Thoracoscopy under Local Anesthesia was Useful for Diagnosing Yellow Nail Syndrome

Shoki Ro, Satoru Ishii, Yukie Hayashi, Konomi Kobayashi, Haruna Masaki, Shion Miyoshi, Yuichiro Takeda, Masayuki Hojo and Haruhito Sugiyama

Abstract

An 80-year-old woman with rheumatoid arthritis and a past history of tuberculosis presented with exertional dyspnea and edema of both legs. Chest X-ray performed on admission showed bilateral pleural effusion. Thoracoscopy under local anesthesia was performed, and vasodilation and non-specific yellowish inflammatory changes were noted in the pleura. A pathological examination showed chronic fibrosing pleuritis in addition to chronic pleural inflammatory changes with lymphoid aggregates. The nails on all fingers and toes were thickened and displayed yellow discoloration, and the edema was resistant to diuretics. Lymphoscintigraphy was conducted, which showed lymphatic drainage abnormalities. The patient was ultimately diagnosed as having yellow nail syndrome.

Key words: thoracoscopy under local anesthesia, yellow nail syndrome, leg edema, pleural effusion

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Introduction

Yellow nail syndrome (YNS) was first described in 1964 by Samman and White (1). It is a syndrome characterized by yellow nails due to nail growth delay and lymphedema. Since Emerson reported respiratory complications of the disease, YNS has been defined by the classical triad of yellow nails, lymphedema and respiratory manifestations (2). The diagnosis of YNS can be made based on the presence of two of the above three symptoms (3), and all three symptoms coexist in only 40-60% of YNS patients (4).

Pleural effusion is present in approximately 40-68% of YNS patients. Thoracentesis and video-assisted thoracoscopic surgery under general anesthesia have been reported to be useful for making the diagnosis, as YNS is associated with a variety of diseases. In this case, thoracoscopy was performed under local anesthesia because it is less invasive and more helpful for diagnosing YNS.

Case Report

An 80-year-old woman with rheumatoid arthritis (RA) treated with methotrexate and bucillamine presented with worsening pleural effusion and edema of both legs. She had been diagnosed as having bladder cancer at 74 years of age and pulmonary tuberculosis at 77 years of age and was treated for tuberculosis for one year. Discoloration of the nails had been present since 78 years of age, and pleural effusion and leg edema had been present since 79 years of age.

The patient was 144 cm tall and weighed 48 kg. Her temperature was 36.9°C. Her blood pressure was 108/77 mmHg, the pulse was regular at 73 beats/min and the respiratory rate was 16/min, with a percutaneous oxygen saturation (SpO₂) of 97% on room air. Respiratory sounds were quieter in the right lower lung, and thickened, curved and yellow discolored nails were observed affecting all fingers and toes. Standard hematological and biochemical tests showed values within the normal ranges (Table), and both serum rheumatoid factor and anti-nuclear antibodies were negative.

Thoracentesis was performed. Exudative pleural effusion with a total protein level of 3.9 g/dL and lactate dehydrogenase (LDH) level of 156 IU/L were observed. The cell count was 150/mm³ with lymphocytic predominance, and a pleural fluid culture and tests for acid-fast bacteria were
negative. No malignant cells were detected, and the adenosine deaminase concentration was within the normal range. However, a chest X-ray showed blunting of the bilateral costophrenic angles (Fig. 1), and computed tomography showed sinusitis and bilateral pleural fluid accumulation (Fig. 2A, B). No nodules, tumor lesions or pleural thickening were seen, and fluorodeoxyglucose positron emission tomography (FDG-PET) revealed no significant FDG uptake in the pleural effusion (Fig. 2C). Nevertheless, mild pericardial effusion was noted on echocardiography, although the systolic function was normal. Since the patient had a history of tuberculosis and bladder cancer and was currently under treatment for RA, thoracoscopy under local anesthesia was performed to differentiate tuberculosis from rheumatic pleurisy and metastasis.

Following drainage of 600 mL of the serous effusion fluid, the right thoracic cavity was examined. The parietal pleura showed an increased number of dilated vessels and marked hyperemia. (Fig. 3A). However, no tumors or nodal pathological changes were seen in the pleura. Yellow tylosis deposits were observed in the pleura, although they could be peeled off easily when performing a biopsy (Fig. 3B). The deposits were different from fat deposits, and gloss was noted. These findings were not compatible with tuberculosis or rheumatic pleurisy.

A histological analysis of the pleural biopsy specimen showed hyperplasia of the mesothelium and collagen fibrosis. Chronic inflammatory changes with notable lymphoid aggregates were observed in the collagenous thickened pleura (Fig. 4). There was no epithelioid granuloma, and auramine staining and tissue cultures were negative. Tuberculous, carcinomatous and rheumatic pleurisy were ruled out based on the above findings.

The patient’s edema was managed with diuretics on admission; however, it was resistant to the medication. Lymphoscintigraphy was carried out to evaluate lymphatic drainage abnormalities. As a result, fewer ilioinguinal lymph nodes were visualized in the left lower extremity two hours after sulfur colloid injection, which indicated a left lower extremity lymphatic drainage delay (Fig. 5).

The patient was diagnosed as having YNS according to the triad of nail discoloration, lymphedema and chronic respiratory disease and treated with 400 mg of clarithromycin (CAM) daily for YNS. An improvement in the nail coloration occurred approximately two weeks after the start of CAM (Fig. 6), and the pleural effusion was controlled. No additional treatment was performed. Although the lymphedema was managed with bandage wrapping and showed an improvement, it persisted.

Table. Laboratory Findings on Admission.

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Immune serum</th>
<th>Laboratory findings of Pleural effusion</th>
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<tbody>
<tr>
<td>WBC 7.270x10^9/µL</td>
<td>Anti-nuclear antibody negative</td>
<td>Color yellow</td>
</tr>
<tr>
<td>Neutrophil 91.30%</td>
<td>P-ANCA &lt;0.5</td>
<td>Gravity 1.018</td>
</tr>
<tr>
<td>Lymphocyte 6.3%</td>
<td>C-ANCA &lt;0.5</td>
<td>Total protein 3.9g/dL</td>
</tr>
<tr>
<td>Eosinophil 0%</td>
<td>C3 100mg/dL</td>
<td>LDH 150IU/L</td>
</tr>
<tr>
<td>Monocyte 2.3%</td>
<td>C4 28.2mg/dL</td>
<td>Total Cholesterol 86mg/dL</td>
</tr>
<tr>
<td>Basophil 0.10%</td>
<td>Rheumatoid Factor 14.1IU/mL</td>
<td>Triglycerides 14mg/dL</td>
</tr>
<tr>
<td>RBC 3.56x10^6/µL</td>
<td>Anti CCP Antibody 30.1mg/dL</td>
<td>Glucose 115mg/dL</td>
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<tr>
<td>Hemoglobin 11.6g/dL</td>
<td>f-T3 1.67pg/mL</td>
<td>WBC 150/mm^3</td>
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<tr>
<td>Platelet 27.4x10^5/µL</td>
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<td>Neutrophil -</td>
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<td></td>
<td>TSH receptor antibody negative</td>
<td>Eosinophil -</td>
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<td></td>
<td>sIL-2R 559U/mL</td>
<td>Lymphocyte 1+</td>
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<td></td>
<td></td>
<td>ADA 8.9IU/L</td>
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<td></td>
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<td>Rheumatoid Factor 23.3IU/mL</td>
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<td></td>
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<td>TB PCR negative</td>
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<td></td>
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QuantiFERON-TB GOLD

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<tr>
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<tbody>
<tr>
<td>Mitogen-nil</td>
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</table>

Figure 1. Chest X-ray shows right side-dominant pleural effusion.
Discussion

YNS is a rare disease characterized by the triad of thickened, slow-growing yellow nails, lymphedema and chronic respiratory manifestations, including pleural effusion, bronchiectasis, rhinosinusitis and recurrent lung infections. All three conditions coexist in only 40-60% of YNS patients (4). According to Hiller’s definition (3), the presence of two of these three symptoms is sufficient for a diagnosis. Individual manifestations of the syndrome can appear at different times, even with an interval of several years. Nail changes are the most common symptom, presenting in 89% of YNS patients (5), while 80% of affected subjects have lymphedema, more often involving the lower limbs. Bilateral lymphocytic-predominant exudative pleural effusion is present in approximately 40-68% of cases of YNS (6, 7). The pleural effusion is either serous or chylothorax, with a higher level of protein than that of LDH in the pleural fluid (7). Spontaneous improvements in the nails are reported in 10-30% of YNS patients, and nail abnormalities have been reported to improve or regress when the associ-
Figure 4. A, B: A histological analysis of the pleural biopsy specimen shows chronic inflammatory changes with lymphoid aggregates. No epithelioid granuloma or rheumatoid nodules are seen.

Figure 5. Abnormal lymphoscintigraphy findings of the left lower extremity. Technetium-99m-labeled nanocolloid was injected subcutaneously into the first web space of the foot. Imaging performed at 15min and two hours after injection shows delayed left lower extremity lymphatic drainage with decreased left ilioinguinal lymph nodes.
Figure 6. A: Yellowish discolored and thickened nails on admission. B: The yellow nails improved after treatment with 400mg of CAM.

ated respiratory disease is treated successfully (8). In contrast, lymphedema and pleural effusion are chronic and persistent; no cases of spontaneous recovery have been reported (9). YNS is linked to a variety of underlying diseases, including connective tissue diseases, such as RA, malignancy, immunodeficiency and endocrine disorders. There are also secondary cases associated with adverse drug effects following the use of penicillamine and bucillamine (8). Underdevelopment of the hypoplastic lymphatic system has been suggested to be the cause of YNS. Since patients with a family history of lymphedema or YNS have been reported, YNS is considered a hereditary disease (10, 11). Although the pathophysiology remains unclear, a recent study argued that YNS is an acquired disease (12). In affected patients, anatomic and functional lymphatic drainage is thought to be obstructed due to infection and/or other systemic disorders. Hence, YNS may occur in infancy, although it is more frequent in middle-aged patients (13).

The current patient had a history of bladder cancer and tuberculosis and was taking bucillamine for RA. It is difficult, but important, to establish the diagnosis, due to the wide spectrum of differential diagnoses, including carcinomatous, tuberculosis and rheumatic pleurisy. Rheumatic pleurisy usually presents with thickening of the parietal pleura with numerous blebs and granules (possibly vesicular granulomatous inflammation). In contrast, the manifestations of tuberculous pleurisy vary. Diffuse white and red nodules in the pleura are strongly suggestive of tuberculosis. In the present case, thoracoscopy showed vasodilation and non-specific yellowish inflammatory changes in the patient’s pleura, and a histological analysis of the pleural biopsy specimen showed non-specific chronic inflammatory changes with lymphoid aggregates, consistent with reported YNS changes (6). Nail discoloration and pleural effusion were present three years ago when she was diagnosed as having tuberculosis. Lymphedema developed two years later. These symptoms appeared at different times and met the criteria for the triad. Therefore, the patient was diagnosed with YNS. In this case, tuberculosis and sinusitis are considered to have caused mechanical disruption of the lymphatic vessels, which resulted in lymphatic congestion and edematous changes. Bucillamine was also a trigger of YNS. Over 90% of patients show an improvement in yellow nails with the discontinuation of bucillamine. However, lymphedema and pulmonary manifestations are reported to be irreversible (8, 14).

Since YNS is associated with a variety of systemic disorders, thoracentesis and video-assisted thoracoscopic surgery under general anesthesia have been reported to be helpful for establishing the diagnosis (6). However, the low sensitivity of pleural fluid staining and tuberculosis pleurisy cultures often makes the diagnosis more difficult.

The use of thoracoscopy with local anesthesia permits a parietal pleural biopsy to be undertaken under direct vision and can be performed without the need for intubation or single-lung ventilation. It is a minimally invasive procedure with a low complication rate (2-5%) and low cost (5). It has also been reported to be the most accurate tool for establishing the diagnosis of tuberculous pleurisy (15).

According to Maldonado et al., YNS progresses slowly, with a median survival of 132 months. Vitamin E (16), 14-membered macrolide antibiotics, such as CAM, and topical corticosteroids have been reported to be effective (17). OK-432 is used for pleurodesis, and good treatment outcomes have been reported in patients with recurrent pleural effusion (7, 18, 19), although there remains no known specific treatment. In this case, the patient had sinusitis and was treated with 400 mg of CAM daily because of its anti-inflammatory actions and effect in inhibiting mucus secretion in the tracheal epithelium. Her symptoms were con-
trolled after CAM therapy was started, and no additional treatment, including the addition of vitamin E or withdrawal of bucillamine, was applied.

YNS is a rare disease. However, when physicians encounter patients with persistent pleural effusion and edema on medication, we should keep in mind the importance of YNS in the differential diagnosis and take care to check the subject’s nails. Thoracoscopy with local anesthesia was useful for establishing the diagnosis of YNS in this case.

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References