Long-term treatment efficacy in a rapid growth malignant undifferentiated lung tumor

Účinnost dlouhodobé léčby u rychle rostoucího maligního nediferencovaného nádoru plic

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Summary

Background: Treatment of patients with malignant undifferentiated lung tumors who also have diffuse lung disease is difficult, especially when the tumor grows rapidly. Herein we present a malignant undifferentiated tumor of the lung with rapid growth. ***Case:*** A 57-year-old man was diagnosed with chronic obstructive pulmonary disease and was receiving inhalation of long-acting muscarinic antagonist / long-acting beta2 agonist. At the age of 65, dyspnea became worse and he had hemoptysis. A chest radiograph revealed an 11 × 9 mm nodule in the right upper lung field. This nodule grew to 89 × 60 mm and 102 × 68 mm on radiographs taken 63 and 79 days after the date of the first radiograph. The volume doubling times were 7 and 23 days, respectively, and it was a rapidly growing, highly malignant tumor. The tissue specimens obtained by percutaneous biopsy from this lesion was pathologically diagnosed as malignant undifferentiated tumor of the lung. Chemotherapy including immune checkpoint inhibitors was effective. Although the patient still has cancer, he is constantly undergoing treatment 2.5 years after its initiation. ***Conclusion:*** It is interesting to note that the course of the rapidly growing lung tumor and the effectiveness of chemotherapy including immune checkpoint inhibitors in patients with such a rapid growth. We believe that information about the clinical course of this patient may provide insight into the treatment of future patients who may have a similar clinical course.

Key words

malignant – undifferentiated tumor – lung – rapid growth – immune checkpoint inhibitor – long-term efficacy

Souhrn

Východiska: Léčba pacientů s maligními nediferencovanými nádory plic, kteří trpí také difuzním onemocněním plic, je obtížná, zejména pokud nádor roste rychle. V tomto článku představujeme případ maligního nediferencovaného nádoru plic s rychlým růstem. ***Případ:*** U 57letého muže byla diagnostikována chronická obstrukční plicní nemoc a pacient byl léčen inhalací dlouhodobě působícího muskarinového antagonisty / dlouhodobě působícího beta2 agonisty. Ve věku 65 let se zhoršila dušnost a objevila se hemoptýza. Rentgen hrudníku odhalil v pravém horním plicním poli nodulus o velikosti 11 × 9 mm. Tento útvar zvětšil svou velikost na 89 × 60 mm a 102 × 68 mm na rentgenových snímcích pořízených 63 a 79 dní po prvním snímku. Doba zdvojnásobení objemu byla 7 a 23 dní, jednalo se o rychle rostoucí, vysoce maligní nádor. Tkáňové vzorky získané perkutánní biopsií z této léze byly patologicky diagnostikovány jako maligní nediferencovaný nádor plic. Chemoterapie s inhibitory imunitních kontrolních bodů byla účinná. Pacient má sice stále rakovinu, ale stále je v léčbě, a to 2,5 roku od jejího zahájení. ***Závěr:*** Je zajímavé sledovat průběh rychle rostoucího nádoru plic a účinnost chemoterapie s inhibitory imunitních kontrolních bodů u pacientů s tak rychlým růstem nádoru. Domníváme se, že informace o klinickém průběhu tohoto pacienta mohou poskytnout poznatky pro léčbu budoucích pacientů, kteří mohou mít podobný klinický průběh.

Klíčová slova

maligní – nediferencovaný nádor – plíce – rychlý růst – inhibitor imunitního kontrolního bodu – dlouhodobá účinnost

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Introduction

The volume doubling time (VDT) for solid tumors is calculated using the Schwartz formula, assuming a spherical shape and constant growth over time [1]. The VDT of non-small cell lung cancer (NSCLC) is reported to be approximately 100–400 days, depending on the histological type [2–4]. However, there were NSCLC patients whose VDT with few days to few weeks [5,6]. They were poorly differentiated lung cancers such as large cell carcinoma [5] and undifferentiated carcinoma [6]. Among the tumors occurring within the thorax, in addition, there were sarcoma patients whose VDT increased within a few weeks [7–9]. Even if the opacity is a solid nodule, if rapid growth is observed, it is necessary to differentiate between infectious diseases in addition to neoplastic diseases [10,11]. Therefore, when diagnosing rapidly growing intrathoracic lesions, it is necessary to include not only neoplastic diseases but also infectious diseases in the differential diagnosis.

We recently encountered a patient with a malignant undifferentiated lung tumor who had a very short VDT. In this patient, a small nodule was detected incidentally on a chest radiograph during the clinical course of chronic obstructive pulmonary disease (COPD). Then, a follow-up chest radiograph taken 2 months later revealed rapid enlargement of the nodule. Because the tumor was growing so rapidly, infectious diseases were initially suspected, but a biopsy revealed that the lesion was a neoplastic disease. The tumor was a rapidly growing, undifferentiated tumor, which raised concerns about the efficacy of treatment. However, the tumor responded well to combination treatment with immune checkpoint inhibitors (ICIs) and cytotoxic antitumor drugs. This patient has survived for more than two years since the initiation of the treatment. We do believe that information about this patient's medical history, disease progression, and treatment course might have implications for the treatment of future patients with a similar clinical course.

Case report

A 57-year-old man presented to our hospital complaining of increasing shortness of breath. He had been a smoker of 60 cigarettes per day until the age of 55. He was diagnosed with COPD and was receiving inhalation of long-acting muscarinic antagonist/long-acting beta2 agonist. At the age of 65, dyspnea became worse and he had hemoptysis. A chest radiograph revealed a nodule measuring 11 mm in diameter in the right upper lung field (Fig. 1A). A chest CT scan taken 8 months before this radiograph showed a significant emphysema in both lungs and a pulmonary cyst in the right upper lobe, but no nodule was identified in the right upper lobe (Fig. 2A). Considering the presence of significant emphysema in both lungs, as well as the difficulty of obtaining tissue samples due to the small nodules in the upper lobe, it was decided to follow up with images. The CT scan taken 2 months later revealed a mass measuring 89 × 60 mm in the upper right lobe that was presumably arising from the cyst wall (Fig. 1B, 2B). The patient was admitted for percutaneous biopsy. A physical examination was unremarkable, and his performance status (PS) was 1. Laboratory data showed a white cell count of 9.8×10^9/L with 76.7% neutrophils and a C-reactive protein level of 0.94 mg/dL. Evaluating the specimens obtained percutaneous biopsy, the mass was diagnosed as a malignant undifferentiated tumor. All interrogable driver genes were negative, and programmed death-ligand 1 (PD-L1) expression had a tumor proportion score (TPS) 1–24%. A positron emission tomography scan confirmed no regional lymph node or distant metastasis, and the tumor was classified as T4N0M0, stage IIIA. The nodule grew to 102 × 68 mm 11 weeks after it was discovered (Fig. 1C, 2C). Fluorodeoxyglucose-positron emission tomography / computed tomography (FDG-PET/CT) showed significant uptake of FDG in most part of the mass (Fig. 2D).

The tumor had grown rapidly, was large, and pathologically determined to be poorly differentiated. Radiation ther-

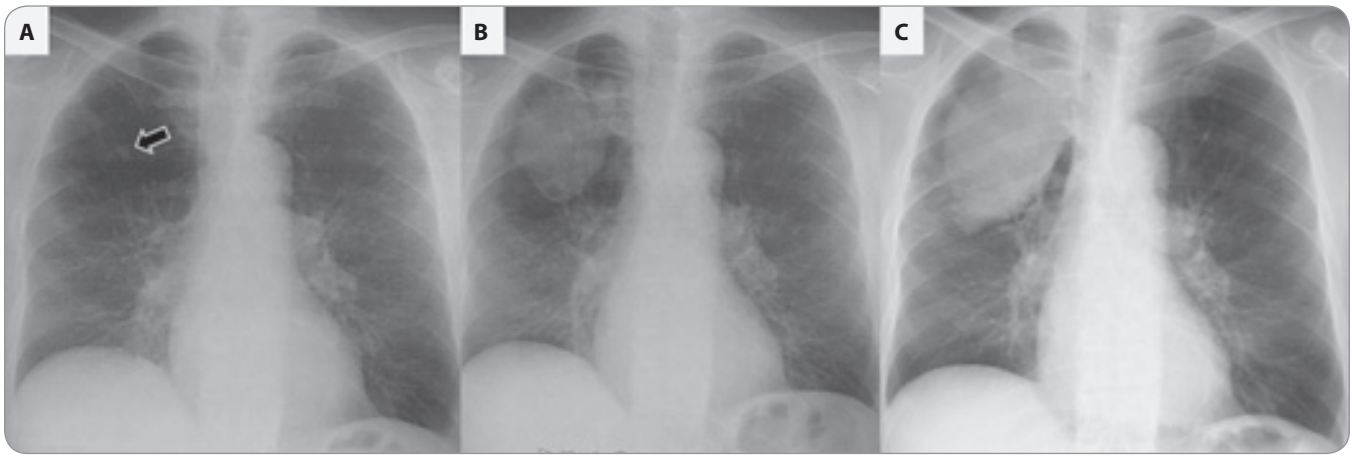

Fig. 1. A chest radiograph taken when shortness of breath increased and bloody sputum appeared showed an 11 × 9 mm nodule in the right upper lung field (A). The nodule grew to 89 × 60 mm 9 weeks after the nodule was discovered (B), and the size of the nodule taken 11 weeks after the nodule increased to 102 × 68 mm (C). Fluorodeoxyglucose-positron emission tomography / computed tomography (FDG-PET/CT) performed before the start of treatment showed significant uptake of FDG in most part of the mass (D).

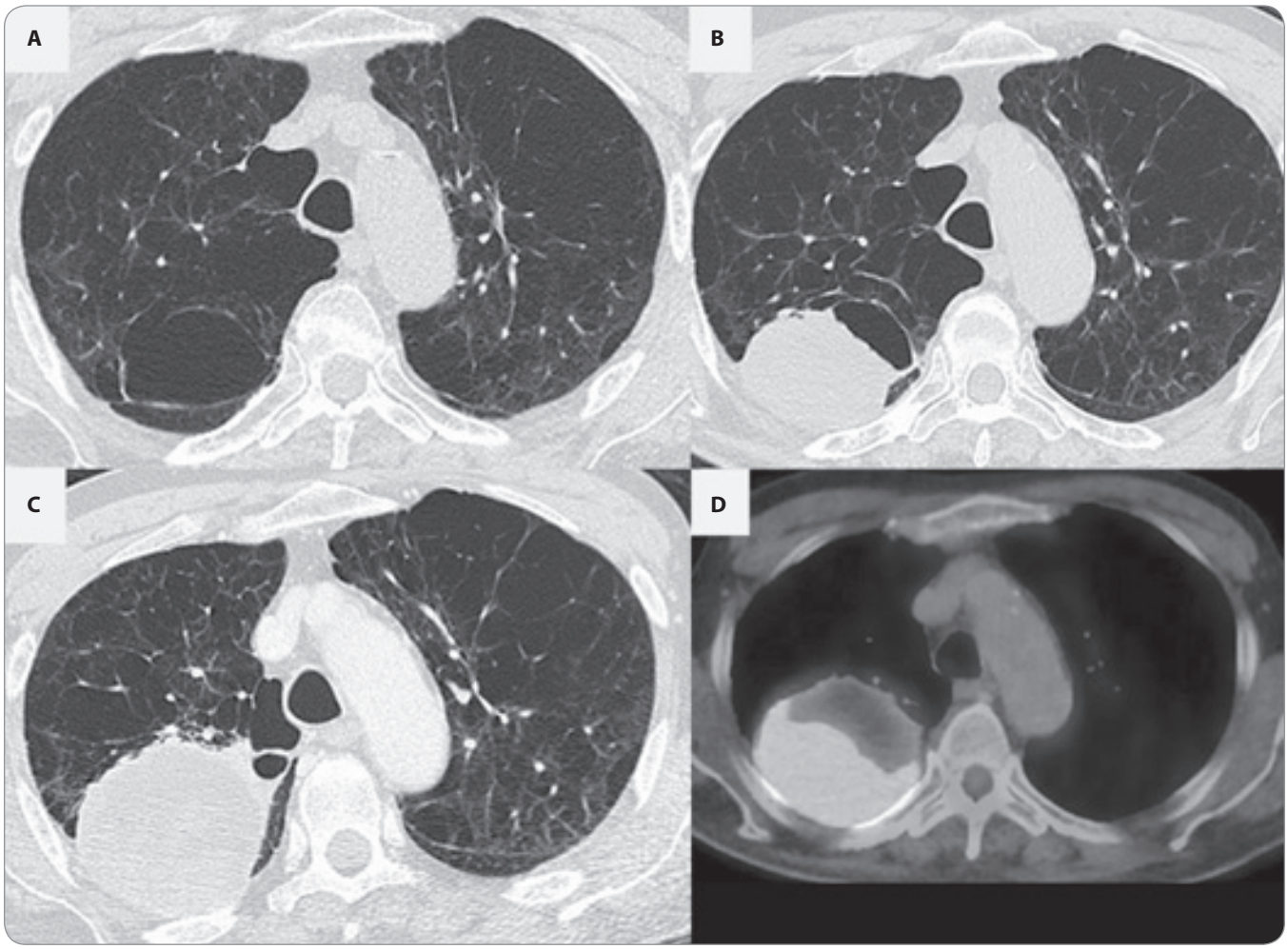

Fig. 2. A CT scan taken 12 months before the nodule of the right lung was discovered showed no nodule in the right upper lobe of the lung (A). CT scan taken 9 weeks after the nodule revealed a mass measuring 89 × 60 mm in the upper right lobe that was presumably arising from the cyst wall (B). Further growth of the tumor was observed in a CT scan taken 11 weeks after the nodule was discovered (C).

apy was not selected due to the extensive area that would require irradiation. Surgery was also deemed inappropriate due to the coexistence of COPD. As his PS was good, therefore, combined immune checkpoint inhibitors and chemotherapeutic drugs were selected as the first-line treatment. One course of chemotherapy with nivolumab, ipilimumab, carboplatin, and paclitaxel was administered, followed by nivolumab and ipilimumab for 2 years. The best treatment outcome was a partial response (Fig. 3A, B). After 29 months, there was no distant metastasis, but the primary tumor had regrown, and second and third lines of chemotherapy were administered, but were ineffective, and brain and skin metastases appeared. The patient passed away from lung cancer 35 months after the start of the treatment.

Pathological findings

A percutaneous core needle biopsy specimen obtained by percutaneous biopsy showed tumor cells had no clear morphological tendency to differentiate, was extremely undifferentiated, and was considered to be a malignant undifferentiated tumor of the lung (Fig. 4A, B). Immunostaining showed that CK7 was focally positive (Fig. 4C). Vimentin was positive (Fig. 4D), and α-SMA was very focally positive. Pankeratin, CK20, TTF-1, napsin A, CK5/6, S100, CD34, calretinin, and D2-40 were all negative. pKi-67 showed a mixture of strongly and weakly positive areas, with a positive rate of 80%. Alcian Blue staining was observed within a small portion of the cytoplasm, but this finding could not be conclusively determined to be mucus. Taking these findings into consideration, the pathological diagnosis was a malignant undifferentiated tumor of the lung, most likely undifferentiated carcinoma.

Discussion

In this patient, there was a rapid tumor growth, which might have been related to poor tumor differentiation [5,6]. In addition, this rapid growth suggested an association with bulla formation [12,13]. The tumor in our patient appeared to have arisen from the bulla wall and grown to fill it. Tumors arising from or near the bulla wall are typically found

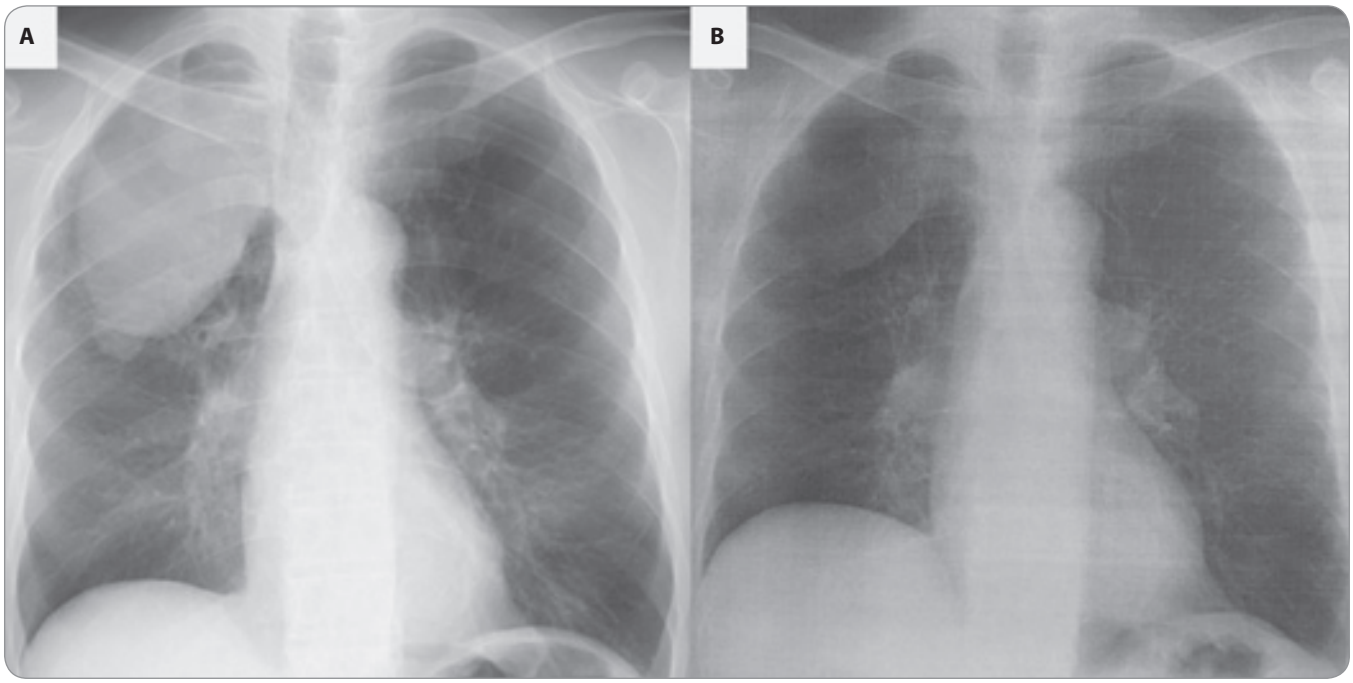

Fig. 3. A chest radiograph taken on the day of the treatment initiation showed further growth of the mass (A). In a chest radiograph taken 25 months after the initiation of chemotherapy, a significant reduction in the tumor size was confirmed (B).

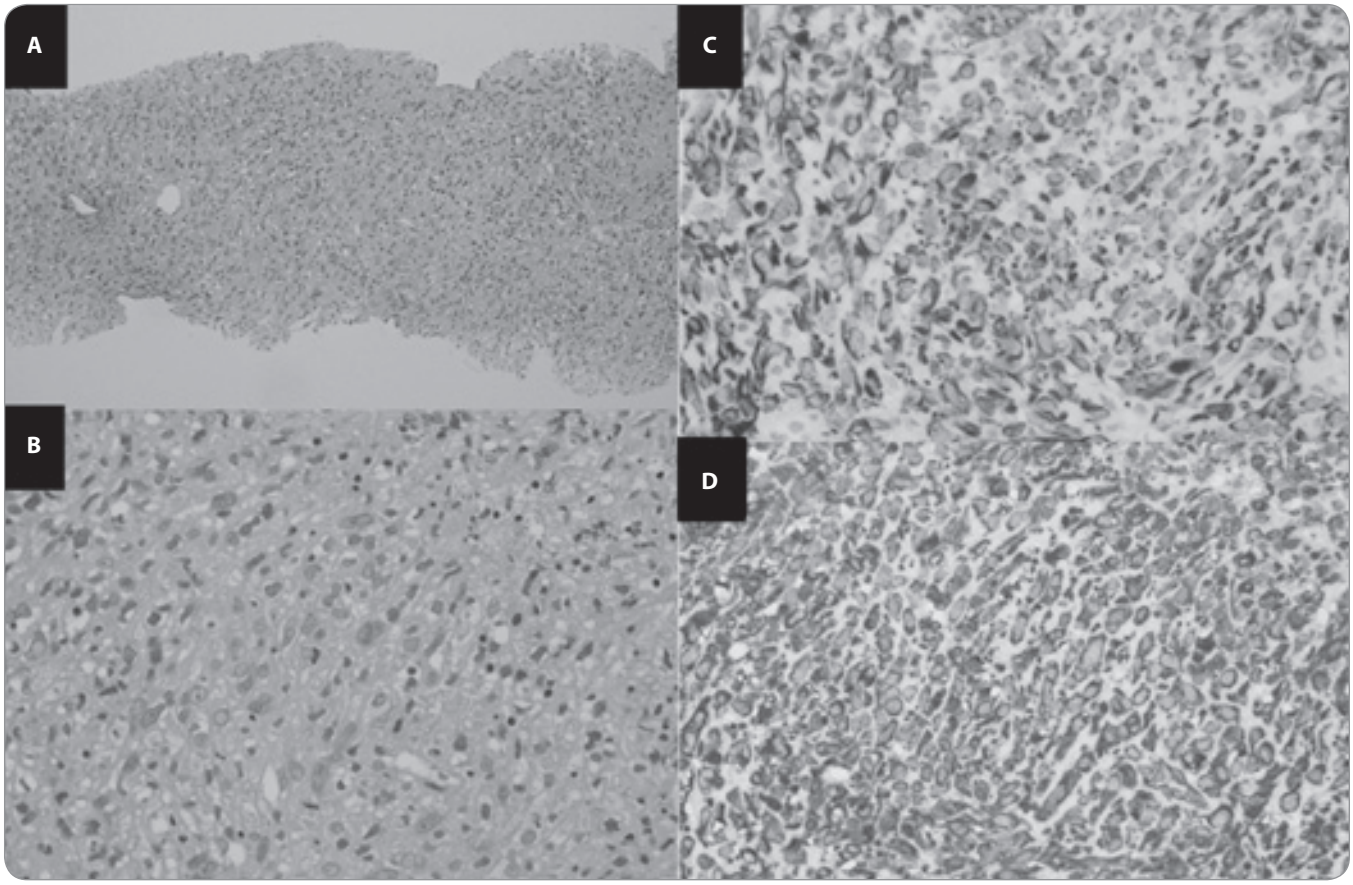

Fig. 4. Hematoxylin and eosin staining of the tissue obtained by percutaneous biopsy – low power (A), high power (B) – showed that the tumor cells had no clear morphological tendency to differentiate, being extremely undifferentiated. The finding was considered to be a malignant undifferentiated tumor, most likely an undifferentiated carcinoma. Immunostaining showed that CK7 was focally positive (C), and vimentin was positive (D).

in men aged 50 or older who are heavy smokers [14,15]. These features were also present in our patient. Tumors associated with the bullae have been reported to have a poor prognosis. This patient had a locally advanced tumor and had underlying lung disease, but survived for more than 2 years.

In this patient, the VDT from the first detection of the nodule until 63 days later was calculated to be 7 days, and that for the following 16 days was calculated to be 27 days. On images, it is difficult to distinguish the necrotic areas caused by rapid growth from the actively proliferating areas of viable cells. In this patient, FDG/PET/CT showed that most part of the mass had taken up FDG, and the increase was determined to be rapid tumor cells themselves and unlikely to be due to residual necrotic material. Shyu et al reported a patient with rapidly growing squamous cell carcinoma of the lung, whose VDT time was 7.5 days [6]. However, except for this case, as far as we could search, there was no report of NSCLC patients whose VDT was only a few days. Therefore, although NSCLC presenting with VDT for several days does exist, it is considered to be extremely rare. Whereas, there have been reports of cases of sarcoma occurring in the thorax which had VDT of several tens of days [7,9]. When encountering a rapidly growing intrathoracic lesion, it is necessary to keep in mind from the perspective of differential diagnosis the possibility of infectious diseases, undifferentiated lung tumors, and neoplastic diseases other than lung cancer.

Taking into consideration the patient's wish to receive aggressive treatment, a treatment regimen combining two ICIs and cytotoxic antitumor drugs were selected as the first-line treatment. Regarding ICIs, it was unclear how the poor degree of differentiation would affect the therapeutic effect, but the positive programmed cell death ligand 1 test also served as a basis for selecting the treatment regimen. Treatment of advanced carcinoma, especially undifferentiated ones, has been extremely difficult, but the situation has improved significantly in recent years with the advent of ICIs [16–19], and there have been reports of patients with these undifferentiated cancers in the otolaryngological field and thyroid gland who have achieved survival times of more than 2 years [16, 18]. Many of these included therapies with one ICI, such as pembrolizumab [19]. However, to our best knowledge, we could not find any reports in which treatment with a combination regimen of two ICIs produced long-term responses in undifferentiated cancers. Perhaps due to the large number of types and the small number of patients, there are no clinical trial results targeting only malignant undifferentiated lung tumors, and there is currently no established standard treatment regimen that could be recommended for these tumors. Considering this patient's clinical course and outcome, we cannot simply recommend this treatment to many other patients. However, the clinical course of this patient was very interesting to us. When it is difficult to choose a treatment for pulmonary anaplastic cancer, the treatment we selected may be considered as one of the options.

Conclusion

We treated a patient with COPD who had a rapidly growing malignant undifferentiated tumor of the lung. The tumor was suggested to be related to the emphysematous bulla. The patient survived for more than 2 years after the treatment with a combination of ICIs and a cytotoxic antitumor drugs. We reported this interesting clinical course.

Statement of ethics: This study was approved by the institutional ethics committee of our institute (NO-1639). Written comprehensive informed consent at the time of admission for obtaining pathological specimens was obtained from the patient.

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Authors' contributions: Yosuke Maezawa and Hiroaki Satoh designed the study. Yosuke Maezawa, Yuika Sasatani, Gen Ohara, Shinichiro Okauchi and Hiroaki Satoh collected the data. Hitomi Kawai was responsible for the pathological diagnosis. Yosuke Maezawa and Hiroaki Satoh prepared the manuscript. All the authors approved the final version for submission.

References

1. Schwartz M. A biomathematical approach to clinical tumor growth. Cancer 1961; 14: 1272–1294. doi: 10.1002/1097-0142(196111/12)14:6<1272::aid-cncr2820140618>3.0.co;2-h.
2. Henschke CI, Yankelevitz DF, Yip R et al. Lung cancers diagnosed at annual CT screening: volume doubling times. Radiology 2012; 263(2): 578–583. doi: 10.1148/radiol.12102489.
3. Miura K, Hamanaka K, Koizumi T et al. Solid component tumor doubling time is a prognostic factor in non-small cell lung cancer patients. J Cardiothorac Surg 2019; 14(1): 57. doi: 10.1186/s13019-019-0879-x.
4. Kanashiki M, Tomizawa T, Yamaguchi I et al. Volume doubling time of lung cancers detected in a chest radiograph mass screening program: comparison with CT screening. Oncol Lett 2012; 4(3): 513–516. doi: 10.3892/ol.2012.780.
5. Lu Y, Sun Z, Li H et al. Radiological evidence of rapid growth acceleration of a small part solid nodule found to be large-cell carcinoma of the lung. J Cardiothorac Surg 2023; 18(1): 236. doi: 10.1186/s13019-023-02290-6.
6. Shyu CL, Lee YC, Perng RP. Fast-growing squamous cell lung cancer. Lung Cancer 2002; 36(2): 199–202. doi: 10.1016/s0169-5002(02)00007-7.
7. Tsunezuka Y, Furusawa T, Yachi T et al. Rapidly growing intrathoracic extraskeletal Ewing's sarcoma. Interact Cardiovasc Thorac Surg 2012; 14(1): 117–119. doi: 10.1093/icvts/ivr023.
8. Uyar E, Carpintieri S, Gomez Veliz A. Rapidly progressive high-grade leiomyosarcoma in an elderly patient. Cureus 2024; 16(8): e67919. doi: 10.7759/cureus.67919.
9. Kim EY, Kim SJ, Choi D et al. Recurrence of retroperitoneal liposarcoma: imaging findings and growth rates at follow-up CT. AJR Am J Roentgenol 2008; 191(6): 1841–1846. doi: 10.2214/AJR.07.3746.
10. Nguyen ET, Kanne JP, Hoang LM et al. Community-acquired methicillin-resistant Staphylococcus aureus pneumonia: radiographic and computed tomography findings. J Thorac Imaging 2008; 23(1): 13–19. doi: 10.1097/RTI.0b013e318149e698.
11. Camargo JJ, Camargo SM, Machuca TN et al. Round pneumonia: a rare condition mimicking bronchogenic carcinoma. Case report and review of the literature. Sao Paulo Med J 2008; 126(4): 236–238. doi: 10.1590/s1516-31802008000400010.
12. Nakamura H, Takamori S, Miwa K et al. Rapid-growth lung cancer associated with a pulmonary giant bulla: a case report. Kurume Med J 2003; 50(3–4): 147–150. doi: 10.2739/kurumemedj.50.147.
13. Nakamura S, Kawaguchi K, Fukui T et al. The development of large-cell carcinoma in the wall of a giant bulla complicated by hemorrhage. Surg Case Rep 2016; 2(1): 22. doi: 10.1186/s40792-016-0151-8.
14. Kaneda M, Tarukawa T, Watanabe F et al. Clinical features of primary lung cancer adjoining pulmonary bulla. Interact Cardiovasc Thorac Surg 2010; 10(6): 940–944. doi: 10.1510/icvts.2010.233551.
15. Hirai S, Hamanaka Y, Mitsui N et al. Primary lung cancer arising from the wall of a giant bulla. Ann Thorac Cardiovasc Surg 2005; 11(2): 109–113.
16. Trinh JQ, Acosta C, Easwar A et al. Durable and dramatic response to checkpoint inhibition combined with COX-2 inhibitor celecoxib in a patient with p16+ metastatic sinonasal undifferentiated carcinoma: a case study. Cancer Rep (Hoboken) 2024; 7(1): e1915. doi: 10.1002/cnr2.1915.
17. Nakane W, Naito Y, Morishita K et al. A case of undifferentiated carcinoma of the bladder treated by combination therapy of surgery, local radiation, and immune checkpoint inhibitors. Nagoya J Med Sci 2022; 84(4): 865–870. doi: 10.18999/nagjms.84.4.865.
18. Ma DX, Ding XP, Zhang C et al. Combined targeted therapy and immunotherapy in anaplastic thyroid carcinoma with distant metastasis: a case report. World J Clin Cases 2022; 10(12): 3849–3855. doi: 10.12998/wjcc.v10.i12.3849.
19. Ooi R, Tobino K, Sakabe M et al. A case of large-cell lung carcinoma successfully treated with pembrolizumab but complicated with cholangitis. Respir Med Case Rep 2020; 31: 101197. doi: 10.1016/j.rmcr.2020.101197.