

[CASE REPORT]

Regression of Lung Squamous Cell Carcinoma after the Withdrawal of Cyclosporin A Combined with Pirfenidone Treatment in a Patient with Idiopathic Pulmonary Fibrosis

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Abstract:

A 72-year-old man was treated with prednisolone and cyclosporine A for idiopathic pulmonary fibrosis. A nodule with a diameter of 19 mm was found in the right lung and diagnosed as lung squamous cell carcinoma. Anti-cancer treatments were not performed because of the presence of advanced interstitial pneumonia and chronic respiratory failure. Cyclosporine A was tapered to avoid suppression of anti-tumor immunity, and pirfenidone was initiated. Within 2 months, the tumor had shrunk to 10 mm in diameter and remained regressed for 9 months. This is the first report of a non-hematologic solid organ tumor responding to the discontinuation of immunosuppressants.

Key words: cyclosporine A, idiopathic pulmonary fibrosis, immunosuppressants, lung cancer, pirfenidone

(Intern Med 60: 617-621, 2021)

(DOI: 10.2169/internalmedicine.5125-20)

Introduction

Idiopathic pulmonary fibrosis (IPF) and other chronic fibroproliferative lung diseases can often be complicated with lung cancer (1), which is the third leading cause of death among IPF patients in Japan (2). A number of risk factors, such as cigarette smoking, age, and genetic factors, are shared between the pathogenesis of IPF and lung cancer (3). Immunosuppressants, including calcineurin inhibitors such as cyclosporine A (CyA) used for the treatment of IPF or other interstitial lung diseases, might be another predisposing factor for carcinogenesis and promote tumor growth (4-6).

Iatrogenic immunosuppression is associated with an increased risk of lymphoproliferative disorders (7) and also cancers in the solid organs or skin, as demonstrated in organ

transplant recipients (8, 9) or patients with collagen-vascular diseases (10, 11). The causative relationship between immunosuppression and tumorigenesis has been further confirmed by the observation that spontaneous regression of lymphoproliferative disorders occurs following the withdrawal of immunosuppressants (12, 13). However, there have been no reports showing that non-hematologic solid tumors regress after the discontinuation of immunosuppressants.

We herein report an IPF case with squamous cell carcinoma in the lung where the primary tumor spontaneously regressed when CyA was tapered and discontinued.

Case Report

A 72-year-old man who was a former smoker (40 pack-years) with type 2 diabetes had been diagnosed with IPF 8

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Received: April 19, 2020; Accepted: August 19, 2020; Advance Publication by J-STAGE: October 7, 2020

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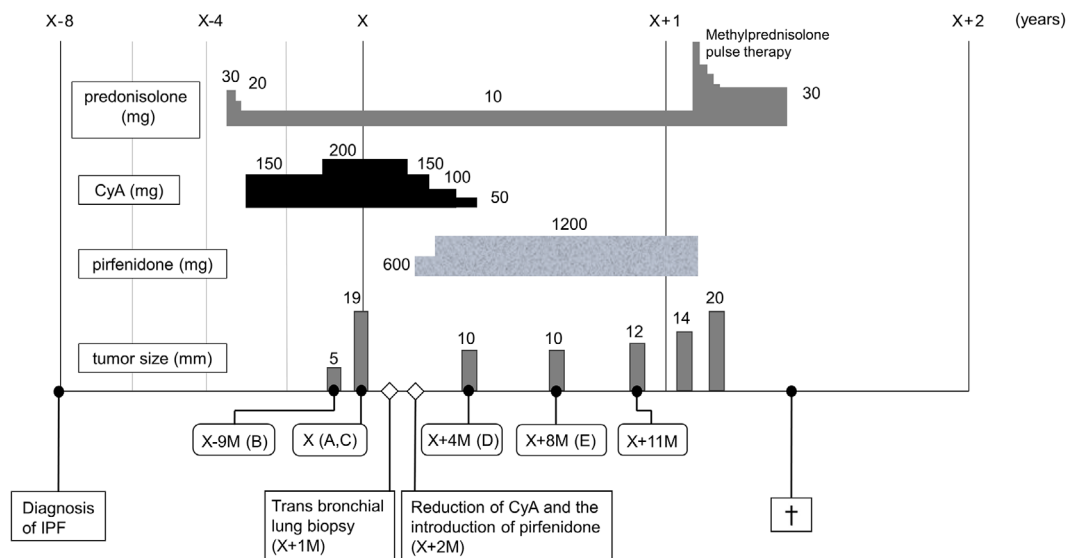


Figure 1. Clinical course. When referred to our hospital (year X), the patient was being treated with prednisolone (10 mg/day) and cyclosporine A (CyA; 200 mg/day). A nodule with a diameter of 19 mm that was diagnosed as squamous cell carcinoma was observed in the right upper lobe of the lung. CyA was tapered and withdrawn, and pirfenidone (1,200 mg/day) was started. The nodule regressed to 10 mm in diameter for 9 months before it started to re-grow. The patient died of acute exacerbation of idiopathic pulmonary fibrosis (IPF) 17 months after he was diagnosed with lung cancer.

years ago based on typical images on thoracic computed tomography (CT), including honeycombing and traction bronchiectasis. Prednisolone, 30 mg per day, was started 3 years ago due to the subacute progression of dyspnea on exertion and appearance of ground-glass opacities in the bilateral lungs. CyA (200 mg/day) was added while the dose of prednisolone was reduced due to the worsened control of diabetes mellitus.

When he was referred to our hospital, he was receiving prednisolone (10 mg/day) and CyA (200 mg/day) (Fig. 1). Fine crackles in the lower lung fields were present, as well as an enhanced pulmonary component of the second heart sounds. Blood tests revealed increased levels of lactate dehydrogenase (320 U/L), Krebs-von-Lungen-6 (2,259 U/mL), and surfactant protein-D (326 ng/mL). An arterial blood gas analysis showed mild hypoxemia at rest with an arterial O₂ partial pressure of 57.9 Torr and difference alveolar-arterial O₂ partial pressure of 39.5. The vital capacity and diffusion capacity of the lungs for carbon monoxide were 63% and 42% of the predicted values, respectively. The six-minute walk distance was 170 m under 4 L/min O₂ supplementation. In addition to honeycombing and traction bronchiectasis in the lower lung fields (Fig. 2A), a nodule with a diameter of 19 mm, which was 5 mm in diameter in a retrospective review of the previous CT scan taken 9 months before the referral (Fig. 2B), was identified in the right upper lobe on thoracic CT (Fig. 2C). A transbronchial biopsy of the nodule was performed, leading to a diagnosis of squamous cell carcinoma in the lung (Fig. 3A), with a clinical stage of IA2 (cT1bN0M0).

The patient was not indicated for surgical treatment or

thoracic irradiation due to the presence of advanced interstitial pneumonia and chronic respiratory failure. CyA was gradually tapered to avoid suppression of anti-tumor immunity, and pirfenidone was started. Two months later, after CyA had been reduced to 50 mg/day, the tumor had shrunk to 10 mm in diameter (Fig. 1, Fig. 2D). CyA was eventually discontinued, and the tumor remained regressed without any additional anti-cancer treatments for nine months (Fig. 1, Fig. 2E). The patient ultimately died of respiratory failure due to acute exacerbation of IPF 17 months after being diagnosed with lung cancer.

Discussion

We present a case of a spontaneous regression of lung squamous cell carcinoma after the withdrawal of CyA. To our knowledge, this is the first report describing a non-hematologic solid organ tumor that responded to the discontinuation of immunosuppressants.

CyA suppresses T cell-mediated immune systems by binding to cyclophilin and forming a complex with calcineurin in T cells, which inhibits the nuclear translocation of a transcription factor, nuclear factor of activated T cells. CyA also promotes the vascular endothelial growth factor expression and neovascularization (4, 6, 14) and induces the release of transforming growth factor (TGF)- β , which increases tumor cell motility, invasiveness, and metastasis (5). A single-center study (15) demonstrated that the incidence of malignancy in 43 patients treated with CyA for interstitial pneumonia was 14% including 4 cases with lung cancer, with more rapid tumor doubling rates of 40-70 days than

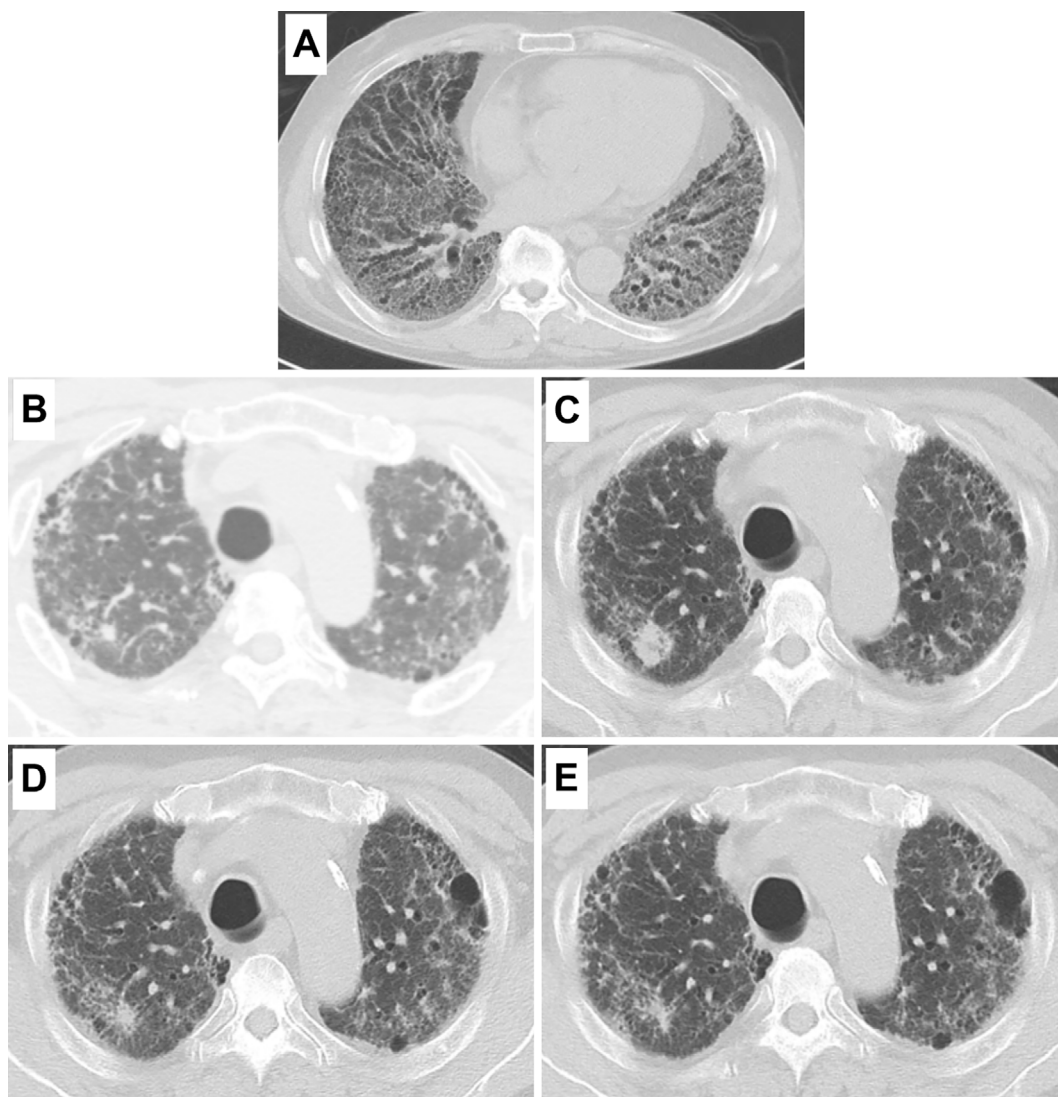


Figure 2. Thoracic computed tomography (CT). Honeycombing and traction bronchiectasis were observed in the bilateral lower lobes (A). A nodule that was eventually diagnosed as squamous cell carcinoma was observed nine months before the referral (B), at referral (C), and two (D) and six (E) months after the tapering of CyA with the concomitant initiation of pirfenidone.

previously reported: 220 days for lung adenocarcinoma and 110 days for lung squamous cell carcinoma (16). In our case, the tumor doubling rate prior to the tapering of CyA was 100 days, which was prolonged to 390 days after CyA withdrawal. The physical stimulus during the transbronchial biopsy may have enhanced the release of new antigens and further activated the anti-tumor immune response (17).

Treatment with pirfenidone might have been another factor that contributed to the regression of lung cancer in our case. Pirfenidone suppresses the production of inflammatory cytokines, enhances the release of anti-inflammatory interleukin-10, and inhibits TGF- β -induced epithelial-mesenchymal transition (18), which might enhance the motility and invasiveness of carcinoma cells (19). The suppression of the TGF- β protein expression in tumor cells by pirfenidone also reduces the levels of matrix metalloproteinase-11, which is related to tumor invasiveness (20, 21). It has been demonstrated that pirfenidone exerts *in vivo* anti-tumor

activity synergistically with cisplatin in a mouse transplanted with human lung or breast cancer cells (22, 23). Although the expression of epithelial-mesenchymal transition markers, such as N-cadherin and vimentin, was not evident in this case (Fig. 3B, C), the introduction of pirfenidone might have affected the tumor regression in combination with the withdrawal of CyA.

Conclusion

Lung squamous cell carcinoma in a patient with IPF was regressed by the withdrawal of CyA and initiation of pirfenidone. When lung cancer develops in the presence of IPF or other chronic fibrotic lung diseases, physicians should consider reducing the dose of immunosuppressive medications as much as possible and starting anti-fibrotic agents in order to enhance anti-tumor immunity and minimize the risk of acute exacerbation accompanied by the tapering of immunosuppressants.

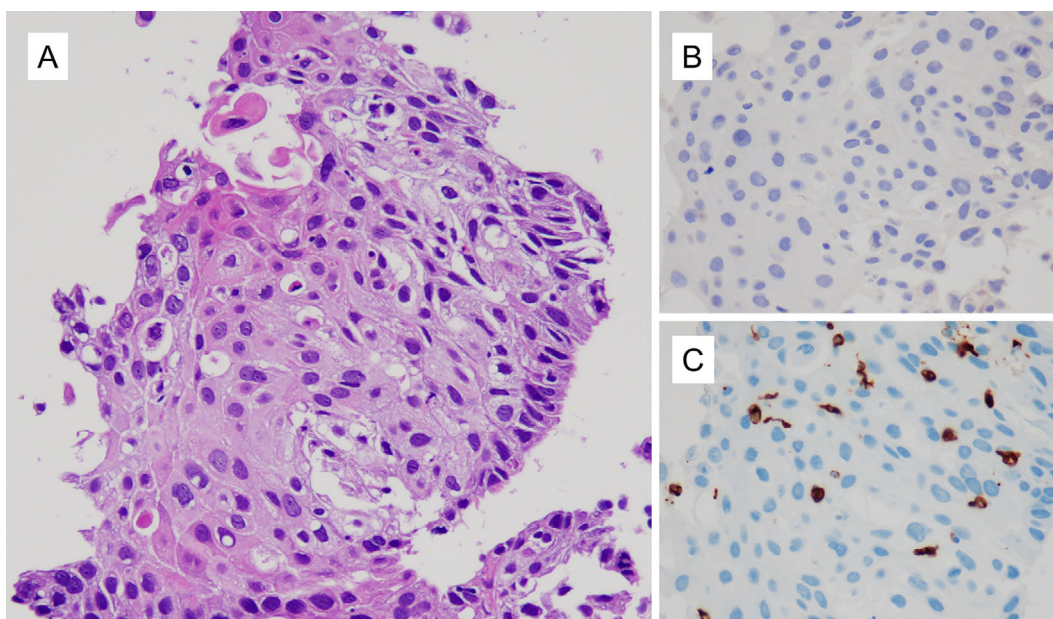


Figure 3. Histopathology of the lung tumor. Hematoxylin and Eosin staining (A) of the lung tumor obtained by a transbronchial biopsy demonstrated cancer cells with a high N/C ratio and eosinophilic cytoplasm as well as keratinization compatible with squamous cell carcinoma. Infiltration of lymphocytes or other inflammatory cells was absent in the interstitium. There was no expression of epithelial-mesenchymal transition markers in the cancer cells, such as N-cadherin (B) and vimentin (C).

The authors state that they have no Conflict of Interest (COI).

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