






RITA SOUSA E SILVA¹ , SARA PEREIRA DA SILVA^{2,3} , RITA LUÍS^{4,5} , CILENIA BALDAIA⁶ ,
SUSANA L. SILVA^{2,3} 

Nodular regenerative hyperplasia in CVID patients: could low-dose oral glucocorticoids be part of the solution?

¹Department of Allergy and Clinical Immunology, Setúbal Hospital Centre, EPE, Setúbal, Portugal

²Serviço de Imunoalergologia, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal

³Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

⁴Centro de Imunodeficiências Primárias, Centro Académico de Medicina de Lisboa, Lisbon, Portugal

⁵Instituto de Patologia, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

⁶Department of Gastroenterology, North Lisbon University Hospital Centre, EPE, Lisbon, Portugal

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Corresponding author

Rita Sousa e Silva

Department of Allergy and Clinical Immunology

Setúbal Hospital Centre, EPE

Rua Camilo Castelo Branco

2910-446 Setúbal, Portugal

ORCID: 0000-0002-8279-4726

E-mail: ritadesousaesilva@gmail.com

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To the Editor,

Common Variable Immunodeficiency (CVID) is the most frequent symptomatic Primary Immunodeficiency, with an estimated prevalence of 1:10,000-100,000 (1). Besides increased susceptibility to bacterial infection (respiratory and/or gastrointestinal mostly), 30% of CVID patients feature clinical manifestations associated with immune dysregulation (2), including autoimmunity, granulomatous disease, lymphoid hyperplasia, enteropathy or malignancy (1). Importantly, immunoglobulin replacement therapy (IgRT) is not sufficient to prevent or contain non-infectious complications that have become major causes of death in CVID (3).

Altered liver function and mild hepatomegaly may be present in up to 50% of CVID patients (3). Although variable amongst cohorts, reported prevalence of liver disease has increased, in association with extended survival in CVID, improved diagnostic capability and disease awareness, among other factors.

Nodular Regenerative Hyperplasia (NRH) is the most frequently diagnosed liver disease in CVID. It is currently thought that in NRH, cytotoxic T cells infiltrate liver sinusoidal endothelium, leading to intra-hepatic vasculopathy with repeated hepatocyte injury and regeneration, and appearance of hepatocellular nodules that further compress peripheral sinuses, portal and central veins. Non-cirrhotic portal hypertension (PTHT) and corresponding

clinical consequences may develop (3). NRH diagnosis requires histopathological evidence of these hepatocellular nodules up to 3 mm compressing peripheral sinuses, without septal fibrosis (3). Single nucleotide polymorphisms in the gene area AK096081-AK124028 have been associated with this complication (4).

Similar phenotype has been reported in HIV infection and in other immune-dysregulation diseases. It is crucial to exclude viral hepatitis B or C, Epstein-Barr virus and Cytomegalovirus infection, non-alcoholic or alcoholic steatohepatitis, autoimmune hepatitis, hereditary haemochromatosis, Wilson's disease, primary biliary cholangitis, sarcoidosis, schistosomiasis, and congenital liver fibrosis (3, 4).

NRH is associated with increased morbi-mortality, particularly when associated with PTHT and/or cirrhosis (3, 5), with reported crude death rates of 26%, *versus* 6% in CVID without liver disease (3). There is no recommended treatment, besides managing complications (3-5), like ascites and oesophageal varices (2), in 32.9% of patients (6).

Importantly, treatments adopted in other chronic hepatic diseases have worse results in CVID, owing to increased infectious risk. Transjugular intrahepatic portosystemic shunt (TIPS) was associated with higher mortality in CVID (2), and NRH recurrence was noticed in transplanted liver (5).

We report a 43 years-old female, non-smoker and with no consumption of alcohol or other drugs. She was diagnosed CVID at the age of 36, after multiple lower respiratory infections. Previous antecedents included autoimmune thyroiditis (at 13 years of age), and refractory Immune Thrombocytopenic Purpura leading to splenectomy at 23 years-old. Chest Computed Tomography revealed bronchiectasis.

CVID diagnosis was based on markedly decreased serum IgG, IgA and IgM and absent response to pneumococcal polysaccharide and tetanus vaccines. Detailed immune phenotype revealed low frequency of switched-memory B cells (0.3% of B cells) and expansion of B cells expressing CD21 with low intensity (29.5%

of B cells) without significant disturbances in major T-cell populations.

Despite optimal intravenous IgRT (IgG 10%, 600 mg/Kg body weight/month, IgG trough level > 800 mg/dL), she maintained recurrent non-infectious diarrhea and elevated fecal calprotectin levels. Colon biopsies revealed areas of erosions, reactive epithelial changes, and mild lympho-plasmocytic infiltrate, suggesting CVID-enteropathy. Upper digestive endoscopy revealed chronic non-atrophic gastritis, *Helicobacter pylori* negative.

Mild hepatomegaly was observed with persistently increased alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (γ GT), punctually increased aminotransferases and normal bilirubin. Extensive evaluation excluded other hepatic diseases namely negative nucleic acid detection of multiple hepatotropic virus and normal levels of serum iron and intra-hepatic copper. Percutaneous liver biopsy revealed altered hepatic structure with granulomas, nodularity, absent fibrosis and lymphoid infiltrates, causing intrahepatic sinusoid compression suggestive of NRH (**figure 1**).

No clinical signs of PTHT were detected and doppler sonography showed preserved portal vein diameter (13 mm) and velocity (average 20 cm/s), without portosystemic collaterals. No ascites or esophageal varices were identified on abdominal ultrasound or endoscopy. Ultrasound based transient elastography (TE) revealed increased liver stiffness (mean 12.0 kPa).

Given the evolving liver condition for over three years, with associated enteropathy, glucocorticoid therapy was considered, as a strategy to control immune-dysregulation. Since there was no evidence of granulomatous disease or lymphoid hyperplasia affecting other organs, the patient was started on oral budesonide, 9 mg/day, a second-generation topical glucocorticoid, as a strategy to avoid broad systemic effects of steroids. The patient has been regularly monitored through abdominal ultrasound with Doppler, ultrasound-based TE, and laboratory evaluation, with progressive decrease in ALP and γ GT.

Figure 1 - The 17 mm hepatic core displayed nodular regenerative hyperplasia, with non-fibrotic nodules outlined by uneven trabeculae and non-necrotizing non-infectious epithelioid granulomas in agreement with clinical diagnosis of CVID.



(A) H&E, 100x; (B) Reticulin stain, 100x; (C) H&E, 400x.

Liver disease, namely NRH, has been increasingly recognized as a relevant complication in CVID (3, 5). ALP alterations are diverse, from persistent increase to a fluctuant profile (3). Liver damage is strongly associated with lymphocytic enteropathy in CVID (7, 8). Although systemic glucocorticoids have been used successfully to treat enteropathy in CVID (9) and granulomatous hepatitis (7), this treatment is associated with important adverse effects, namely increased infectious risk. First-pass hepatic metabolism significantly reduces systemic bioavailability of oral budesonide (10). Low-dose oral budesonide is used to manage ileocecal disease or colitis in inflammatory bowel conditions and autoimmune liver diseases with well-documented T-cell involvement (4, 10, 11), like autoimmune hepatitis, but to our knowledge its use in NRH has not been reported.

The patient we report developed enteropathy and NRH during follow-up for CVID. Treatment with 9 mg oral budesonide has been maintained for 24 months, allowing remission of diarrhea and improvement of liver enzymes alterations. Based on this positive evolution, we suggest oral budesonide may be an option in patients combining NRH and enteropathy. Regular laboratory evaluation, particularly ALP, and non-invasive liver monitoring, provide reliable information on liver disease progression (3). During follow-up, ursodeoxycholic acid may also be added if histopathology reveals biliary damage (7), as well as anticoagulation, to prevent further intrahepatic venule obliteration and portal vein thrombosis, although benefits should be carefully balanced.

NRH treatment options are scarce and some are even associated with worse results in CVID. We reason that low-dose oral budesonide treatment is associated with minimal adverse effects and may contribute to limit gut inflammation and its putative impact on liver disease. Systematic longitudinal analysis of CVID patients with NRH submitted to different treatment approaches will be instrumental to learn about this complication and improve its management.

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Contributions

RSeS: writing - original draft. SPdaS, SLS: conceptualization, writing - review & editing, supervision, validation. RL: resources, writing - review & editing. CB: conceptualization, writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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