Yellow nail syndrome

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Purpose of review

The yellow nail syndrome (YNS) is a rare disorder of unknown cause characterized by the triad of yellow and thickened nails, lymphedema and respiratory manifestations. We review the current state of knowledge, particularly regarding the diagnosis and management of this disorder.

Recent findings

Available data suggest acquired lymphatic dysfunction to be the predominant mechanism underlying the clinical manifestations of YNS. The clinical features are variable among individuals diagnosed to have this disorder, and these features can vary over time. Although many disorders have been reported to be associated with YNS, there is no consistent theme in these associations. Longevity of patients with YNS is modestly reduced when compared with a control population. There is no specific treatment for YNS, but most patients can be managed with supportive measures aimed at ameliorating various clinical manifestations.

Summary

The pathogenesis of YNS remains poorly defined. The diagnosis is established on the basis of characteristic clinical features including abnormal nails, lymphedema and respiratory manifestations. The clinical course is generally benign, and current treatment aims to control the various clinical manifestations of this obscure disease process.

Keywords

chylothorax, lymphedema, pleural effusions, yellow nail syndrome

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Introduction

The yellow nail syndrome (YNS) is a rare disorder of unknown cause characterized by the triad of yellow and thickened nails, lymphedema and respiratory manifestations [1–3]. It was first described by Samman and White [3] in 1964, and approximately 150 cases have been reported in the literature, consisting of small case series or isolated case reports. Hence, the pathogenesis, clinical presentations and natural history of this disorder remain, for the most part, obscure. Available data suggest acquired lymphatic dysfunction to be the predominant mechanism underlying the clinical manifestations of YNS.

Historical aspects

Although Samman and White [3] are usually credited for introducing the term 'yellow nail syndrome' and providing the original description of the disorder, the first reported cases can probably be attributed to Heller who in 1927 described two patients with abnormal yellow nails and peripheral edema. In a review article on nail disorders published in 1962, Samman and Strickland [4] presented 41 patients with various nail abnormalities, four of whom also had evidence of lymphedema, a condition thought to result from impaired peripheral circulation. Samman and White [3] published the first case series of YNS in 1964. Thirteen cases were presented, all having in common the presence of thickened yellow and slow-growing (<0.25 mm/week) nails, in association with lymphedema in 10 of 13 patients. Lymphangiographic data were presented for four of these 13 patients and were abnormal in all, revealing diffusely hypoplastic lymphatic vessels. Impaired lymphatic drainage was offered as the explanation for the diffuse peripheral edema observed in these patients, but whether it could also explain the nail findings was unclear.

In 1966, Emerson [1] reported the association of YNS with pleural effusions, a frequent manifestation of the syndrome. Runyon, in 1979, suggested that a triad of symptoms including yellow nails, lymphedema and pleural effusions was the most characteristic presentation of YNS. Finally, the observation that some of these findings may resolve over time led Hiller *et al.* to suggest that the presence at any given time of two of these three manifestations was sufficient to establish the diagnosis of YNS [2].

Pathogenesis

As stated above, the prevailing concepts regarding the pathogenesis of YNS are based on the presence of anatomic or functional lymphatic abnormalities thought to be responsible for the various manifestations observed. The initial lymphangiographic characteristics of four of the 13 patients described by Samman and White [3] in 1964 constitute the cornerstone of this hypothesis. Nordkild *et al.* [5] in 1986 reviewed the lymphangiographic data available in the medical literature and noted that anatomic abnormalities of the lymphatic ducts were noted in the majority of cases (15 of 18 patients) and included lymphatic hypoplasia, dilatations and extensive collateral lymphatic network. These anatomic abnormalities, however, are not universally described in cases of YNS and can be difficult to reconcile with the frequent improvement of peripheral edema over time, a phenomenon rarely encountered in other forms of lymphedema. Functional lymphatic abnormalities have been suggested as a more likely explanation and have been documented in some cases of YNS via lymphoscintigraphy. For example, Bull *et al.* [6] reported 17 cases of YNS of whom nine had lower extremity swelling and two had features of lymphedema. Interestingly, lymphatic drainage as assessed by lymphoscintigraphy was reduced in the legs of patients with YNS when compared with normal controls, albeit not to the level typically observed in lymphedema.

Runyon *et al.* [7] analyzed pleural fluid turnover using a protein-bound dye and demonstrated decreased lymphatic flow to be responsible for the development of pleural effusion and appeared to support the notion of functional lymphatic abnormality in YNS. The biochemical feature of pleural effusions in YNS, characterized by a high protein content but transudative by all other criteria, would be consistent with this explanation. Histologic investigations pertaining to the lymphatic dysfunction hypothesis have yielded conflicting results. Solal-Celigny *et al.* [8] reported light and electron microscopy findings in a patient with YNS after a pleurectomy was performed for recurrent pleural effusions in 1983. The pleura was thickened with chronic inflammation, and dilated lymphatic capillaries were observed, similar to previous reports. In a recently published case series, pleural biopsy specimens were available for seven of 41 patients [9••]. Although chronic pleural inflammation was again noted, lymphatic vessels appeared grossly normal. Functional lymphatic disorder, rather than structural disease, is currently favored as the shared pathogenic mechanism for the development of pleural effusions and lymphedema.

The nail manifestations are more difficult to explain solely on the basis of lymphatic dysfunction. Ectatic endothelium-lined vessels, possibly lymphatic in nature, have been described in the nailbed of patients with YNS [10]. The nail manifestations of YNS appear to vary over time and have occasionally been reported to evolve in parallel with the respiratory manifestations of the syndrome [8,9••]. Some authors have suggested that oxidation of lipids in the nail plate may lead to accumulation of lipofuscin, a pigment responsible for the characteristic discoloration of the nails [11].

Likewise, the mechanism of recurrent upper and lower airway infections frequently encountered in this syndrome is unclear. Impaired lymphatic drainage at the microcirculation level may delay bacterial clearance of bacteria and promote microbial proliferation, ultimately leading to the well recognized complications of bronchiectasis and chronic sinusitis observed in this disease [12].

Recent studies have suggested that microvasculopathy with protein leakage, rather than lymphatic dysfunction, may be a more likely explanation for the various manifestations of YNS, based on the observation that more than 20% of patients with lymphedema have evidence of protein-losing enteropathy due to small bowel lymphangiectasia [12,13]. Several such cases of YNS with exudative enteropathy have been described. The resultant hypogammaglobulinemia and lymphopenia were thought to contribute to the high rate of respiratory infections observed in patients with YNS. Although this is an interesting hypothesis, hypoalbuminemia and microvasculopathy are uncommonly observed in YNS [9••].

Few case reports of familial YNS have been described; an autosomal dominant pattern of transmission is sometimes mentioned in the literature, in spite of scarce evidence to support YNS as an inheritable disorder [9••,14–16]. Most cases are sporadic with clinical manifestations occurring relatively late. Very few pediatric cases have been reported [17].

Overall, the evidence to date suggests that the lymphatic dysfunction observed in YNS is an acquired disorder rather than a congenital one. No environmental exposure has been implicated, and smoking does not seem to play an important role in the pathogenesis of the disease. The frequent observation that severe respiratory infections predate the development of lymphedema suggests that infections may serve as a trigger to overwhelm an already 'saturated' dysfunctional lymphatic network. These conclusions are speculative as our understanding of the pathogenesis of YNS is primarily based on anecdotal observations.

Clinical features

Males and female patients are equally affected and typically present between the 4th and 6th decades

Table 1 Clinical features of yellow nail syndrome

Abnormal nails	Lymphedema	Respiratory manifestations
Yellow discoloration	Lower extremities, upper extremities or face	Cough or shortness of breath
Slow growth (<0.25 mm/week)	Hypoplastic or dilated lymphatic ducts or both on lymphangiography	Pleural effusion (chylous or nonchylous)
Abnormal thickening	Delayed lymphatic drainage on lymphoscintigraphy	Bronchiectasis
Transverse ridging		Chronic sinusitis
Excessive curvature		
Onycholysis		

[9••]. A preceding severe respiratory illness is occasionally described. Clinical features of YNS are outlined in Table 1.

Nail findings

The 'yellow nail' terminology only captures some of the nail changes observed in YNS. More consistent is the abnormally slow growth of the nails (<0.25 mm/week), as described in the original report by Samman and White in 1964 and later confirmed by other authors [2,3,5]. Most reported cases include patients manifesting abnormal nails, as the diagnosis is hardly ever considered otherwise. Other nail findings include thickening, transverse ridging, excessive curvature from side to side, uneven pigmentation, diminished lunulae and onycholysis. Severe transient pain of the nail beds may precede these findings (personal observation). Fungal cultures of the nails, by definition, do not demonstrate any microbial growth. The nail changes are variable over time. In fact, several authors have reported some improvement in the nail abnormalities with better control of the respiratory manifestations or decongestive therapy for lymphedema [8,9••,18].

Lymphedema

Lymphedema is present in the vast majority of patients with YNS (80%) and is the presenting symptom in one-third of the cases [11]. It is nonpitting and typically involves the lower extremities in a symmetric fashion. Lymphedema has also been described in the upper extremities, face and occasionally in the peritoneal cavity with ascites. Pericardial effusions may also occur (up to 10% in the largest case series) [9••].

A typical lymphangiographic finding is the local persistence of the dye in the dorsum of the feet, months after injection [19]. Other abnormal features include dilated or hypoplastic lymphatic ducts, but these studies may also yield unremarkable results. Lymphoscintigraphy may reveal delayed lymphatic drainage, occasionally in an asymmetric fashion, but may also be normal [5,6,18,20,21].

One characteristic of the lymphedema associated with YNS is its potential for improvement, a characteristic generally not observed in other forms of lymphedema. As described for the nail changes, improvement of lymphedema has been observed with better control of respiratory manifestations, supporting the hypothesis that a precipitating factor may lead to decompensation of a deficient lymphatic network (second-hit hypothesis). Soft tissue infections of the lower extremities from chronic stasis are rarely observed.

Respiratory manifestations

Respiratory manifestations are diverse. Cough and shortness of breath are the most common presenting symptoms. Pleural effusions, usually bilateral, are relatively common (40% of cases). Pleural fluid is typically exudative by the protein criterion but in the transudative range by cholesterol and lactate dehydrogenase criteria. Lymphocytic predominance is the rule on cellular analysis. Chylothorax accounts for 30% of all pleural effusions [9••]. Infections of the pleural space are exceedingly rare. The management of these pleural effusions can be difficult, with a tendency to recur. In most cases, symptomatic pleural effusions can be managed by serial thoracenteses, pleurodesis or thoracic duct ligation (for chylous effusions) [9••].

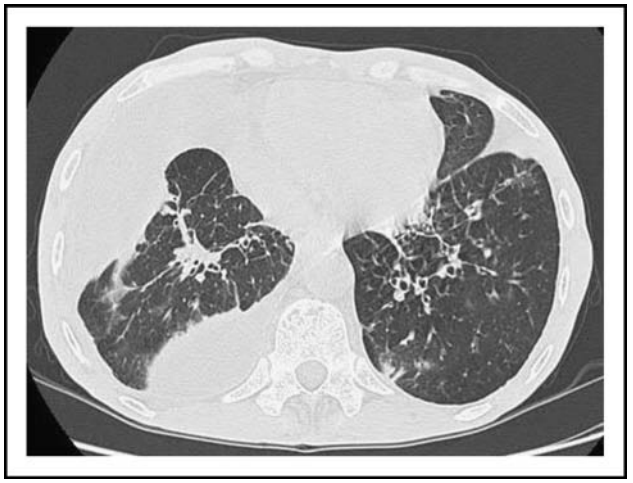
Bronchiectasis and recurrent lower respiratory tract infections are present in almost half of the patients. The bronchiectasis tends to affect lower lobes bilaterally, as evidenced by high-resolution CT in patients with YNS (Fig. 1) [9••,22]. Lower respiratory tract infections consist of exacerbations of bronchiectasis or pneumonias. *Staphylococcus aureus*, *Haemophilus influenzae* and *Moraxella catarrhalis* are the commonly encountered pathogens [9••]. Chronic colonization by *Pseudomonas aeruginosa* has also been described [23]. Chronic sinusitis is present in 40% of patients [9••].

Pulmonary function studies are frequently abnormal (80% of patients) and typically reveal an obstructive pattern that may respond to bronchodilators [9••,11]. Restrictive lung defects are less common and usually are associated with the presence of pleural effusions.

Disorders associated with yellow nail syndrome

YNS has been described in association with a variety of conditions, but most of these associations are probably spurious.

Figure 1 Chest CT of a patient with yellow nail syndrome demonstrating bronchiectasis involving both lower lobes and bilateral pleural effusions (larger in the right chest and partly loculated)



Reported associations with yellow nail syndrome are as follows:

(1) malignancies,
(2) immunodeficiency states,
(3) connective tissue diseases,
(4) diabetes mellitus,
(5) thyroid dysfunction,
(6) hemochromatosis,
(7) obstructive sleep apnea,
(8) Guillain–Barré syndrome,
(9) xanthogranulomatous pyelonephritis,
(10) tuberculosis,
(11) myocardial infarction,
(12) nephrotic syndrome,
(13) exudative enteropathy,
(14) hypoalbuminemia,
(15) drugs (thiol compound therapy).

Reports on associated conditions have included several malignancies, such as bronchogenic carcinoma [24], breast cancer [25], endometrial carcinomas [26] and lymphoproliferative disorders [27,28]. Others have included immunodeficiency states [28–30], connective tissue diseases [4,31,32], endocrine disorders [5,30,33,34], obstructive sleep apnea [35], Guillain–Barré syndrome [36], xanthogranulomatous pyelonephritis [37] and tuberculosis [38]. It is interesting to note that the original description of YNS occurred in association with Raynaud's phenomenon, and that some authors have described dilated capillary loops in the nails of patients with YNS [4,10], similar to that seen in Raynaud's phenomenon, perhaps supporting the hypothesis of microvasculopathy.

Diagnostic criteria

The diagnosis of YNS is essentially a clinical one and based on the presence of characteristic findings including abnormal nails, lymphedema and respiratory manifestations that may include pleural effusions, bronchiectasis and sinusitis among others. The early recognition that some of the manifestations of YNS are inconsistent and variable over time has led to the general consensus that two of the three manifestations of YNS may be sufficient to strongly suggest the diagnosis in the absence of another plausible explanation [2]. Nonetheless, it would be difficult to suggest the diagnosis of YNS in the absence of nail abnormalities. However, the nail findings in YNS seem to be the most variable finding, and a history of nail changes should be sought in the presence of other suggestive manifestations [9••]. Most reported cases of YNS have included patients with obvious clinical manifestations and may not reflect the true spectrum this disorder. It appears likely that patients with more subtle features continue to elude proper diagnosis.

Treatment

Respiratory manifestations of bronchiectasis can be controlled with a combination of postural drainage and other bronchopulmonary hygiene measures, in combination with the judicious use of antimicrobial therapy. The management of pleural effusions is tailored to the size of the effusions, symptoms and the clinical context. Therapeutic thoracenteses may suffice in controlling symptomatic pleural effusions, with pleurodesis being considered for managing recurrent effusions. Thoracic duct ligation is also an option in the treatment of recurrent symptomatic chylothorax. The role of low-fat diet or total parenteral nutrition in the management of chylothorax is not entirely clear.

The nail manifestations eventually improve in the majority of patients, often without specific treatment. This improvement may follow better control of respiratory and lymphatic manifestations, which has led some authors to describe the nail manifestations as the 'barometer' of YNS [8]. The use of topical steroids or vitamin E has been described though the evidence supporting their use remains scarce [9••,18]. Lymphedema tends to persist, though dramatic and durable improvements have sometimes been noted with decongestive therapy.

Prognosis

Relatively little is known about the natural history of YNS. The largest case series suggests that life expectancy is modestly reduced when compared with that of the general population [9••]. Progression of respiratory manifestations to respiratory failure is rare.

Conclusion

The YNS remains a rare and intriguing disorder of unclear cause. Lymphatic dysfunction probably represents the pathogenic mechanism responsible for the various clinical manifestations associated with this disorder. Most clinical manifestations of YNS are generally manageable with supportive measures, and the long-term prognosis appears favorable.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 395).

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