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Yellow nail syndrome in a patient with membranous glomerulonephritis

Zespół żółtych paznokci u chorego na błoniaste kłębuszkowe zapalenie nerek

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Abstract

Yellow nail syndrome (YNS) is a condition characterized by yellow-green coloration of nails, respiratory manifestations, and lymphedema. This article presents a case of a 52-year-old patient with membranous glomerulonephritis, hospitalized at the National Research Institute for Tuberculosis and Lung Diseases in Warsaw because of suspected allergic aspergillosis. Based on clinical and radiological findings, diagnosis of YNS was established. Treatment of renal disease did not affect the course of yellow nail syndrome. During the two-year follow-up, despite stable renal parameters, progression of respiratory manifestations (bronchiectasis, pleural effusions) was observed.

Key words: yellow nail syndrome, lymphedema, pleural effusion

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Introduction

Yellow nail syndrome (YNS) is an uncommon clinical syndrome characterized by yellow-green discoloration of nails and the presence of respiratory tract lesions, pleural effusions, and lymphedema [1, 2]. In 1964 Samman and White for the first time described 13 patients with coexistent leg oedema and yellow nails [2–5]. Further publications described other components of this syndrome, concerning the respiratory tract, which include pleural effusions and recurrent upper and lower respiratory tract infections. Diagnosis is made based on the presence of clinical criteria, after other possible causes of the above-mentioned symptoms are excluded [1, 2]. The aetiology of YNS remains unclear. Developmental or functional abnormali-

ties of the lymphatic system were suggested, possibly manifesting in the course of chronic inflammation [2, 6]. Given the low number of known cases (approx. 200 cases described) and unclear disease aetiology, no accepted standards of YNS treatment exist [2]. Attempted treatment is most often aimed at alleviating symptoms [2, 3]. Spontaneous remissions were also observed [3]. The presented report describes a patient with YNS and membranous glomerulonephritis.

Case report

A fifty-two-year-old male smoker (JK) was admitted to the National Research Institute for Tuberculosis and Lung Diseases in November 2009 with suspected allergic bronchopulmonary asper-

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gillosis (ABPA). The patient gave anamnesis of recurrent symptoms from both upper and lower respiratory tract since 1993 (chronic cough, purulent rhinitis, airway infections). Prior to admission, the patient had three episodes of pneumothorax. Chronic obstructive pulmonary disease (COPD) was diagnosed in June 2006, with introduction of bronchodilators and inhaled corticosteroid. During the following months the patient experienced headaches, purulent nasal exudation, and yellow discoloration of nails. Computed tomography (CT) disclosed the presence of polyps in the paranasal sinuses, thickening of perimural mucosa, and fluid in the maxillary and sphenoid sinuses. A dermatology consultant suggested yellow nail syndrome (YNS). Before 2008 the patient had two episodes of acute respiratory tract infection necessitating hospitalization and parenteral antibiotic administration. Massive proteinuria was observed in June 2008, and six months later diagnosis of membranous glomerulonephritis was made based on histopathological examination of renal biopsy. Immunosuppression with pulses of methylprednisolone, prednisone and chlorambucil perorally was commenced. Treatment was complicated by diabetes and marked oedema, particularly in the lower limbs. Medical therapy was modified, with the introduction of cyclophosphamide pulses, which resulted in partial regression of proteinuria. Respiratory symptoms (cough, effort dyspnoea) and purulent rhinitis persisted. Marked progression of symptoms occurred in November 2009, with resting dyspnoea, heavy cough with purulent expectorate, and fever. The patient was hospitalized in the department of nephrology, which followed him up for immune suppression. Bronchoscopy revealed copious thick, purulent exudate and deposits of pus in the small bronchioles. Chest CT showed bilateral pleural effusion, with fibrous and emphy-

sematous lesions in lung parenchyma. Immunosuppression was ceased, and antibiotics and antimycotics were administered, which resulted in an improvement in the patient's general condition, but admission to a lung clinic with suspected ABPA was planned.

On the day of admission, the patient was in good general condition. Yellow discoloration of nails was observed. The nails were thickened and plates were protruding (fig. 1 A, B). The patient also had mild leg oedema, increased percussion over upper lung lobes, decreased vesicular sound, and single rhonchi over the entire lung area. Laboratory investigations showed *white blood* cells (WBC) of $3.8 \times 10^9/L$ (49% neutrophils, 32% lymphocytes, 12% monocytes, 5% eosinophils), red blood cells (RBC) of $3.98 \times 10^{12}/L$ and platelet count (PLT) of $181 \times 10^9/L$. Further analyses showed signs of inflammatory reaction, decreased total protein content (5.9 g%; 47% albumins, 16% a1-globulins, 14% b-globulins, 13% g-globulins, 8% a1-globulin alpha 1), and proteinuria of 1.07 mg/dl. Blood gasometry was normal. Spirometry showed signs of mild obturation: forced expiratory volume in one second (FEV1) of 2.74 (77%), forced vital capacity FVC) of 4.88 (110%), and FEV1/FVC of 56%. Chest CT showed peribronchial thickening in lower lobes, with possible bronchiectasis. In addition, inflammatory lesions were found in the lower left lobe, consistent with bronchopneumonia, emphysema with the presence of bullae, scarring in apical regions, and a small amount of fluid in the right costophrenic angle. Laboratory investigations also showed slightly increased IgE (immunoglobulin E, 128 IU/ml), with normal concentration of IgE specific for *Aspergillus fumigatus* (1.43 IU/ml), and trace amounts of anti-nuclear antibodies (ANA). Microbiological analyses showed no presence of fungal antigens (*Candida*,

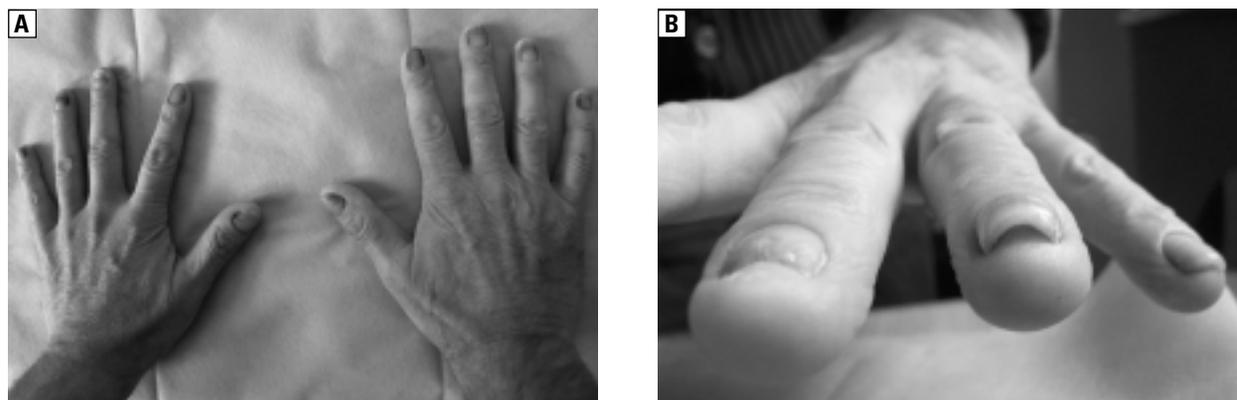


Figure 1 A, B. Thickened, elevated, yellow-coloured nails in a patient with yellow nail syndrome

Aspergillus, *Cryptococcus*) in serum. Ultrasound examination visualized fluid in the right pleural cavity (up to 22 mm). Based on these findings and anamnesis, ABPA was excluded. The observed respiratory tract lesions (bronchiectases, chronic paranasal sinusitis, recurrent pleural fluid, and lower leg oedema) were assigned to YNS. The diagnosis of moderate COPD was also sustained. The patient was in good general condition and had only mild lower leg oedema and little pleural effusion; therefore, he was discharged with recommended nephrological and pulmonological follow-up. There were no indications for immunosuppression. A chest X-ray from April 2011 showed an increasing amount of right-sided pleural effusion, and the patient was hospitalized again in an out institution. The patient complained of progressing effort dyspnoea and mild productive cough with mucous expectorate. Physical examination revealed dampened percussion sound and dampened vesicular sound at the base of right lung, mild oedema of the lower legs, and yellow discoloration and deformation of nails on the fingers and toes.

Laboratory investigations showed slightly increased markers of inflammatory reaction, with CRP of 18 mg/l, WBC of $10.57 \times 10^9/L$ (76% neutrophils, 17% lymphocytes, 4% monocytes, 1% eosinophils), and proteinuria of 0.33 g/l. Chest CT showed subpleural rounded consolidations on the right side, consistent with marginal emphysema, with bronchiectases in the lingual and left lower lobe, with exudate deposition in some areas. Pleural effusion was observed on both sides but was more prominent in the right pleural cavity (fig. 2A, B; 3A, B). Given the asymmetric pleural effusion accumulation, puncture and biopsy of pleura on the right side was performed. Aspiration yielded 1,420 ml of yellowish, cloudy fluid biochemically consistent with exudate, with 79% lymphocytes in smear preparations. Bacteriological cultures were negative. Histopathological examination showed fibrotic parietal pleura with chronic inflammatory infiltrates. No signs of malignancy were identified. The patient improved clinically and was discharged home with recommended follow-up in an outpatient service.

Discussion

Yellow nail syndrome mainly affects middle-aged persons, but some cases were described in children or the elderly [7, 8]. The disease is seen more commonly in women, with a female/male ratio of 1.6:1 [1, 8]. Its aetiology is unknown. Developmental or functional anomalies of the lym-

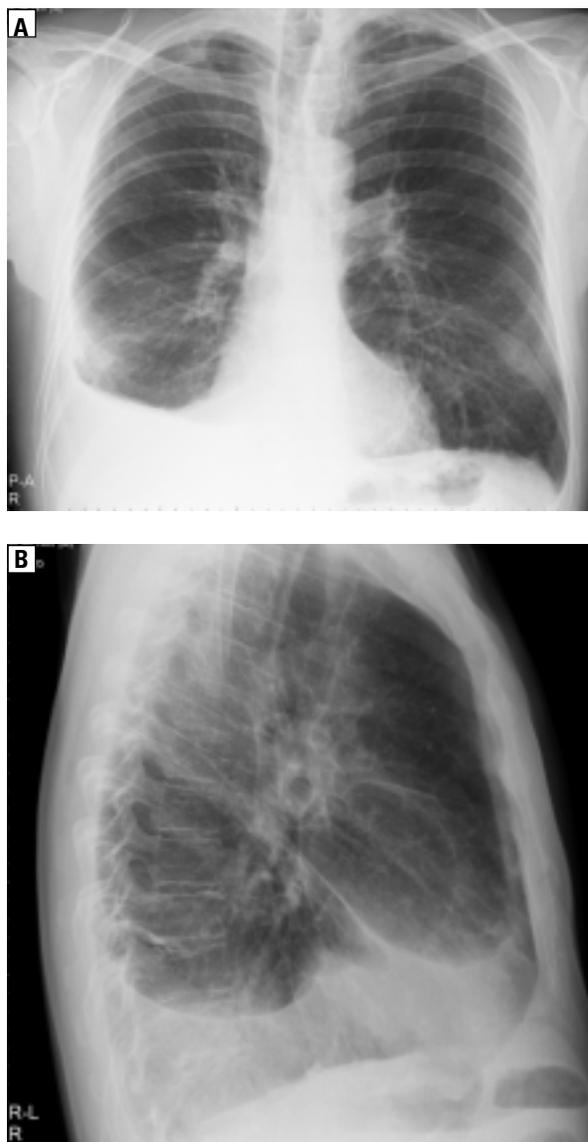


Figure 2 A, B. Chest X-ray: effusion in the right pleural cavity, fracture of the tenth left rib, emphysema, peribronchial thickening in the lower zones, apical scars

phatic system were suggested, but the results of lymphographic examinations performed in some patients did support this hypothesis [2, 4, 9]. A triad of symptoms is characteristic for YNS: yellow discoloration of nails, pleural effusions, and lymphedemas. Since the first published report in 1964, further clinical characteristics have been added, including chronic paranasal sinusitis, chronic airway inflammation, and bronchiectases. Diagnosis is made based on clinical findings, and at least two of the three classical symptoms need to be confirmed [2]. The most typical and characteristic feature is yellow-greenish discoloration of the nail plates, with thickening, shrinking, and decreased nail growth rate (< 0.25 mm/week) as well as

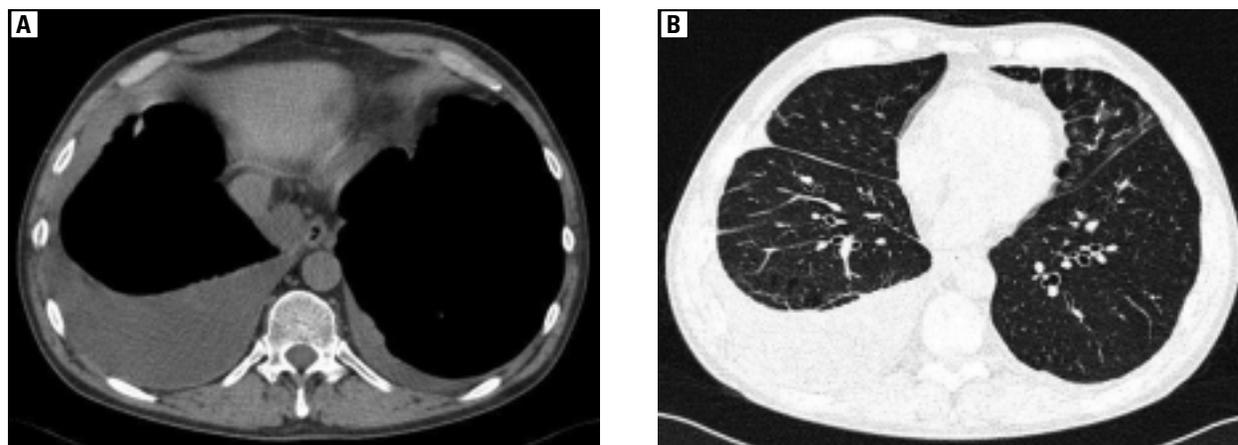


Figure 3 A, B. A — computed tomography of the chest, mediastinum window: bilateral pleural effusion, more prominent on the right; B — computed tomography of the chest, lung window: diffuse bronchial thickening; bronchiectasis in the lower left lobe and lingual, locally filled with fluid

atrophy of lunula and eponychium [1, 7, 10]. These features can be found in 89% of YNS patients [1] but can spontaneously regress in 7–30% of cases [10]. Lymphedema is present in 80% of patients and concerns mainly the upper and lower limbs; however, oedema of other body parts (e.g. eyelids) can also be present [1, 2, 11]. Signs of respiratory tract affection are found in 63% of patients [1]. Pleural effusion was the first ever described abnormality in YNS. Effusion is most often of exudate type, contains mostly lymphocytes, and the lactate dehydrogenase level is increased. High albumin content in effusion can be related to protein leakage at the capillary level, as suggested by some authors [12]. Pleural biopsies show unspecific histopathological pictures, most often normal or with chronic inflammatory infiltrates and pleural thickening [2, 9]. Symptoms and signs from the respiratory tract were added to the classical clinical picture of YNS, including chronic paranasal sinusitis, recurrent respiratory tract infections, and bronchiectases. Pathogens most commonly isolated from sputum and bronchial secretions include *Staphylococcus aureus*, *Haemophilus influenzae* and *Moraxella catarrhalis*. Colonization of the bronchial tree by *Pseudomonas aeruginosa* was also described. The reasons underlying development of bronchiectasis remain unknown. Impaired lymph circulation with diminished bacterial clearance in bronchi has been suggested, as these phenomena can facilitate the development of chronic inflammation, which can then damage bronchial walls [4]. Computed tomography scans show bronchiectasis most often in the lower lobes, pleural effusion, and focal infiltrates in lung parenchyma [9]. The presented patient had a classical constellation of YNS symptoms, with yellow discoloration

and impeded nail growth, pleural effusions, recurrent respiratory tract infections, and chronic paranasal sinusitis. Oedemas were least prominent, and were observed mostly in the legs for the entire follow-up period. The characteristics of pleural effusion and the microscopic findings in his pleural biopsy were also consistent with reports from literature.

Coincidence of YNS with autoimmune diseases, and malignancy of chronic inflammatory diseases, has been pointed out by some reports in literature [2, 9, 5]. Renal diseases have also been described in YNS patients, which was the constellation observed in our patient [13–15]. Given the low incidence of YNS, it cannot be confirmed that all the clinical issues described in these patients are aetiologically connected to the syndrome, or should it be perceived as coincidence? However, a common denominator for all of them is chronic inflammatory reaction, which can be a suspected trigger underlying YNS development. Spontaneous remissions were noted in some patients [15]. In the presented patient, immunosuppressive treatment had no impact on YNS symptoms.

The natural course of YNS was not well studied. Descriptions concerning the largest groups of patients suggest that their life expectancy might be only slightly shorter than that of the general population [4].

As the cause of YNS development remains unknown and its incidence is low, no treatment strategy was ever established. Symptomatic treatment was most commonly applied. Nail lesions can be treated with vitamin E, steroid ointment, zinc preparations, or antimycotica [2, 16, 10, 17]. Positive effects were observed following enteral administration of zinc and vitamin E or with topical

steroids [2, 17]. A single case of successful treatment with intramuscular stilbestrol injections was described in 1972 [7]. The greatest clinical concerns are, however, related to recurrent pleural effusions, as pleural cavity drainage gives only short-term improvement in most cases; pleurodesis appears to be more effective. Some authors successfully administered bleomycin, tetracyclin, and OK-432 [18, 19]. Pleuro-peritoneal shunts can be implanted, with alternative shunts between the venous system and the pleural or peritoneal cavity [2, 19]. Gravitational drainage or other procedures facilitating drainage of the bronchial tree as well as periodic antibiotic administration aimed at inhibiting development of bronchiectases [4]. Lymphedemas are treated mainly through compression [11]. Administration of diuretics had no impact on the disease course [2].

Yellow nail syndrome is a rare clinical entity but should be taken into consideration in patients with recurrent pleural effusions, bronchiectases, and persistent lymphedemas.

Conflict of interests

The authors declare no conflicts of interest.

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