





CASE REPORT

Lung adenocarcinoma coexisting with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia manifesting as multiple pulmonary nodules: A case report

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Abstract

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), a rare condition, is characterized by pathological proliferation of neuroendocrine cells. Some of them are localized to the airway mucosa, and others locally infiltrate to form tumorlets and nodules. Here, we present a patient with lung adenocarcinoma accompanied by DIPNECH, making the latter difficult to distinguish from multiple pulmonary metastases. The patient, a 72-year-old Japanese woman, was diagnosed as having stage IVA lung adenocarcinoma because she had multiple nodules in both lungs. Mutation of epidermal growth factor receptor gene having been found in the primary tumor, treatment with osimertinib was started. This resulted in shrinkage of the primary tumor, but not the multiple pulmonary nodules. To determine whether these lung nodules were indeed lung metastases, we performed right upper lobectomy with lymphadenectomy and wedge resection of the right lower lobe. On pathological examination, the primary tumor was diagnosed as invasive adenocarcinoma, whereas the multiple pulmonary nodules were diagnosed as DIPNECH manifesting as tumorlets. Therefore, the final diagnosis was stage IA1 lung adenocarcinoma accompanied by DIPNECH. The patient had no recurrences 1 year after the operation without any additional treatment. This is a rare case of lung adenocarcinoma accompanied by DIPNECH presenting as multiple pulmonary nodules. DIPNECH should be included in the differential diagnosis of multiple pulmonary nodules.

KEYWORDS

diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, epidermal growth factor receptor, lung adenocarcinoma, tyrosine kinase inhibitor

INTRODUCTION

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), a rare condition, is characterized by pathological proliferation of neuroendocrine cells.^{1,2} Some of them are localized to the airway mucosa, and others locally infiltrate to form tumorlets and nodules. Here, we present a patient with lung adenocarcinoma accompanied by DIPNECH, making the latter difficult to distinguish from multiple pulmonary metastases.

Case report

A 72-year-old Japanese woman who had never smoked was diagnosed with lung adenocarcinoma in 2019. Computed tomography (CT) showed a tumor in the right upper lobe and multiple nodules in both lungs. She was diagnosed as having stage IVA lung adenocarcinoma (Figure 1). Mutation of epidermal growth factor receptor gene (exon 19 deletion) having been found in the tumor cells, treatment was started with osimertinib (80 mg/d).

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FIGURE 1 Radiological images at the time of initial diagnosis. (a) There is a solid 3.8 cm-diameter nodule in the right upper lobe. (b)–(d) The multiple nodules in both lungs (arrow heads) were diagnosed as pulmonary metastases

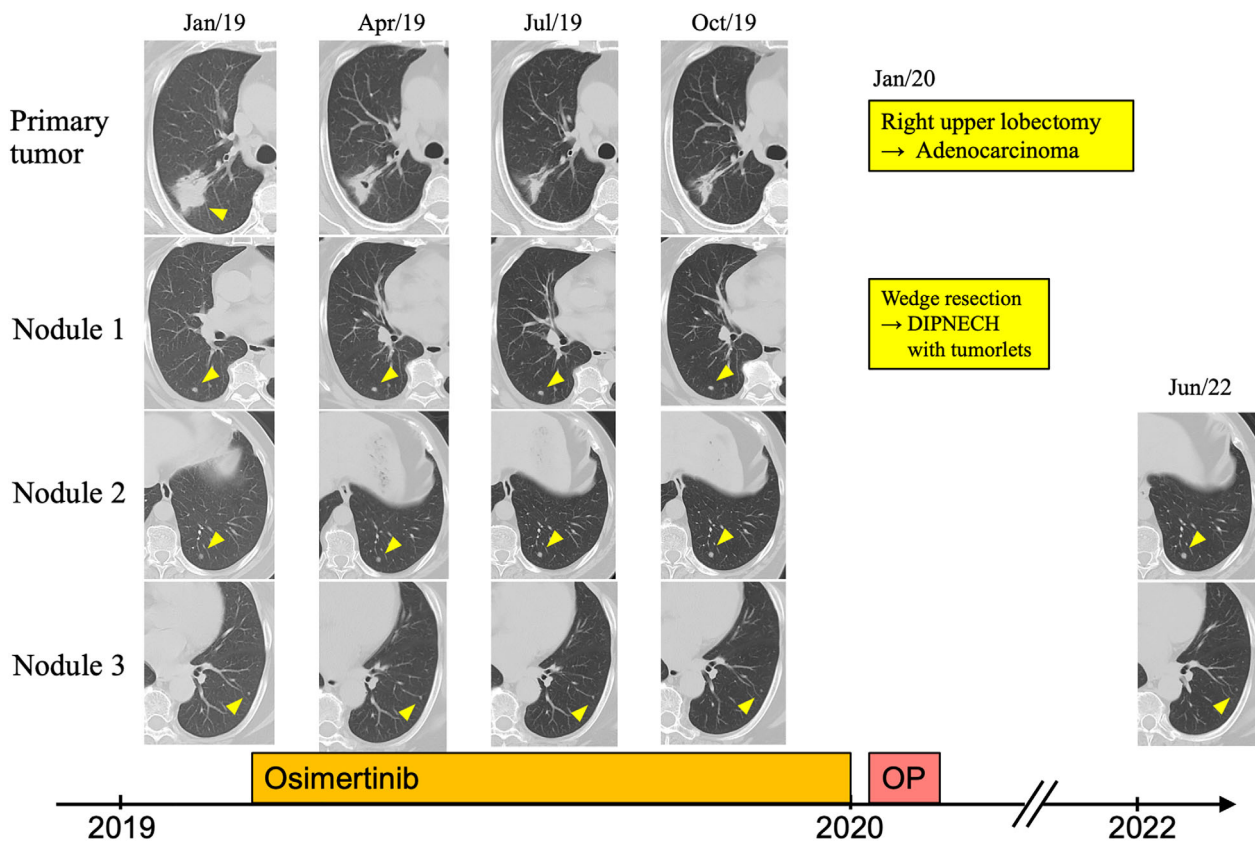
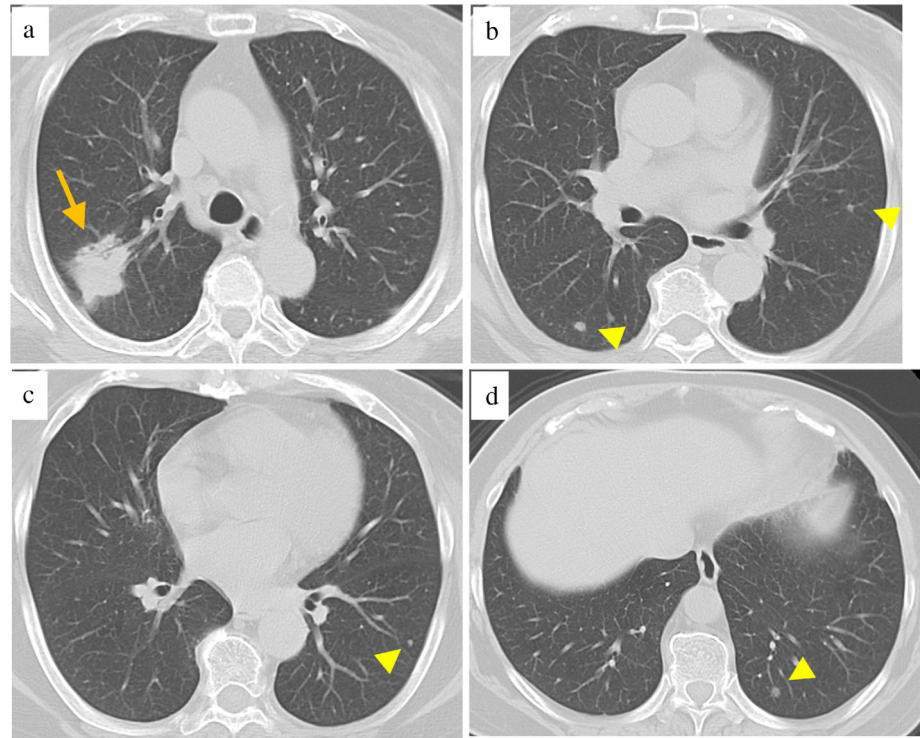


FIGURE 2 Patient's clinical course. After a diagnosis of clinical stage IVA lung adenocarcinoma, the patient was treated by osimertinib. The primary tumor shrank after administration of osimertinib, whereas the multiple pulmonary nodules did not change. Therefore, we performed surgical resection of the primary tumor and wedge resection of some of small nodules. The patient was followed up without any additional treatment after the multiple nodules were diagnosed of DIPNECH. The patient has had no recurrences 1 year after the operation with no additional treatment. DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia.

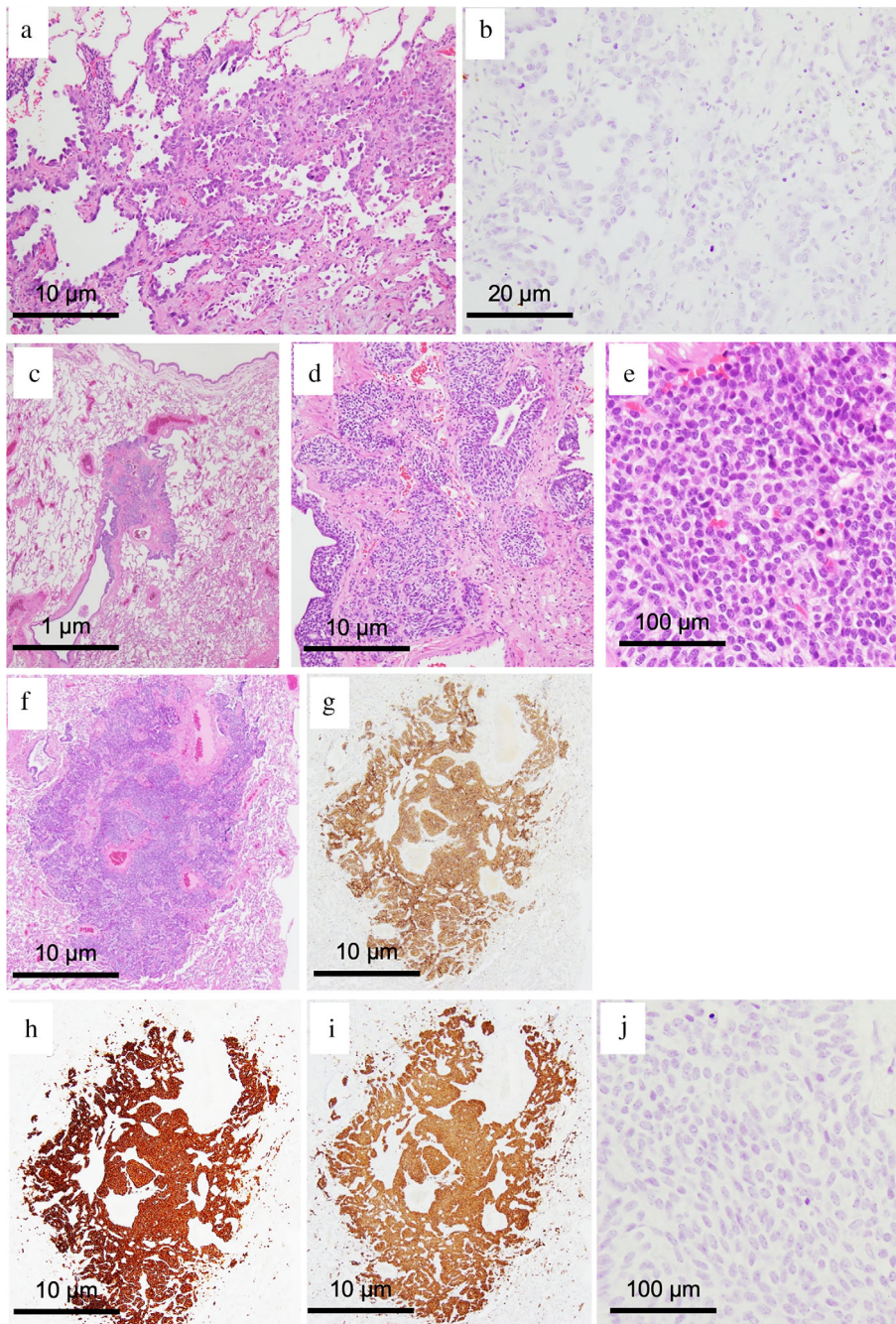


FIGURE 3 Pathology of resected tumors. (a) The primary tumor was diagnosed as invasive adenocarcinoma (papillary 70%, lepidic 30%) without lymph node metastasis, pT1aN0M0, stage IA1. (b) The primary tumor was negative for ACTH. (c)–(e) The nodule in the right lower lobe comprises cells with fine granular chromatin proliferating in the bronchiolar epithelium. (f)–(i) the nodules were strongly positive for the neuroendocrine marker of CD56 (g), synaptophysin (h) and chromogranin (i). All nodules being 3 mm or less in diameter, DIPNECH with multiple tumorlets was diagnosed. (j) DIPNECH tumors were negative for ACTH. DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia.

This resulted in shrinkage of the primary tumor, but not the multiple pulmonary nodules (Figure 2). Suspecting that the multiple lung nodules were not lung metastases, we performed right upper lobectomy with lymphadenectomy and wedge resection of the right lower lobe to establish a definitive diagnosis. On pathological examination, the primary tumor was diagnosed as invasive adenocarcinoma (papillary 70%, lepidic 30%) without lymph node metastasis according to the Union for International Cancer Control criteria (version 8) (Figure 3A). Moreover, the multiple nodules in the right upper and lower lobe consisted of small round cells with eosinophilic cytoplasm and round nuclei with fine

granular chromatin, proliferating in bronchiolar mucosa (Figure 3(c)–(f)). These cells were strongly positive for neuroendocrine marker CD56, synaptophysin, and chromogranin, and all nodules were 3 mm or less in diameter (Figure 3(g)–(i)). Accordingly, she was diagnosed as having DIPNECH manifesting as tumorlets. Therefore, the final diagnosis was stage IA1 lung adenocarcinoma accompanied by DIPNECH. Both primary lung adenocarcinoma and DIPNECH tumors were negative for adrenocorticotropic hormone (ACTH) (Figure 3(b) and (j)). The patient has had no recurrences 1 year after the operation with no additional treatment.

DISCUSSION

DIPNECH belongs to a spectrum of conditions characterized by pulmonary neuroendocrine hyperplasia. These include neuroendocrine cell proliferation, neuroendocrine tumorlets, and pulmonary carcinoid tumors.^{1,3} To the best of our knowledge, there are few published reports concerning differentiating DIPNECH manifesting as multiple pulmonary nodules from multiple pulmonary metastases (Table).^{2,4} Whenever a patient has lung cancer with multiple pulmonary nodules, DIPNECH should be included in the differential diagnosis.⁴ Reported features of DIPNECH are as follows: (1) most affected patients are women in their 50s to 70s; (2) 70% of affected patients have never smoked; (3) chronic cough is a characteristic symptom; (4) the condition is characteristically accompanied by obstructive pulmonary disease; (5) high serum concentrations of progastrin-releasing peptide; and (6) multiple pulmonary nodules of diameter 5 mm or less located around the lower lung field or bronchi.^{3,5} The current patient demonstrated all of these features except for obstructive respiratory disorder, and the past reported patients in Table seem to have some of those features. Therefore, in patients who are suspected of having pulmonary metastases on the basis of CT findings, but whose lesions have not changed substantially over time, as was the case with the present patient, DIPNECH should be considered and material obtained for histopathological examination. Regarding DIPNECH-related immunophenotype and paraneoplastic syndrome, there is a paper presenting DIPNECH as an unusual cause of cyclical ectopic ACTH syndrome.⁶ We additionally performed immunohistochemical staining of ACTH for both primary lung adenocarcinoma and DIPNECH tumors, whereas neither were negative. The current patient was asymptomatic except cough and sputum, so we did not perform further examination for other paraneoplastic syndromes.

In conclusion, we present a rare case of a patient with lung adenocarcinoma accompanied by DIPNECH presenting as multiple pulmonary nodules. DIPNECH should be included in the differential diagnosis of multiple pulmonary nodules.

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DISCLOSURE

The authors have no conflicts of interest.

INFORMED CONSENT

The patient has given written consent to publication of details of her case.

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