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Clinical note

Nodular regenerative hyperplasia associated with common variable immunodeficiency and other comorbidities☆

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ABSTRACT

Background and objective: Currently, there are not many data on the evolution of nodular regenerative hyperplasia (NRH) associated or not with underlying diseases and in particular that associated with common variable inmunodeficiency (CVID). Twenty cases of NRH are presented, and the differences between the cases associated with CVID and those related to other diseases are analysed.
Methods: Retrospective and descriptive study over a period of 14 years.
Results: Twelve out of the 20 patients were men; the median age was 51 years. CVID was the main illness associated with NRH. In patients with CVID and NRH, gastrointestinal haemorrhage was more common, all the patients had high gamma glutamyl transferase and alkaline phosphatase and none had altered albumin and bilirubin levels compared to the patients without CVID. On follow-up, 50% of patients with CVID (2/4) had died compared to 33.3% (5/15) without CVID.
Conclusions: NRH in patients with CVID seems to have more biochemical data of anicteric cholestasis and portal hypertension and could be associated with lower survival.

Hiperplasia nodular regenerativa hepática asociada a inmunodeficiencia común variable y a otras comorbilidades

Palabras clave:
Hiperplasia nodular regenerativa
Inmunodeficiencia común variable
Hipertensión portal

RESUMEN

Fundamento y objetivo: Actualmente no se dispone de muchos datos sobre la evolución de la hiperplasia nodular regenerativa (HNR) asociada o no a enfermedades de base, y en concreto de la asociada a inmunodeficiencia común variable (IDCV). Se presentan 20 casos de HNR y se analizan las diferencias entre los casos asociados a IDCV y los relacionados con otras enfermedades.
Métodos: Estudio retrospectivo y descriptivo durante un período de 14 años.
Resultados: De los 20 pacientes, 12 eran hombres; la mediana de edad fue de 51 años. La IDCV fue la principal enfermedad asociada con HNR. En los pacientes con IDCV y HNR la hemorragia gastrointestinal fue más común, todos tenían elevación de FA y GGT y ninguno tenía valores de albúmina y bilirrubina alterados comparados con los pacientes sin IDCV. De los pacientes con HNR en seguimiento han fallecido el 50% de los asociados a IDCV (2/4) frente al 33,3% (5/15) sin IDCV.
Conclusiones: La HNR en los pacientes con IDCV parece manifestarse más con datos bioquímicos de colestasis anictérica e hipertensión portal y podría asociar una supervivencia menor.

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Introduction

Regenerative nodular hyperplasia (RNH) is the leading cause of non-cirrhotic intrahepatic portal hypertension in western countries; it comprises 27% of all cases of non-cirrhotic portal hypertension in Europe and about 14% in Japan.[1–5]

It is characterised by benign transformation of the heptic parenchymal into small regenerative nodules evenly distributed throughout the entire liver with minimal or no fibrosis in periportal or perisinusoidal areas, accompanied by areas of regenerative hyperplasia that alternate with other atrophy areas.[1] RNH is associated with intrasinusoidal T cell infiltration, portal vein endotheliitis, autoimmune disease and peripheral lymphocyte abnormalities, evidence of an autoimmune mechanism.[6]

Although our current knowledge is limited to individual case reports and case series, the number of patients diagnosed with RNH has increased significantly in recent years.[1,6] RNH may develop as a result of a generally autoimmune and inflammatory underlying disease or one with neoplastic origins.[7,8] There are several diseases and conditions associated with RNH, such as pulmonary hypertension, rheumatoid arthritis, HIV infection, lupus erythematosus, Crohn's/colitis disease or celiac.[1]

Common variable immunodeficiency (CVID) is associated with a defect in B lymphocytes and the production of antibodies, as well as cellular immune system defects.[9] It manifests with recurrent bacterial infections, especially sinopulmonary infections, gastrointestinal manifestations and autoimmune and neoplastic diseases. Upon reviewing Hartleb et al.[1] on RNH, we found that they only included 2 cases of CVID. However, Ward et al.[10] and Malamut et al.[11] showed that RNH was the main liver disease in patients with CVID and liver enzyme abnormalities of unknown origin in which a liver biopsy was performed.

The aim of this paper is to present a series of 20 diagnosed cases of RNH in our hospital from the last 14 years and analyse the differences between the cases associated with CVID and other related diseases.

Methodology

Design

A retrospective and descriptive study was conducted from January 2000 to December 2013. For this, a search was conducted in the General Hospital Universitario de Alicante (Spain) Pathology Department database, identifying patients with a histological diagnosis of RNH in reports of liver biopsies performed during the study period. It is important to note that the main indication for liver biopsies in these patients was non-cirrhotic portal hypertension and/or unexplained enzymatic alteration. In January 2013, the hospital provided medical care to a population of 215,000 inhabitants according to the census for Alicante city and its surroundings. The hospital has 735 beds and has been a referral centre for patients with severe hepatic impairment susceptible to liver transplantation since December 2012.

Variables

The variables recorded were age, sex, history of alcoholism, associated diseases, presence of oesophageal varices, gastrointestinal bleeding due to portal hypertension, ascites; liver function tests: aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), Quick index, platelet count, white blood cells, albumin and serology of hepatitis B and C viruses.

Statistical analysis

Statistical analysis was performed using SPSS® 22.0 (IBM, Chicago, Illinois, USA). A descriptive analysis of RNH cases was conducted. The qualitative variables were represented by absolute values and percentages, and the quantitative variables as median and interquartile range (IQR). For the bivariate comparison between patients with CVID and RNH and those who did not have CVID, the Chi square test and the Mann–Whitney *U* test was used for qualitative and quantitative variables, respectively. Survival was assessed by Kaplan–Meier curves.

Results

20 cases of RNH were reviewed, of which 12 were men and 8 women; the median age was 51 years (IQR 40–73.3). Six (30%) patients were over 70 years old. The main diseases associated with RNH in our series were haematologic and immunodeficiency (n = 8; 40%). CVID was the main disease associated with RNH (n = 4), followed by inflammatory bowel disease, Crohn's/ulcerative colitis (n = 2). The characteristics of all patients with RNH are present in Table 1. 70% of patients had oesophageal varices and 25% had gastrointestinal bleeding. 70% of patients had splenomegaly, 50% ascites and 40% haepatomegaly. Pancytopenia was present in 45% of patients.

During the study period, 30 cases of CVID were diagnosed in our hospital, of which four (13.3%) underwent a liver biopsy which all had RNH (4/4, 100%). Of the four cases with CVID, 2 were male with a median age of 42.5 years (range 37–76 years), half of them had oesophageal varices and none had gastrointestinal bleeding upon diagnosis. One patient had ascites, three splenomegaly, two haepatomegaly and three pancytopenia. All had increased ALP and GGT. Bilirubin and albumin values were normal in all patients. Table 2 shows the differences in patients with CVID and other underlying causes of RNH. Gastrointestinal bleeding was more common in CVID, all patients had elevated ALP and GGT and none had values of albumin < 30 g/l and total bilirubin > 1.3 mg/dl compared to those with RNH associated with other diseases. Two of the four patients with CVID passed away, occurring at three and 16 months after diagnosis because of complications unrelated to RNH; the other two patients have been monitored for 38 and 44 months. Of the 16 patients without CVID, one was not monitored. Five of 15 (33.3%) being monitored passed away, two of these deaths were related to a complication of the portal hypertension (upper gastrointestinal bleeding). The median of patient monitoring was lower in those with CVID than in the rest of the patients (Table 2). In the Kaplan–Meier survival curve (Fig. 1) we can see a lower survival rate in patients with CVID, without reaching statistical significance ($p = 0.21$).

Discussion

RNH is an abnormality characterised by alterations in microvascular perfusion, leading firstly to damage in the haepatocytes and secondly, to their regeneration. This results in the formation of nodules that compress the surrounding liver parenchyma as well as the portal vein and the central veins, which affects the development of portal hypertension.[7] Characteristically there is no thickening of the portal venules nor fibrosis.

CVID is an alteration of the function of B cells and hypogammaglobulinemia, but many patients have abnormalities in T cells or antigen presenting cells.[2,12] This hipogammaglobulinemia and other immunological disorders predispose patients who did not start substitution treatment with immunoglobulins to the development of bacterial infections, especially sinopulmonary, and also