Nodular regenerative hyperplasia of the liver and cutaneous T-cell lymphoma: An unreported association

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ABSTRACT

Nodular regenerative hyperplasia of the liver –a type of non-cirrhotic portal hypertension– is a rare condition of unknown etiopathogenesis that has been associated with multiple disorders, including diverse types of hematologic disease. We report the case of a 36-year-old female patient diagnosed with cutaneous T-cell lymphoma of the mycosis fungoides variety, staged as T2N0M0B0, where a transjugular liver biopsy demonstrated the presence of nodular regenerative hyperplasia with a hepatic venous pressure gradient of 15 mm Hg. The study was triggered by the incidental radiologic finding of hepatomegaly with indirect evidence of portal hypertension. We are not aware of any previous reports on the association of nodular regenerative hyperplasia with mycosis fungoides in the medical literature.

Key words: Nodular regenerative hyperplasia. Cutaneous T-cell lymphoma. Vitamin A. Mycosis fungoides.

INTRODUCTION

Primary cutaneous lymphomas –whether B-cell or T-cell– are only second to gastrointestinal lymphomas as the most common extranodal non-Hodgkin type, with an annual incidence estimated around 1/100,000. Mycosis fungoides and Sézary syndrome are both the most common varieties of cutaneous T-cell lymphoma (CTCL). Their prognosis depends not only upon the type and extent of skin lesions but also on extracutaneous involvement, for which histologic confirmation is also recommended; hepatosplenic involvement is, however, an exception to this rule as it usually manifests as nodules in imaging studies, hence biopsy is not essential (1,2).

Nodular regenerative hyperplasia (NRH) is one of the categories included in the syndrome known as non-cirrhotic portal hypertension (NCPH), which requires absence of spleno-portal axis vein thrombosis and exclusion of an established cause of liver disease (3). In NRH, by definition, fibrosis is minimal or even absent. This is an uncommon condition in the Western world that has been associated with multiple disorders (infectious, genetic, autoimmune), various immune deficiency states, and exposure to a wide range of drugs and toxics. Occasionally, different potential etiologies are concurrently present in one patient. An association of NRH with a variety of hematological conditions is also well documented, and an underlying -ever so often manifest- thrombophilic status is posited in such cases as a key etiopathogenic factor (4). However, the description of an association between NRH and CTCL in the medical literature has never been made known to us.

CASE REPORT

A 36-year-old woman was referred from our dermatology and hematology clinics for the study of an incidental case of hepatomegaly on radiologic images. For approximately three years the patient had suffered from eczematous, erythematous, scaling, scarcely pruriginous, circular plaque-like skin lesions, some of them pigmented, on virtually all of the trunk and both upper and lower limbs. She had previously undergone two skin biopsies that yielded nonspecific findings (parakeratotic foci, minimal superficial perivascular lymphocytic infiltration with eosino-
phils, and mild epidermal hyperplasia), and the diagnoses of chronic eczema (perhaps due to contact atopy) versus atypical pityriasis rosea; she had received treatment mainly with various topical corticoids. Four months before our first encounter she was eventually diagnosed with CTCL of the mycosis fungoides variety. On this occasion a skin biopsy showed dense inflammatory infiltration of the superficial dermis with lymphocytes and exocytosis, that was minimal in the epidermis but well established in hair bulbs; the immunophenotype of the lymphocytic component was predominantly CD3/CD4 over CD8, with a scarce representation of CD20; the mitotic index (ki-67) was 25-30%. An amplification of the VJ segment in the hypervariable region of the TCR-γ (T-cell receptor-gamma) gene was carried out by PCR with specific primers and successive fragment analyses, using the ABI Prism® 3730 sequencer (Applied Biosystems, Foster City, CA, USA) and the commercially available MAD-003994TP-2/5® kit (Master Diagnóstica, Granada, Spain). The sample had tumor cellularity in excess of 70% with a DNA level of 21.2 ng/μl. A T lineage-specific monoclonal rearrangement was confirmed: the material analyzed showed an amplification fragment that was 156 base pairs in size.

At the time the diagnosis with CTCL was confirmed the patient was 26 weeks pregnant, which limited therapy options. As part of the staging process a CT scan with IV contrast was scheduled that also had to be delayed until after delivery, but that eventually identified a homogeneous hepatomegaly with no space-occupying lesions as sole significant finding. Stage at diagnosis was determined to be T2 (involvement greater than 10% of body surface), N0, M0 (no lymphocytic infiltration in nodes or other organs), B0 (no changes in T-cells or CD4/CD8 ratio on cytofluorometry and normal peripheral blood smear). When our first interview took place the patient had completed a course of 24 phototherapy sessions with ultraviolet-B radiation (cumulative dosage of 19,804 MJ), which resulted in significant improvement. She was otherwise asymptomatic, with no palpable adenopathies or abdominal masses and no stigmata of chronic liver disease on inspection. Her body mass index was 20.6 kg/m². All three series in the blood panel were normal and routine parameters suggested a rigorously preserved liver function. Liver enzymes were normal. Serologies for hepatitis B and C viruses were negative, as also were liver disease-related autoantibodies. Neither iron overload nor changes in the proteinogram or immunoelectrophoresis were found.

At three months following light therapy completion the patient experienced a severe recurrence of skin lesions wherefore she underwent treatment with bexarotene (150 mg/m²: 225 mg daily, adjusted to body surface area [1.6 m²]), thyroxine (25 μg daily), fenofibrate (180 mg daily) and omega-3 triglycerides (1,000 mg daily) together with psoralen and ultraviolet-A radiation (PUVA). Concomitantly, a repeat CT scan with IV contrast was performed where previously absent radiographic portal hypertension (PHT) evidence was comparatively ascertained (increased portal vein caliber and splenomegaly); hepatomegaly persisted but now with a peripheral nutmeg liver pattern of enhancement that suggested potential veno-occlusive hepatic disease (Fig. 1). Here a transjugular liver biopsy was performed with simultaneous measurement of suprahepatic vein wedged (25 mm Hg) and free (10 mm Hg) pressures: The resulting hepatic venous pressure gradient (HVPG) was 15 mm Hg. No sedation was used for this procedure. Five liver tissue fragments with
sizes between 5 and 10 mm were histologically studied: An architectural distortion could be seen that included a changed relationship between central veins and portal tracts and no fibrosis was present (Fig. 2).

No gastroesophageal varices or other PHT manifestations were documented by oral endoscopy. An abdominal sonogram revealed no evidence of steatosis. Liver stiffness as measured by transient elastometry (TE) was 6.1 kilopascals (kPa) with an interquartile range of 0.8 kPa. Baseline urinary Na/K excretion was 132/141 mmol/24 hours. No changes worth mentioning were found in a complete hypercoagulability study including antithrombin III, proteins C and S, homocysteine, antiphospholipid antibodies and both prothrombin and factor V Leiden gene mutations. No complications have arisen after six months following her diagnosis with NRH.

**DISCUSSION**

Hepatic distortion in NRH results from diffuse parenchymal transformation into regeneration nodules (single-acinus, smaller than 3 mm) with central hyperplasia alternating with tissue atrophy areas; typically, in contrast with cirrhosis, nodules are not separated by fibrosis (5). The most commonly accepted hypothesis regarding their genesis considers NRH a consequence of generalized tissue adaptation (hyperplastic liver cells and/or atrophy) to a disruption or heterogeneous distribution of blood flow secondary to the obliteration, luminal narrowing and destruction of smaller portal veins (up to 0.2 mm in diameter). Regardless of the underlying disorder, the unifying histology of NRH is therefore obliterating portal vein disease (6), without significant septal fibrosis, probably associated with a baseline prothrombotic status (7). These changes, however, are not pathognomonic and also develop in other NRH-related conditions (8). The clinical behaviour of NRH is usually silent with long symptom-free periods lacking specific laboratory or radiologic changes. Nevertheless, most patients (50-70%) eventually develop irreversible PHT signs or complications. Ascites is peculiarly uncommon and prognosis is never as poor as for liver cirrhosis, likely because liver function is usually preserved until end-stage disease. Otherwise, recommendations regarding the prophylaxis and management of PHT clinical manifestations are similar to those established for patients with cirrhosis (3). Consequently, a high level of suspicion is necessary in routine clinical practice regarding the prophylaxis and management of PHT in patients with NRH: direct sinusoidal compression by regeneration nodules may as well develop. Some authors (11) posit a mixed (presinusoidal and sinusoidal) component for NCPH, and the result may depend on the measuring of pressures for the predominant mechanism in each individual case, and/or disease progression stage: 6 of 21 (28.6%) patients in the study by Bissonnette et al. had a HVPG higher than 10 mm Hg, some of them with no esophageal varices, as in our case. Recently, promising evidence has emerged on the capacity of TE to discriminate between liver cirrhosis and NCPH (12): Seijo et al., using HVPG measurements and TE, studied a cohort of 27 patients with NCPH (7.1 ± 3.1 mm Hg and 8.4 ± 3.3 kPa, respectively) and compared their findings with those from a cohort of cirrhotics with PHT (17.0 ± 3.0 mm Hg and 40.9 ± 20.5 kPa, respectively) finding statistically significant differences in both cases. Only 5/27 (18.5%) patients with NCPH had an HVPG above 10 mm Hg and only two patients had a liver stiffness value greater than 13.6 kPa. Therefore, in patients with unequivocal PHT evidence, HVPG and/or liver stiffness values below those consid-
ered significant for cirrhosis should raise suspicion for a condition within the NCPH syndrome complex.

In summary, NRH (as other forms of NCPH) is a condition that entails a serious prognosis, likely remains underdiagnosed and may be easily mistaken for liver cirrhosis. Diagnostic tools available to us include biopsy, liver hemodynamics, and –of late– TE, but the disease may manifest with a wide range of nonspecific data that, on occasion, may even look conflicting. Describing the association of NRH with other conditions (e.g., with CTCL, as in our patient) may foster understanding for this still puzzling disease on whose etiopathogenesis all theories remain merely guesswork. Its treatment currently consists of the generic management of PHT, but the hypothesis that anticoagulation therapy may be beneficial is overtly appealing (3).

REFERENCES