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A Case of Yellow Nail Syndrome Accompanying Idiopathic Interstitial Pneumonia; Successful Treatment with Clarithromycin, Methylprednisolone, and Alpha-Tocopherol

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Abstract

A 51-year-old woman presented with complaints of dyspnea, fatigue, and non-productive cough. Chest X-ray showed bilateral lung infiltrates. Nonspecific air-space consolidation on anterior segment of the right lower lobe, bilateral bronchiectasis and infiltrates, patchy ground-glass opacities, and interstitial thickening were reported on thorax computed tomography which was non-responsive to antibiotics. After tru-cut biopsy which only revealed a single granuloma in a particular area, alveolar septal thickening and fibrosis, slight chronic inflammation with findings of congestion, lung involvement was considered to be associated with nonspecific interstitial pneumonia. The nails on all fingers displayed yellow discoloration with mild edema in the face and the legs. The final diagnosis was yellow nail syndrome. Short-term clarithromycin and long-term oral methylprednisolone with vitamin E treatment were successful. After 4 months, all components of the syndrome almost completely regressed.

Keywords: Alpha tocopherol, clarithromycin, idiopathic interstitial pneumonia, methylprednisolone, treatment, yellow nail syndrome

INTRODUCTION

Yellow nail syndrome (YNS) is a rare disorder usually characterized by thickened yellow nails, edema of the extremities (lymphedema), and pulmonary manifestations, especially bronchiectasis or pleural effusion. Since the complete triad is only observed in about one-third of the patients, two of these symptoms are required for the diagnosis (1). The syndrome was first described by Samman and White in 1964.

The etiology is still unknown. Available data suggest that acquired lymphatic dysfunction is the predominant mechanism underlying the clinical manifestations of YNS. Some researchers believe that YNS is a sporadic acquired condition. However, it was previously reported to run in families, which suggests that genetic factors may play a role in the development of the disorder (2). It is usually diagnosed in the fourth or sixth decades, but childhood cases were also seen. *In utero* existence of YNS is hypothesized to be associated with fetal hydrops. Lung involvement may be associated with asthma, lymphedema, exudative pleural effusion, bronchiectasis, recurrent pneumonia, and lipoid pneumonia with or without recurrent sinusitis. To the best of our knowledge, this is the first case reporting the YNS and idiopathic interstitial pneumonia coexistence.

CASE PRESENTATION

A 51-year-old woman with complaints of dyspnea, fatigue, and non-productive cough was admitted to our clinic on October 2015. Before her admission, oral steroids and salmeterol fluticasone inhaler treatment were prescribed because of bronchiectasis and non-resolving consolidation on the right lower lobe which was not responsive to antibiotics. The patient did not continue using oral steroids because of their side effects which was prescribed before she was referred by her physician. She was working as a lecturer at a university's philosophy department. She had no history of chronic diseases,

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had never owned pets or traveled abroad, and had never undergone surgery. She denied smoking or any addictive substance abuse. She had no history of dust or volatile gas inhalation. Her sister had pulmonary tuberculosis which was successfully treated 13 years ago. Her initial vital signs (blood pressure: 129/70 mmHg, heart rate: 72/min, body temperature: 36.8°C, and respiratory frequency: 20/min) were stable. Physical examination revealed mild non-pitting edema and erythema of the face. The fingernails were yellow and thickened with exfoliating skin of the fingertips (Figure 1). Chest auscultation revealed bilateral Velcro crackles on lung bases. Oxyhemoglobin saturation was 96% at rest but was noted to be as low as 86% during the six-minute walking test. A chest X-ray showed bilateral lung infiltrates. Nonspecific air-space consolidation on anterior segment of the right lower lobe, bilateral bronchiectasis and infiltrates, patchy ground-glass opacities, and interstitial thickening were reported on thorax computed tomography (CT). Lung volumes measured by pulmonary function test conducted on December 2015 were as follows: Forced vital capacity (FVC): 2180 mL, 78%; Forced expiratory volume in 1 second (FEV_1): 1860 mL, 78%; and FEV_1/FVC ratio: 85%. No biochemical abnormalities were detected on routine serum analysis. Serum rheumatoid factor, antinuclear antibody, angiotensin-converting enzyme, and tumor markers were also negative. Bronchoscopy revealed no endobronchial lesion, and the culture of bronchial lavage fluid was positive for *Pseudomonas spp*. An open-lung biopsy was recommended for differential diagnosis, but the patient preferred to undergo a tru-cut biopsy which only revealed a single granuloma in a particular area, alveolar septal thickening and fibrosis, and slight chronic inflammation with findings of congestion (Figure 2). The ultimate diagnosis was YNS with nonspecific interstitial pneumonia. Oral methylprednisolone of 48 mg daily, 100 I.U alpha-tocopherol, and 1000 mg of clarithromycin were prescribed on December 2015. She was also seen by a dermatologist and prescribed oral acitretin, anti-histaminic drugs, and local treatments for healing and moisturizing her psoriatic skin lesions. Nail involvement of psoriasis was excluded by the dermatologist. On her second monthly visit, she complained of proximal muscle weakness suggesting steroid myopathy; therefore, the steroid dosage was tapered gradually and discontinued in 2 months. After 4 months of steroid and tocopherol, 3 months of acitretin, 2 months of anti-histaminic drugs, and 2 weeks of clarithromycin treatment, her pulmonary and cutaneous symptoms completely regressed. A control chest CT revealed minimal ground-glass opacities with a fibrotic scar lesion on the right lower lobe (Figure 3). Lung auscultation was normal, and the lowest measure of oxygen saturation on the 6-minute walking test was 95%. Pulmonary function test conducted on May 2016 revealed: FVC: 2260 mL, 81%; FEV_1: 1940 mL, 82%; and FEV_1/FVC: 86%. She was asked to return for control visits after 3 months and was prescribed inhaled salmeterol fluticasone 50/500 mcg/bid and 100 I.U. of oral tocopherol daily until next visit. A written informed consent was signed by the patient before this article was prepared for publishing.

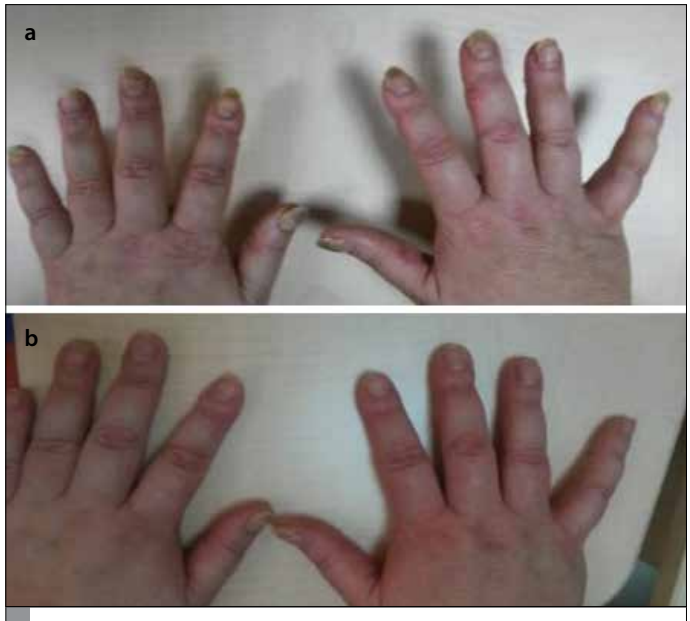

Figure 1. a, b. (a) Greenish yellow discoloration and thickening of nail fingers (before treatment), (b) Complete resolution of ungual findings (after treatment)

DISCUSSION

The triad of yellow nails, lymphedema, and pulmonary involvement is present in only 25% of the patients with YNS. As some of the find-

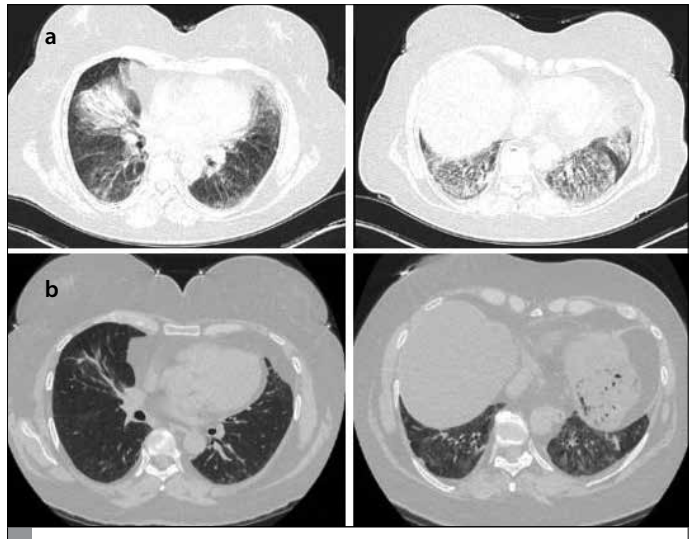

Figure 3. a, b. High-resolution CT (HRCT) findings of the lungs before (a) and after (b) the treatment

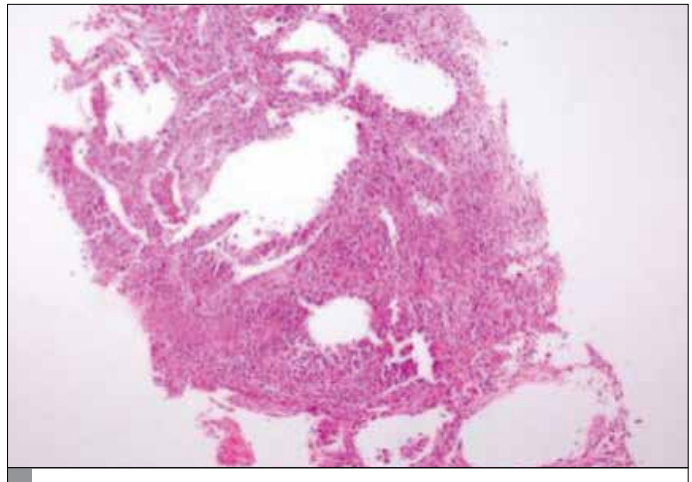

Figure 2. A single granuloma surrounded by chronic inflammatory cells with alveolar septal thickening. Hematoxylin and eosin staining of tru-cut lung biopsy (x100)

ings may resolve over time, it has been suggested that the presence of two over three manifestations was sufficient to establish the diagnosis. Emerson added pleural effusion as the third element of YNS, and he has attributed the pleural fluid accumulation to a deficiency of the lymphatics draining the pleural space (3). Although our case did not have pleural effusion, it is commonly associated with YNS. The effusions are mostly lymphocytic exudative, and chylous effusion is more often encountered than it is in any other disorder.

Lung involvement in YNS is often associated with asthma, lymphedema, pleural effusion, bronchiectasis, recurrent pneumonia, and lipoid pneumonia with or without recurrent sinusitis (4). Infections such as otitis media might be associated with pulmonary infections. Gupta and colleagues have hypothesized that patients with YNS have frequent sinopulmonary infections due to immunodeficiency. The lymphedema and the pleural effusion of two immunocompromised patients were treated with intravenous immunoglobulin (IVIG) and responded well to this therapy (5). In this study, we report a case of YNS with bronchiectasis and idiopathic interstitial pneumonia which resolves after oral steroid and alpha-tocopherol treatment.

In a study performed between 2001 and 2006 on 165 patients with bronchiectasis, four patients were found to have YNS (6). Studies showing coexistence of rheumatoid arthritis and YNS, in which pulmonary involvement consists of interstitial lung disease with ground-glass opacity on high-resolution CT, are found in the literature. Rheumatoid arthritis or use of drugs, such as D-penicillamine, might be related to this interstitial involvement unlike our study, in which the interstitial involvement is fully idiopathic (7). To the best of our knowledge, this is the first case in the literature reporting the coexistence of idiopathic interstitial pneumonia and the YNS.

Interstitial lung diseases are rarely accompanied with cutaneous manifestations. Pulmonary cutaneous syndromes, such as sarcoidosis, Hermansky–Pudlak syndrome, tuberous sclerosis, neurofibromatosis, dyskeratosis congenita, scleroderma, systemic lupus erythematosus, and dermatomyositis, are reported to be associated with interstitial lung involvement (4). In our case, sarcoidosis was excluded. The patient's history revealed no childhood or genetic diseases, such as Hermansky–Pudlak syndrome, tuberous sclerosis, neurofibromatosis, or dyskeratosis congenita. Serum markers associated with collagen vascular diseases were negative, and no other clinical findings associated with these diseases were present.

In YNS, pathophysiology may also be associated with an unknown mechanism affecting collagen synthesis. The changes affecting the dense fibrous tissue found in the nail bed and the pleura are hypothesized to be associated with primary stromal sclerosis which may lead to lymphatic obstruction, thus explaining the clinical manifestations (8). Alpha-tocopherol, which is the only medical agent that seems to be successful for the treatment of YNS, may also be effective in an unknown mechanism related to collagen metabolism. After 4 months of 100 I.U./day alpha-tocopherol treatment, our patient's nail findings returned to normal. Lymphedema of the face and lower extremities disappeared, which was mild in the initial examination. It has been reported that congenital malformations and a secondary dysfunction of lymphatic vessels may be responsible for the syndrome, but the exact mechanism is still not known (9). In successfully treated cases of YNS, all components of the syndrome seem to be reversible which suggest a functional, rather than anatomical, impairment of the lymphatics.

Edema is resistant to diuretics in some patients. Lymphoscintigraphy is a valuable tool for diagnosing lymphatic drainage abnormalities where edema may not be apparent or is hard to attribute to the YNS (10). The edema may however not appear until some years after the nails have become abnormal. In our case, there was mild edema of the lower extremities, therefore no diuretic treatment was necessary. Some case reports declare recovery of the pulmonary symptoms and edema after definite treatment modalities, but minimal or no change may be observed on the nail findings (7). The resolution of the nail findings has also been reported after successful management of the underlying respiratory disturbance which might be the answer to how our case responded well to clarithromycin + oral steroids + alpha-tocopherol (Figure 1). However, cases declare spontaneous resolution of nail abnormalities up to 30%, but vitamin E remains the best pharmacological choice.

CONCLUSION

Although bronchiectasis and pleural effusion are the most common types of lung involvement in YNS, idiopathic interstitial pneumonia may also accompany may also accompany this syndrome. The combination therapy of clarithromycin, vitamin E, and steroids taken orally may be helpful in improving the pulmonary cutaneous findings and lung functions. Further studies are needed to elicit standard treatment modalities.

Informed Consent: A written informed consent was obtained from the patient who participated in this case.

Peer-review: Externally peer-reviewed.

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