A 53-year-old female never-smoker presented with back pain and dyspnea. Computed tomography revealed a right upper-lobe mass, mediastinal lymphadenopathy, pericardial effusion, and a thoracic epidural soft-tissue mass. The patient underwent corpectomy of the epidural mass and surgical pathology revealed that this was a keratinizing squamous cell carcinoma (SCC), cytokeratin (CK)5/6+, p63+, thyroid transcription factor 1 (TTF1)− (Fig 1A). Subsequently, the patient underwent a pericardiocentesis, and cytology from the pericardial fluid showed an adenocarcinoma (ADC), CK7+, TTF1+ (Fig 1B). There was insufficient material for molecular testing of ADC, thus the SCC surgical specimen was evaluated for epidermal growth factor receptor (EGFR) mutations, which revealed that the SCC harbored a L858R mutation in exon 21 of the EGFR gene (Fig 2A). Subsequently, the pericardial effusion cytology was also evaluated and demonstrated a very low positive signal for the L858R mutation, but this was below the limit of detection of the assay, given that the sample contained less than 3% neoplastic cells.

The second patient is a 61-year-old female never-smoker who presented with right supraclavicular and hilar masses and a malignant pleural effusion. A core needle biopsy of the supraclavicular mass revealed an SCC (Fig. 1C) and subsequent cytologic evaluation of the pleural fluid revealed an ADC, TTF1+ (Fig 1D). Molecular testing of the supraclavicular SCC and the pleural ADC specimens revealed that these were both positive for an EGFR exon 19 deletion of 15 base pair (Fig 2B). Both patients were initiated on single-agent erlotinib, and imaging studies after 2 months of therapy demonstrated significant tumor response in the pulmonary lesions and in the metastatic sites. After 4 months of therapy, the imaging studies of the first patient demonstrated stable disease whereas the second patient continued to demonstrate further partial response.

DISCUSSION

We present two cases of adenosquamous lung cancer (ADSCC) in never-smokers, which initially presented as pure SCC in the metastatic site. These patients were initially thought to have two synchronous malignancies, given the distinct histologic subtypes at different disease sites. However, molecular profiling revealed that both the ADC and SCC tumor samples harbored the same EGFR mutation, indicating that these likely arose from the same original malignant clone. EGFR mutations occur rarely in SCC with reported frequency of less than 5%,1 thus routine molecular testing is not usually recommended for SCC histology.2 In contrast, several studies have reported the presence of EGFR mutations in ADSCC, especially among never-smokers.3 Other molecular abnormalities, including an ALK rearrangement in ADSCC have been reported.4 ADSCC comprises approximately 1% to 2% of all non–small-cell lung cancers and the current World Health Organization definition of ADSCC requires at least 10% SCC and ADC by light microscopy.5 However, the abovementioned cases demonstrate that ADSCC may present as pure SCC, even in large surgical specimens. One other study has reported the presence of EGFR mutations in SCC specimens that were later found to be ADSCC on further pathologic evaluation,6 which indicates that this is a clinically significant occurrence that warrants attention. This case report demonstrates that a biopsy of SCC in never-smokers should raise the suspicion of an ADSCC and illustrates the importance of molecular testing of non–small-cell lung cancers in never-smokers regardless of the histological subtype to provide the optimal therapy in this patient population.
REFERENCES


