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CASE REPORT

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Successful treatment with atezolizumab combination chemotherapy in a patient with high-grade fetal adenocarcinoma of the lung: A case report

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Abstract

High-grade fetal lung adenocarcinoma (H-FLAC) is a rare tumor, with little known of its response to chemotherapy with or without an immune checkpoint inhibitor or of its molecular profile. We report the first case of a 56-year-old man with stage IV H-FLAC who was successfully treated with carboplatin plus nab-paclitaxel in combination with atezolizumab. In addition, the tumor was found to be positive for amplification of the human epidermal growth factor receptor 2 gene.

KEYWORDS

atezolizumab; case report; high-grade fetal lung adenocarcinoma (H-FLAC); human epidermal growth factor receptor 2 (HER2, ERBB2); immunotherapy

INTRODUCTION

High-grade fetal lung adenocarcinoma (H-FLAC) is a rare tumor that accounts for 0.1–0.4% of all lung cancers.[1] Given its rarity, little is known of the genomic signature of H-FLAC or of its response to chemotherapy regimens. We here report a case of atezolizumab combination chemotherapy in *HER2*-amplified H-FLAC.

Case report

A 56-year-old man with no serious medical history but with a 38-pack-year current smoking history developed dizziness and vomiting 10 days before admission. He was transferred to our hospital because of a high-density area found on the head computed tomography (CT) scan. Contrast-enhanced magnetic resonance imaging (MRI) of the head showed a 45-mm mass in the left cerebellar hemisphere, and thoracoabdominal CT revealed a 14 mm nodule in the right lung segment 6, enlarged mediastinal and right subclavian lymph nodes, and an enlarged left adrenal gland (Figure 1a–c). Serum analysis showed an elevated level of α-fetoprotein (AFP, 1537 ng/ml). Resection of the metastatic brain tumor was performed to control cerebellar ataxia.

Pathological analysis of the surgical specimen of the cerebellar tumor revealed diffuse proliferation of glycogen-rich cylindrical tumor cells with papillary glandular duct structures and transition to a fuller growth with necrosis (Figure 2a). Immunohistochemistry (IHC) showed that the tumor was negative for thyroid transcription factor-1 (TTF-1) and positive for cytokeratin AE1/AE3, glypican-3, caudal-type homeobox-2 (CDX-2), AFP, and Sal-like protein 4 (SALL4) (Figure 2b–g). Given that gastrointestinal

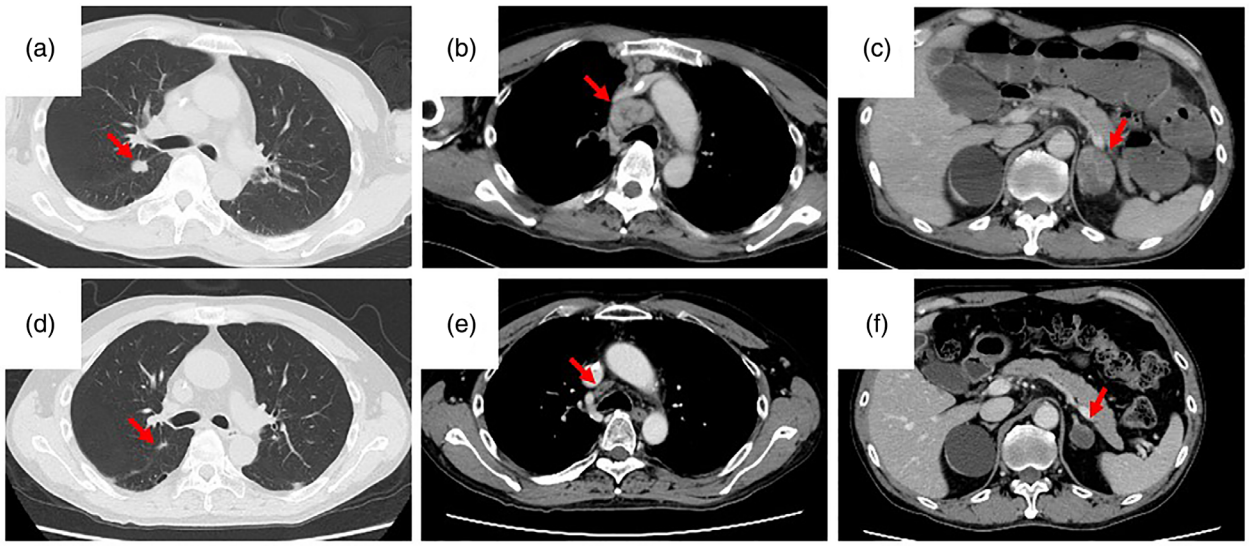

FIGURE 1 Response evaluation for the patient. (a) Baseline chest computed tomography (CT) showing a 14-mm nodule in right S6 (arrow). (b, c) contrast-enhanced CT of the chest (b) and abdomen (c) showing mediastinal lymph node enlargement (arrows) and left adrenal enlargement (arrow). (d–f) Thoracoabdominal CT after four courses of treatment revealed a partial response (48% reduction in the sum of diameters of target lesions). Images correspond to those in (a) through (c)

endoscopy and CT showed no obvious abnormality in the gastrointestinal tract, we diagnosed the patient with the latter condition. A diagnosis of H-FLAC was then made on the basis of morphological features and positivity for AFP and glypican-3. The tumor proportion score (TPS, 22C3) for programmed death-ligand 1 (PD-L1) was <1%, and no gene alteration was identified in the tumor by targeted next-generation sequencing (NGS) with the Oncomine Dx Target Test Multi-CDx System. Given that human epidermal growth factor receptor 2 (HER2) positivity has been described for AFP-producing gastric cancer,[2] and H-FLAC has been suggested to be the counterpart of this malignancy in the lung, we performed HER2 staining. The IHC staining score for HER2 was 2+ (Figure 2h), and we further detected *HER2* amplification in the tumor by fluorescence in situ hybridization (FISH, *HER2*/*CEP17* = 2.8) (Figure 2i).

After recovering from surgery, chemotherapy with carboplatin (area under the curve of 6) plus nab-paclitaxel (100 mg/m^2) combined with atezolizumab (1200 mg/body) was initiated. Radiotherapy was not performed after brain metastases resection since it was fully booked and was not available within a reasonable time.

After four courses of chemo-immunotherapy, RECIST evaluation[3] revealed a partial response (Figure 1d–f, 48% reduction), and the patient was transitioned to atezolizumab monotherapy for consolidation. His serum AFP level decreased gradually during the treatment period (minimum of 6.6 ng/ml). He experienced neutropenia, vomiting, and anorexia, each of grade 3, during the first course of treatment, which occasioned a reduction in the dose of carboplatin and nab-paclitaxel from the second course. All subsequent adverse events were of grade 1 or 2. After 10 courses of the treatment, he experienced primary hypoadrenocorticism and was treated with oral hydrocortisone. The adverse event might be dur to adrenal metastasis or immune checkpoint inhibitor.

We also conducted comprehensive genomic profiling of the tumor with the FoundationOne CDx assay (Table 1). After 10 courses of treatment, a thoracoabdominal CT scan showed progressive disease (37% increase), and the patient was referred to a university hospital for participation in a clinical trial. The treatment was effective overall for 8.0 months. The patient provided informed consent to publication of his case details.

DISCUSSION

H-FLAC is a rare tumor reported to occur almost exclusively in middle-aged male smokers.[4] Some cases of H-FLAC have been reported to be associated with hepatoid adenocarcinoma, choriocarcinoma-like features, or large cell neuroendocrine carcinoma-like differentiation, and they form a closely related clade. These features are highly similar to those of primary AFP-producing tumors of the stomach, and H-FLAC can be considered as a pulmonary counterpart of these tumors.[5]

The molecular profile of FLAC is not well understood, with its target antigens thus remaining to be identified. To our knowledge, there has been no previous report of *HER2* FISH analysis or NGS for H-FLAC. A previous study found that all five cases of H-FLAC examined were negative for HER2 by IHC,[6] but the details of the analysis were not provided. In the present case, HER2 expression was analyzed on the basis of ASCO/CAP guidelines. The patient was found to have a HER2 IHC score of 2+ and *HER2* amplification was confirmed by FISH.

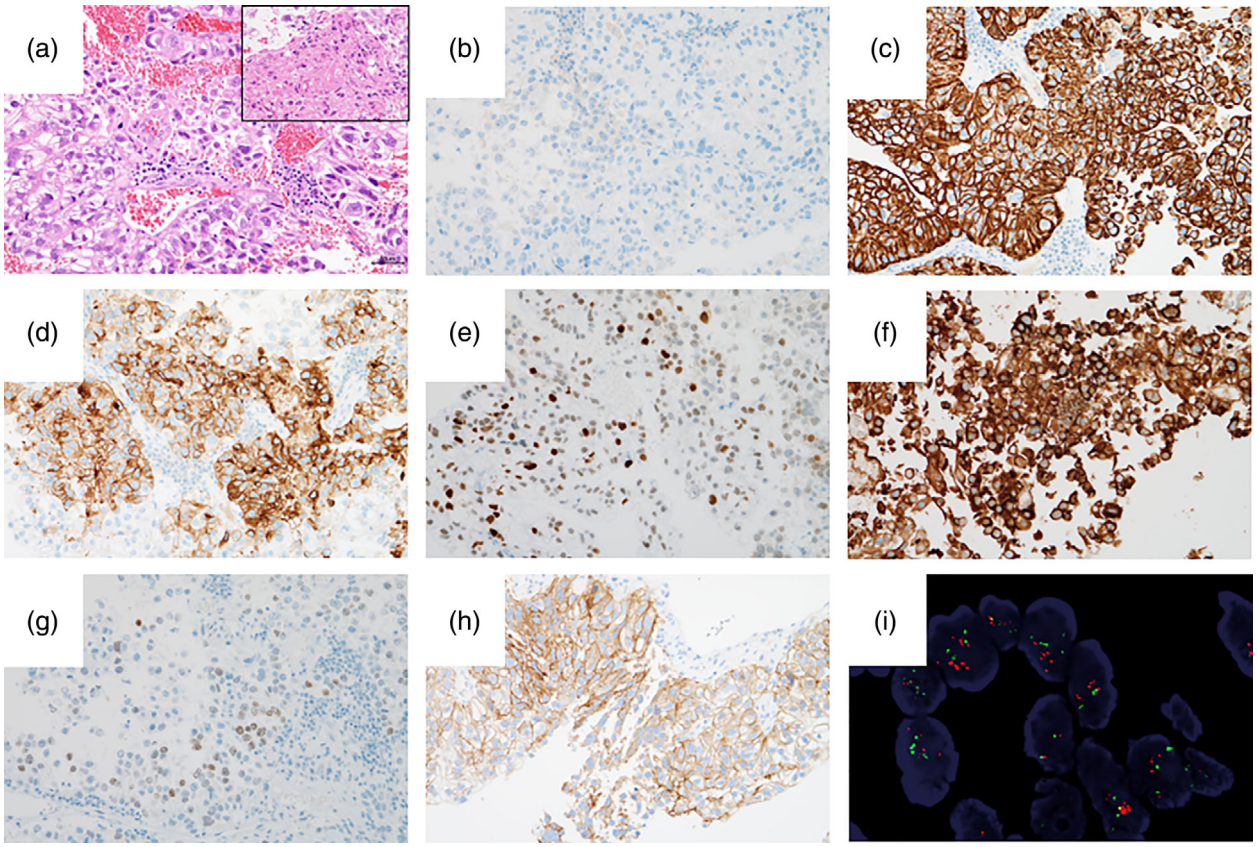

FIGURE 2 Pathological findings for the surgical tumor specimen. (a) Hematoxylin–eosin staining showing diffuse proliferation of glycogen-rich cylindrical tumor cells with papillary glandular duct structures and a transition to a fuller growth with necrosis (inset). (b–h) Immunohistochemistry staining was negative for thyroid transcription factor-1 and positive for cytokeratin AE1/AE3, glypican-3, caudal-type homeobox-2, α-fetoprotein, Sal-like protein 4, and human epidermal growth factor receptor 2 (HER2), respectively. (i) Fluorescence in situ hybridization analysis of the surgical tumor specimen. Amplification of the HER2 gene (*ERBB2*, red) relative to a centromere control (green) was apparent in the tumor cells.

TABLE 1 Results of FoundationOne CDx analysis of the surgical tumor specimen

Microsatellite instability	Stable
Tumor mutation burden	25 mutations/Mb
Genomic findings	*ARAF* amplification, *ASXL1* G646fs*12, *ATRX* R808*, *CDK4* amplification, *ERBB2* amplification, *FGFR1* amplification, *GATA4* G93*, *KRAS* amplification, *MAP3K1* E53*, *NSD3* (*WHSC1L1*) amplification, *TP53* L35fs*9, *ZNF703* amplification Variants of unknown significance: *AKT3* E352Q, *ATRX* E1218D and G175L, *BCL6* D297Y, *CDK12* amplification, *EPHB1* D243_G244 > EL, *FAM46C* H36Y, *FGF19* P191A, *FLT1* rearrangement, *FLT3* W196C, *JAK2* G968D, *KIT* G886C, *LTK* R658P, *MERTK* R775Q, *MET* S794C, *MITF* C12S, *MLL2* L1935V and amplification, *NF2* D567V, *NOTCH1* S1900T, *NTRK2* L788Q, *PIK3C2G* D638Y and amplification, *POLE* Q687H, *PTPRO* R709K, *RAD21* R427T, *SMO* L312M

The efficacy of chemotherapy or immunotherapy for metastatic H-FLAC has not been determined. Two cases of stage IV hepatoid adenocarcinoma of the lung, which is considered to be embryologically similar to FLAC, have suggested that it responds to immune checkpoint inhibitors, despite its low expression level of PD-L1.[7,8] In the present case, although the PD-L1 TPS was <1%, a durable response was achieved after conversion to maintenance with atezolizumab monotherapy, with this response possibly having been due to the high tumor mutational burden (TMB).

In conclusion, this is the first case of H-FLAC found to show a durable response to the combination of carboplatin–nab-paclitaxel and atezolizumab. Genomic profiling, revealing a high-TMB and *HER2* amplification, was also performed for H-FLAC for the first time. Further study is needed to clarify the best treatment strategy for, as well as the molecular profile of, H-FLAC.

AUTHOR CONTRIBUTIONS

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Kana Fujimoto: Investigation, writing—original draft preparation. Satomi Watanabe: Conceptualization, writing—reviews & editing. Yuto Yasuda: Writing—original draft preparation—reviews & editing. Emi

Date: Data curation, writing—reviews & editing. Yasuhiro Kawabata, Hiroaki Kanemura, Takayuki Takahama, and Kimio Yonesaka: Data curation. Norishige Iizuka, Ken-ichi Takahashi, Osamu Kawakami, and Kazuhiko Nakagawa: Supervision.

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CONFLICT OF INTEREST

Satomi Watanabe, Takayuki Takahama, and Kimio Yonesaka received honoraria from Chugai Pharmaceutical Co., Ltd. Kazuhiko Nakagawa received grants and honoraria from Chugai Pharmaceutical Co., Ltd. The other authors declare no conflicts of interest.

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