNA of 320 cases of neuroendocrine carcinoma, including 70 cases of pulmonary neuroendocrine carcinoma, and found *BRAF* mutations in 28 cases.[17] Furthermore, Chae *et al* analysed 300 cases of LCNEC and reported that 13 cases had *BRAF* mutations. Targeted therapy was effective in a case with a non-V600E mutation.

In clinical practice, LCNEC is often treated with cytotoxic drugs similar to those of small cell lung cancer. However, it may also be treated as NSCLC. Platinum-based chemotherapy for LCNEC was effective but insufficient. Thus, the development of additional treatments is expected. A clinical trial of DT in patients with previously treated *BRAF* V600E mutant metastatic NSCLC showed an overall response rate of 63.2% in a cohort of 57 patients.[18] Furthermore, DT in patients with previously untreated *BRAF* V600E mutant metastatic NSCLC had an overall response rate of 64% in a cohort of 36 patients.[4] Our

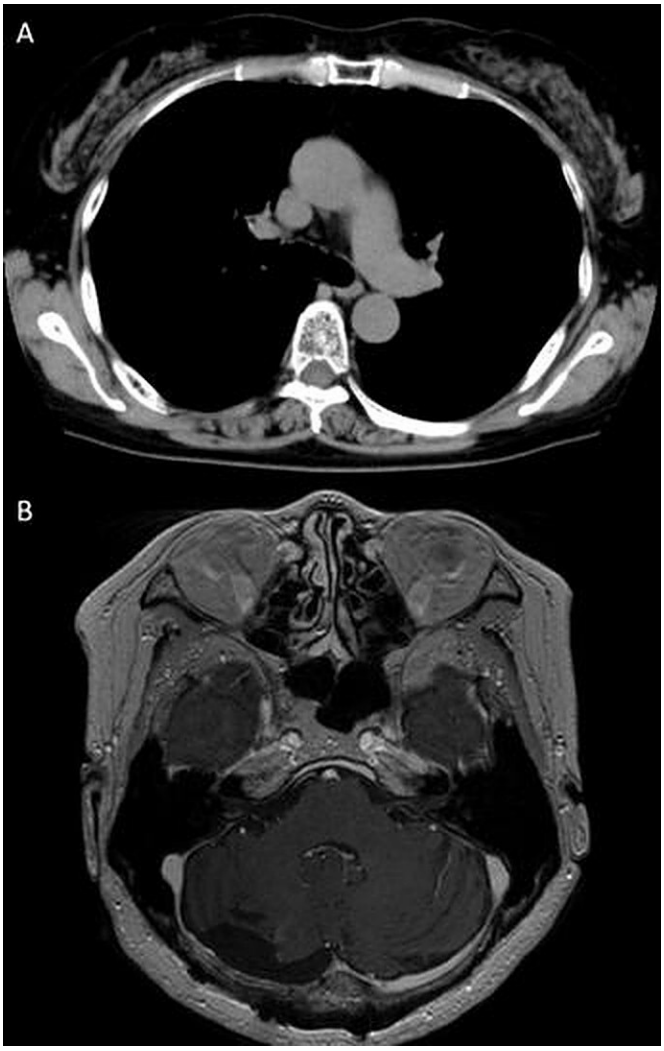

Figure 3 (A) A CT 10 weeks after the start of dabrafenib and trametinib therapy confirms a shrinkage of the tumour, which corresponds to a partial response. (B) An MRI showed no recurrence after surgical removal at diagnosis.

patient underwent routine multiplex gene analysis as NSCLC prior to initial treatment.

In this case, multiplex somatic mutation testing allowed the patient to receive *BRAF*-targeted therapy, which resulted in improvement. This encounter showed that LCNEC should also be treated based on the results of multiplex somatic mutation testing.

Learning points

- This is a case of combined large cell neuroendocrine carcinoma in which dabrafenib and trametinib therapy was effective.
- Multiplex somatic mutation testing prior to initial treatment provided one more option before cytotoxic anticancer drugs.
- Patients with large cell neuroendocrine carcinoma should be given the same opportunity to undergo multiplex somatic mutation testing as patients with non–small cell lung carcinoma.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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