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CASE REPORT

Paraneoplastic Yellow Nail Syndrome: A Case Report

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Abstract

Yellow Nail Syndrome (YNS) is a rare clinical condition affecting multiple districts. Distinctive signs include nail abnormalities, pulmonary manifestations, and lymphedema. The aetiology is unknown; usually presents isolated or as a paraneoplastic syndrome.

There is no established treatment and resolution is limited. Low dose azithromycin with mucolytics and long-acting muscarinic antagonist could improve the respiratory component of the YNS when present. Here we describe a case of paraneoplastic YNS presenting with cough, sputum, rhinosinusitis, and nail discoloration appearing after a recent history of breast cancer.

In a patient with an oncological history, nail abnormalities associated with pulmonary manifestations and/or lower limbs lymphedema, the diagnosis of paraneoplastic YNS should be considered.

Abbreviations

YNS: Yellow Nail Syndrome; CT: Computed Tomography; OMIM: Online Mendelian Inheritance In Man

Introduction

Yellow Nail Syndrome (YNS) is a rare disorder characterised by the triad of yellow and thickened nails, respiratory manifestations and lower limbs lymphedema [1]. Two of these three clinical characteristics are required for a diagnosis [1]. Less than 400 cases have been described in literature, with a prevalence of < 1/1,000,000 [2]. The diagnosis is clinical, particularly based on nail abnormalities, pulmonary manifestations, lymphedema and sinusitis [2]. YNS is a condition of unknown aetiology that is usually sporadic or presents as a paraneoplastic syndrome [2,3]. Currently, there is no specific treatment for YNS [2]. Resolution has been observed in up to 30% of patients with paraneoplastic condition, either spontaneously or after cancer treatment [2]. Here we present a paraneoplastic case of YNS in a 67-years old never-smoker female who complained of chronic productive purulent cough for the last two years, after being diagnosed with breast cancer.

Corresponding author(s)*Alfano Franco**, Pulmonary Division, Emergency Department, University of Ferrara, St. Anna University Hospital, Ferrara, Italy**Email:** franco.alfano@edu.unife.it**DOI:** 10.37871/jbres2028**Submitted:** 15 October 2024**Accepted:** 24 October 2024**Published:** 27 October 2024**Copyright:** © 2024 Franco A, et al. Distributed under Creative Commons CC-BY 4.0 ⓘ**OPEN ACCESS****Keywords**

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Case Report

Case history

A 67-years old never-smoker female was referred to a respiratory outpatient clinic complaining of productive purulent cough for the last two years, despite treatments with antitussives. Two years earlier, the patient was diagnosed with left ductal mucinous breast cancer (G2 pT1No) and underwent quadrant surgery and local radiotherapy. The patient had been in remission since then and is currently receiving hormonal therapy with anastrozole. She had a history of atrial fibrillation (treated with warfarin), otitis, and sinusitis of recent onset (3 months). Family history was silent. High-resolution thoracic Computed Tomography (CT) revealed bronchiectasis in the lower right inferior bronchus with mucus plugs. Spirometry performed under stable conditions revealed mild obstruction. A short course of oral clarithromycin was ineffective in reducing respiratory symptoms. A thoracic CT scan performed after 6 months showed parenchymal consolidation (organising pneumonia) in the lower right lobe (Figure 1A). At this stage the patient was referred to our outpatient clinic.

She reported that during the last year, her nails had turned yellow, thicker and frail, with slowed growth of both fingers and toenails (Figure 1B). Onychomycosis was excluded by dermatologic evaluation and the Wood's lamp test. Chest examination showed expiratory rhonchi at the basis. No history of lower-limb lymphedema was reported, laboratory investigations showed no abnormal values. Owing to

persistent respiratory symptoms that were resistant to antibiotic therapy, bronchoscopy was performed, which showed purulent material dripping from the nasal districts and mucous-purulent secretions in the lower right bronchus in the absence of signs of malignancy. Based on the strict association between xantonychia, bronchiectasis, sinusitis, and recent breast cancer detection, in the absence of other concurrent diseases, a diagnosis of paraneoplastic YNS was made.

A short course of azithromycin (500 mg once daily for 3 days) was initiated, although the Bronchoalveolar Lavage (BAL) culture was negative. This resulted in partial remission of the productive cough. The patient was subsequently chronically treated with low-dose oral azithromycin (500 mg twice weekly), repeated regular courses of 600 mg N-Acetyl-L-Cysteine + Lactoferrin + Resveratrol combination, repeated regular courses of 100 mg oral Vitamin E, and daily 55 mcg of inhaled umeclidinium. Six-months after treatment initiation, the patient reported remission of the chronic productive cough, otitis, and sinusitis, but the yellow nails remained unchanged. The patient continues regular oncologist follow-ups and remains in remission.

Discussion

Yellow Nail Syndrome (YNS) - OMIM 153300; ORPHA662 - is a rare disorder characterised by a triad of yellow and thickened nails, respiratory manifestations and primary lymphedema [2]. Two out of these three clinical characteristics are required to diagnose YNS [2,3], as in the case here reported.

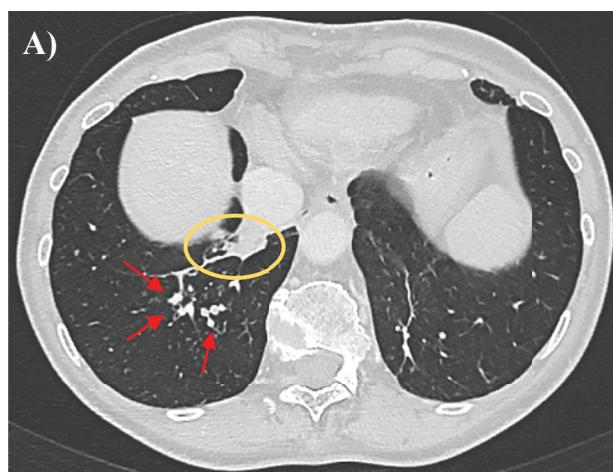


Figure 1 1A: Lower right lobe organizing pneumonia (yellow circle) with mucous plug bronchiectasis (red arrows). **1B:** Yellow fingernails with discoloration (chromonychia and xantonychia).

First described in 1927, this definition dates back to 1966 [4]. Fewer than 400 cases have been described in literature, with a prevalence of less than 1/1,000,000. YNS is a condition of unknown aetiology, is usually sporadic, and affects adults over 50 years of age worldwide, with no sex predominance [2].

The completed triad is present only in 27–60% of cases, with nail chromonychia being the main clinical manifestation, present in more than 85% of cases [2]. The diagnosis is clinical and based on nail abnormalities, pulmonary manifestations, lymphedema, and sinusitis. Chromonychia (nail discolouration), xantonychia (yellow nail coloration), progressive thickening and hardening of the nail plate, and slow growth (reduced by half) are the main characteristics of YNS [1,2,5]. Respiratory manifestations occur in 60–70% of patients, with chronic cough as the most frequent symptom [1,6]. Pleural effusion is present in up to 46% of cases, usually bilateral, with a latescent appearance (chylothorax) and bronchiectasis in 44% [1,2]. Both chronic and acute rhinosinusitis are common, presenting in 14 to 83% of cases with daily mucopurulent rhinorrhea and nasal obstruction [2].

Lower bilateral limb lymphedema is generally present in 29 to 80% of cases [2]. Lymphatic disorders with defective lymphatic drainage have been hypothesised as the causes of lymphedema, pleural effusion, and subungual tissue sclerosis with nail alterations [2,3]. Another hypothesis considers micro vasculopathy and protein leakage [3,6]. Replacement of the normal subungual stroma by fibrous and dense collagen deposits may reflect the lymphatic obstruction, leading to thickened and slow growth nails [7]. High titanium levels were also detected in the nails of YNS patients, possibly reflecting exposures to implants or surgical staples, medication excipients, food and cosmetics [2].

YNS may present as a paraneoplastic syndrome, associated with malignant diseases, such as lung and breast cancer or non-Hodgkin lymphoma [2]. Reviewing the current literature, we identified 20 cases of paraneoplastic YNS, 3 involving breast cancer (Table 1) [8–25]. The complete triad was present in half of the patients (10/20). In all these cases, paraneoplastic YNS was considered only when the malignancy was diagnosed in the intervening months during the YNS assessment. The paraneoplastic presentation could

Table 1: Yellow nail syndrome cases published in literature, associated with malignancies and clinical manifestations. YN yellow nails, including nail abnormalities, n/a information not available.

Patient	Associated malignancy	Age (years), sex	Features of YNS	Complete triad
#1	Lung [8]	n/a	YN, n/a	n/a
#2	Lung [9]	59, M	YN, pleural effusion, cough, lymphedema	Yes
#3	Lung [10]	51, M	YN, pleural effusion, lymphedema	Yes
#4	Lung [11]	66, M	YN, bronchiectasis, lymphedema	Yes
#5	Breast [12]	62, F	YN, chronic cough, sinusitis	No
#6	Breast [13]	52, F	YN, tracheobronchitis, lymphedema	Yes
#7	Breast [14]	n/a, F	YN, giant cell interstitial pneumonia	No
#8	Lymphoma [15]	39, M	Pleural effusion, lymphedema	No
#9	Lymphoma [16]	78, F	YN, pleural effusion, lymphedema	Yes
#10	Lymphoma [17]	61, M	YN, bronchiectasis	No
#11	Lymphoma [18]	72, M	YN, bronchitis, lymphedema	Yes
#12	Melanoma [19]	56, M	YN, bronchiectasis, rhinosinusitis	No
#13	Melanoma [20]	31, F	Bronchitis, pleural effusion, lymphedema	No
#14	Myeloma [21]	53, M	YN, pleural effusion, lymphedema	Yes
#15	Gastric [19]	71, M	YN, pleural effusion, sinusitis, lymphedema	Yes
#16	Fibrosarcoma [22]	72, M	YN, pleural effusion, lymphedema	Yes
#17	Kidney [13]	83, M	YN, bronchiectasis, pleural effusion	No
#18	Larynx [23]	66, M	YN, bronchiectasis	No
#19	Gallbladder [24]	54, F	YN, bronchiectasis, sinusitis	No
#20	n/a, probable endometrium [25]	n/a, F	YN, bronchiectasis, pleural effusion, lymphedema	Yes

be due to lymphatic micro-obstruction, possibly correlated with circulating tumour micro emboli [26], or due to cancer histopathology. Other diseases associated with YNS are autoimmune disorders and immunodeficiency [1,2]. The differential diagnosis is broad and includes asbestos-related disease, heart failure, connective tissue diseases, malignancies, and onychomycosis are the main ones [1]. Differential diagnosis of nail discolouration includes also planus lichen, chronic paronychia, psoriasis or alopecia areata and anti-rheumatoid drugs containing thiol compounds such as penicillamine, bucillamine and tiopronin [2].

To date there is no specific treatment for YNS [1]. Resolution has been observed in up to 30% of patients with paraneoplastic conditions, either spontaneously or after cancer treatment [2]. Oral α -tocopherol (vitamin E) at 1,000-1,200 IU/day, is considered the only partially effective agent on nail alterations [2,5]. Regular antifungal treatment (itraconazole or fluconazole) and oral zinc sulphate have also been attempted with little success [2]. A randomised study using a topical vitamin E preparation showed no difference compared to a placebo [27]. Acute exacerbations of bronchiectasis and sinusitis can be treated with antibiotics and symptomatic drugs, whereas for recurrent respiratory flare-ups or poor symptom control, low dose oral azithromycin (250 mg three times/week), and a physiotherapy program should be prescribed. Flu and pneumococcal vaccinations are recommended [2]. Surgical intervention for recurrent or large pleural effusions can be useful, while somatostatin analogues, such as octreotide, or ligation of the thoracic duct can be attempted for chylothorax [1,5]. Complete decongestive therapy is an option for lymphedema volume reduction [1,2].

Conclusion

Paraneoplastic YNS is a rare and often misdiagnosed syndrome of unknown origin characterised by yellow nails, pulmonary manifestations, and lymphedema. To date, only 20 cases are reported in literature. Treatment is generally supportive and spontaneous resolution may occur in up to 30% of cases. We report a paraneoplastic case of YNS that started with chronic cough and sputum production, rhinosinusitis, and nail discolouration. Respiratory symptoms improved with long-term antibiotic treatment in association with inhaled antimuscarinics and mucolytics.

Declaration of Interest

F. Alfano and G.L. Casoni have no conflicts of interest to declare. A Papi received grants for research from Chiesi, AstraZeneca, GSK, Sanofi and AIFA; consulting fees from Chiesi, AstraZeneca, GSK, Novartis, Sanofi, Avillion, Elpen Pharmaceuticals; lecture fees from Chiesi, AstraZeneca, GSK, Menarini, Novartis, Zambon, Mundipharma, Sanofi, Edmond Pharma, IQVIA, Avillion, Elpen Pharmaceuticals; advisory boards from Chiesi, Astrazeneca, GSK, Novartis, Sanofi, IQVIA, Avillion, Elpen Pharmaceuticals.

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