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Methamphetamine-induced Fibrotic Hypersensitivity Pneumonitis

Metamfetaminin İndüklediği Fibrotik Hipersensitivite Pnömonisi

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Abstract

We present here a case of fibrotic hypersensitivity pneumonitis in a patient with a 7-year history of daily inhaled crystal methamphetamine abuse. The patient's history of chronic exertional dyspnea attributable to progressive methamphetamine abuse, family history and autoimmune features pointed to methamphetamine as the initiator of fibrotic hypersensitivity pneumonitis. After excluding other causes, the patient's clinical, laboratory, radiological and histopathological findings indicated that the fibrotic hypersensitivity pneumonitis had been induced by methamphetamine.

Keywords: *Methamphetamine, drug abuse, hypersensitivity pneumonitis, talc, fibrosis.*

Öz

Yedi yıl günlük inhale kristal metamfetamin kullanma öyküsü olan bir hastada fibrotik hipersensitivite pnömonisi olgusunu sunuyoruz. Hastanın metamfetamin kullanımı ile başlayıp ilerleyen kronik efor dispnesi öyküsü, aile öyküsü ve otoimmün özellikleri hipersensitivite pnömonisinin metamfetaminden kaynaklanmış olabileceği şüphesini uyandırdı. Diğer nedenler dışlandıktan sonra hastanın klinik, laboratuvar, radyolojik ve histopatolojik bulguları, fibrotik hipersensitivite pnömonisini amfetaminin indüklediğini gösterdi.

Anahtar Kelimeler: *Metamfetamin, madde bağımlılığı, hipersensitivite pnömonisi, talk, fibrozis.*

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Hypersensitivity Pneumonitis (HP) is defined as "an inflammatory and fibrotic disease that affects the small airways and lung parenchyma. In susceptible individuals, it usually arises from an immune-mediated response triggered by an overt or occult inhaled antigen". In recent guidelines, HP has been categorized as non-fibrotic or fibrotic HP, based on the presence of radiological and/or histopathological findings of fibrosis (1). The most severe clinical findings of Fibrotic HP (FHP) are cough and dyspnea, and the prognosis is worse when compared to non-fibrotic HP (NFHP) (2).

The causes of FHP remain unclear, although hypothyroidism, coexisting autoimmune disorders and an inability to specify inciting antigens are potentially involved (3-5). The clinical factor identified as the greatest contributor to FHP survival is the identification of the inciting antigen (6). More than 200 environmental and occupational sensitizing antigens of HP have been defined to date, the most common of which are fungi, bacteria, protozoa, probiotics, animal proteins and low-molecular-weight chemicals (7). FHP results primarily from long-term, low-level exposure to most commonly birds or molds in the home. The exact time to FHP onset is uncertain, although it has been reported to develop days, months, or even years after exposure (8).

We report here on the first case of inhaled methamphetamine-incited FHP supported by clinical history combined with laboratory, radiological, and histopathological findings in the absence of other causes.

CASE

A male patient in his 50s was suffering from exertional dyspnea on admission to the chest diseases outpatient clinic. He had smoked crystal MA every day for 6 years and had quit 7 years ago and developed exertional dyspnea after 1 year of MA abuse that progressively worsened, leading him to quit the drug. His dyspnea worsened 1 year after quitting, leading to him being prescribed oral prednisolone for 2 weeks in another center, but without a definite diagnosis, and partially recovered under the treatment. The patient had a 30-pack/year cigarette smoking history and had quit smoking 7 years ago. He had no other diseases and a test for human immunodeficiency virus was negative. The patient was working as an English teacher but had been previously employed as a hospital blood center technician in a mechanized laboratory for 15 years, but quit this job 12 years ago. He had no history of animal contact. In his family history, his mother had been diagnosed with rheumatoid arthritis and psoriasis, and his sister had also been diagnosed with psoriasis. The patient stated that his brother had also been abusing inhaled MA, and was undergoing treatment for exertional dyspnea in another hospital.

The only physical examination finding was clubbing. There was no auscultation sign. The O_2 saturation measured via pulse oximetry was 96 %, and cardiac pulse/min was 116. The patient's biochemical lab and total blood test results were unremarkable, aside from a mildly elevated C-reactive protein (7.8 mg/L, standard: 0-5). A moderate restrictive respiratory disorder was noted during respiratory functional tests, and the diffusion capacity of carbon monoxide was moderately low at 53% (average: 80-140%). Chest X-ray showed bilateral peripheral ground-glass opacities prominent on the basales and reticular opacities (Figure 1). Thorax high-resolution computed tomography revealed bilateral, peripheral and disseminated subpleural interlobular septal thickening and ground-glass attenuation with small centrilobular nodules, as well as ground-glass attenuation on the basales (Figure 2).

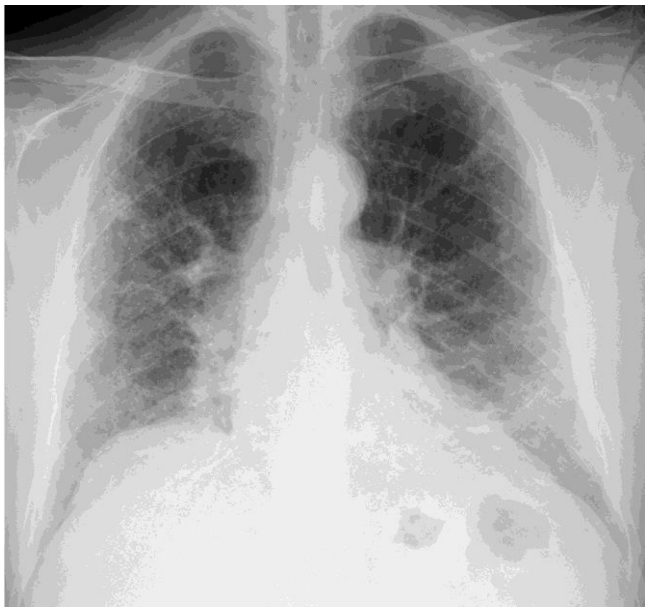

Figure 1: Chest X-ray revealing bilateral reticular opacities and peripheral ground-glass attenuation

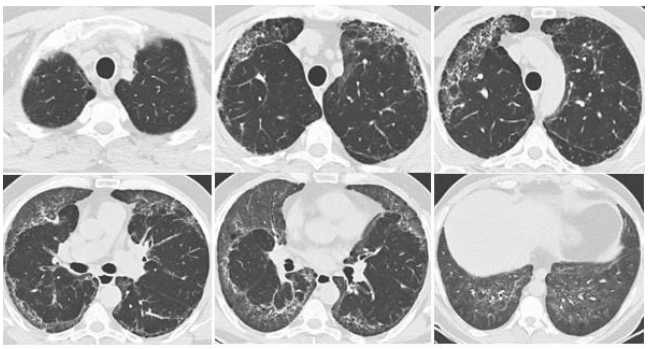

Figure 2: HRCT revealing bilateral peripheral subpleural interlobular septal thickening and ground-glass attenuation without the apices involvement and ground-glass attenuation on the basales

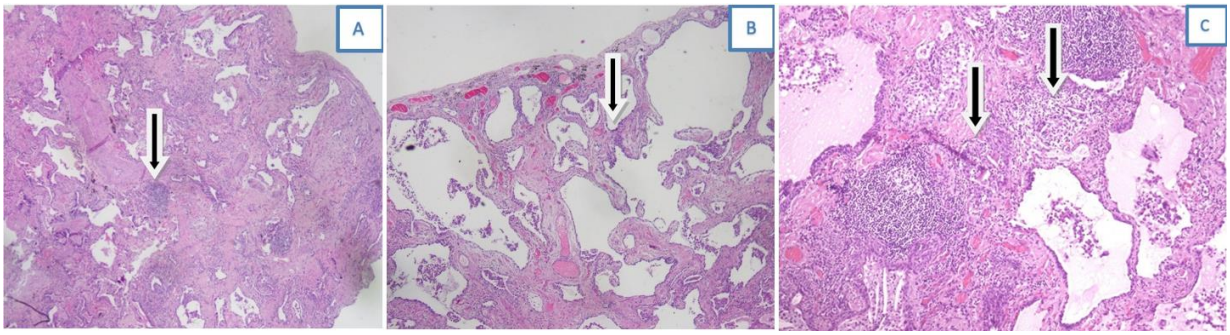

Figure 3a, b, and c: *Interstitial fibrosis, subpleural microscopic honeycomb pattern and lymphoid aggregates (arrowed), H&E 4x10* **(A)**; *Interstitial fibrosis, subpleural microscopic honeycomb pattern, and hyperplasia of type-2 pneumocytes (arrowed), H&E 4x10* **(B)**; *Peribronchiolar loose granuloma structures (arrowed) and lymphoid follicles, H&E 10x10* **(C)**

Real-time polymerase chain reaction tests for respiratory syncytial virus, influenza and COVID were found negative. Rheumatologic markers revealed a positive antinuclear antibody (ANAs:1/80 titer, standard:<1/80), mildly elevated rheumatoid factor (27.9 IU/mL, standard: <14) and angiotensin-converting enzyme (82 U/L, standard:13-64), leading the patient to be referred to a rheumatologist for an investigation of connective tissue diseases, but no such diseases were found. A fiberoptic bronchoscopy was performed for bronchoalveolar lavage (BAL) from the right lung middle lobe, and the blood cell profile of the BAL fluid was as follows: lymphocyte: 11%, macrophage: 62%, neutrophil: 20% and eosinophil: 0%. The CD4/CD8 value (0.94, standard:1.2–1.8) was low in the BAL fluid, and the findings from the BAL fluid were not specific for HP. The patient thereupon underwent video-assisted thoracoscopic surgery for a diagnostic biopsy, and the histopathology of the wedge resection samples from the right lung's upper and lower lobes revealed interstitial fibrosis, subpleural honeycomb pattern, peribronchiolar granulomas and lymphoid follicles, which were appropriate for FHP (Figure 3A, B, C). Treatment with oral prednisolone 32 mg and oral azathioprine 100 mg was initiated, and the patient was taken under close outpatient clinic follow-up.

DISCUSSION

Recreational drug use is a widespread problem. MA is a stimulant drug with similarities to cocaine, amphetamine and 3,4-methylenedioxymethamphetamine. Short-term or long-term MA abuse has many health complications. An earlier study of a large sample reported that people with histories of MA abuse are at greater risk of such lung diseases such as empyema, lung abscess and pneumonia than those with non-MA drugs abuse (9).

Inhaled stimulants have also the potential to cause HP by inciting immunologic response (10). Among the amphetamine-derived stimulants, only cocaine-induced NFHP has been reported in literature (11). MA is frequently mixed or "cut" with microparticles, including corn starch, cellulose and talcum, known as "fillers" (12). As FHP develops, Type-3 allergic and Type-4 lymphocytic reactions occur. Granuloma is an important tissue marker for Type-4 immune responses (13). Associations between pulmonary granulomatosis and exposure to corn starch, cellulose and talc have been reported (14-16). In our case, granulomas were observed in the histopathology of the VATS biopsy sample. We believe that the patient was sensitized to the fillers, as potential causes of granulomatous immune reactions, leading to the development of FHP. Non-asbestiform talc has been reported to contribute to pulmonary fibrosis in several degrees (17). A previous study reported on a case of interstitial pulmonary fibrosis and progressive massive fibrosis related to inhaled MA (12), similar to the present study. We hypothesize that the long-term recreational use of MA "cut" with talcum can result in the inhalation of sufficient talcum to cause pulmonary fibrosis.

Among the autoantibodies, RF, ANAs, Scl-70, cyclic citrullinated peptide, SS-A/Ro, or SS-B/La are more common in some HP patients, and are associated with poorer outcomes (4,18). The autoimmune features of the presented case, including high RF and ANAs values, were in line with the findings of previous studies.

Furthermore, the thorax computed tomography (CT) scans of two separate patients with a history of MA abuse revealed interlobular septal thickening in one, and ground glass attenuation in the other (19,20). In our case, both of the mentioned CT findings associated with FHP were observed.

CONCLUSION

The recent increase in MA abuse has led to the frequent identification of various associated lung involvements. In the present study, we report on the ability of MA and "fillers" to incite antigens leading to fibrotic hypersensitivity pneumonitis, with a poor prognosis.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - H.A., F.T.A., N.F.; Planning and Design - H.A., F.T.A., N.F.; Supervision - H.A., F.T.A., N.F.; Funding -; Materials - H.A., N.F.; Data Collection and/or Processing - H.A., N.F.; Analysis and/or Interpretation - H.A.; Literature Review - H.A.; Writing - H.A.; Critical Review - H.A., F.T.A.

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