

## CASE REPORT

# Yellow nail syndrome in rheumatoid arthritis: an aetiology beyond thiol drugs

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## Abstract

Yellow nail syndrome (YNS) is a rare entity characterized by a triad of nail changes, lymphoedema and lung involvement. We report a 57-year-old man with rheumatoid arthritis (RA) and YNS. We have reviewed the previous case reports of RA and YNS and discuss the pulmonary manifestations.

## INTRODUCTION

Yellow nail syndrome (YNS) is characterized by a triad of slow-growing yellow nails, lymphatic oedema and sinopulmonary manifestations like sinusitis, bronchiectasis and pleural effusion. It has been associated with various malignancies and autoimmune diseases. Rheumatoid arthritis (RA) has been the most common association among autoimmune diseases. YNS has been reported to occur spontaneously or after initiation of treatment for RA. There are no case reports of spontaneous YNS with RA and bronchiectasis.

## CASE REPORT

A 57-year-old gentleman, a non-smoker, presented with persistent productive cough with mucoid sputum of 16 years duration. He had no associated symptoms of dyspnoea, fever, chest pain or haemoptysis. He had noticed progressive symmetric, swelling of both his lower limbs and discolouration of the nails for the past 6 years. He also complained of a symmetric inflammatory polyarthritis with involvement of small joints of the hand for 1 year. He did not have any family history of RA or YNS. On examination, his vitals were stable, and physical examination revealed bilaterally symmetric non-pitting pedal oedema extending to the lower

one-third of the thigh (Fig. 1). Cutaneous examination revealed the presence of dystrophic nails characterized by thickened nail plates with yellowish discolouration and an increased transverse curvature involving all finger and toe nails (Fig. 2). Musculoskeletal system examination revealed the presence of tenderness and limitation of movement of the bilateral metacarpophalangeal, elbow and knee joints. The rest of the systemic examination including respiratory system examination was within normal limits. Routine blood and urine investigations were normal. He was found to have high titres of rheumatoid factor (>736 IU/ml) and anti-cyclic citrullinate peptide (89 RU/ml). Sputum examination for acid fast bacilli was negative. Imaging of the thorax revealed multilobar peribronchial thickening with cylindrical and cystic bronchiectasis with no evidence of pleural effusion (Fig. 3). His spirometry showed obstructive airway disease. An echocardiogram ruled out cardiac impairment and pulmonary hypertension. A diagnosis of YNS with treatment-naive RA was made. Further investigations including HIV, HBsAg, anti-nuclear antibody, and anti-neutrophil cytoplasmic antibody done to rule out other associations were non-contributory. He was started on hydroxychloroquine, sulfasalazine and oral steroids for his RA. He was started on vitamin E 400 mg once daily for his yellow nails. He was initiated on tiotropium and deriphyllin along with

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Figure 1: Clinical photograph showing bilateral non-pitting pedal oedema.



Figure 2: Clinical photograph showing dystrophic nails characterized by thickened nail plates with yellowish discoloration and an increased transverse curvature involving all finger and toe nails.

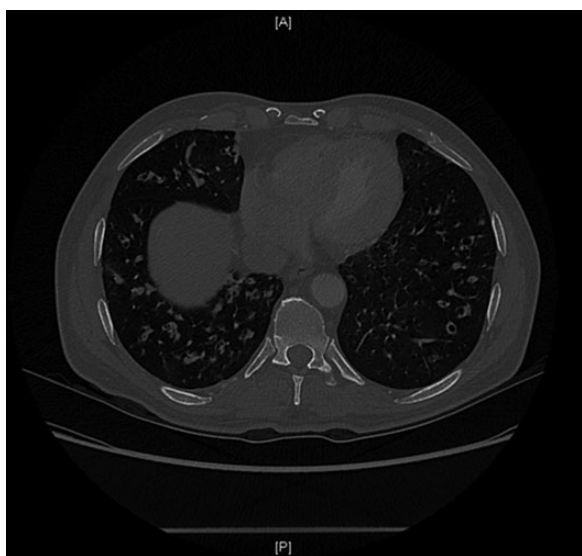


Figure 3: Computed tomography scan of the thorax showing multilobar peribronchial thickening with cylindrical and cystic bronchiectasis.

bronchial hygiene and pulmonary rehabilitation. He was advised compression stockings, manual lymphatic drainage measures and leg end elevation for his lymphoedema.

## DISCUSSION

YNS was first described by Samman and White. This syndrome comprises three elements namely yellow nails, lymphoedema and pleuropulmonary disease [1]. YNS commonly affects patients in the age group between the fourth and sixth decades, though it can occur at any age and involves both the sexes equally. In a case series of 97 patients, Nordkild identified that yellow nails, lymphoedema and respiratory involvement were present in 99, 80 and 63% of patients, respectively [2]. Only 40–60% of patients with YNS have the full triad of yellow nails, lymphoedema and chronic respiratory manifestations [3]. As some of the manifestations of YNS are inconsistent and variable over time, it has been proposed that the presence of any two of the three manifestations in the absence of other contributory causes can strongly suggest the diagnosis.

The pathogenesis of YNS is considered to be secondary to impaired lymphatic drainage secondary to anatomical or functional abnormalities in the lymphatic system. This is considered to be the cause of the peripheral oedema and the pleural effusions that are seen in most patients with YNS. Classical non-pitting, non-tender lymphoedema is mostly localized to both the lower limbs and has been attributed to dysfunction of the lymphatic vessels, which in itself could be spontaneous or secondary to other mechanism [4]. There is a report of ectatic endothelium-lined vessels being found in the nail bed of patients with YNS. The oxidation of lipids in the nail plate to lipofuscin is considered to be the cause of the yellowish discoloration of the nails. The nail manifestations that have been described in the literature include the following: thickening of the nail plate, transverse ridging, increased lateral curvature, diminished lunulae, chronic paronychia and onycholysis [4]. The rate of nail growth is said to be very slow (0.1–0.25 mm/week) when compared with the normal (0.5–2 mm/week) [5].

YNS has been known to be associated with various malignancies, connective tissue diseases and endocrine abnormalities. It can also be induced by certain drugs [4]. RA has been described as the most common connective tissue disorder associated with YNS. David et al. in 2002 described 24 patients with RA and YNS [5]. Sixteen more cases fulfilling the triad of YNS in patients with RA have been reported till 2015 (Table 1) [3, 6–9, 11–14]. YNS in RA has been subdivided into two types: drug-induced and spontaneous [5]. Most of the reports of YNS in RA are drug induced, which have been attributed to be secondary to drugs such as penicillamine, gold, bucillamine and tiopronine [5]. The most common drug implicated in drug-induced YNS in RA has been bucillamine. This drug has been developed and approved for RA in Japan; therefore, most cases of bucillamine-induced YNS in RA have been reported in the Japanese literature [8]. Most of the drugs causing drug-induced YNS in RA belong to the thiol group of drugs, and it has thus been postulated that their characteristic structure may be implicated in the pathogenesis [10]. Of the 29 patients of YNS in RA represented in Table 1, the mean age was 62 years [30–81]. As described by Nakagomi, we also found a female preponderance of cases with a male to female ratio of 1:3 [8]. The most common drug causing YNS was bucillamine (50%) followed by penicillamine (10%), gold, tiopronine and methotrexate (7% each). Of the 28 patients with RA who had the complete triad of YNS, only 3 were treatment naive. We report the fourth patient of treatment-naive RA who developed spontaneous YNS.

Maldonado analysed chronic respiratory manifestations of 41 patients with YNS and reported pleural effusion, bronchiectasis, chronic sinusitis and recurrent pneumonia in 46, 44, 41 and 22%,

Table 1: YNS in association with RA

| Number | Study (year)                         | Patient age | Sex | Pulmonary manifestation                       | Treatment                   |
|--------|--------------------------------------|-------------|-----|---|-----------------------------|
| 1      | Sharwill et al. [5] (1966)           | –           | F   | +   | Gold                        |
| 2      | Mattingly et al. [6] (1979)          | 30          | F   | Pleural effusion                              | Penicillamine               |
| 3      |                                      | 56          | F   | Pleural fibrosis and adhesion                 | Penicillamine               |
| 4      |                                      | 59          | F   | Pleural effusion                              | –                           |
| 5      | Dreno et al. [7] (1981)              | 77          | M   | +   | –                           |
| 6      |                                      | 66          | F   | +   | –                           |
| 7      | Dubost et al. [5] (1990)             | 59          | F   | +   | Penicillamine               |
| 8      | Kikuchi et al. [5] (1990)            | 46          | F   | Pleural effusion                              | Bucillamine                 |
| 9      | Tojo et al. [8] (1993)               | 48          | F   | Chronic bronchitis                            | Bucillamine                 |
| 10     |                                      | 67          | F   | Interstitial lung disease                     | Bucillamine                 |
| 11     |                                      | 58          | F   | Pneumonia                                     | Bucillamine                 |
| 12     | Tujiya [8] (1997)                    | 59          | F   | Chronic bronchitis                            | Bucillamine                 |
| 13     | Launay et al. [9] (1997)             | 66          | M   | +   | Gold                        |
| 14     | Harada et al. [8] (2000)             | 70          | F   | Bronchiectasis                                | Bucillamine                 |
| 15     |                                      | 65          | F   | Chronic bronchitis                            | Bucillamine                 |
| 16     | Iwahori et al. [8] (2001)            | 50          | F   | Pleural effusion                              | Bucillamine                 |
| 17     | Nakatsue et al. [8] (2001)           | 46          | F   | Pleural effusion                              | Bucillamine                 |
| 18     | Lehuede et al. [10] (2002)           | 72          | F   | +   | Tiopronine                  |
| 19     |                                      | 74          | F   | +   | Penicillamine               |
| 20     | David-Vaudey et al. [5] (2002)       | 75          | M   | Bronchiectasis and bilateral pleural effusion | Tiopronine                  |
| 21     | Chuujuo et al. [8] (2004)            | 71          | F   | Pleural effusion                              | Bucillamine                 |
| 22     | Tanaka et al. [8] (2006)             | 45          | F   | Pneumonia                                     | Bucillamine                 |
| 23     | Isozaki et al. [11] (2010)           | 67          | F   | Bronchiectasis                                | Bucillamine                 |
| 24     | Giulia Carnassale et al. [12] (2011) | 66          | M   | Bronchiectasis                                | Methotrexate                |
| 25     | Hirofumi Taki et al. [3] (2012)      | –           | –   | Bronchiectasis                                | Thiol compound therapy      |
| 26     | Samjot SD et al. [13] (2012)         | 73          | F   | Bronchiectasis and pleural effusion           | Methotrexate and infliximab |
| 27     | Ariyoshi et al. [14] (2013)          | 81          | M   | Bilateral pleural effusion                    | Bucillamine                 |
| 28     | Nakagomi D et al. [8] (2013)         | 75          | M   | Bilateral pleural effusion                    | Bucillamine                 |
| 29     | Mishra AK et al.                     | 57          | M   | Bronchiectasis                                | –                           |

respectively [4]. Our findings were similar to more than 45% having pleural effusion. Pleural effusion either unilateral or bilateral is the most common respiratory manifestation even in the subgroup of patients with RA-associated YNS [4]. While the previous three treatment-naïve patients had pleural effusion, this is the first report of RA-associated spontaneous YNS presenting with bronchiectasis.

Management of YNS in drug-induced RA includes discontinuation of the offending agent [15]. Nakagomi reported that discontinuation of bucillamine resulted in improvement of yellow nail, lymphoedema and pulmonary manifestations in 90, 31 and 35% patients, respectively [8]. The pathogenesis of YNS is heterogeneous, and further research needs to be done to elucidate the exact pathogenesis of the disease, in particular the drug-induced subset. There are anecdotal reports of treatment of the nail involvement with azole group of antifungals, vitamin E, zinc and intralesional triamcinolone. Management of pleural effusion has been chemical pleurodesis with agents like tetracycline and talc powder [6, 16, 17].

We report this case owing to its rarity. The patient described in this report is the fourth patient of RA in the literature developing spontaneous YNS and the first case report of treatment-naïve RA with YNS and bronchiectasis.

## CONCLUSION

YNS is a rare clinical entity, which has been known to be associated with various autoimmune diseases, prime among them being RA. YNS in RA can be broadly classified into spontaneous

or drug induced. The most common drug implicated in the drug-induced variant of YNS in RA is bucillamine. Pleural effusion is the commonest pulmonary manifestation in both the subsets of YNS in RA. The patient described in this report is the fourth patient of RA in the literature developing spontaneous YNS and the first case report of treatment-naïve RA with YNS and bronchiectasis.

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## CONFLICT OF INTEREST STATEMENT

None declared.

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Self.

## ETHICAL APPROVAL

Ethical clearance was obtained from Institutional Review Board of Christian Medical College and Hospital, Vellore.

**CONSENT**

Patient consent was obtained.

**GUARANTOR**

Leni George.

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