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The Changing Shape of Disease: Non-alcoholic Fatty Liver Disease in Crohn's Disease A case series and review of the literature

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Abstract

Background—With improvements in therapy for inflammatory bowel disease (IBD) and changes in the prevalence of obesity, the phenotype of Crohn's Disease (CD) is changing. These changes may herald an increase in the incidence of non-alcoholic fatty liver disease (NAFLD) in this population.

Methods—Over a ten-month period we identified seven patients with CD who required liver biopsy for elevated liver function tests (LFTs), with an ultimate diagnosis of NAFLD. We performed a retrospective chart review and literature search to identify relevant data on NAFLD and CD. Specifically, we abstracted prior and current IBD-related medication exposures, disease severity, and the presence of typical comorbidities associated with NAFLD.

Results—We describe seven patients with CD and biopsy-proven NAFLD. The majority of these patients were overweight or obese, had quiescent CD, and were more likely to be receiving a tumor necrosis factor-alpha inhibitor. Review of the literature produced a total of 29 articles describing NAFLD in IBD patients, primarily restricted to historical autopsy and surgical series. Limited contemporary studies highlight the rising prevalence of NAFLD in treated IBD populations.

Conclusions—NAFLD is increasing in incidence and prevalence among the general population. With improvements in therapy, NAFLD is likely increasing among the CD population as well. When evaluating an IBD patient with abnormal LFTs, clinicians need to consider NAFLD. NAFLD may impact IBD management in the future if therapeutic modalities are limited due to elevated LFTs. Further, patients should be monitored for excessive weight gain and counseled regarding healthy dietary and exercise habits.

Keywords

NAFLD; NASH; IBD; Crohn's Disease; Liver

Introduction

Patients with inflammatory bowel disease (IBD) are at risk of developing extra-intestinal complications of disease, with primary sclerosing cholangitis, autoimmune hepatitis, and

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adverse treatment-related effects among the most frequently recognized conditions affecting the hepatobiliary system.[1] Non-alcoholic fatty liver disease (NAFLD), the most common liver disorder in industrialized Western countries,[2] is infrequently described in patients with IBD. However, with improvements in treatment, in particular the advent of the tumor necrosis factor-alpha (TNF-a) inhibitors and in conjunction with larger societal trends in weight gain, the phenotype of IBD may be changing. Though traditionally viewed as underweight and/or malnourished, IBD patients today are more likely to exhibit rates of overweight and obesity on par with the general population.[3-5] Consequently, these patients are at risk of developing NAFLD. The hepatic inflammation and abnormal liver function tests (LFTs) that often accompany a diagnosis of NAFLD may complicate treatment decisions, influence pharmaceutical choices, and potentially predispose IBD patients to develop cirrhosis. We describe seven patients with Crohn's disease (CD) and biopsy-proven NAFLD, with the aim to describe potential risk factors including medication exposures, clinical CD course, and related comorbidities, and to raise awareness of this infrequently recognized complication that is likely increasing in incidence.

Materials and Methods

We identified a total of seven Crohn's disease patients evaluated at the University of North Carolina between December 2009 and October 2010 for abnormal liver function tests, with liver biopsy identifying non-alcoholic fatty liver disease. Patient characteristics, medical co-morbidities, CD severity, current and past medications, and laboratory and pathologic results were extracted from the medical record.

To identify existing literature, a Medline MeSH search was performed using the terms “inflammatory bowel diseases” and “fatty liver.” Abstracts were searched to identify relevant articles, with pertinent ones reviewed. Additional queries were performed using a combination of MeSH terms including “Crohn disease,” “ulcerative colitis,” and “liver diseases.” Individual bibliographies were hand-searched to identify additional associated articles.

Results

A total of seven Crohn's disease patients with biopsy-proven NAFLD were identified. A summary of the clinical characteristics of each patient is provided in Table 1. Five patients were female; all were Caucasian. The mean age at time of NAFLD diagnosis was 35 (range: 23 to 49). Mean duration of CD was 11 years (range: 6 to 17). Obesity was defined in standard fashion using the following body mass index (BMI) cut-points: normal BMI <25, overweight BMI 25 – 29.9, obese BMI >30.[6] Five of seven patients were obese (mean BMI: 35), one was overweight, and one was of normal body mass. Six of seven patients had normal BMI at the time of IBD diagnosis; mean BMI increased by 7 kg/m^2 from IBD onset to time of NAFLD diagnosis. Four patients were receiving TNF-alpha inhibitors at the time of biopsy, and 2 were receiving azathioprine (AZA) or 6-mercaptopurine (6-MP). All seven patients were treated with corticosteroids in the course of their CD, though only a single patient received them within the preceding 12 months. Four patients were in asymptomatic remission from their CD at the time of liver biopsy.

A Medline MeSH search using terms “inflammatory bowel diseases,” “Crohn disease,” “ulcerative colitis,” “fatty liver,” and “liver diseases” yielded 17 relevant manuscripts. Review of individual bibliographies identified 12 related articles. A summary of the 29 included articles is provided in Table 2. Twenty-one articles were published prior to 1972, with only 4 published in the last decade. The majority were case reports or case series involving autopsy and/or surgical specimens. The prevalence of biopsy-proven NAFLD in

these series was as high as 89%[7], and was attributable to severe IBD and malnutrition. Lower rates of NAFLD, on the order of 2% – 6%, were noted in less-ill populations.[8-11] More recent studies, utilizing sonographic diagnosis, identified NAFLD in approximately 40% of IBD patients.[12,13]

Discussion

NAFLD and IBD in the medical literature

In this series, we highlight seven cases of biopsy-proven non-alcoholic fatty liver disease in patients with underlying Crohn's disease. Though liver dysfunction is a recognized complication of IBD,[13,14] reports of NAFLD as the primary abnormality have been infrequently described in the medical literature, and rarely in patients with treated, inactive disease.

The first known description of hepatic steatosis in IBD was reported in 1873 by CH Thomas, who described a young patient with “ulceration of the colon,” with autopsy revealing “a much enlarged fatty liver.”[15] Subsequent autopsy series reported a prevalence of hepatic steatosis in 15% to 88% of IBD patients, representing the most common pathologic abnormality. [16-26] Steatosis was presumed secondary to severe illness, with malnutrition and hypoproteinemia primarily responsible.[17] Further series examining liver biopsies at the time of bowel resection supported this hypothesis.[7,27-32] However, the presence of hepatitis steatosis is less frequent when considering more diverse IBD populations, with 2% to 6% prevalence in representative biopsy-based cross-sectional studies.[8-11] The inclusion of less-ill patients, compared to prior reports, may explain this discrepancy. Notably, these studies preceded the obesity epidemic later observed in western countries.

More recent studies utilizing ultrasound diagnosis suggest a higher prevalence of NAFLD. In a large, single-center study of 511 patients with IBD, sonographic evidence of hepatic steatosis was detected in 40% of CD patients, with severe steatosis in 12%. Though patients with underlying obesity and/or metabolic disorders were excluded from this study, nearly two-thirds of patients were receiving corticosteroids, a factor that may have contributed to these findings.[12] Similar rates of steatosis have been observed in other ultrasound-based studies.[13,33,34]

Therefore, available evidence would suggest that NAFLD is not uncommon in IBD. The majority of these studies, however, were conducted in patients with active, severe, even life-threatening disease. Our series includes primarily treated, asymptomatic patients, highlighting the occurrence of NAFLD in less-ill patients.

The rise of overweight and obesity in IBD

Traditionally, patients with inflammatory bowel disease have been viewed as underweight or malnourished, particularly in the setting of active disease. In fact, weight deviation is one of the eight components of the Crohn's Disease Acivity Index.[35] This viewpoint was supported by epidemiologic data from Scotland in the 1970s, where 28% and 57% of juvenile CD patients fell below the 3rd percentiles for height and weight, respectively.[36] These changes persisted into adulthood, irrespective of disease activity, with average weight remaining below normal at a mean of 14 years follow-up. [37]

However, more contemporary data suggest that the typical IBD phenotype may be evolving. A subsequent study of IBD patients in Tayside, Scotland, found that rates of overweight and obesity were 38% and 18%, respectively, equivalent to those in the general population.[3] Similar findings were noted in a Netherland's cohort of CD patients in remission.[4] A more

recent cohort of pediatric patients in the United States under medical treatment for IBD demonstrated a rate of overweight or obesity of 23.6%, comparable to the general population.[38]

The patients in our series are no exception to this trend, six of which were either overweight or obese. Obesity, along with diabetes mellitus, hypertension, and dyslipidemia, is a known risk factor for NAFLD and patients with IBD are not exempt from this risk. Recognizing the epidemic of overweight and obesity in modern society, with 68% of the adult population of the United States affected,[39] IBD patients may simply be mirroring larger trends. However, other factors may be at play, including the direct and indirect role of pharmacotherapeutic agents.

Pharmacotherapy: direct and indirect effects on hepatic steatosis

Medications used in the treatment of IBD carry a known risk of hepatoxicity.[40] However, NAFLD is an infrequently recognized complication of their use. Yet, specific agents may directly contribute to hepatic steatosis, or indirectly induce weight gain, a principle factor in its development.

Corticosteroids, a mainstay of IBD treatment, are known to produce weight gain and steatosis.[41,42] However, newer steroid-sparing therapies have reduced dependence on their use. This is evident in our series, where only 1 patient was actively receiving a corticosteroid, and the remaining 6 patients had been corticosteroid-free for a median of 3 years. The role of corticosteroids in the pathogenesis of NAFLD in IBD patients may be less relevant today.

Methotrexate, which one patient in our series was actively receiving, has a well-recognized risk of hepatotoxicity, particularly with prolonged administration.[43] Observed histological changes may overlap with those seen in NAFLD, including steatosis, inflammation, and fibrosis.[40] Further, concomitant obesity and diabetes mellitus may potentiate this risk.[44] The thiopurines (AZA and 6-MP), used by two patients in our series, have known liver toxicities, including hepatocellular injury and cholestatic disease.[13,45] However, hepatic steatosis is not an identified risk.

The biologic agents, in particular the TNF-alpha inhibitors, have emerged as important modalities in the treatment of moderate to severe Crohn's disease, allowing for induction and maintenance of remission, and improved quality of life.[46] Adverse hepatic effects associated with their use include reactivation of viral hepatitis, direct hepatoxicity, and autoimmune hepatitis.[47] Furthermore, use of these agents may induce weight gain. Known also as cachectin, TNF-alpha is an important mediator of muscle wasting and protein depletion in states of inflammation and infection.[48] Inhibition of its effects, then, could lead to changes in body mass. In patients with rheumatologic disease, TNF-alpha inhibitors are linked to increased body weight.[49-52] This change was not observed with other agents, including methotrexate.[50,51]

Few data are available regarding TNF-alpha-related weight changes in IBD patients. A small, prospective study of infliximab use in 20 CD patients documented increase in body weight at 4 weeks.[53] Unpublished retrospective data from Isaacs, et al, examined infliximab use in patients with Crohn's disease and rheumatoid arthritis (RA). Over the 4-year study period, CD patients gained significantly more weight than RA patients (5kg vs. 1.2kg; p=0.0049). The authors suggest that this difference may be explained by improvement in mucosal function, leading to nutrient absorption and weight gain, perhaps more than a direct medication effect.[54] Additionally, treatment with TNF-alpha inhibitors may affect circulating levels of leptin, a peptide that plays a central role in appetite control and insulin

resistance, though evidence has been conflicting.[53,55] Interestingly, the TNF-alpha inhibitors have shown promise in the treatment of non-alcoholic steatohepatitis (NASH), with limited evidence indicating a biochemical and histologic benefit.[56-59] It is unclear how these benefits might be outweighed by the risks associated with weight gain, at least in the treatment of IBD patients.

In summary, treatment modalities for IBD have established adverse hepatic effects. Perhaps most relevant to our case series, though, is their effectiveness in inducing and maintaining remission, which may promote weight gain and contribute the development of fatty liver disease.

Summary and Implications

Our case series highlights the existence of overweight, obesity, and non-alcoholic fatty liver disease in patients under medical therapy for Crohn's disease. Though originally described in patients with severe, active colitis, NAFLD is likely to increase in incidence among less-ill IBD patients, particularly given rising rates of obesity, and the effectiveness of newer treatment modalities in inducing remission. Obesity itself is a known risk factor for increased anoperineal disease, earlier surgical interventions, and greater surgical complications among Crohn's disease patients.[60-62] Additionally, the abnormal LFTs that frequently accompany NAFLD may make utilization of some drugs like AZA or MTX more complicated. This, coupled with the potential morbidity and mortality related to NAFLD, including cirrhosis and its complications, raises significant implications related to the health of this population.

Conclusions

The phenotype of the inflammatory bowel disease patient is changing. With the emergence of more effective pharmacotherapy, coupled with larger trends in society, IBD patients are no longer underweight or malnourished. With rates of overweight and obesity now on par with the general population, NAFLD – an important complication of weight gain – needs to be recognized. When evaluating an IBD patient with abnormal liver function tests, clinicians need to consider this entity. Further, patients should be monitored for excessive weight gain and be counseled regarding healthy dietary and exercise habits.

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Abbreviations

IBD	Inflammatory Bowel Disease
NAFLD	Non Alcoholic Fatty Liver Disease
TNF-a	Tumor Necrosis Factor-alpha
NASH	Non Alcoholic Steatohepatitis
CD	Crohn's Disease
BMI	Body Mass Index
AZA	Azathioprine

6-MP	6-Mercaptopurine
6-MMP	6-Methylmercaptopurine
RA	Rheumatoid Arthritis
UC	Ulcerative Colitis

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Table 1

Patient Characteristics

Age/Gender	CD Duration(years)	BMI (Diagnosis)	BMI (Biopsy)	DM	HTN	Current Medications	TNF-a†	MTX†	AZA/6-MP†	Max AST	Max ALT	Biopsy‡
29 M	10	---	31.8	No	Yes	Natalizumab	2 yr	No	Yes	88	207	Grade 1, Stage 1
26 F	13	22.9	35.3	No	No	Adalimumab AZA	1 yr	No	Yes	75	96	>75% Steatosis
33 M	13	24.3	36.5	No	Yes	6-MP	No	No	Yes	99	195	Grade 1, Stage 1
42 F	10	35.6	39.3	No	Yes	None	2 yr	3 yr	Yes	53	72	Grade 1, Stage 1
49 F	17	21.8	24.2	No	Yes	Adalimumab Prednisone	4 yr	3 yr	No	57	52	Grade 2, Stage 1
46 F	6	27.9	33.5	Yes	No	MTX	1 yr	1 yr	Yes	105	127	Grade 1, Stage 2-3
23 F	13	21.7	26.36	No	No	Adalimumab	4 yr	1.5 yr	Yes	106	176	Grade 1, Stage 1

All patients are Caucasian and carry the diagnosis of Crohn's disease. None of the patients carry a known diagnosis of hyperlipidemia.

All patients were previously treated with oral steroids with one patient receiving them currently.

BMI: Body Mass Index, DM: Diabetes Mellitus, HTN: Hypertension, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, MTX: Methotrexate, 6-MP: 6-Mercaptopurine, AZA: Azathioprine,, TNF-a: Tumor necrosis factor-alpha inhibitor

† Duration of prior use

‡ Histologic classification according to Brunt criteria (Brunt EM, et al. Am J Gasroenterology 1999; 94:2467)

Table 2

Publications Reporting Hepatic Steatosis in IBD Patients

Author	Year	No. of Subjects	Prevalence of Steatosis (%)	IBD Subtype	Diagnostic Modality
Thomas[15]	1873	1	1 (100)	UC	Necropsy
Logan et al[16]	1919	13	10/13 (77)	UC	Necropsy
Ross et al[17]	1948	27	11/27 (41)	UC	Necropsy
Pollard et al[18]	1948	17	15/17 (88)	UC	Necropsy
Warren et al[19]	1949	60	33/60 (55)	UC	Necropsy
Dyson et al[20]	1950	3	1/3 (33)	UC	Necropsy
Jones et al[21]	1951	91	47/91 (52)	UC	Necropsy
Kleckner et al[63]	1952	32	9/32 (28)	UC	Biopsy
Kimmelstiel et[22] al[22]	1952	93	14/93 (15)	UC	Necropsy
Parker et al[23]	1954	39	13/39 (33)	UC	Necropsy
Chapin et al[24]	1956	39	20/39 (51)	CD	Necropsy
Monto et al[25]	1959	100	80/100 (80)	UC	Necropsy
Palmer et al[26]	1964	50	25/50 (50)	UC	Necropsy
De Dombal et al[27]	1966	58	48/58 (83)	UC	Biopsy*
Dordal et al[28]	1967	103	22/103 (21)	Both	Biopsy
Eade et al[29]	1970	132	59/132 (45)	UC	Biopsy*
Eade et al[30]	1971	20	8/20 (40)	CD	Biopsy*
Dutt et al[7]	1983	29	26/29 (89)	Both	Biopsy*
Mattila et al[31]	1994	59	9/59 (15)	UC	Biopsy*
Perrett et al[9]	1971	100	4/100 (4)	CD	Biopsy
Perrett et al[8]	1971	300	19/300 (6)	UC	Biopsy
Wee et al[10]	1985	107	2/107 (2)	UC	Biopsy / Necropsy
Broome et al[11]	1990	74	3/74 (4)	UC	Biopsy
De Fazio et al[33]	1992	74	10/74 (14)†	Both	Ultrasound

Author	Year	No. of Subjects	Prevalence of Steatosis (%)	IBD Subtype	Diagnostic Modality
Riegler et al[34]	1998	484	58/484 (12)†	Both	Ultrasound
Bargiggia et al[12]	2003	511	194/511 (38)	Both	Ultrasound
Candelli et al[42]	2003	1	1 (100)	UC	Biopsy
Scalone et al[32]	2003	21	4/21 (19)	UC	Biopsy*
Gisbert et al[13]	2007	786	49/120 (41)‡	Both	Ultrasound

Inflammatory bowel disease (IBD), Ulcerative colitis (UC), Crohn's Disease (CD)

*Biopsy at time of colectomy or bowel resection

†Bright liver pattern on ultrasound

‡Ultrasound restricted to patients with abnormal liver tests