Clinical Course of Nodular Regenerative Hyperplasia in Thiopurine Treated Inflammatory Bowel Disease Patients

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Nodular regenerative hyperplasia (NRH) is a poorly understood liver condition, which is increasingly recognized in thiopurine-treated patients with inflammatory bowel disease (IBD).[1] It is difficult to establish an optimal approach to NRH patients, because its manifestations are highly variable (from asymptomatic to symptoms of noncirrhotic portal hypertension [NCPH]) and the prognosis is unknown.[2] The aim of this study was to identify NRH cases in IBD patients treated with azathioprine, mercaptopurine, and/or thioguanine, and to describe its clinical course.

Methods

All 81 Dutch hospitals with a gastroenterology and hepatology department were requested to report NRH cases with detailed (follow-up) data. Collected data included demographics; disease and (historical) treatment characteristics; and clinical, laboratory, imaging, endoscopic, and histopathologic findings. Manifestations of NRH (signs or symptoms of NCPH or asymptomatic [ie, biochemical abnormalities in the absence of clinical signs of liver disease]) before diagnosis and during follow-up were documented. Solely cases of histopathologically proven NRH (grade 3 micronodularity in the absence of bridging fibrosis[3]) without concomitant liver pathology, as diagnosed by the pathologist at location, were included.

Results

Seventy-two hospitals (89%) reported a total of 43 NRH cases in thiopurine-treated IBD patients. Their baseline characteristics are detailed in Table 1. Eighteen patients (42%) were treated with thioguanine. Notably, almost 90% of them had previously received azathioprine and/or mercaptopurine. At time of NRH diagnosis, 17 patients (40%) were asymptomatic, whereas 26 (60%) presented with symptoms of NCPH, being splenomegaly in 23 (88%), ascites in 4 (15%), and esophageal varices in 19 (73%), with variceal bleeding in 11 patients (42%). Patients with NCPH had lower hemoglobin (7.3 vs 8.5 mmol/L; $P < .05$) and platelet count (90 vs 172 $\times$ 10^9/L; $P < .001$), but liver biochemistry did not differ between asymptomatic and NCPH patients.

After a median follow-up of 5.5 years (range, 2–13 years), signs and symptoms of NCPH resolved in 8 patients (31%). Initially, NRH was complicated by thrombocytopenia and splenomegaly in all 8 patients; 6 patients had esophageal varices as well. In these 8 patients, aspartate aminotransferase (48 vs 30 U/L) and

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Table 1. Baseline Characteristics, Liver Biochemistry, and Imaging at Time of Diagnosis and Follow-up (n = 43)

Sex, male	33 (77)	
Age at NRH diagnosis, *y*	49 (17–74)	
IBD disease duration, *y*	15 (3–44)	
IBD (CD/UC/IBDu)[a]	30 (70)/12 (28)/1 (2)	
CD behavior (B1/B2/B3)	13 (43)/14 (47)/5 (17)	
CD location (L1/L2/L3/L4)	14 (47)/6 (20)/8 (27)/2 (7)	
UC extent (E1/E2/E3)	0 (0)/5 (42)/7 (58)	
UC severity (S0/S1/S2/S3)	4 (33)/1 (9)/4 (33)/3 (25)	
Thiopurine use (AZA/MP/TG)	30 (70)/13 (30)/18 (42)	
AZA dose (*mg*) and duration (*mo*)	150 (100–300)	48 (1–204)
MP dose (*mg*) and duration (*mo*)	75 (25–100)	33 (1–78)
TG dose (*mg*) and duration (*mo*)	21 (20–48)	38 (12–84)
Laboratory findings	At diagnosis	Follow-up
Hb (7.5–11 mmol/L)	8.2 (4.3–10.1)	8.5 (5.2–10.1)
PC (150–400 × 10^9/L)**	115 (43–346)	160 (28–319)
ALT (<45 U/L)***	45 (15–104)	34 (12–87)
AST (<40 U/L)***	44 (18–78)	30 (17–95)
GGT (<55 U/L)***	107 (16–497)	47 (12–272)
AP (<120 U/L)	126 (55–316)	94 (14–344)
Bilirubin (<20 μmol/L)*	16 (4–328)	12 (4–48)
Imaging findings	At diagnosis	Follow-up
No abnormalities*	17 (40)	27 (63)
Splenomegaly*	23 (54)	11 (26)
Heterogeneous parenchyma*	22 (51)	13 (30)
Bleeding varices	11 (26)	5 (12)
Ascites	4 (9)	3 (7)

NOTE. Categorical characteristics are depicted as numbers and percentages, continuous characteristics as medians with ranges.
Significance: *$P < .05$; **$P < .01$; ***$P < .001$.
ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; AZA, azathioprine; CD, Crohn's disease; GGT, γ-glutamyltransferase; Hb, hemoglobin; IBD, inflammatory bowel disease; MP, mercaptopurine; NRH, nodular regenerative hyperplasia; PC, platelet count; TG, thioguanine; UC, ulcerative colitis.
[a]Disease-specific characteristics are depicted using the Montreal classification for CD and UC.

alkaline phosphatase (127 vs 90 U/L, both $P < .05$) decreased, and there was a statistic trend toward a higher platelet count (99 vs 182 × 10^9/L; $P = .06$) during follow-up. Five patients (19%) experienced recurrent variceal hemorrhages, of which 3 had a recurrence of ascites, despite secondary prophylaxis. All 5 patients had been exposed to azathioprine; 3 patients had been exposed to thioguanine as well.

The 17 patients without clinical signs of liver disease at diagnosis did not develop complications during follow-up. Overall, liver enzymes normalized and platelet count improved over time (Table 1). None of the patients received a liver transplantation, developed hepatocellular carcinoma, or died during the long-term course.

Discussion

The pathogenesis and prognosis of NRH are widely unknown, which makes it difficult to establish an optimal approach to patients with NRH.[4] In this study, a relatively small number of 43 NRH patients were identified in a nationwide cohort, of which 26 patients (60%) presented with symptoms of NCPH at diagnosis. During a follow-up of 66 months, symptoms of NCPH resolved in 8 (31%) and recurred in 5 patients (19%). Both liver biochemistry and platelet count normalized in most patients.

Thiopurines are effective in maintaining remission in IBD, but concerns about adverse events, such as NRH, have impaired their use. Especially thioguanine, a thiopurine-derivative used as a rescue drug, has been related to hepatotoxicity, which has limited its use in IBD.[5] In this cohort, 90% of thioguanine-exposed patients had previously used azathioprine and/or mercaptopurine. The causative factor of NRH in these cases, and in the available literature (incidence rates, 0%–62%), is questionable, because azathioprine and IBD itself have been related to NRH as well.[6,7]

Our cohort was characterized by a predominance of male sex and stricturing disease phenotype. Furthermore, we showed a significant reversibility of NCPH symptoms. In a systematic French study on NRH and azathioprine, NRH was mainly identified in male patients with stricturing Crohn's disease.[6] In both their and our cohort, patients with asymptomatic NRH at time of diagnosis remained asymptomatic during extensive follow-up. Ferlitsch et al[8] reported on improvement of portal pressure in thiopurine-exposed NRH patients, after the cessation of thiopurines. In our study, portal venous pressure was not measured, but we observed reversibility of NRH-related complications (especially in young patients), indicative for portal pressure decrease.

In conclusion, in the long-term follow-up of 43 NRH patients, predominantly male with (stricturing) Crohn's disease, liver biochemistry and platelet count normalized after thiopurine discontinuation. Symptoms of NCPH resolved in one-third and recurred in 5 patients (with pre-existing severe NCPH at diagnosis).

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Conflicts of interest
These authors disclose the following: Annemarie C. de Vries has served as a speaker, member of advisory board, or consultant for Takeda, AbbVie, Tramedico, Dr Falk, and Jansen. Frank Hoentjen has served as a speaker, member of advisory board, or consultant for MSD, Takeda, Celltrion, Teva, Sandoz, Dr Falk, and Celgene. Gerard Dijkstra has received unrestricted research grants from AbbVie and Takeda; has served as a member of the advisory board for Mundipharma and Pharmacosmos; and has received speaker fees from Takeda and Janssen. Jeroen M. Jansen has served as a speaker, member of advisory board, or consultant for AbbVie, Janssen, Ferring, Pfizer, Takeda, and MSD. Bas Oldenburg has served as a speaker, member of advisory board, or consultant for AbbVie, Ferring, Janssen, MSD, Pfizer, and Takeda. Nanne K. H. de Boer has served as a speaker for AbbVie, Takeda, and MSD; has served as consultant and principal investigator for Takeda and TEVA Pharma BV; and has received research grants from Dr. Falk and Takeda. Chris J. J. Mulder has served a principal investigator for TEVA Pharma BV. The remaining authors disclose no conflicts.