

Role of Titanium in the Development of Yellow Nail Syndrome

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Key Words

Nail · Yellow nail syndrome · Titanium

Abstract

Yellow nail syndrome (YNS) is characterized by the triad of nail changes, lymphedema and respiratory tract involvement. Several hypotheses have been postulated to explain the findings in YNS including lymphatic drainage abnormalities along with microvasculopathy. The most recent hypothesis, proposed by Berglund and Calmark [Biol Trace Elem Res 2011;143:1–7], suggests a role of titanium dioxide in the development of YNS. This study showed elevated titanium levels (ranging from 1.1 to 170 µg/g of nail plate) in nail clippings or pieces of shed nail from 30 patients with YNS. Titanium was not found in the nails of healthy patients. Complete resolution was seen in 4 patients after removal of their titanium implants. Titanium dioxide is commonly found in cosmetics, sunscreens, medications, confectionaries and joint implants. Exposure to titanium can lead to its ions being released by galvanic action of dental gold or amalgam through the oxidative stress of fluorides. It is hypothesized that this galvanic interaction may lead to the yellow discoloration. At this point, cause and effect is speculative, but titanium may play a role in a subgroup of patients with YNS.

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Introduction

The triad of yellow nails, lymphedema and respiratory tract involvement characterizes the yellow nail syndrome (YNS). Most of the cases are sporadic with the clinical manifestations occurring later in life [1]. Lymphedema and respiratory symptoms may precede nail changes by many years. The pathogenesis is largely unknown, but several hypotheses suggest anatomic or functional lymphatic drainage abnormalities. These hypotheses are not able to explain nail changes or respiratory issues. Recent literature suggests a relationship between elevated titanium levels and the onset of YNS.

Case Report

A 67-year-old woman with a past medical history of hypertension presented with an 18-month history of 'nail loosening' and discoloration along with a 5-year history of bronchitis and sinusitis. Initial presentation consisted of a persistent cough treated with inhaled corticosteroids without improvement. Three years after the initial respiratory symptoms, the patient started experiencing nail changes including complete loss of the lunula, yellow discoloration of the nail plates, loss of the cuticles, shedding of multiple nails and marked reduction of growth rate of all nail plates (fig. 1, 2). Since the onset of nail changes, the patient's course has been complicated by *Pseudomonas aeruginosa* bronchitis and sinusitis.



Fig. 1. Absence of cuticles, yellow discoloration, nail plate thickening and increased transverse curvature seen in a 67-year-old female with YNS (right foot).



Fig. 2. Absence of cuticles, yellow discoloration, nail plate thickening and increased transverse curvature seen in a 67-year-old female with YNS (left foot).

She did not have any features of lymphedema. Treatment with vitamin E 1,600 IU/day was started. Titanium levels of nail clippings were analyzed by energy-dispersive X-ray fluorescence and found to be elevated at 4 $\mu\text{g/g}$ of nail plate (normal level 0.0 μg titanium/g of nail plate). The patient had 8 silver amalgam dental fillings and reported daily use of toothpaste containing fluoride. She also gave a history of regular titanium dioxide ingestion through cetirizine 10 mg daily and 4–8 pieces of chewing gum daily [2].

Discussion

Samman and White [3] first described YNS in 1964, and to date, there are approximately 150 reported cases. The characteristics include nail changes, lymphedema and respiratory tract involvement. The dermatologic manifestations of YNS are slow/arrested growth of the nail unit, increased transverse curvature, nail plate thickening, absence of cuticles and yellow discoloration [4]. The yellow discoloration of the nails is often a late manifestation and not necessary for the diagnosis. Pleural effusions are the most common lung changes. Bronchiectasis, sinusitis, chronic cough and recurrent pulmonary infections have also been reported. More recently, chronic sinusitis has been one of the early occurrences. Lymphedema is symmetric and nonpitting; lower extremities are affected more commonly than upper extremities. Both respiratory manifestations and lymphedema may precede nail changes by many years. Current treatment options for nail complications, such as pulse itraconazole/fluconazole and/or vitamin E 1,600 IU/day are controversial and without controlled clinical trials [5].

The first case series published in 1964 by Samman and White [3] showed diffusely hypoplastic lymphatics in 4/13 patients with YNS. A study completed by Nordkild et al. [6] in 1986 reviewed lymphangiographic data in the literature and found that 15 out of 18 patients with YNS had abnormalities of the lymph ducts that included lymphatic hypoplasia, extensive collateral networks and dilatation. Another study by D'Alessandro et al. [7] examined the pleural fluid from patients with YNS and found a higher protein content in patients with YNS suggesting microvasculopathy. However, none of these hypotheses explain the nail changes nor the improvement in lymphedema that can be seen with the treatment of respiratory problems.

The most recent hypothesis centers on the role of titanium in the development of YNS after a study by Berglund and Carlmark [8] showed elevated levels of titanium in the nails of their patients. The titanium levels of the nail clippings or small fragments of nails from 30 patients with one or more symptoms of YNS were measured by energy-dispersive X-ray fluorescence with a detection limit of 1 $\mu\text{g/g}$ of nail plate. The level of titanium ranged from 1.1 to 170 $\mu\text{g/g}$ of nail plate with shed nails having high levels. There was no correlation between the titanium levels and the yellowness or thickness of the nails. Sinusitis was the most common symptom. Exposure to titanium was from confectionaries, medications and titanium implants with concurrent gold dental inlays. Titanium was not found in the nails of healthy patients, even those exposed to titanium and gold.

Table 1. Exposure to titanium dioxide

Foods	Chewing gum Candy (especially the outer shell) Chocolate Products with white icing or powdered sugar topping Powdered product mixed into foods
Personal care items	Sunscreen Moisturizers Deodorants Shampoo Lip balms Toothpaste
Medications	Multivitamins Oral capsules Suspensions Tablets

Titanium is a low-density, high-strength transition metal with a silver color and can exist in many different forms. One of the most important forms is titanium dioxide, commonly found in sunscreen, medications, candy and color additives for cosmetics. Despite its strength, titanium dioxide is very susceptible to galvanic corrosion by fluorine and other metals.

Galvanic reactions can take place between metals with different reduction potentials either within the body or across the skin. Berglund [9] hypothesized that titanium ions are released due to the galvanic action of dental gold or amalgam through the oxidative stress of fluorides. Amalgam is an alloy of mercury and other metals used in

dental fillings. Exposure to titanium dioxide occurs from orthopedic implants along with ingestion of some medications or foods (table 1). Reports in the literature have suggested a role of medications in the development of YNS [10–12]. Initially thought to be secondary to the active ingredient, it may in fact be due to the presence of titanium dioxide in the formulation. In all of the cases, withdrawal of the medications led to the resolution of the patient's symptoms.

The low incidence of YNS seen in the overall population suggests that affected individuals are more susceptible to galvanic erosion, but the pathogenesis has not been elucidated. Cause and effect is speculative, but the role of titanium may play a role within a subgroup of patients. It is suggested here that amalgam and gold give rise to galvanic interaction between titanium dioxide and the yellow nail color. In the previously mentioned study by Berglund and Carlmark [8], 4 patients with titanium implants showed complete resolution of their symptoms after gold dental work was removed.

Additional studies need to be completed before a direct cause and effect relationship can be established. YNS is a distressing condition. Functional limitations can occur secondary to the respiratory issues and lymphedema; nail changes can often lead to cosmetic concerns. Dermatologists should consider the role of titanium dioxide in their YNS patients and take a thorough history to determine the amount of exposure. This entails asking about orthopedic implants, medication history along with diet history (focusing on candy and gum intake). Treatment options are limited at this time, but this hypothesis could change the way YNS is managed and treated.

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