

A Case of Metastatic Submandibular Salivary Duct Carcinoma that Completely Responded to Pembrolizumab Monotherapy

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Salivary gland carcinoma is a rare cancer and has more than 20 histopathological types. Although chemotherapy has been the mainstay of treatment for unresectable carcinomas such as multiple recurrence and distant metastasis, no standard regimen is available. In this article, we report a case of poorly differentiated salivary duct carcinoma of the submandibular gland with distant metastases that was successfully treated with pembrolizumab monotherapy. A 66-year-old man became aware of a left submandibular mass 2 months before his first visit to our department. A needle biopsy at a previous hospital revealed carcinoma, not otherwise specified. The combined positive score on a programmed death ligand-1 immunohistochemistry test was 1-10%. The patient was referred to our department for further treatment. Computed tomography revealed left level II and IV neck lymphadenopathy, bilateral lung shadowing, and osteolytic changes in the 12th thoracic vertebra. Needle biopsy showed poorly differentiated carcinoma, positive human epidermal growth factor receptor 2, and positive androgen receptor, which suggested salivary duct carcinoma. These findings indicated a diagnosis of submandibular carcinoma T4aN2bM1 stage IVC. Pembrolizumab monotherapy was started, and tumor shrinkage was observed after three courses of treatment. At 1 year, complete response was achieved without adverse events, and treatment is ongoing. Despite a lack of evidence for the efficacy of immune checkpoint inhibitors in salivary gland carcinoma, the present case suggests that some patients might respond to this treatment. Hence, clinical trials are warranted. (*J Nippon Med Sch* 2023; 90: 356–362)

Key words: salivary gland cancer, pembrolizumab, immune checkpoint inhibitor, distant metastasis

Introduction

Salivary gland carcinoma (SGC) is a rare cancer (age-adjusted incidence rate: 12/1,000,000 person-years)¹. There are over 20 types of SGC, with varying grades and clinical characteristics. Among the major SGCs, the most frequent histopathological subtypes are, in descending order, mucoepidermoid carcinoma, acinic cell carcinoma, adenocarcinoma, adenoid cystic carcinoma, and carcinoma ex pleomorphic adenoma². Regarding treatment, radiation sensitivity is generally low, and if the lesion is resectable, surgery with or without postoperative irradiation has been the basic treatment³. However, chemotherapy remains the treatment mainstay for unresectable

SGCs such as postoperative recurrence and distant metastasis, although no regimen has achieved consensus. Previous studies of chemotherapy have investigated cisplatin/doxorubicin/cyclophosphamide (CAP) therapy for cytotoxic anticancer agents; the response rate (RR: complete + partial response) was 27%⁴. Some recent reports suggest that trastuzumab/docetaxel therapy is effective for positive human epidermal growth factor receptor 2 (HER2) carcinoma and that anti-androgen therapy could be effective for positive androgen receptor (AR) carcinoma; both can be expected to be effective for some carcinomas^{5,6}. Immune checkpoint inhibitors (ICI), which were developed more recently, are expected to be effective

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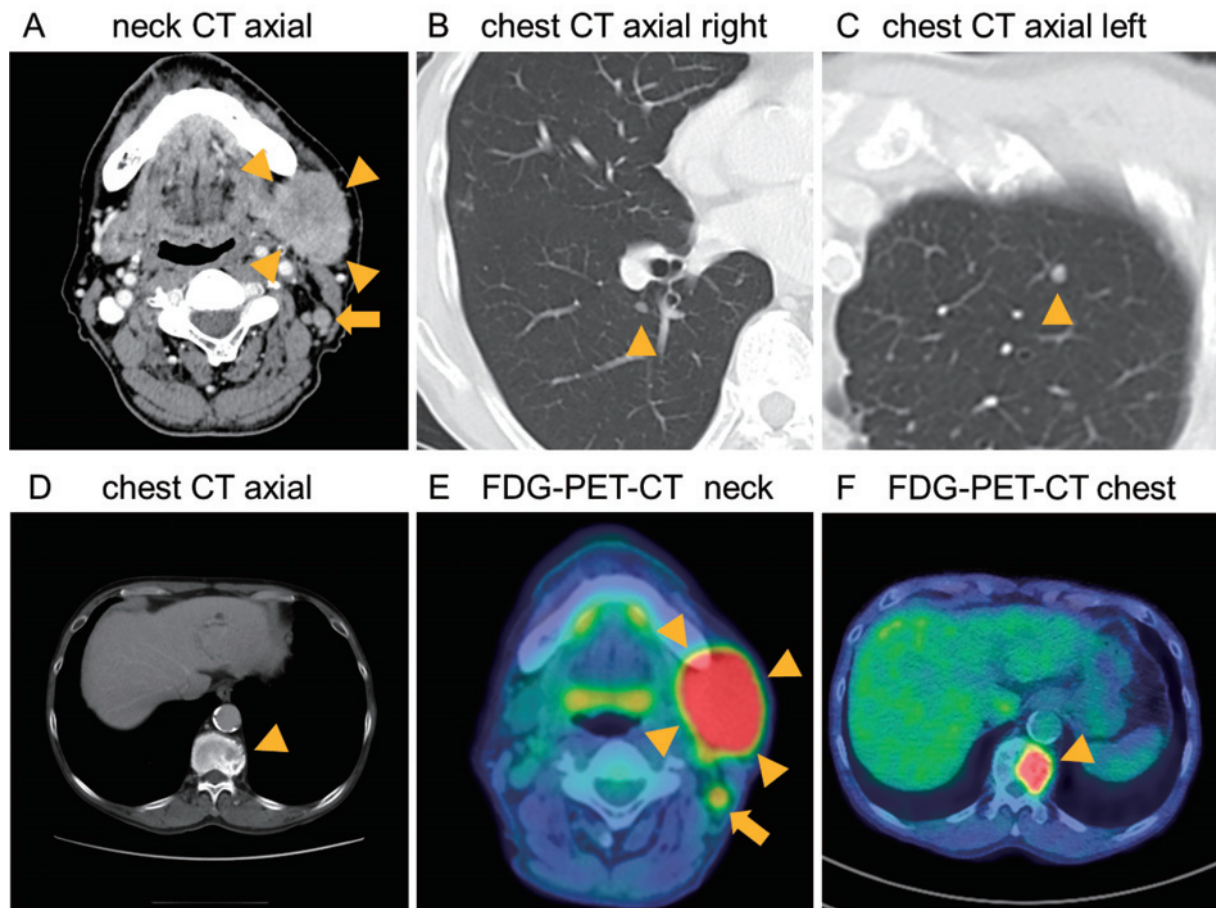


Fig. 1 Imaging findings before treatment

- A: Neck computed tomography (CT) showed a 7-cm neoplastic lesion replacing the left submandibular gland (arrowheads) and left level II lymphadenopathy (arrow).
 B: Chest CT showed a right lung nodule (arrowhead).
 C: Chest CT showed a left lung nodule (arrowhead).
 D: Chest CT showed a mixed osteolytic and osteoblastic bone lesion in the 12th thoracic vertebra.
 E: ^{18}F -deoxy-2-D-glucose positron emission tomography-CT (FDG-PET-CT) showed marked accumulation in the left submandibular gland tumor (arrowhead) and the left neck lymph node (arrow).
 F: FDG-PET-CT showed marked accumulation in the 12th thoracic vertebra (arrowhead).

tive regardless of carcinoma type, unlike conventional anticancer agents. However, the efficacy of ICIs for SGC has not been thoroughly investigated, and much remains unclear. Here, we report a case of poorly differentiated salivary duct carcinoma (SDC) of the submandibular gland with distant metastasis in which a complete response (CR) was achieved with pembrolizumab monotherapy.

Case Report

The patient was a 66-year-old man who became aware of a left submandibular mass 2 months before his first visit to our department. He visited his previous doctor, and fine-needle aspiration cytology revealed malignant findings. A needle biopsy of the submandibular gland tumor indicated carcinoma, not otherwise specified, and the

combined positive score (CPS) on programmed death ligand-1 (PD-L1) immunostaining was 1-10%. He was referred to our department with a diagnosis of left submandibular gland carcinoma. His medical history included hypertension, angina pectoris (after stent insertion), and spontaneous pneumothorax. He had smoked 30 cigarettes a day for 20 years until age 46 years. Physical examination revealed an elastic, hard mass with poor mobility in the left submandibular region and paralysis of the mandibular branch of the left facial nerve. Neck and chest computed tomography (CT) showed a 7-cm neoplastic lesion replacing the left submandibular gland, left level II and IV lymphadenopathies (Fig. 1A), bilateral lung nodules (Fig. 1B, C), and a mixed osteolytic and osteoblastic bone lesion in the 12th thoracic vertebra (Fig. 1D). ^{18}F -deoxy-2-D-glucose positron emission tomography-

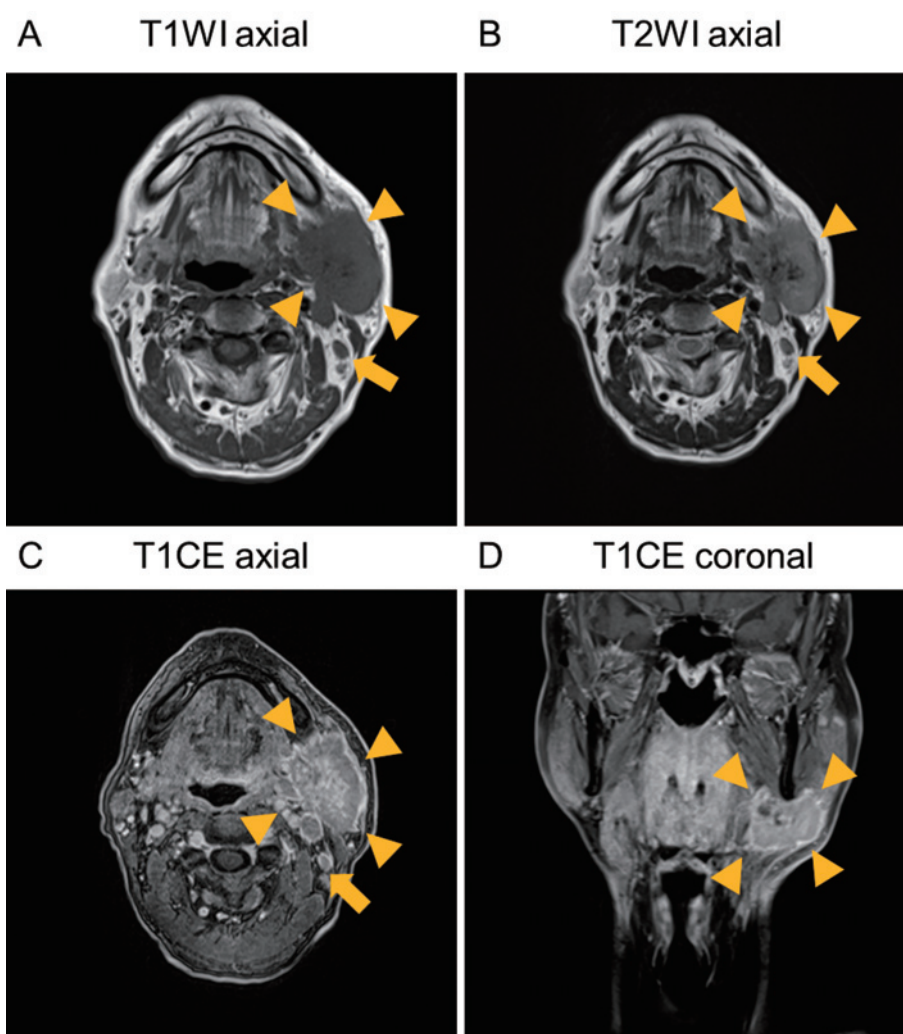


Fig. 2 Magnetic resonance imaging (MRI) findings before treatment

- A: Neck MRI showed a submandibular gland tumor with low intensity on T1-weighted images.
 B: The tumor showed medium intensity on T2-weighted images.
 C: The tumor showed strong contrast on gadolinium contrast imaging.
 D: Coronal view of the tumor.

CT (FDG-PET-CT) showed marked accumulation in the left submandibular gland tumor (maximum standardized uptake value [SUVmax]: 14.28), left neck lymph nodes (SUVmax: 6.82), and thoracic spine (SUVmax: 9.21) (Fig. 1E, F), suggesting involvement of the neck lymph nodes and distant metastasis of submandibular gland carcinoma. Neck magnetic resonance imaging (MRI) showed a submandibular gland tumor with low intensity on T1-weighted images (Fig. 2A), isointensity on T2-weighted images (Fig. 2B), and strong contrast on gadolinium contrast imaging (Fig. 2C, D). Histopathological findings for a needle biopsy specimen of the left submandibular gland tumor showed a solitary to sheet-like tumor composed of atypical cells with round or distorted nuclei and acidophilic cytoplasm and a background of reactive

stroma. It was difficult to identify any specific differentiation (Fig. 3A). Immunohistochemical findings revealed positivity for HER2 (Fig. 3B) and AR (Fig. 3C), and poorly differentiated SDC was diagnosed. The Ki-67 index was 20-30% (Fig. 3D). In sum the findings were consistent with a diagnosis of submandibular gland carcinoma T4aN2bM1, stage IVC. Surgery and radiation therapy for bone metastases were not indicated. In the absence of an established chemotherapy regimen at that time, the patient requested outpatient treatment and was started on pembrolizumab monotherapy (pembrolizumab 200 mg/body administered every 3 weeks); blood testing and chest radiography were performed every 3 weeks to assess adverse events. The primary lesion started to shrink after the third treatment course, which was con-

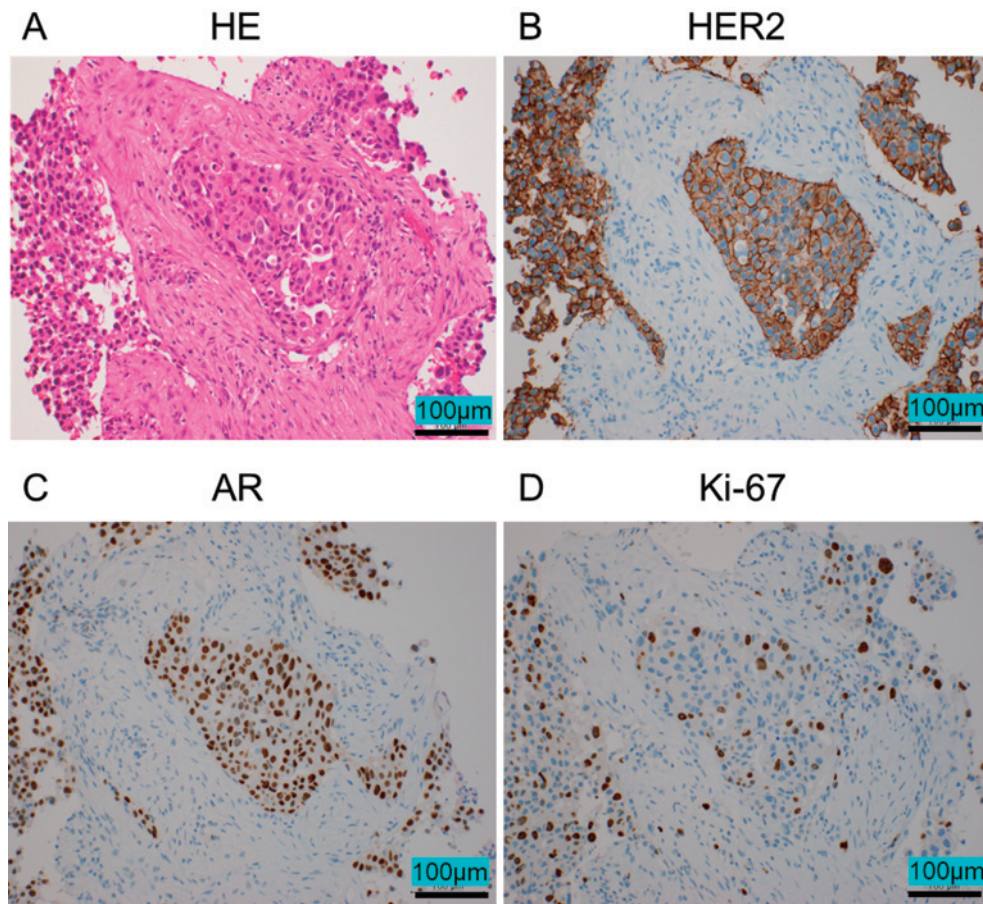


Fig. 3 Histopathological findings of a needle biopsy specimen

- A: The tumor had a solitary to sheet-like appearance and comprised atypical cells with round or distorted nuclei and acidophilic cytoplasm against a background of reactive stroma, which made it difficult to identify specific differentiation.
- B: Immunohistochemical findings revealed human epidermal growth factor receptor 2 (HER-2) positivity.
- C: Immunohistochemical findings revealed androgen receptor (AR) positivity.
- D: The Ki-67 index of the tumor was 20-30%.

firmed on CT 3 months after starting treatment (Fig. 4). The neoplastic lesion disappeared on CT (Fig. 5A, B, C) and MRI 1 year after the start of treatment. The 12th thoracic vertebral metastasis was classified as CR on the MD Anderson classification^{7,8}, because all osteolytic areas were calcified (Fig. 5D). Furthermore, PET-CT showed no obvious accumulation (Fig. 5E, F). We thus concluded that CR had been achieved. Additionally, no adverse events, such as immune-related adverse events, were observed during treatment. Treatment is ongoing at this writing, 17 months after the start of treatment.

This case report was prepared in accordance with ethical guidelines for clinical research and was approved by the institutional review board of Nippon Medical school (reference number: B-2019-080). Informed consent to use the photographs for publication in the article was provided by the patient.

Discussion

The present patient with metastatic SDC of the submandibular gland achieved a CR after treatment with pembrolizumab alone. To our knowledge, this is the first report of a CR after initial treatment with pembrolizumab alone for SDC. With a reported 5-year survival rate of 35% and median survival of 13 months among patients with distant metastasis, SDC remains one of the most aggressive malignant tumors among SGCs⁹. However, an increasing number of reports have described successful chemotherapy with trastuzumab/docetaxel for HER2-positive tumors and combined androgen blockage (CAB) therapy for AR-positive tumors. Trastuzumab/docetaxel therapy, a well-established regimen for ductal carcinoma of the mammary gland, has been adapted for SDC because the histological characteristics of SDC are similar to those of mammary gland ductal carcinoma and HER2-

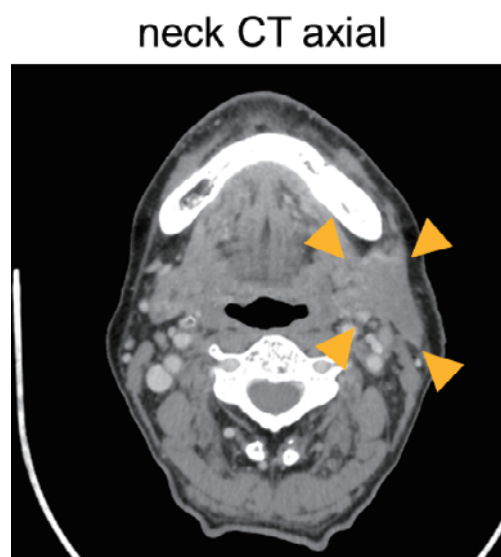


Fig. 4 CT image at 3 months of pembrolizumab monotherapy
Neck CT showed shrinkage of the primary lesion.

positive cases, which are quite common. One study showed that the RR of this therapy for HER-2 positive SDC was 70.2%, indicating that it is a promising treatment⁵. In a study of CAB therapy for AR-positive SGC patients (including 34 SDC patients among a total of 38 patients), Fushimi et al. reported an RR of 41.7%, which suggests that it, too, is a promising treatment for AR-positive SGCs⁶. Because the present patient was HER2-positive and AR-positive, there was a possibility that this treatment would be successful. Although these treatments were not covered by Japanese national health insurance at the start of treatment, trastuzumab/docetaxel therapy for HER2-positive SGC is now covered. Therefore, we are considering using this regimen if the present cancer progresses. ICIs useful for head and neck cancer include nivolumab for recurrent metastatic CDDP-refractory disease and pembrolizumab. However, these regimens are used mainly for squamous cell carcinomas because their effectiveness for other cancers, including SGC, has not been demonstrated. Regarding the usefulness of nivolumab in SGC, a retrospective study of 24 patients (including 20 with SDCs) reported an RR of 4.2%¹⁰. Moreover, Sato et al. reported a case of submandibular gland SDC with distant metastasis in which nivolumab monotherapy promoted CR for residual disease after radiation¹¹. Regarding pembrolizumab for head and neck carcinoma, one study recommended combination therapy with CDDP + 5-FU for patients with a CPS <1% and combination therapy or monotherapy for pa-

tients with CPS $\geq 1\%$ ¹². Regarding the efficacy of pembrolizumab in SGC, the KEYNOTE-028 study of 26 patients with PD-L1-positive salivary gland cancer (including 1 with SDC) reported that treatment with pembrolizumab alone promoted an RR for 12%¹³. Furthermore, a phase II trial reported an RR of 16% for 25 patients with recurrent/metastatic SGC (none with SDC) treated with pembrolizumab and vorinostat¹⁴. Harwood et al. reported that, after several systemic treatments, a patient with SDC of the parotid gland that was treated with pembrolizumab monotherapy for 2 years maintained a good response (nearly CR) and stable disease 1 year after discontinuation¹⁵. Most importantly, only a few studies have investigated the efficacy of ICIs, especially pembrolizumab, for SDC. Similar to our patient, other patients may respond to ICIs. Thus, future studies should attempt to identify predictors of response to ICI therapy.

Conclusion

Despite limited evidence for the efficacy of ICIs in SGC, such treatment might be effective for some patients, as it was for our patient, indicating the need to accumulate evidence from clinical trials. Furthermore, because ICI treatment can be administered on an outpatient basis and results in few adverse events, it might help maintain patient quality of life.

Author Contributions: MN, KS, and AS contributed to patient diagnosis and treatment. MN and KS prepared the draft of the paper and KS is responsible for writing the paper. MT is responsible for the pathological findings. MN, KS, AS, TM, and KO collected the findings and drafted the manuscript. All authors revised the paper, approved the final manuscript, and consented for publication.

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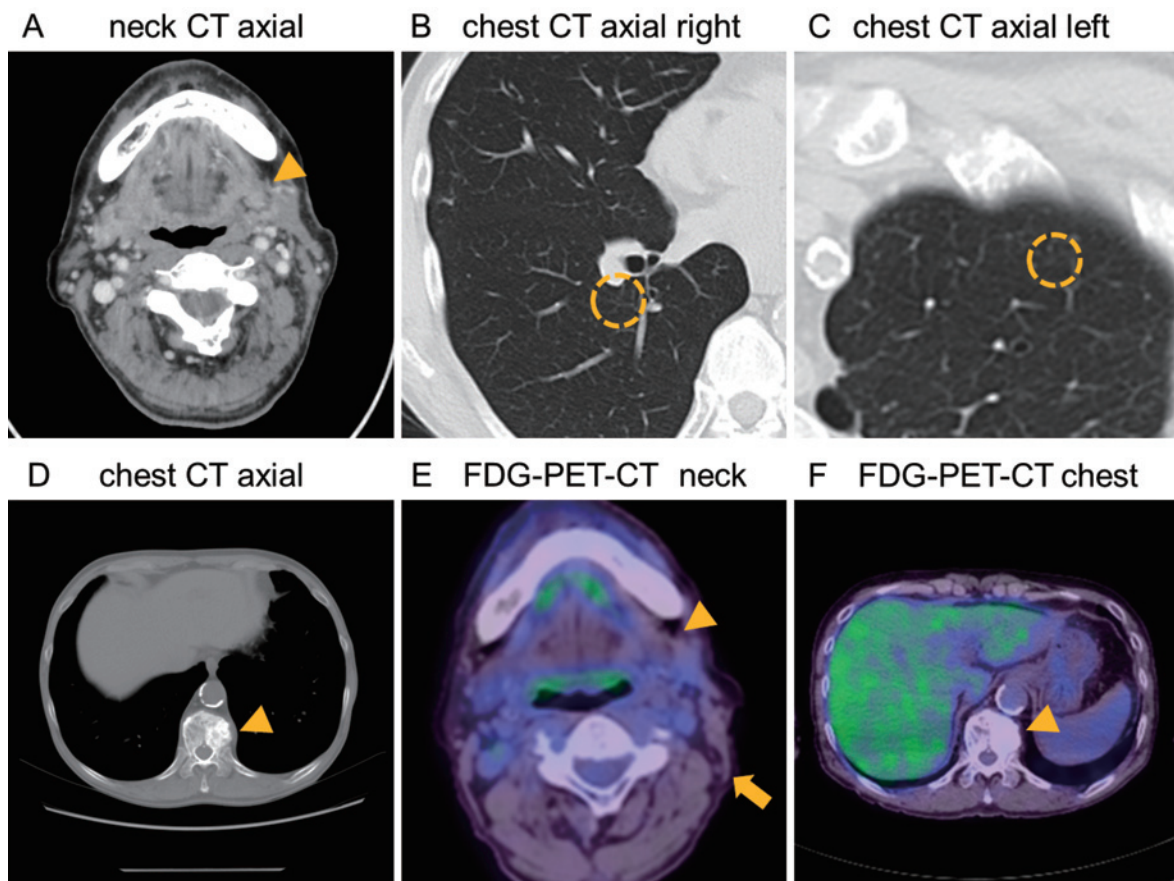


Fig. 5 Imaging study after 1 year of pembrolizumab monotherapy

- A: Neck computed tomography (CT) showed no neoplastic lesion in the left submandibular region or lymph node.
 B: Chest CT showed disappearance of the right lung nodule.
 C: Chest CT showed disappearance of the left lung nodule.
 D: Chest CT showed a bone lesion in the 12th thoracic vertebra, which was classified as CR on the MD Anderson classification because all osteolytic areas were calcified (arrowhead).
 E: ¹⁸F-deoxy-2-D-glucose positron emission tomography-CT (FDG-PET-CT) showed no obvious accumulation in the left submandibular gland and neck lymph node.
 F: FDG-PET-CT showed no obvious accumulation in the 12th thoracic vertebra (arrowhead).

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