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【 CASE REPORT 】

Yellow Nail Syndrome in Which Intranodal Lymphangiography Contributed to the Diagnosis

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Abstract:
Yellow nail syndrome (YNS) is a rare disease comprising the clinical triad of yellow nail discoloration, pleural effusion, and lower limb lymphedema. We encountered a difficult-to-treat case of YNS in which the diagnosis was finally made based on intranodal lymphangiography. An 84-year-old man was admitted to our hospital with pleural effusion and yellow-green discoloration of the nails, accompanied by onychomycosis and limb lymphedema. Intranodal lymphangiography revealed a slow contrast flow and narrowing of the thoracic duct, suggesting lymphatic duct dysplasia and leading to the diagnosis of YNS.

Key words: intranodal lymphangiography, yellow nail syndrome

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Introduction

Chylothorax represents an accumulation of lymphatic fluid in the pleural space due to disruption or obstruction of passage through the thoracic duct and intrathoracic lymph vessels. Among a variety of causes for chylothorax, yellow nail syndrome (YNS) is a rare disease that presents as the clinical triad of yellow nail discoloration, pleural fluid and lower limb lymphedema. Here, we report a case in which the diagnosis was difficult and intranodal lymphangiography proved key to the eventual diagnosis of YNS.

Case Report

An 84-year-old man was referred to a local hospital because of worsening dyspnea, more than 1 year before admission to our hospital. At one year before admission to our hospital, bilateral pleural effusion was identified. He was admitted twice to the previous hospital to investigate the cause of this bilateral pleural effusion. At the first admission, the pleural fluid appeared red, and the pleural fluid was exudative in nature. All fingers and toes showed thickening and yellow-green discoloration of the nails. Tinea albicans was diagnosed after the detection of fungus in nail specimens under microscopy. His symptoms improved after antifungal treatment, but the yellow-green discoloration and thickening of the nails remained.

At the second admission, the appearance of the pleural fluid had changed to milky white. Because of the increased level of triglycerides (TG) in his pleural effusion, chylothorax was diagnosed. The cause of the chylothorax was evaluated, but no specific cause was determined, so idiopathic chylothorax was diagnosed. As outpatient follow-up, the decision was made to perform pleural punctures as needed when pleural effusion increased.

Two months before admission to our hospital, the period of pleural effusion accumulation gradually shortened, and the frequency of thoracentesis increased from once every two weeks to once every three days. Along with the increase in pleural effusion, edema appeared in both legs. Because of the worsening of the chylothorax, he was referred to our hospital for the investigation of the cause.

The patient had a history of hypertrophic cardiomyopathy, abdominal aortic aneurysm, and bladder cancer. His consciousness was clear, blood pressure was 150/90 mmHg, heart rate was regular at 89 beats/min, respiratory rate was 20 breaths/min, and peripheral oxygen saturation (SpO_2) was

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97% on room air. Thickening and yellow-green discoloration of the nails were observed on all fingers and toes (Fig. 1), and limb edema was present.

Both upper limbs showed edema with no laterality, and both lower limbs had edema with predominance of non-pitting edema in the right lower extremity. The right lower limb showed an appearance similar to lymphostatic elephantiasis, and Stemmer's sign was present. Blood testing showed elevated concentrations of B-type natriuretic peptide (BNP) and low levels of both total protein and albumin (Table). The pleural fluid showed milky-white coloration and a turbid appearance. We diagnosed him with chylothorax based on the concentration of TG in the pleural fluid (328 mg/dL) and his pleural fluid cholesterol-to-serum cholesterol ratio (0.58) (Table). Pleural fluid culture and testing for acid-fast bacteria yielded negative results. No malignant cells were detected.

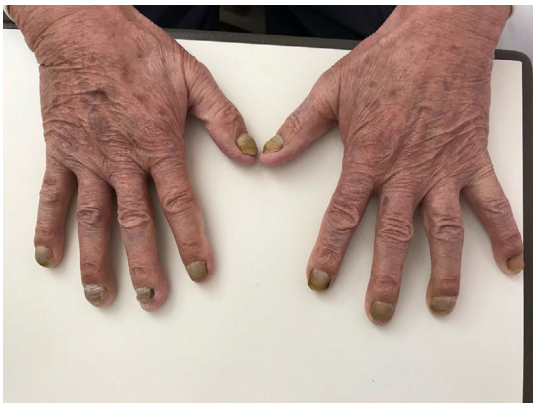

Figure 1. Thickened nails showing yellow-green discoloration on admission.

Chest roentgenography showed dullness of the bilateral costophrenic angles (Fig. 2). Computed tomography (CT) showed right-dominant bilateral pleural effusions. No tumor lesions were seen on CT, and fluorodeoxyglucose-positron emission tomography showed no uptake in the pleural effusion. Both the systolic and diastolic functions on echocardiography were normal. The goal of this admission was to reach a definitive diagnosis and achieve control of the chylothorax. Known causes of chylothorax include trauma, malignant diseases, and diseases such as cirrhosis and tuberculosis, along with idiopathic cases. The patient reported no history suggestive of traumatic chylothorax, such as surgery, falls, or accidents. Regarding malignant diseases, the patient had a history of prostate cancer, but no recurrence was observed.

We initially planned to perform a pleural biopsy under local anesthesia to reach a diagnosis. Thoracoscopy under local anesthesia was performed on hospital day 3. A histological analysis of the pleural biopsy specimen showed only inflammatory changes, with no malignant lesions or lymphatic vessel abnormalities.

If lymphatic leakage were present, treatments such as thoracic duct embolization or surgical thoracic duct ligation might be effective, so we next planned lymphangiography. On day 13 after admission to our hospital, intranodal lymphangiography was performed to try to identify the location of leakage from the thoracic duct (Fig. 3) using ethiodized oil contrast medium (Lipiodol®; Guerbet Japan, Tokyo, Japan). This procedure was performed in a fluoroscopy room.

Table. Laboratory Findings on Admission.

Laboratory findings for blood				Laboratory findings for pleural effusion	
WBC	4,620 /μL	Creatinine	0.89 mg/dL	Color	Yellow-white
Neutrophils	61.7 %	CRP	0.20 mg/dL	Specific gravity	1.034
Lymphocytes	25.1 %	Na	143 mEq/L	Total protein	4.8 g/dL
Eosinophils	3.9 %	K	3.9 mEq/L	LDH	2.4 U/L
Monocytes	9.1 %	Total cholesterol	159 mg/dL	Total cholesterol	103 mg/dL
Basophils	0.2 %	Triglycerides	52 mg/dL	Triglycerides	328 mg/dL
RBC	4.58×10^4 /μL	Anti-nuclear antibody	Negative	Glucose	93 mg/dL
Hemoglobin	14.0 g/dL	P-ANCA	<1.0 U/mL	WBC	67 /μL
Platelets	16.0×10^4 /μL	C-ANCA	<1.0 U/mL	Mono	64 /μL
Total protein	5.7 g/dL	Rheumatoid factor	<5.0 IU/mL	Poly	3 /μL
Albumin	2.6 g/dL	CEA	0.7 ng/mL	AMY	28 U/L
AST	23 U/L	SCC	0.5 ng/mL	ADA	15.3 U/L
ALT	10 U/L	CYFRA	1.4 ng/mL	CEA	0.5 ng/mL
LDH	135 U/L	ProGRP	48.4 pg/mL		
BUN	12.8 mg/dL	sIL-2R	399 U/mL		
		BNP	305 pg/mL		
		T-SPOT®.TB test	Negative		

WBC: white blood cells; RBC: red blood cells, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, CRP: C-reactive protein, P-ANCA: perinuclear antineutrophil cytoplasmic antibody, C-ANCA: cytoplasmic antineutrophil cytoplasmic antibody, CEA: carcinoembryonic antigen, SCC: squamous cell carcinoma, CYFRA: cytokeratin 19 fragment, ProGRP: pro-gastrin-releasing peptide, sIL-2R: soluble interleukin-2 receptor, BNP: brain natriuretic peptide, Mono: mononuclear leukocytes, Poly: polymorphonuclear leukocytes, AMY: amylase, ADA: adenosine deaminase

The inguinal lymph nodes were visualized using ultrasonography with a high-frequency linear transducer. Lidocaine (1%) was subcutaneously injected for local anesthesia at the puncture site of the inguinal region. The inguinal lymph node was punctured using a Cathelin needle under ultrasound guidance, and then Lipiodol was injected manually under fluoroscopy. Since the lymphatic vessels were able to be visualized during the injection, the injection needle was considered to have been placed at the position of a lymph node. Of note, if the injected Lipiodol® shows granular nodules at the start of injection and lymphatic vessels continuous with these are observed, lymph node puncture can be considered successful, and injection can be continued. Lipiodol® flows in from the inguinal lymph nodes to the lumbar lymph vessels, chylothorax, and thoracic duct in that order. Lipiodol® showing spreading, lobulated nodular pooling with no visualization of lymphatic vessels would indicate unsuccessful puncture, in which case the injection should be stopped. In the present case, Lipiodol® injection was continued manually at a rate of 1 mL/3 min. The upper limit for the dose of Lipiodol® was 15 mL, and the final dose in the present case was about 13 mL. First, the right inguinal lymph node was punctured under ultrasonographic guidance, and Lipiodol® was slowly injected. The lymph flow appeared to be very gradual. The Lipiodol® flow stagnated at the level of the third lumbar vertebra (L3), with no flow superiorly. The chylothorax and lumbar lymph vessels can develop differently on the left and right sides. Since the flow of the thoracic duct was unclear on the right side, lymphangiography from the left inguinal lymph node was added, considering the possibility of left-side predominance. The lymphatic flow was extremely gradual, and the thoracic duct was visualized, but narrowing of the thoracic duct was evident above the L3 level. No site of rupture showing evidence of Lipiodol® leakage was apparent from the thoracic duct. These results from intranodal lymphangiography suggested lymphatic duct dysplasia.

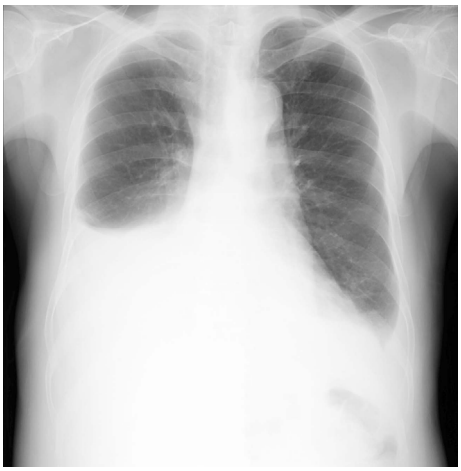

Figure 2. Chest roentgenogram showing right-dominant pleural effusion.

Abnormalities in the nails, pleural effusion, and edema were observed. Edema was identified from the physical findings. We diagnosed the patient with possible lymphedema based on Stemmer's sign and the similarity to lymphatic elephantiasis. Lymphedema is frequently localized, and the findings in this case were atypical. Causes of systemic edema include heart failure, cirrhosis, and nephrotic syndrome. Edema due to heart failure was considered a differential diagnosis because of the elevated levels of BNP in blood and the history of hypertrophic cardiomyopathy. However, in our case, both the systolic and diastolic functions appeared normal on echocardiography, and the heart function was not worsened compared with previous hospital data. However, lymphography suggested lymphatic dysplasia, and lymphatic stagnation was considered present, so the edema was considered to represent lymphedema. In addition, a pleural biopsy excluded malignant disease and tuber-

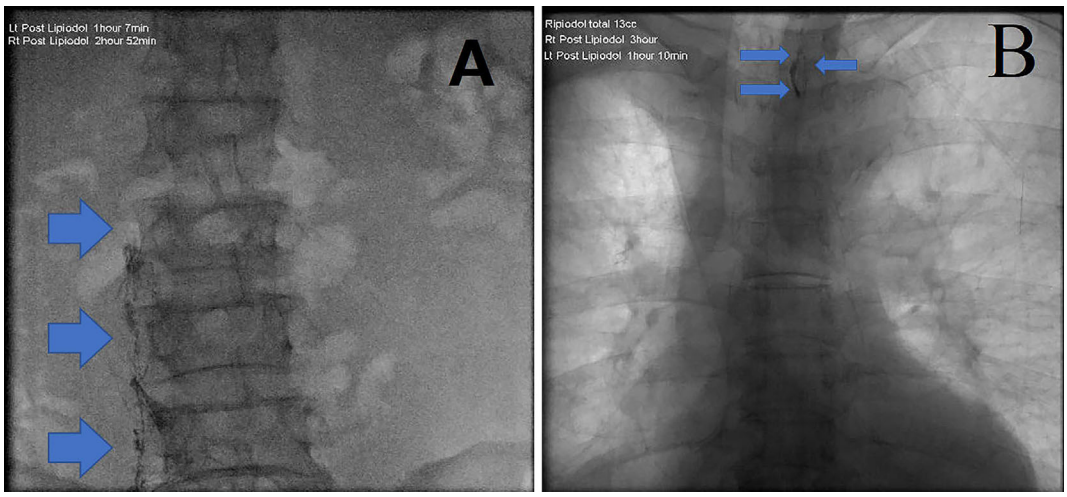

Figure 3. Intranodal lymphangiogram on hospital day 13 indicating lymphatic duct dysplasia. Intranodal lymphangiogram reveals lymph flow is very slow and stagnant at the L3 level. A) The thoracic duct above the L3 level is narrow. B) Most of the thoracic duct above the L3 level is not visualized. Leak location cannot be identified.

culosis lesions. Lymphatic dysplasia was thus considered to be the pathological condition and was assumed to have led to chylothorax. Regarding thickening of the nails, a microscopic examination was performed again and confirmed the absence of dermatophytes. Based on these findings, YNS was diagnosed.

The patient declined pleurodesis. Treatment with a combination of octreotide and a low-fat diet reduced the volume of pleural effusion during admission, and he was discharged on hospital day 17.

Discussion

Chylothorax represents an accumulation of lymphatic fluid in the pleural space due to either disruption or obstruction of the thoracic duct and intrathoracic lymph vessels. Chylothorax can be diagnosed by demonstrating a pleural fluid TG concentration >110 mg/dL and a pleural cholesterol-to-serum cholesterol ratio ≤1.0. In cases with large amounts of chylothorax and showing leakage or a point of damage in the thoracic duct, ligation or embolization of the thoracic duct can be considered. YNS is a rare disease that can cause chylothorax. The first description of YNS was probably made by Heller et al. in 1927 (1). YNS is usually diagnosed based on the three symptoms of yellow nail discoloration, pleural fluid, and lower limb lymphedema. This syndrome primarily affects individuals over 50 years of age. No exact data are available to clarify the prevalence of YNS, although the prevalence is estimated to be about <1/1,000,000.

Our case seems important in two regards. First, YNS may not show the full triad of symptoms at the time of the initial diagnosis, and the diagnosis may be difficult in cases complicated by onychomycosis. Second, intranodal lymphangiography proved useful in reaching the eventual diagnosis in this case.

YNS can be diagnosed in the presence of two of the three triad symptoms (2). If all three symptoms are noted at the time of admission, the diagnosis of YNS may be readily made. However, the three symptoms may not be apparent at the same time and may occur at different times over several years (3). In our case, lymphedema of the lower extremities was noted after the identification of pleural effusion and nail abnormalities. The diagnosis of nail changes was also hampered by the complications of tinea unguium. Dermatophyte infection is a differential condition for nail changes in YNS. Anti-fungal drugs for tinea unguium have also been reported to be effective in treating YNS (4), and in the present case, the fact that the symptoms were improved with anti-fungal drugs was one of the causes of the difficulty in reaching the correct diagnosis.

Intranodal lymphangiography is useful for the diagnosis of YNS. Lymphangiography includes bipedal and intranodal lymphangiography. Bipedal lymphangiography is a procedure to detect lymph ducts in the dorsum of the foot using dye and injecting contrast agent into the lymph ducts. This procedure is very difficult to perform, requires time to visualize the thoracic duct, and is available in very few hospitals. Intranodal lymphangiography was first reported by Rajebi et al. in 2011 (5) as a procedure to puncture a normal inguinal or proximal lymph node under ultrasonographic guidance and inject the node with a contrast agent. Bipedal lymphangiography is a simpler, quicker, and less-invasive procedure than intranodal lymphangiography and is currently being performed at a gradually increasing number of hospitals. In our case, lymphatic leakage was investigated using intranodal lymphangiography. Based on the intranodal lymphangiography findings, hypoplasia of the lymph ducts was suspected due to the delay or stagnation of Lipiodol®, and we were finally able to diagnose YNS. No previous cases have described intranodal lymphangiography assisting in the diagnosis of YNS, so this case is considered to be the first of its kind.

The exact etiology of YNS remains uncertain. Some researchers have considered the syndrome to be suggestive of lymphatic dysfunction. Lymphangiography of the lower limb with bipedal lymphangiography has shown dysplasia of the lymph ducts in most cases (6). Emerson et al. reported that lower respiratory tract infection causes lymphatic damage, which impairs lymphatic drainage from the thoracic cavity and results in chylothorax (7). A biopsy of the parietal pleura reportedly showed obstruction of lymphatic flow pathways (8). Limb lymphoscintigraphy reveals lymphatic disorder, such as tortuousness or hypoplasia, or defective lymph drainage (9). In our case, we were able to visualize the thoracic duct rather than the lower limb by intranodal lymphangiography. Delayed or stagnated lymphatic flow suggestive of dysplasia was seen around the thoracic duct. Any of these findings would suggest thoracic lymphatic disorder. Lymphatic dysplasia in YNS may occur not only in the lymph ducts of the lower limb visualized by bipedal lymphangiography but also in the trunk lymph ducts visualized by intranodal lymphangiography. Intranodal lymphography facilitates visualization of lymph duct dysplasia in the trunk of the body.

We encountered a case in which intranodal lymphangiography assisted in the diagnosis of YNS. We believe that YNS should be listed as a differential diagnosis if delayed contrast flow or narrowing of the thoracic duct of the lymphatic system is seen without thoracic duct leakage on intranodal lymphangiography.

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

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