

YELLOW NAIL SYNDROME IN ASSOCIATION WITH PROTEIN-LOSING ENTEROPATHY IN A DIABETIC PATIENT

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The yellow nail syndrome is a rare disorder which is characterized by the triad of yellow nails, lymphedema and pleural effusion. The etiology of the syndrome is unknown, but impaired lymphatic drainage may play a role in its pathogenesis. The yellow nail syndrome has been reported in association with various conditions such as thyroid disease, hypogammaglobulinemia, nephrotic syndrome, rheumatoid arthritis, obstructive sleep apnea, keratosis obturans in the external ear, carcinoma of the gall bladder, xantho-granulomatous pyelonephritis, onychomycosis and protein-losing enteropathy (PLE) in the literature.¹⁻³ A case of a diabetic woman with chronic recurrent pleural effusion, lymphedema, yellow discolored nails, chronic sinusitis, bronchiectasis and PLE is presented here.

Case Report

A 65-year-old woman who had productive cough, dyspnea, diarrhea and leg swelling was admitted to our hospital. Her other previous illness was a type II diabetes mellitus which had been diagnosed two years earlier. Her mother was also diabetic. On examination, her nails were yellowish-green in color and dystrophic in appearance, and was thickened and excessively curved from side to side (Figure 1A). She also had manifest edema of her lower extremities, especially on the right (Figure 1B). Chest radiograph showed bilateral pleural effusion with mildly enlarged cardiac silhouette (Figure 2), which was confirmed by CT scan, together with mild bronchiectasis of both lower lobes. The CT scan of paranasal sinuses showed bilateral sinusitis. Biochemical studies were normal except total protein at 5.8 mg/dL, albumin 2.5 mg/dL, and glucose at 259 mg/dL. There was no hypogammaglobulinemia on the protein electrophoresis. The urine analysis was normal except glucosuria. Pleural fluid was a serous exudate with no chylothorax. Cytologic examination of pleural fluid demonstrated predominantly lymphocytes. Lymphoscintigraphy using intradermal ^{99m}Tc colloid revealed absence of lymphatic drainage of lower extremities and no

FIGURE 1B. Manifest lymphedema of lower extremities, especially on the right side, and yellow toe nails.

visualization of inguinal lymph nodes, especially on the right (Figure 3). Barium contrast radiography demonstrated jejunal and ileal abnormalities. Subsequent jejunal biopsies showed the presence of dilated lymphatic vessels in the lamina propria and the submucosa. The diagnosis of PLE was confirmed by chromium-51 chloride technique as described by Eustace et al.⁴ Chromosomal analysis was found normal at cytogenetics examination. The patient was treated medically by antibiotic, antidiabetic, diuretic, bronchodilator-expectorant, postural drainage, and low-fat dietary therapy. External elastic support was applied to her affected extremities. Chemical pleurodesis with tetracycline was carried out bilaterally. The dyspnea clearly improved. Pleural effusion regressed on radiography, especially on the left side after the pleurodesis (Figure 4).

FIGURE 2. Chest radiograph showing bilateral pleural effusion with mildly enlarged cardiac silhouette.

FIGURE 3. Lymphoscintigraphy obtained 24 hours after ^{99m}Tc colloid injection, showing absence of lymphatic drainage of lower extremities and no visualization of inguinal lymph nodes, especially on the right side.

FIGURE 4. Chest radiograph obtained two weeks after completion of chemical pleurodesis showing almost complete radiological clearance, especially on the left side.

Discussion

In 1986, Nordkild et al. reviewed the reports of all the 97 yellow nail syndrome patients described in the literature.¹ The disorder appears to be congenital and may have a genetic component which has yet to be defined.⁵ Two siblings have been described and this familial occurrence is unique among the cases reported to date.⁶

The basic abnormality responsible for this syndrome appears to be defects of the lymphatic vessels. The recurrent pleural effusions are also most likely due to hypoplastic lymphatics. Light and electron microscopy show dilatation of both visceral and parietal pleural lymphatics associated with perilymphatic inflammation, and the pleural fluid characteristically contains a high percentage of lymphocytes.⁷

Patients often give a history of recurrent attacks of bronchitis and may have chronic sinusitis, bronchiectasis, and recurrent pneumonia. The present case also had chronic sinusitis and mild bronchiectasis. The pathogenesis of the bronchiectasis is unknown, although it has been attributed either to hypoplasia of the lymphatic system with altered lung

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FIGURE 1A. Patient's nails showing typical signs of abnormalities of the yellow nail syndrome.

drainage or to immunologic deficiencies.¹ Hiller et al. have suggested the possibility of underlying mucociliary dysfunction.⁶ Miro et al., however, have found that the ciliary beat frequency was within normal limits, and thought that abnormal ciliary motility is not a pathophysiologic mechanism of recurrent sinopulmonary infections in yellow nail syndrome.⁸

Primary intestinal lymphangiectasia is a rare condition of uncertain etiology characterized by dilated small bowel lymphatics and often complicated by anomalous lymphatics elsewhere, typically in the limbs. Over 20% of patients with primary lymphedema have PLE resulting from lymphangiectasia of the small bowel. With significant loss of protein, these patients develop hypoproteinemia as well as hypogammaglobulinemia,⁹ but there was no hypogammaglobulinemia in the present case. Whipple's disease, on the other hand, is a systemic bacterial infection and the common though not invariable manifestations are diarrhea, weight loss, abdominal pain, and arthralgia. A small bowel biopsy is often diagnostic. The characteristic histopathological features are variable, villous atrophy and distension of the normal villous architecture by an infiltrate of foamy macrophages which stain a brilliant magenta color with PAS. These pathognomonic PAS-positive macrophages may also be present in the peripheral and mesenteric lymph nodes and various other organs.¹⁰ There were no arthralgia and abdominal pain in our patient. Our jejunal biopsies were also excluded from the Whipple's disease because of the absence of these foamy macrophages.

Review of the literature revealed that there were only two documented reports about the yellow nail syndrome in association with PLE. In 1985, Battaglia et al. presented the first case of yellow nail syndrome in association with PLE.³ Subsequently, Malek et al. claimed the first description of the yellow nail syndrome associated with a diffuse lymphangiectasia involving the whole small bowel, by performing jejunal and duodenal biopsies.⁹ We believe that the present case is the third documented report of the condition in association with PLE. Moreover, the patient was also a diabetic. Whether there was any causal relationship between the disorder and the yellow nail syndrome is a matter of conjecture.

Diabetes mellitus is a common disease. Its association with the yellow nail syndrome may be merely a coincidence. However, some genetics factors may play a role although we have not observed an evident finding in cytogenetic examination. We believe that the present patient is an interesting case and suggest further studies to investigate the association between these disorders.

There is no specific treatment for the syndrome. Interestingly, improvement in treatment with oral zinc supplementation has been reported by Arroyo and Cohen.¹¹ Pleural effusion secondary to lymphedema may be chronic, symptomatic and refractory to treatment, occasionally requiring invasive and painful procedures such as chemical pleurodesis, pleural abrasion or pleurectomy, and

pleuroperitoneal shunting to achieve control of the effusion and gain symptomatic relief.¹² We preferred chemical pleurodesis by using tetracycline.

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