

REVIEW

Characteristics of patients with yellow nail syndrome and pleural effusion

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ABSTRACT

Yellow nail syndrome (YNS) can be associated with a pleural effusion (PE) but the characteristics of these patients are not well defined. We performed a systematic review across four electronic databases for studies reporting clinical findings, PE characteristics, and most effective treatment of YNS. Case descriptions and retrospective studies were included, unrestricted by year of publication. We reviewed 112 studies (150 patients), spanning a period of nearly 50 years. The male/female ratio was 1.2/1. The median age was 60 years (range: 0–88). Seventy-eight percent were between 41–80 years old. All cases had lymphoedema and 85.6% had yellow nails. PEs were bilateral in 68.3%. The appearance of the fluid was serous in 75.3%, milky in 22.3% and purulent in 3.5%. The PE was an exudate in 94.7% with lymphocytic predominance in 96% with a low count of nucleated cells. In 61 of 66 (92.4%) of patients, pleural fluid protein values were >3 g/dL, and typically higher than pleural fluid LDH. Pleurodesis and decortication/pleurectomy were effective in 81.8% and 88.9% of cases, respectively, in the treatment of symptomatic PEs. The development of YNS and PE occurs between the fifth to eighth decade of life and is associated with lymphoedema. The PE is usually bilateral and behaves as a lymphocyte-predominant exudate. The most effective treatments appear to be pleurodesis and decortication/pleurectomy.

Key words: chylothorax, decortication/pleurectomy, empyema, pleural effusion, pleurodesis, yellow nail syndrome.

Abbreviations: ADA, adenosine deaminase; LDH, lactate dehydrogenase; PE, pleural effusion; PF, pleural fluid; YNS, yellow nail syndrome

INTRODUCTION

The yellow nail syndrome (YNS) is a rare disorder characterized by the presence of the triad of thickened, slow-growing yellow nails, lymphoedema and chronic respiratory symptoms. The latter include rhinosinusitis, chronic cough, recurrent pulmonary infections, bronchiectasis and pleural effusion (PE).^{1,2} Samman and White³ described the first cases, but it was Emerson who demonstrated the association of YNS and PE.⁴ Up to 2009, an estimated 150 cases of YNS have been published.⁵ The pathophysiology of the disease is unclear, although it has been suggested that it is due to different disorders, both functional and anatomical, of lymphatic drainage.^{6–8} Recent speculation suggests that there may be a contributing increase in microvascular permeability.⁹ Although there are some cases of family YNS,¹⁰ the most accepted hypothesis is that it is an acquired rather than hereditary disease.¹¹ Cases of YNS have been associated with connective tissue diseases,¹² neoplasms,^{13,14} immunodeficiencies,¹⁵ endocrine diseases or drugs,¹⁶ among others, but a relationship has yet to be established.¹ The diagnosis of YNS is established with the presence of two of the three elements of the triad simultaneously;² and all characteristics are observed in only one-third of patients.⁴

PE is present in about 40–50% of cases of YNS.^{5,17} There are no sufficiently large series describing its features and our aim was to document the characteristics of patients with YNS and PE, evaluate the characteristics of the pleural fluid (PF) and elicit the most effective treatment for recurrent, symptomatic PE.

MATERIAL AND METHODS

This systematic review employed a methodology based on the principles of the PRISMA study.¹⁸ Because there are insufficient large series that respond to the needs of the study, the cases described in the literature were added using this methodology.

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Selection criteria

Deemed eligible for inclusion were all cases described as YNS or hereditary lymphoedema and PE of any age published in any format, except abstracts of papers presented at conferences and editorials, reviews or letters to the editor that did not document new cases.

Sources of information

The search strategy included several sources of free databases available by the year of publication, although the full text of the study had to be in English, Spanish, German, French, Italian or Portuguese. The literature search included the following electronic databases (online): Medline (through Pubmed interface), Embase, Scopus and Web of Science. Searches were conducted between September 1 and October 31, 2013. The following search terms were adopted for each database:

- pleural effusion AND
- yellow nail syndrome OR hereditary lymphoedema

In addition to the electronic data bases consulted, a manual search was performed of reference lists of the included articles. We included any studies fulfilling the above criteria, and then independently screened and assessed each article identifying those potentially relevant. Studies were reviewed in three stages based on the title, abstract and then full text with consensus sought at each stage of review.

Data collection process

Data from selected studies were extracted electronically (Microsoft Excel 2010, Microsoft Corp, USA). The information extracted included the following: authors, year and number of cases in the series; age, gender and smoking history of the subjects; presence of yellow nails, lymphoedema, chronic cough, sinusitis, bronchiectasis, recurrent pneumonia and immunodeficiency; family history related to the disease, laterality of PE, PF appearance; description of whether the fluid was a transudate or exudate; nucleated cell differential; levels of total protein in PE, lactate dehydrogenase (LDH), albumin, cholesterol, triglycerides, glucose, pH and adenosine deaminase (ADA); presence of ascites, culture results, cytology and pleural biopsy, treatments received and their response, and complications.

Methodological quality of individual studies

Because the articles reviewed were mostly case descriptions, their quality was not assessed in relation to study type, internal validity, generalizability, accuracy and heterogeneity.

Outcomes of interest

Outcomes of interest were to know the demographic characteristics of patients; associated diseases; family history; biochemical, microbiological and cytological behaviour of the PE, and the response to various treatments.

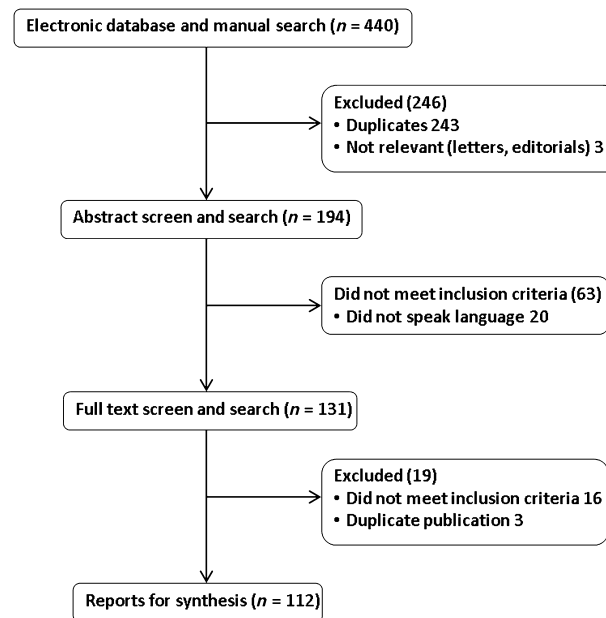


Figure 1 PRISMA flowchart of evidence synthesis.

Statistical analysis

Due to the wide heterogeneity and descriptive nature of the studies, a simple description (proportion, median and range) of each outcome of interest was calculated.

RESULTS

One hundred and twelve studies involving 150 patients were selected for review, spanning a period of nearly 50 years. Figure 1 presents a flow chart for the complete breakdown in the identification of appropriate studies.^{1,2,4,7-9,11-15,17,19-119} They all corresponded to the description of isolated case reports (between 1 and 4 per item) and a retrospective series of 19 patients.¹⁷

Demographic and clinical characteristics

Clinical and demographic characteristics of the 150 patients included in the study are shown in Table 1, and their age distribution appears in Figure 2. The median age was 60 years (range: new-born to 88). The disease occurred in all age groups, but in 78.7% (100/127), it was between 41–80 years. The population consisted of 68 males (55%) and 56 females (45%) (ratio 1.2/1). Gender was not available for 26 patients. All patients with YNS and PE had lymphoedema, while 14.4% (18/125) did not have yellow nails.^{2,4,7,15,19,20,25,35,47,56,67,74,87,107}

Pleural effusion

PE was bilateral in 95 patients (68.3%), right-sided in 20 and left-sided in 17. In the other seven, PE was unilateral (not stated whether right or left), and 11 did not specify whether it was unilateral or bilateral. In

Table 1 Demographic and clinical findings of patients with yellow nail syndrome and pleural effusion

Characteristics	Data
Age, years (median) (range)	60 (New-born, 88)
Gender (male/female)	68/56
Smoking (smokers or ex-smokers/non-smokers)	21/20
Yellow nails (yes/no)	107/18
Lymphoedema (yes/no)	123/0
Chronic cough (yes/no)	53/10
Sinusitis (yes/no)	33/11
Bronchiectasis (yes/no)	24/25
Recurrent pneumonia (yes/no)	22/15
Immunodeficiency (yes/no)	5/25
Family history of YNS (yes/no)	9/24
Pleural effusion	20/17/95 [†]
Neoplasia	14
Ascites	11 [‡]
Pericardial effusion	11
Hypothyroidism	6
Pneumothorax	5
Erysipelas	4
Rheumatoid arthritis	2
Parental consanguinity	2

YNS means yellow nail syndrome.

[†] right/left/bilateral.

[‡] 7 chylous.

the 85 cases of patients with PE and descriptions of its appearance, 64 (75.3%) were serous, 17 milky, (16 chylothorax^{17,38,42,47,59,64,74,75,86,88,99,108} (18.8%), one pseudochylothorax⁹¹) and three empyemas.^{11,52,110} A single patient with bilateral PE presented with a milky appearance on the right and serous on the left.¹¹² The PE was described as an exudate in 54 patients (94.7%) and a transudate in three patients (5.3%).^{17,90,112} PF culture was positive in four cases for anaerobic *streptococcus* and *fusobacteria*,²⁸ *streptococcus pneumoniae*,⁵² *escherichia coli*⁵⁶ and *Pseudomonas Aeruginosa*.¹¹⁰ Cytology was negative for malignancy in 59 patients in which it was described and pleural biopsy was normal or did not provide any further diagnostic information in 10 cases;^{2,4,14,23,35,38,45,48,65} 40 patients showed findings compatible with chronic fibrosing pleuritis, and metastatic melanoma was observed in one patient.⁶³ The nucleated cell count was low (median 1,540 cells/mm³; range 240 to 8,000) with a cell predominance largely lymphocytic (48/50 patients, 96%). In the other cases, the prevalence was polymorphonuclear.^{62,89} Protein levels in the PF were described in 66 patients, while in two cases it was only noted that they were elevated. The median was 4.2 g/dL (range: 1.6 to 9⁴). In 92.4% of patients (61/66), protein values were ≥ 3 g/dL. The other five cases corresponded to a single transudate (proteins 1.9 g/dL) and the remainder did not specify whether they were exudates or transudates; however, the LDH values in two cases were 315 and 330 IU/L (proteins 2.2 and 1.6 g/dL, respectively) (Table 2).^{89,107}

LDH values in the fluid were provided in 30 patients, although two only state that they were

elevated. Except in one case in which the LDH was 2,609 IU/L,⁶² the range of the remaining 27 was 55–410 IU/L. Pleural cholesterol was determined in 19 patients (the value specified was high in only one). One case was a transudate (cholesterol <45 mg/dL),⁹⁰ and in the remaining 17, the median was 72 mg/dL (range 58 to 170 mg/dL). Of patients with chylothorax, triglyceride levels were available in five cases and all were elevated.^{42,47,64,86,99} In serous PE, triglyceride levels were determined in 16 patients. All had levels below 110 mg/dL, except one (111 mg/dL, but with absence of chylomicrons).⁵⁶ In two other cases the levels of 'fat' were considered normal.^{2,20} Glucose levels were determined in 37 patients and only three had values below 40 mg/dL.^{28,65,88} The pH and adenosine deaminase (ADA) were determined in only eight and six patients, respectively. The lowest pH value was 7.35 and the highest 7.80.⁹⁴ The highest value of ADA was 33.4 U/L.¹⁰⁵

Treatment of pleural effusion

The therapeutic measures used to control the PE and symptoms were highly variable over the years, with mixed results. Table 3 summarizes the most frequently used treatments for the control of the pleural effusion and their response (favourable: total or partial control of PE or symptoms; unfavourable: no control or recurrence of symptoms).

DISCUSSION

Published cases of YNS with PE correspond to small series or isolated case reports, so key points of the disease, such as its clinical behaviour, PE characteristics or the most effective treatments, are relatively unknown. This systematic review of the literature highlights several interesting aspects of the disease.

The underlying pathophysiology of YNS is poorly understood, and its diagnosis is clinical, (the classic triad of yellow, dystrophic and/or slow growth nails, lymphoedema and respiratory symptoms in the absence of other more likely explanations).^{1,3,37} Because the three criteria are not always present simultaneously, the existence of two is sufficient to establish the diagnosis.² In our review, 18/125 patients (14.4%) did not have yellow nails. By contrast, all reported YNS and PE had lymphoedema. The presence of PE and lymphoedema could be explained by an impairment of lymphatic drainage, a theory considered to be the underlying cause of the disease.³

Some authors consider YNS to be a hereditary disease with an autosomal dominant pattern. In our series, we found nine patients with a family history of lymphoedema or YNS.^{4,15,22,35,56,68,74,89} However, a recent study challenges this theory and argues that it is an acquired disease.¹¹ As in all cases of YNS, those that occur with PE may also have chronic cough, bronchiectasis, rhinosinusitis, bronchiectasis, recurrent pneumonia and immunodeficiency (Table 1). Because of impaired lymphatic drainage, a delay of bacterial clearance promoting microbial growth could lead to the development of these complications

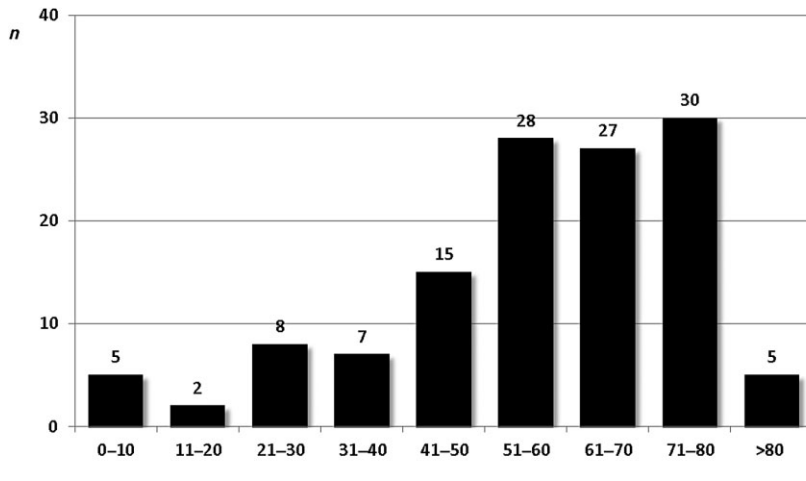


Figure 2 Age distribution of patients with yellow nail syndrome and pleural effusion.

Table 2 Descriptive analysis of the parameters determined in the pleural fluid

Parameter	n	Median	Range	Comments
Nucleated cells (cells/mm ³)	19	1540	240, 8000	Low cell count
Differential count (%)	50	NA	6, 100	Predominantly lymphocytes: 48/50 cases (96%)
		NA	4, 94	Predominantly polymorphonuclear: 2 cases (4%)
Proteins (g/dL)	66	4.2	1.6, 9	92.4% of cases (61/66) ≥ 3 g/dL
LDH (IU/L)	30	208	55, 2609	Low values. Only two cases with values >400 U/L
Cholesterol (mg/dL)	18	72	<45, 170	A transudate with cholesterol value <45 mg/dL
				Exudates with values >55 mg/dL
Triglycerides (mg/dL)	16	NA		All chylothorax with high values (>110 mg/dL). All serous effusions with levels <110 mg/dL, except one (111 mg/dL, without chylomicrons)
Glucose (mg/dL)	37	99	8, 150	Only three patients with values below 40 mg/dL
pH	8	7.45	7.35, 7.80	No case with low pH
ADA (U/L)	6	12.8	7.3, 33.4	No case with high values

NA indicates Not Available; LDH, lactate dehydrogenase; ADA, adenosine deaminase.

and infections.³⁷ Multiple clinical associations have been described in patients with YNS. The most common among those who present with PE were neoplasms, hypothyroidism, pneumothorax, erysipelas and connective tissue disorders, similar to those described in all YNS cases.¹⁷

Although the disease can occur at any age (from birth to age 88 years in our review), the greatest number of cases occur after the fifth decade of life and especially between the sixth and eighth decade (Fig 2).

PE in patients with YNS acts generally as a paucicellular, lymphocyte-predominant, protein-discordant exudate with protein levels that are usually higher than those of pleural fluid LDH. This characteristic PFA is representative of either an increased capillary permeability or lymphatic dysregulation, rather than pleural space inflammation. Pleural fluid glucose, pH and ADA may be useful to exclude other diseases, but not to confirm the diagnosis. Cytology and PF culture are negative. A chylothorax can be seen in 19% (16/85) of cases, which could be justified by the existence of alterations in the lymphatic drainage of the pleural space.

For this reason, the PE may be accompanied by ascites,^{38,51,59,64,70,75,89,99,108,112} which in some cases may also be chylous.^{38,51,59,64,70,75,112} Although this is the general behaviour of the PE, there are exceptions as noted in the 'Results' section.

The most effective treatments for PE appear to be pleurodesis and decortication/pleurectomy. Therapeutic thoracentesis was not effective in any case due to re-occurrence. Only one patient reportedly experienced a period of four years stability with later recurrence of a symptomatic PE.¹¹² A total of 81.8% patients treated with pleurodesis (27/32) progressed favourably (partial or complete),^{1,2,9,30,41,42,44,54,59,65,71-73,75,76,81-83,92,98,101,103,104,112,118,119} while six patients had a poor outcome.^{9,40,51,84,108} Another technique with a generally favourable response was decortication/pleurectomy (8 patients;^{2,8,19,21,28,58,98,110} 89%), although not in all cases.¹⁵ A large retrospective review of 19 patients with YNS and PE described four pleurectomies/decortications and six pleurodesis, without providing data on outcomes.¹⁷ Risks of infection or obstruction are well described,^{53,85} but in some cases, it may be effective.^{53,85,88,107}

Table 3 Established treatments for the control of pleural effusion associated with yellow nail syndrome

Treatment	n	Favourable [†] (%)	Unfavourable [†] (%)
Therapeutic thoracentesis	48		48(100)
Pleurodesis [‡]	33	27 (81.8)	6 (18.2)
Diuretics [§]	25	7 (28)	18 (73)
Thoracic drainage	10	3 (30)	7 (70)
Decortication/pleurectomy	9	8 (88.9)	1 (11.1)
Antituberculosis drugs	8		8 (100)
Pleural-peritoneal shunt	6	4 (66.7)	2 (33.3)
Corticosteroids	6	3 (50)	3 (50)
Antibiotics [¶]	5	2 (40)	3 (60)
Pericardial procedures ^{††}	5	3 (60)	2 (40)
Immunoglobulins	4	3 (75)	1 (25)
Octreotide	4	3 (75)	1 (25)

[†] Favorable means complete or partial response; Unfavourable means not controlled or relapse.

[‡] includes pleurodesis with tetracycline, talc, bleomycin, iodized solution, rifamycin, coparvax (*corynebacterium parvum*) and OK-432 (one case associated with a tunnelled catheter and another with thoracic duct ligation).

[§] associated or not with elastic stockings, corticosteroids, thyroid or vitamin E.

[¶] associated with or without chest or postural drainage.

^{††} includes pericardiocentesis, pericardial effusion, pericardiomy and pericardial window.

Three patients presented with a pericardial effusion.^{61,67,82} In one case, both pericardiocentesis and pericardial drainage were not effective, so clinicians had to resort to a pericardiomy.⁶¹ In the other two, pericardial drainage⁷² and performing a pericardial window⁸² led to favourable progress.

Immunoglobulins^{67,82,108} and octreotide^{70,86,93,112} also have been used in some cases with mixed results (Table 3) and cases of favourable progression of PE have even been described without any treatment.¹⁹

Our review has significant limitations. The most important was a reliance on descriptions of case reports, instead of case series or comparative trials. Therefore, the evaluation of the quality of the reported literature would limit internal validity, generalizability, and accuracy. In addition, some articles highlight the clinical characteristics of patients, while others stress diagnostic and therapeutic aspects. Due to the heterogeneity of the reported information, it does not possible to provide detail required, making it difficult to correctly classify some effusions or evaluate the response to a particular treatment.

In summary, patients with YNS and PE present with lymphoedema and the highest incidence is observed after the age of fifty. Clinical symptoms of other unrelated conditions are similar to those described in YNS, with or without PE. The PE is usually bilateral and behaves like a pauci-cellular exudate, either serous or chylothorax, lymphocyte-predominant and with proportionately higher levels of proteins as compared to LDH. The most effective treatments for PE appear to be pleurodesis and decortication/pleurectomy.

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