Case Report

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A rare cause of pleural effusion; yellow nail syndrome

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Abstract:

Yellow nail syndrome (YNS) is a rare syndrome characterized by yellow-thick nails, lymphedema, and recurrent respiratory symptoms. Respiratory symptoms occur due to asthma, bronchitis, bronchiectasis, pneumonia, sinusitis, pleural, and pericardial effusion. Pleural effusion is usually bilateral, exudative, and lymphocyte-predominant. Although about half of patients have pleural effusion, it is not a component of the triad. Two of the classical triad, yellow-thick nails, lymphedema, and recurrent respiratory symptoms, is enough for the diagnosis. About a hundred cases have been reported in the literature and all what we know is based on these case reports. There is no specific treatment for YNS; the goal is symptom control. Here, we report a successful pleurodesis in a 58-year-old male patient with YNS.

Keywords:

Lipofuscin, lymphedema, lymphoscintigraphy, pleural effusion, yellow nail

Introduction

Yellow nail syndrome (YNS) is a rare syndrome characterized by yellow-thick nails, lymphedema, and recurrent respiratory symptoms. The disease was first described by Samman and White in 1964.[1] The relationship between nail changes, lymphedema, and pleural effusion was first noticed by Emerson.[2] Since then, about 100 cases have been reported, and all what we know is based on these case reports. Based on the reports, some authors suggested that YNS might be related to some comorbidities such as connective tissue disease, malignancy, immunodeficiency, endocrine disease, or titanium exposure. There is no sufficient evidence that all these are accidental or causal.[3-6] Whatever the reason, the result is the same, anatomical or functional lymphatic drainage disorder,[7] that results in recurrent respiratory symptoms, yellow and thick nails, and lymphedema.

Respiratory symptoms occur due to asthma, bronchitis, bronchiectasis, pneumonia, sinusitis, pleural, and pericardial effusion, that all are the results of lymphatic drainage disorder. Approximately 40%–50% of the patients with YNS have pleural effusion, which it is not a component of the triad.[8] Pleural effusion is usually bilateral, exudative, and lymphocyte-predominant but sometimes chylous. Nail changes may be in the form of slow growth, excessive thickening, stiffness, transverse contour, extreme fragility, onycholysis, paronychia with the absence of lunula. Yellow color in the nails depends on the molecule called lipofuscin, which is formed by the oxidation of lipids by free radicals. Due to the deterioration of the lymphatic drainage in YNS, free radicals increase, and hence, the lipofuscin that gives the yellow

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discoloration to the nails, increase. Lymphedema occurs generally in the lower extremities but may be present in both upper and lower extremities or less often only in upper extremities. Lymphatic system drainage can be evaluated by lymphoscintigraphy, which demonstrates a decrease or total loss of lymphatic flow. However, the scintigraphic evaluation is not necessarily for the diagnosis.

There is no consensus about the treatment. In the literature, the disappearance of nail findings through long-term clarithromycin, local steroid treatment, Vitamin D, Vitamin E or zinc supplementation was reported. Spontaneous remission without any intervention was reported also.[9-13] The drugs used for nail discoloration have no or limited effect on the respiratory symptoms and the pleural effusion. However, the prognosis in YNS, is determined by the respiratory system malfunction. So far, diuretics, octreotide, long chain fat free diet chemical pleurodesis, pleuroperitoneal shunt have been tried to cope with pleural effusion.[13-17] Here, we present a case with the classical YNS triad and pleural-pericardial effusion, in the light of literature.

Case Report

A 58 year-old male patient admitted to our out-patient clinic with progressive dyspnea and swelling in the feet that had started about 3 years ago. Previously, the patient was evaluated in another center for similar complaints, pleural effusion was detected and pleural and pulmonary wedge biopsies were performed. Histopathological examination revealed only mesothelial cell proliferation, chronic lymphocytic infiltration, sentriaciner emphysema, and anthracosis. He had recurrent respiratory symptoms such as cough and dyspnea that were not accompanied by sputum, chest pain, and hemoptysis. He had no additional disease except diabetes mellitus (DM) and benign prostatic hyperplasia (BPH). He was not taking any medication other than metformin, gliclazide, and alfuzosin. He had previously gone to a dermatologist for his yellow nails, which he considered as a cosmetic problem. Dyspnea and edema in his legs were not so much at that time. He had used terbinafine several times for the diagnosis of onychomycosis, but his nails had not improved. He had a 60 pack-year history of smoking but quite 17 years ago. He had pulmonary tuberculosis 35 years ago. Of these, his medical history was unremarkable, with no occupational and environmental exposure, no pet at home, and no recent travel history. Physical examination revealed decreased breath sounds at posterior basal region bilaterally, edema in bilateral lower extremities, excessive thickening, and yellow discoloration of four extremity nails [Figure 1]. Biochemical test results and blood cell count were normal except borderline neutrophilic leukocytosis. Echocardiography revealed,

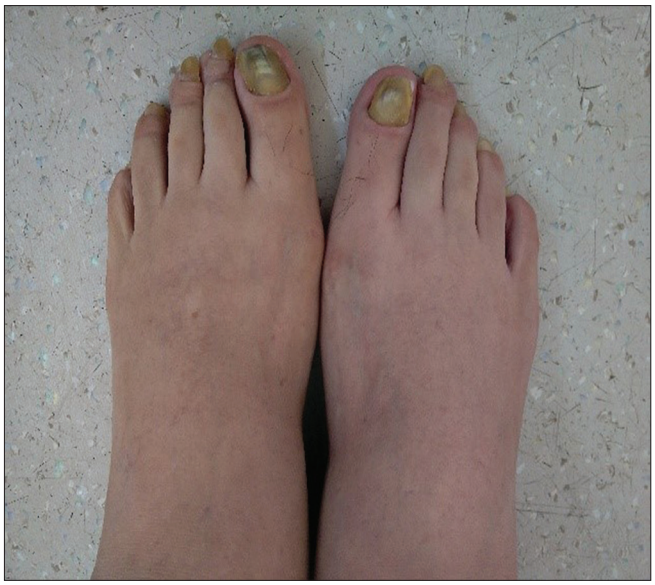

Figure 1: Edema and nail thickening and yellow discoloration in bilateral lower extremities

noncompressive pericardial effusion with normal systolic function and low probability for pulmonary hypertension. In thorax computed tomography of the thorax, only pleural and pericardial effusion was detected without any parenchymal abnormality [Figure 2]. There was no FMF gene mutation, and rheumatological and tumor biomarkers were negative. The rheumatologic disease was ruled out by a rheumatologist. He was evaluated in detail by a dermatologist due to nail changes and yellow discoloration once more. Terbinafine treatment was discontinued due to a lack of growth in nail fungus culture. No other dermatological disease could be detected, explaining these symptoms other than YNS. The pleural fluid was exudative by Light's criteria, with a total protein level of 5 g/dl. Cytology was negative for malignancy, as was testing for adenosine deaminase. There was no growth in pleural fluid culture. AARB and *Mycobacterium tuberculosis* polymerase chain reaction were negative. Cytological examination revealed lymphocyte-predominance, among inflammatory cells without any evidence of malignancy. At regular intervals, therapeutic thoracentesis was re-performed. Respiratory symptoms and radiological findings regressed a few days after every drainage. Abdominal ultrasonography revealed a 1–2 cm free fluid between the bowel loops. In the paranasal and maxillofacial sinus CT, densities in the frontal and bilateral maxillary sinus and a significant increase in mucosal thickness in the left side of the sphenoid sinus was detected. Blood flow was normal, with no insufficiency or obstruction in both lower-extremity venous and arterial Doppler ultrasonography. No lymphatic flow was detected in the bilateral lower-extremity lymphoscintigraphy [Figure 3]. After these evaluations, we considered the diagnosis as YNS. We performed talc pleurodesis and follow-up the

patient. The patient is comfortable with a loculated, small in amount, nonprogressive pleural fluid with no respiratory symptoms, in the 3rd year of pleurodesis [Figure 4]. He was advised by a gastroenterologist to take a diuretic for the 1–2 cm, nonprogressive ascites all the time.

Discussion

YNS is a rare syndrome that should be considered in the presence of yellow and thick nails and lymphedema in the patient who has got recurrent respiratory complaints. Respiratory symptoms are present in 25%–75% of patients. Two of the classical triad, yellow-thick nails, lymphedema, and recurrent respiratory symptoms, is enough for the diagnosis. In our case, all components of the triad were present. Although it is thought that the diagnosis can be made clinically with these findings, further investigations are recommended to rule out alternative diagnoses and to determine the etiology.

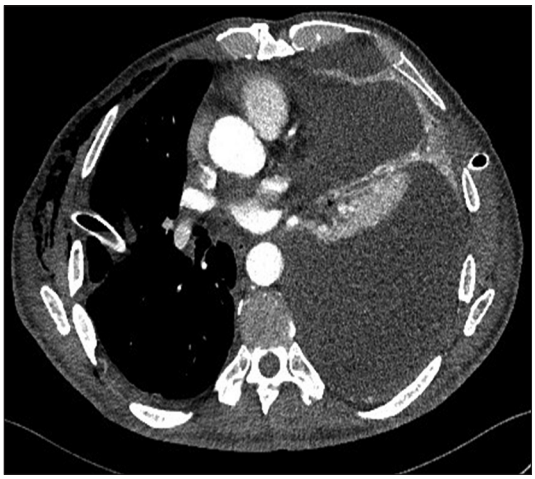

Figure 2: Massive pleuropericardial effusion and bilateral tube thoracostomy

YNS cases reported in the literature are mostly male patients. Although familial cases have been reported, most of them were sporadic and noncongenital. In terms of these features, our case is similar to the reported cases. Although previously some autoimmune diseases, immunodeficiencies, malignancies, inflammatory diseases, hematological diseases, and a number of environmental exposures have been reported in some cases, it is not known whether they are coincidental or they are the factors or co-factors involved in the pathogenesis. In a previous study, due to the disappearance of nail findings and respiratory symptoms after cessation of bucillamine that had been used for rheumatoid arthritis, it was declared that YNS in these cases were related to bucillamine usage.[18] Hence in every YNS suspected patients, a detailed evaluation of comorbidities, medications, exposures

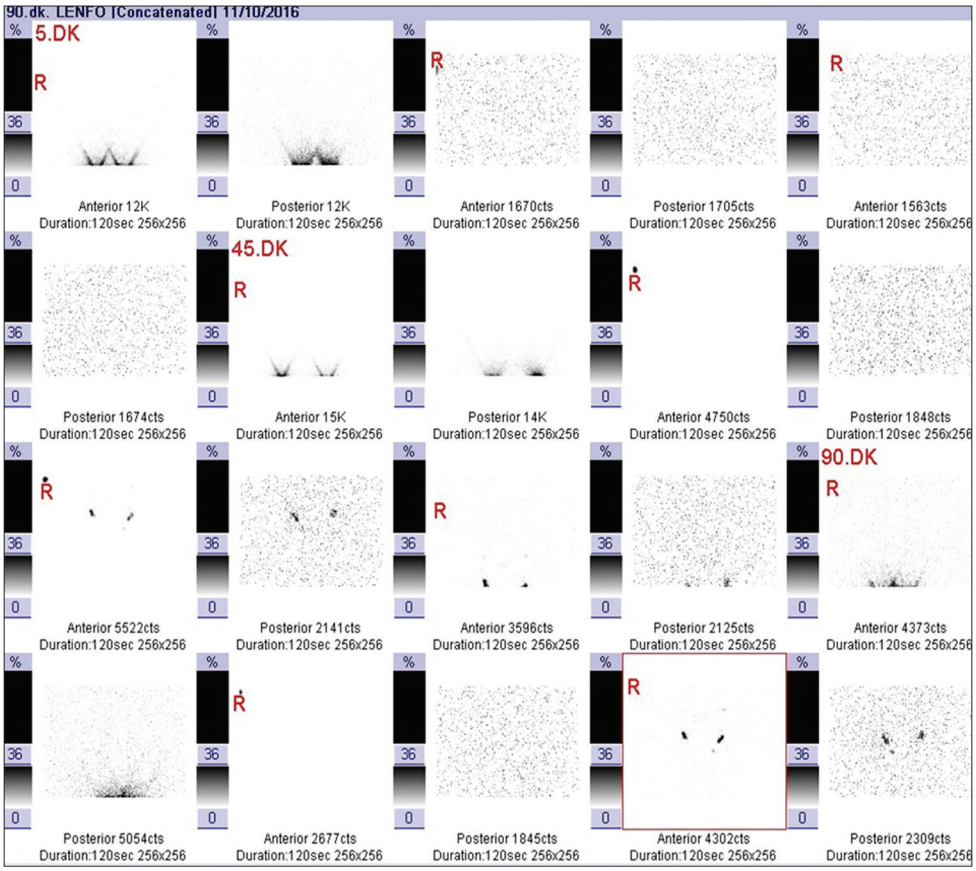

Figure 3: No lymphatic flow in bilateral lower-extremity lymphoscintigraphy

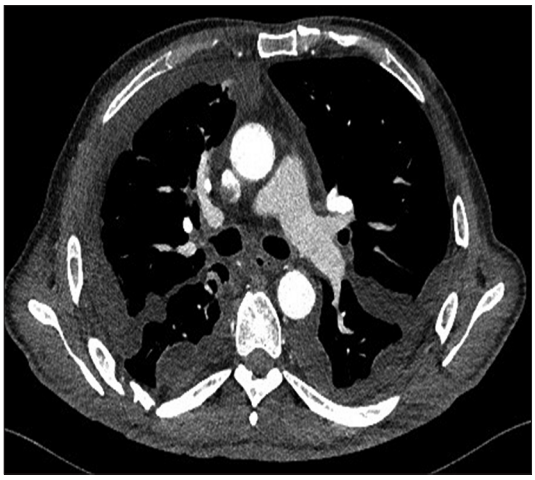

Figure 4: Loculated, small in amount, nonprogressive pleural fluid after pleurodesis

is advised in order both for the diagnosis and the treatment. Our patient had a history of tuberculosis, and his comorbidities were DM and BPH, and no autoimmune disease or immunodeficiency was detected after a detailed investigation.

Pleural effusion develops up to 40%–68% of YNS. Although it is such common in YNS, it is not a component of the triad. It is generally bilateral and exudative and sometimes chylous. In a previous study of 41 cases, pleural effusion was detected in 47% of YNS patients, and the effusion was bilateral in 72% and exudative and lymphocyte-predominant in 83% of the cases. About one-third was chylous.[8] In our patient, pleural fluid was bilateral, exudative, lymphocyte-predominant also. Other causes of exudative, lymphocyte-rich pleural effusion, such as rheumatoid arthritis, malignancy, and tuberculosis, were ruled out. Pleural fluid was analyzed for chylothorax, pseudochylothorax, and urinothorax also. So far, pleurodesis, pleuroperitoneal shunt, octreotide, and macrolide treatment have been used for pleural effusion in YNS. We preferred talc pleurodesis in our patients. It seems a good intervention as no relapse of pleural effusion have occurred after then and the patient cope well with the small amount ascites by diuretic treatment.

Nail discoloration, varying from whitish-yellow to yellow-green and thickening, can be present in fingernails or toenails or all four. Patients often receive onychomycosis treatment for these signs as a result of misdiagnosis, but onychomycosis treatment is not effective in YNS. Similarly, our patient had been treated as if he had onychomycosis several times before. For the diagnosis of YNS, onychomycosis should be excluded. In our patient, the lack of growth in the nail fungus culture and the lack of response to multiple fungal treatment were excepted enough for the exclusion of onychomycosis.

Upper airway pathologies can be present in 25%–83% of YNS patients.[19] Chronic rhinosinusitis is the most common one. We performed a paranasal-maxillofacial sinus CT scan for sinusitis symptoms in our patient and detected intense densities and significant mucosal thickness in sinuses that were compatible with sinusitis also.

Lymphedema, a component of the triad, is thought to be caused by anatomical or functional impairment in lymphatic drainage. It has also been suggested that microvasculopathy causing protein leakage may be the reason for lymphedema. It is usually pitting and present in the bilateral lower extremities. It usually does not respond sufficiently to diuretic therapy. Manual lymphatic drainage with a low-pressure compression pump can be tried in these conditions. In refractory cases, as the reason of unresponsiveness is the irreversible hypertrophy of the connective tissue, Homan's or Charles Procedures, which are surgical interventions to the edematous skin, subcutaneous tissue, and muscle, can be applied.[13] In our case, we performed lower-extremity venous and arterial Doppler for differential diagnosis and did not detect any pathology. Hence, the lower-extremity edema is not related to arterial or venous system of the extremities. We did not detect any other disease that can be related to lower-extremity edema, such as the heart, kidney or liver failure, and hypothyroidism. We found that there was no lymphatic drainage in the lower-extremity lymphoscintigraphy. Lymphedema is stable, not progressive, and the patient is quite mobile despite the lymphedema.

Conclusion

YNS is one of the rare causes of pleural effusion. Although pleural effusion is not a component of the triad, about half of YNS patients have pleural effusion. Hence, in the differential diagnosis of a pleural effusion, YNS must be kept in mind, in any case with any component of the classical triad, yellow-thick nails, lymphedema, and recurrent respiratory symptoms. Although the diagnosis can be made clinically with these findings, further evaluation should be performed to rule out other similar diseases and to identify the possible etiology.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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