

# Titanium Dioxide in Toothpaste Causing Yellow Nail Syndrome

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Yellow nail syndrome (YNS) is an uncommon disorder, the classic triad of which consists of yellow nails, lymphedema, and respiratory symptoms. Few pediatric cases have been reported. We report a 9-year-old girl with yellowish nail discoloration for 1 year accompanied by respiratory symptoms, including chronic cough, recurrent pneumonia, bronchiectasis, and chronic sinusitis. The patient was diagnosed with YNS. Knowing that a relationship between YNS and titanium has been reported, we collected her nail clippings and detected titanium in them by energy dispersive radiograph fluorescence. This patient's titanium exposure may have come from her habit of swallowing children's toothpaste. With meticulous avoidance of swallowing toothpaste, she had amelioration of her yellow nail discoloration as well as diminution of her respiratory symptoms. We reevaluated her nail clippings for titanium 3 years later, and no titanium was detected. This observation suggests that avoiding titanium exposure could alleviate the symptoms of YNS. This is the first report of YNS in a pediatric patient that demonstrates a relationship between YNS and titanium. We review the previous reports of pediatric patients with YNS.

Yellow nail syndrome (YNS), first described by Samman and White in 1964,<sup>1</sup> is an uncommon disorder characterized by the classic triad of yellow and dystrophic nails, lymphedema, and respiratory symptoms. It mainly affects people 40 to 60 years of age and is rare in the pediatric population.<sup>2</sup> Its pathophysiology and etiology remain unknown. In 2011, Berglund and Carlmark<sup>3</sup> described the relationship between YNS and titanium in adults. All of their patients with YNS had a history of exposure to titanium (by implants in the teeth or elsewhere) or titanium dioxide (by ingestion of drugs and confectionaries), and titanium was detected in the nails of each patient. Until now, the relationship between YNS and titanium had never been reported in children. In this report, we describe a 9-year-old girl who presented

with chronic cough and recurrent pneumonia. Dystrophic yellow nails were noted. YNS was diagnosed and additional respiratory imaging studies were evaluated. Titanium was detected in the patient's nail clippings. The association between titanium and the development of YNS may provide a new way to manage this condition.

## CASE PRESENTATION

Our research was reviewed and approved by the MacKay Memorial Hospital institutional review board. Informed consent was obtained from the patient's mother. The patient is a 9-year-old girl who presented with a spiking fever for 2 days and chronic cough for 6 months. One month before presentation, she was admitted to another hospital with lobar pneumonia and was treated with oral antibiotics after discharge. However,

## abstract

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**DOI:** 10.1542/peds.2016-0546

Accepted for publication Aug 31, 2016

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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**FINANCIAL DISCLOSURE:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** No external funding.

**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

**To cite:** Hsu T, Lin C, Lee M, et al. Titanium Dioxide in Toothpaste Causing Yellow Nail Syndrome. *Pediatrics*. 2017;139(1):e20160546



**FIGURE 1**  
Toenails and fingernails show typical features of YNS.

her productive cough and purulent nasal discharge did not improve. Physical examination was notable for coarse breath sounds with crackles in both lower lung fields. Chest radiograph disclosed pneumonia in the lower lobes bilaterally.

On admission, we noticed yellowish discoloration and thickening of nail plates in all of her fingernails and toenails (Fig 1). This manifestation was first noted 1 year previously, and the growth of her nails had been slow. High-resolution computerized tomography revealed bronchiectasis in the right middle lobe, left lingula, and lower lobes bilaterally (Fig 2). Bilateral air-fluid levels in a Waters' view of the maxillary sinuses suggested bilateral maxillary sinusitis (Fig 3).

Because the patient had yellow nails and respiratory manifestations, the diagnosis of YNS was made. Lymphedema was not observed in our patient, and none of her family members had YNS. The relationship between titanium exposure and YNS had been reported in a recent study,<sup>3</sup> so we collected the patient's



**FIGURE 2**  
Chest computed tomographic demonstrating bronchiectasis in the right middle lobe, left lingula, and bilateral lower lobes. R, right side; L, left side.

nails for additional evaluation. Nail clippings analyzed by energy dispersive radiograph fluorescence showed an elevated level of titanium ( $11.48 \mu\text{g/g}-1$ ). Titanium was not found in the nails of her family and 6 other healthy people. We therefore obtained a detailed exposure history of titanium. The patient had no history of orthopedic or dental implants. Her parents also denied a history of long-term use of antibiotics or other drugs, but she took antibiotics intermittently for pneumonia in the last month. There was no history of massive consumption of confectionaries or chewing gum. However, we surmised that when our patient brushed her teeth, she had a habit of swallowing a significant amount of children's toothpaste that contained titanium dioxide, which may be the source of titanium detected in her nail clippings.

In addition to optimal control of sinusitis and bronchiectasis with antibiotics and bronchopulmonary hygiene measures, we encouraged the patient to avoid the habit of swallowing toothpaste. The yellow discolored nails gradually detached from the nail bed in 2 to 3 months, and new nails grew in normally after she discontinued swallowing toothpaste. Her respiratory symptoms also improved over time. We reexamined her nails 3 years later, and no titanium was detected.



**FIGURE 3**  
Waters' view shows bilateral maxillary sinusitis. R; right side.

## DISCUSSION

YNS is an uncommon disorder. More than 300 cases have been reported in literature. In 1964, Samman<sup>1</sup> described 13 patients, all of whom had thickened and slow-growing yellow nails, and 10 of whom also had lymphedema. This was the first reported case series of YNS. In 1966, Emerson<sup>4</sup> added pleural effusion as a frequent feature of YNS. In 1979, Runyon et al<sup>5</sup> described the classic triad of YNS: yellow nails, lymphedema, and pleural effusion. Later, bronchochiectasis, rhinosinusitis, recurrent pneumonia, and chronic cough were also recognized as frequent manifestations of YNS.<sup>6</sup> Current opinion supports the replacement of pleural effusion with respiratory manifestations as the third criterion. The clinical features of YNS are variable among individuals and can vary over time. Only 27% of YNS patients have all 3 classic symptoms simultaneously.<sup>7,8</sup> Hiller et al<sup>6</sup> suggested the diagnosis of YNS can be made when a patient presents with 2 of the 3 classic symptoms at any given time without another explanation.

In a previous study, 89% of patients with YNS had yellow nail discoloration.<sup>9</sup> Typical abnormalities of the nails included yellow discoloration, thickening, slow

growth, transverse ridging, excessive curvature, and onycholysis.<sup>10</sup> YNS usually affects all 20 nails. Improvement of nail symptoms is often associated with treatment of the respiratory syndrome.<sup>11</sup> Lymphedema usually involves the lower limbs symmetrically, but it can also affect the upper limbs, face, and eyelids.<sup>12</sup> About 40% of patients with YNS present with pleural effusion. Most of the pleural effusions are bilateral (68.3%), consisting of exudates with lymphocytic predominance.<sup>13</sup>

The pathogenesis of YNS remains unknown. Some familial cases have been described<sup>14</sup>; however, most cases are sporadic or acquired. The hypothesized mechanisms of YNS include anatomic or functional lymphatic abnormalities and microvasculopathy with protein leakage.<sup>9,15,16</sup> However, these mechanisms cannot explain the nail abnormality, because patients who have lymphedema of any other etiology do not present with yellow nail discoloration.

Recently, a relationship between titanium and the development of YNS was reported. In 2011, Berglund and Carlmark<sup>3</sup> reported that all of their patients with YNS had a history of titanium exposure. In their 34 patients, 26 had received titanium implants; the other 8 patients were exposed to high amounts of titanium dioxide either in drug tablets or in confectionaries. Nail clippings of these patients were analyzed by energy dispersive radiograph fluorescence, and titanium was detected in all samples (range: 1.1–170 µg/g–1). Titanium was not found in the nails of healthy people, even those exposed to titanium.

Titanium is a lustrous metal with a silver color, low density, and high strength. In medical uses, titanium can be alloyed with aluminum or iron, among other elements, to produce strong, lightweight alloys for orthopedic or dental

implants. Berglund and Carlmark<sup>3</sup> hypothesized that titanium ions are released from titanium implants by galvanic actions with dental gold or amalgam implants or by the oxidative action of fluorine. Removal of gold could alleviate the symptoms of YNS. After Berglund and Carlmark's study,<sup>3</sup> there have been 3 subsequent reports that support their findings.<sup>17–19</sup> All of the reported patients had a history of titanium exposure preceding the development of YNS. The titanium levels from the patients' fingernails were all elevated. Withdrawal of titanium exposure led to improvement of the symptoms in the early stage of the disease,<sup>18</sup> but did not help in a patient with advanced disease.<sup>19</sup>

Another source of titanium exposure is by uptake of titanium dioxide from the digestive tract. The brightness and high refractive index of titanium dioxide have made it widely used as a color additive or coating agent in sunscreen, toothpaste, medication tablets, chewing gum, confectionaries, and cosmetics. YNS that is associated with taking medical tablets containing titanium dioxide has been repeatedly reported, and symptoms are at least partially reversible after discontinuing these drug tablets.<sup>3,20</sup> For our patient, a thorough history of titanium exposure suggested that swallowing of toothpaste was the potential cause of her YNS. With meticulous avoidance of swallowing toothpaste, she had amelioration of her yellow nail discoloration and her respiratory symptoms also improved over time. Furthermore, no titanium was detected in the nails 3 years later.

The hypothesis that YNS is related to titanium exposure may explain some characteristics of this syndrome. Most patients with YNS are middle-aged adults or elderly adults, and these groups of patients have a greater prevalence of implants. YNS

has been reported to be associated with other systemic diseases, such as malignancy,<sup>21,22</sup> thyroid disease,<sup>9</sup> nephrotic syndrome,<sup>23</sup> rheumatoid arthritis,<sup>20</sup> obstructive sleep disorder,<sup>24</sup> and tuberculosis.<sup>25</sup> The possible explanation is that patients with systemic diseases are more likely to be taking medicines that contain titanium dioxide.<sup>20</sup>

By contrast, YNS is rarely reported in children. In reviewing the 19 pediatric cases of YNS reported in the literature (Table 1), we found that 6 of them had a history of family tendency. Yellow nails and recurrent respiratory infections were the most common presentations. Lymphedema was present in 12 cases. Pleural effusion was present in 5 cases (4 at birth and 1 later). Bronchiectasis was diagnosed only in 4 cases. We find that there are 2 age peaks in the incidence of YNS. Most pediatric cases of YNS presented at birth, and 2 affected infants were born to mothers who had YNS.<sup>26,27</sup> Fetal hydrops may be the clinical presentation of lymphedema in newborns. We speculate that titanium may cross through the placenta from mother to baby. Another peak of incidence of YNS is between 6 and 10 years of age, which may be explained by the fact that children at this age have had exposure to candy or children's toothpastes that contain titanium dioxide.

Titanium is a widely used material, but YNS is a relatively rare syndrome. Only rarely do people exposed to titanium ever develop YNS. The duration and amount of titanium exposure, sensitization to titanium or titanium dioxide, susceptibility to galvanic erosion, and other coexisting factors may be responsible for development of YNS. It is likely that specific patients may have an underlying genetic or immunologic susceptibility to develop YNS when exposed to titanium or titanium dioxide. Additional research is warranted to determine the

**TABLE 1** Pediatric Cases of YNS

Ref. No.	Age at Presentation	Yellow Nails	Lymphedema	Respiratory Manifestations			Family History of YNS
				Pleural Effusion	Bronchiectasis	Recurrent Infection	
26	Neonate		V (fetal hydrops)	V			Yes (mother)
27	Neonate		V (fetal hydrops)			V	Yes (mother)
28	Neonate	V	V (fetal hydrops)			V	No
28	Neonate	V	V (fetal hydrops)			V	No
29	Neonate	V	V (fetal hydrops)	V			Siblings
29	Neonate	V					Yes (siblings)
29	Neonate	V					Yes (siblings)
30	Neonate	V		V			No
31	Neonate		V	V		V	Not mentioned
32	Neonate	V					No
33	Neonate	V			V	V	Not mentioned
34	Neonate	V	V			V	Not mentioned
12	7 mo		V	V			No
35	6 y	V	V		V	V	Not mentioned
36	6 y	V	V			V	Yes (father)
37	7 y	V				V	No
38	10 y	V	V		V	V	No
3	15 y	?	V				Not mentioned
Our case	8 y	V			V	V	No

V, symptom present; ?, not recorded.

relationship between YNS and titanium exposure.

Our patient presented with sinusitis and chronic cough, which are common findings in children. Without noting the nail changes, YNS can be easily overlooked and underdiagnosed by a physician. Therefore, we suggest that the diagnosis of YNS should be considered in children with chronic respiratory manifestations. If nail changes are found, energy dispersive radiograph fluorescence is an appropriate tool to analyze the titanium level in nail clippings.<sup>39</sup> Currently, there is no specific treatment for YNS; treatment decisions are always based on clinical judgment, and the responses are variable. Based on the hypothesis that YNS may result from titanium, physicians should trace the possible source of titanium dioxide exposure for their patients. Avoiding exposure to titanium dioxide may benefit children with this rare syndrome.

**ACKNOWLEDGMENT**

We thank Garefully Technology Co, Ltd, for their assistance in the analysis of the nail sample.

**ABBREVIATION**

YNS: yellow nail syndrome

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*Pediatrics* 2017;139;  
DOI: 10.1542/peds.2016-0546 originally published online December 7, 2016;

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