LETTER TO THE EDITOR

Immunoglobulin replacement therapy for yellow nail syndrome

Dear Editor,

We read with interest the recent article from Gupta et al.\(^1\) reporting innate and adaptive immunological alterations occurring in patients with yellow nail syndrome (YNS). The authors observed that immunoglobulin administration, in the subset of YNS patients with immunoglobulin deficiency, may result not only in decreased frequency and severity of infections but also in an impressive effect on lymphoedema and pleural effusion recurrence. They described a single patient.\(^1\)

Yellow nail syndrome has an estimated prevalence of <1/1 000 000,\(^2\) and <400 patients have been reported in the literature.\(^3\) YNS most often occurs in adults over 50 years, with no sex predominance.\(^2,5\) The etiopathogenesis is unclear although it has been related to impaired lymphatic and vascular drainage and with immunological defects, including both T and B lymphocyte defects.\(^1,4\) Respiratory tract involvement may include unilateral or bilateral pleural effusion(s), recurrent pneumonias, bronchiectasis, chronic cough and chronic sinusitis.\(^6\) Lymphoedema may manifest many years after the nail changes. YNS is a suggested paraneoplastic syndrome.\(^3,7\) Unfortunately, there is no specific therapy for the disease. Symptomatic relief, such as topical vitamin E and antifungal therapy, has been proposed, without clear benefits.\(^7\)

Here, we report the history of a 74-year-old patient presenting with chronic cough, bronchiectasis, idiopathic recurrent pleural effusion, thickened yellow nails associated with pathological nail discoloration, lower limb lymphoedema and immunoglobulin G deficiency. The examination revealed lower limb lymphoedema, especially below the knees. His finger nails were dry, rigid and thickened with brown vertical ridging; his toe nails were thickened, yellow-pigmented and presented onycholysis (Figure 1). A nail biopsy excluded onychomycosis and demonstrated hyperpigmentation. Inflammatory and autoimmune markers (erythrocyte sedimentation rate, C-reactive protein, ferritin, antinuclear antibody, rheumatoid factor and antineutrophil cytoplasmic antibody) were all negative. Proteinuria was absent while total proteins, gammaglobulines and albumin concentrations were reduced.

The patient had been referred for lymphoedema already in 1993, 1 year after a trip in Guinea Bissau. The patient was then investigated for filariasis and other tropical infective diseases, all with negative results. The patient further reported high frequency and severity of respiratory infections. Serum IgA and IgM concentrations were normal while serum IgG levels were reduced (total IgG 420 mg/dL with IgG-1 357 mg/dL and IgG-2 119 mg/dL). A computed tomography of the chest showed bilateral pleural effusions and bronchiectasis, predominantly in the lower lobes. Fluorodeoxyglucose positron emission tomography (FDG-PET) revealed no pulmonary FDG uptake. A thoracocentesis was performed, and an analysis of pleural fluid revealed total proteins 26 g/L, LDH 51 U/L, glucose 174 g/L, differential leucocyte count 96/μL, polymorphonuclear cells 17% and mononuclear cells 83%. The cytological and microbiological examinations of pleural fluid were all negative. A pleural biopsy showed unspecific chronic eosinophilic and lymphocytic inflammation associated with lymphoid aggregates of the pleura. The patient was diagnosed with yellow nail syndrome based on the contemporary presence of the triade: nail alterations, lymphoedema and pleural effusion. This triade is seen in one-third (27%-60%) of patients.\(^8,9\)

After reading the article by Gupta et al.,\(^1\) we decided to treat the patient with monthly intravenous injections of
immunoglobulin (IVIG), observing an early improvement in YNS clinical manifestations. In particular, after the first 3 months of therapy, the lymphoedema and pleural effusion stopped to worsen and the patient no longer required pleural drainage or high dose of diuretics. IVIG treatment also resulted in decreased frequency and severity of respiratory infections, which previously had recurred every 3-4 weeks. A significant reduction in antibiotic use was observed, which was associated with an increase in IgG levels (total IgG 650 mg/dL). Until now, no improvements in nail alterations were observed.

In conclusion, in selected patients with YNS, the intravenous immunoglobulin administration may be successfully used to improve the clinical manifestations of this rare disease through a potential immunomodulatory effect potentially associated with Fc receptors regulation, neutralization of potential autoantibodies as well as inhibition of complement activation.

CONFLICT OF INTEREST
The authors have no conflict of interest to declare related to this manuscript.

ORCID
E. Bargagli
http://orcid.org/0000-0002-8351-3703

REFERENCES