Yellow Nail Syndrome – Diagnosis, Differential Diagnosis, Treatment Options

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Abstract
Yellow nail syndrome (YNS) is a rare, but relatively well characterized triad of slow growing yellow nails, lymphedema of the distal portions of the upper and lower limbs as well as chronic infection of the respiratory tract and/or pleural effusion. The most characteristic features of this syndrome are the nail changes that allow the diagnosis to be made even if the triad is not complete. Yellow discoloration of the nails is nonspecific and often seen in onychomycosis, nail psoriasis, a variety of other conditions that are associated with onycholysis. Distal limb edema may not be very pronounced. In addition to the bronchopulmonary disorders, malignancies, chronic heart conditions and gastrointestinal diseases may occur. Treatment after exclusion of non-YNS conditions is aimed at finding the underlying systemic disorder, which usually requires a very long therapy and a lot of patience both from the patient as well as the treating physician.

Key words: Yellow nails, lymphedema, pleural effusion, sinubronchial syndrome, nail growth rate, chronic infection, long-term antibiosis, clarithromycin, azole antifungals

Introduction

Nail changes are often related to systemic diseases although the number of nail patients without associated general diseases is much higher. Yellow nail syndrome (YNS) (OMIM 153300) is one of the characteristic nail conditions that are virtually always associated with internal diseases, most commonly chronic infections of the rhino-sinu-bronchial system. It was first described as scleronychia in 1927 [1], then as the triad of yellow nails, lymphedema and chronic respiratory symptoms in 1964 [2, 3].The challenge is to make the diagnosis as early as possible to save the patient a long period of unnecessary suffering.

Frequency

YNS is a rare syndrome with an estimated prevalence of less than 1:1,000,000. YNS occurs worldwide. There is no sex predilection. Most patients are adults over 50 years of age [4]. It is very rare in children [5]. Whether congenital cases should really be considered true YNS remains to be clarified [6]. Although there are a few familial cases there is probably no genetic component [7].

Etiology

The cause of YNS is not exactly known. Genetic alterations have not been proven although some authors claimed a relation to *FOXC2* mutation, which is seen in the remotely similar distichiasis – lymphedema syndrome [8]. Whether or not associated disorders such as malignant tumors, hormonal diseases, immunodeficiencies, nephrotic syndrome, tuberculosis, and rheumatoid arthritis or their treatment are causally related remains to be proven [9]. In 2011, titanium ingestion was claimed to be responsible for the nail changes in adults [10, 11], and recently high nail titanium levels were found in a child with YNS who used to swallow her titanium-containing toothpaste; 3 years after stopping this habit the nails looked normal again and were free of titanium [12]. Another study did not find an association of YNS with titanium [13]. Yet another report described the disappearance of respiratory symptoms after removal of titanium containing dental fillings while the nails remained unchanged [14].

Pathogenesis

The pathogenesis of the characteristic nail changes is the matter of much debate. The nails grow slowly, are harder and thicker, become intransparent, turn yellow and lose the contact with the nailbed. They are more curved from side to side, often develop a hump in the longitudinal axis. Due to the extremely slow nail growth, the cuticle is no longer formed and the free margin of the proximal nail fold rounds up. A split between the undersurface of the proximal nail fold and the underlying proximal nail plate develops allowing bacteria and other exogenous substances to get under the eponychium. Together with the often very pronounced onycholysis this loosens the nail so that it may eventually fall off spontaneously. The nail changes are so characteristic that the diagnosis of YNS can be made from them alone. Some authors claim that a disturbed lymph circulation with protein loss through leakage would be the cause. This theory is based on the finding of hypoplasia, malformation or obstruction in very few patients examined by lymphography [2]. Histopathology of two nail biopsies demonstrated many dilated endothelium-lined vascular spaces in a fibrotic tissue [15]. Others favor the theory that lipofuscin, which is accumulated in many tissues with age would be responsible for the yellow color [16];

however, lipofuscin granules are more brownish than yellow and exhibit a bright orange autofluorescence in tissue. The greenish tinge often seen in long-standing YNS is due to colonization by *Pseudomonas aeruginosa* of the nails. The lymphedema pathogenesis is not exactly known. Pericardial effusion, which is also sometimes associated with the yellow nails and completes the triad is linked to defective lymph drainage as sclerosis and lymphatic stasis with dilated lymph vessels are also seen in the parietal pleura of some YNS subjects [17]. Although some cases of YNS were seen in patients with immunodeficiency disorders of various types most YNS individuals do not suffer from overt immunocompromise thus chronic respiratory system infections are not proven to be associated with immunological impairment [18]. Other concomitant disorders described in YNS patients were various cancers, gastrointestinal, renal and hormonal disorders [19].

Course

YNS is a chronic progressive condition with a low chance of spontaneous regression. There is often a long lag period between the nail changes and lymphedema and/or chronic respiratory disease. Indeed, it is the author's view that the diagnosis of YNS cannot be made with certainty without the nail changes even if a patient presents with lymphedema and chronic respiratory symptoms [20]. As the nails may only mildly be affected and many patients only come to the dermatologist after a year-long course the rate of undiagnosed YNS is probably relatively high [19]. However, as outlined above, the nail alterations are characteristic enough for an unequivocal diagnosis.

Management

Since its first description as a syndrome in 1964 [2], no therapeutic consensus has been achieved. This is, at least in part, due to the rarity of the condition and the different views as to its etiopathogenesis. It is thus no wonder that various treatments were proposed on an anecdotal basis and also reflect the therapeutic possibilities of their time.

Complex decongestion treatment is generally recommended to improve the lymphedema [21]. Compression garments and low-stretch bandages, if needed supported by manual lymph drainage, are usually effective. Octreotide, a somatostatin analogue capable to inhibit lymph secretion, was given in patients with pleural effusion [22].

Spontaneous resolution of the nail changes has been observed in less than one third [7]. Topical vitamin E alone rarely improved the nails and the remaining YNS symptoms [23], but systemic a-tocopherol in a daily dose of 1000 mg was beneficial [16,24]. The combination of vitamin E with systemic itraconazole also improved the nails [25]. Local injections with triamcinolone were performed with inconsistent results [26]. Although there are case reports of improvement of the nail changes during/after successful therapy of the chronic respiratory symptoms this is by far not always the case [27]. Treatment of the bronchopulmonary infections with clarithromycin, which is effective in infections of the lower respiratory tract, led to dramatic improvement of the nail discoloration [28]; however, long-term treatment in a sufficiently high dose is mandatory. Surgical correction of a septum deviation led to a dramatic improvement of YNS [29]. Successful carcinoma therapy caused the disappearance of paraneoplastic YNS [30]. As slowed nail growth is one of

the major nail signs attempts were made to speed the growth rate up. Some systemic azole antifungals, particularly itraconazole [31] and fluconazole in higher doses, were observed to cause faster nail growth and their administration combined with topical vitamin E [32] improved the nails in some cases. Oral zinc in a dose of 300 mg per day was also touted to improve the nails and lymphedema [33]. The role of titanium elimination is also controversial. Titanium is used widely in daily life, mostly as titanium dioxide. It is contained in endoprostheses and dental fillings, in cosmetic and daily care products, in candies etc [34]. For an etiological role, its distribution is too wide as to be the sole cause of YNS. Furthermore, even high amounts of titanium in the body were not associated with yellow nails [13].

Prognosis

Fingernails have a better chance to normalize than toenails, probably because their physiologic growth rate is three times faster than that of toenails. Often, only one component of the YNS improves while the remaining ones do not respond. There are few long-term investigations as to the life expectancy of YNS. It appears, however, that they die earlier than age-matched controls [4].

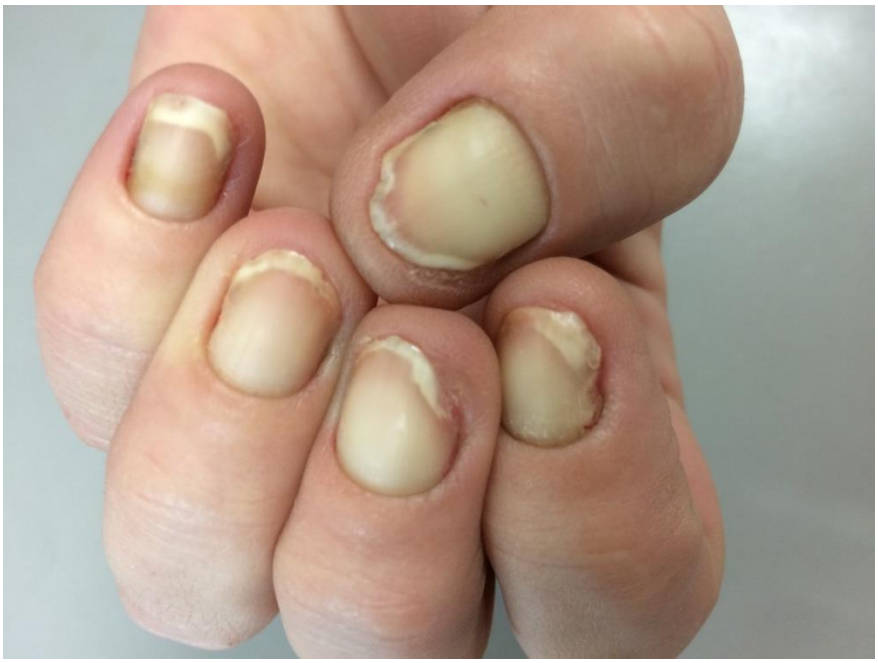

Figure 1. Fingernails in a 51-year-old female patient with lymphedema of the lower legs, chronic productive cough since more than 10 years and long-term tobacco smoking. Note the yellowish milky, intransparent nails and the loss of the cuticles.

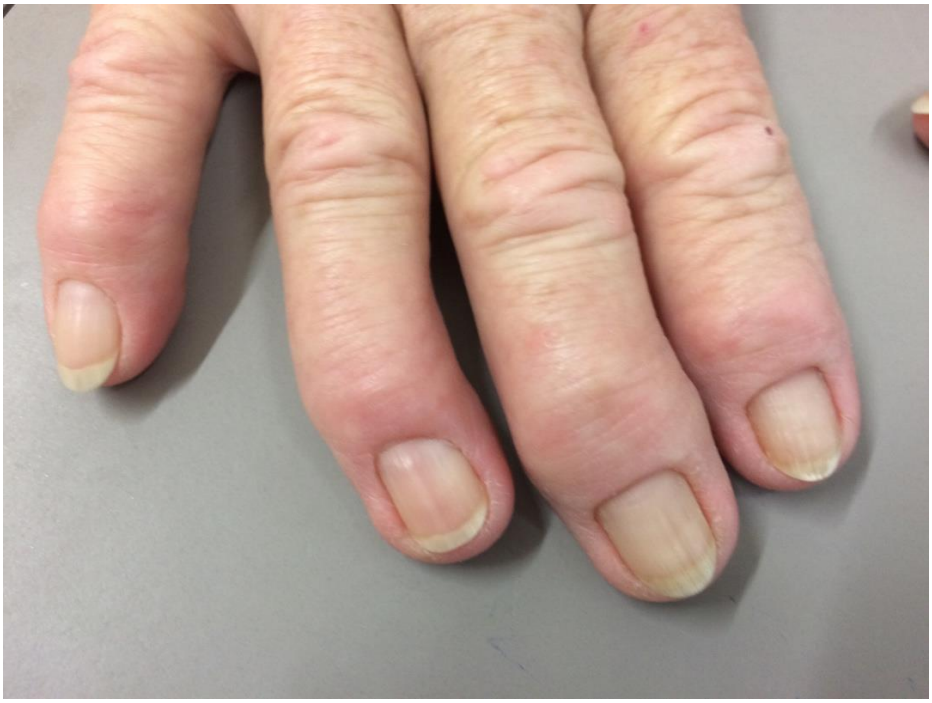

Figure 2. Fingernails of a 66-year old patient with early yellow nail syndrome. She had chronic cough and sinusitis as well as lymphedema of the lower legs and forearms. The nails of the index and middle fingers are whitish, the lunula is no longer visible, the cuticles are gone.

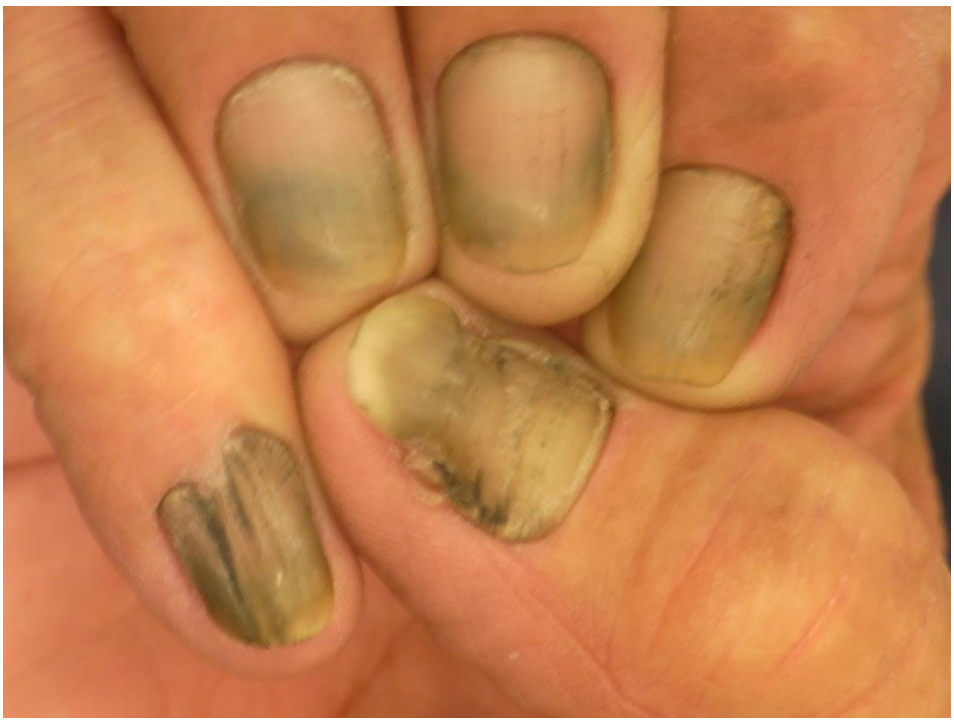

Figure 3. Fingernails of a 60-yer old man with yellow nail syndrome. He had chronic sinubronchitis and mild lymphedema of the lower leg. The nails are yellow with a distinct greenish tinge of the distal third to half, the cuticles are lost, the lunulae are not visible.

Conclusion

Yellow nail syndrome is a rare condition characterized by the triad of yellow nails, edema of the distal limbs and chronic bronchopulmonary infection. Although the full triad only exists in about 40% of the cases the nail changes are typical enough to allow a correct diagnosis to be made. The nails grow very slowly if at all, they become hard, detach from the nail bed, over curve both in transverse as well as longitudinal direction, and the cuticle disappears. The edema may be very mild and escape the patient's notice. Chronic infection of the airways, from sinusitis to bronchiectasia, is common and may be etiologically related; however, oncologic, hormonal, gastrointestinal and renal diseases were also observed. The importance of the yellow nail syndrome is that it has to prompt thorough internal medicine examinations.

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