A unique combination of celiac disease, mesenteric lymph node cavitation, splenic atrophy and necrotizing hepatitis

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Abstract

We report on a patient who was diagnosed six years before with celiac disease, with a current combined problem of asplenism, mesenteric cysts and elevated liver function tests. The implications of splenic atrophy mimic those of post-splenectomy patients. Mesenteric lymph node cavitation is a rare complication of celiac disease that is most often associated with splenic atrophy. The pathogenesis is unknown. The clinical implications of the cavitated mesenteric lymph nodes are unclear. The association of celiac disease with liver disease was reported many years ago, but only recently these associations have been more clearly defined. Liver involvement shows a clinical spectrum varying from nonspecific reactive hepatitis, chronic active hepatitis, steatohepatitis to frank cirrhosis. Associations with autoimmune hepatitis, autoimmune cholangitis, primary biliary cirrhosis and primary sclerosing cholangitis have been described. In our patient, we found no obvious cause for the necrotizing hepatitis and the negative auto-antibodies made it impossible to firmly establish the diagnosis of autoimmune hepatitis. The causal relationship with celiac disease, if any, remains unproven. (Acta gastroenterol. belg., **2008**, 71, **267-270**).

Introduction

Celiac disease is a complex, multifactorial, chronic inflammatory disease of the small intestine induced by dietary proteins in wheat, rye and barley. Immuno-dominant dietary (wheat gliadin) peptides resistant to intestinal enzymatic breakdown and modified by tissue transglutaminase – which are presented to T cells by HLA-DQ2 – are considered key steps leading to the intestinal inflammatory response. Although potentially disease causing grains are present in substantial quantity in most Western diets, the prevalence of disease among Caucasians is less than 1% [1]. Histology of the small intestine typically shows villous atrophy and an elevated number of intra-epithelial lymphocytes [2]. Laboratory findings consist of the presence of antibodies against gliadin, endomysium and tissue transglutaminase. The disease may lead to the clinical syndrome of malabsorption [3], an increased incidence of malignancy and extraintestinal manifestations, including liver disease. Therapy consists of a life-long gluten free diet and vitamin supplementation (1). We report on an unusual association in an elderly female patient of celiac disease with mesenteric lymph node cavitation, splenic atrophy and necrotizing hepatitis.

Case report

A 68-year old woman was referred in April 2004 to our hospital by her family doctor. She had been complaining of weight loss, general weakness, anorexia, cachexia and oedema of the lower limbs since the last year.

When she was 14 years old, she underwent an appendectomy. In 1998, age 62 years, the diagnosis of celiac disease was made on duodenual biopsy because of complaints of epigastric discomfort and anorexia. She was started on a gluten free diet and followed this for eighteen months. In 1999 Computerized Tomography (CT) of the abdomen revealed multilocular cysts. A laparoscopy in 2000 done because of an elevated serum CA 125, showed chylous ascites in the Douglas (triglycerides of 256 mg/dl in the ascitic fluid), multilocular mesenterial cysts and no ovarian masses. Pathological examination of the ascites was normal. A repeat laparoscopic diagnostic intervention with cyst biopsy was proposed in 2001 because of further weight loss and cachexia but the patient refused. In 2003 she underwent a vaginal hysterectomy because of a vaginal prolapse ; the surgeon described multiple masses and pathological examination of one mesenteric mass showed a chylous mesenterial cyst.

Patient currently presented on examination with a weight of 33 kg. Her normal body weight ranged around 40 kg. There was tense ascites and malleolar oedema. She was cachectic with pronounced muscular atrophy, and she was slightly jaundiced. There were no spider naevi or liver palms and no enlarged lymph nodes were felt. Treatment on admission was spironolactone 100 mg per day. Laboratory findings are given in table 1 and showed signs of malabsorption with low values of albumin, vitamin A, E, D and secondary hyperparathyroidism. The

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Table 1

	Normal values	April 2004	June 2004	September 2004
Hemoglobin	(12 – 16 g/dl)	11.4		
Platelets	(150,000-450,000/µl)	129.000		
Calcium	(8.6 – 10.3 mg/dl)	7.6		
Albumin	(35 – 52 mg/dl)	31.7		
Alkaline Phosphatase	(< 240 U/l)	3623	1580	611
AST	(< 32 U/l)	348	201	32
ALT	(< 31 U/l)	355	190	34
Gamma GT	(< 35 U/l)	573	214	50
Total bilirubin	(< 1 mg/dl	2.18	1.5	0.53
LDH	(240 – 480 U/l)	680	647	306
Prothrombin time (PT)	(70-100%)	46	95	58.9
PT (after vitamin K administration)		63		
Parathormone	(3 – 40 ng/l)	133.7		
25 OH vitamin D	(7 – 60 µg/l)	< 2.5		
Vitamin B12	(170 – 800 ng/l)	266		
Folic acid	(170 – 480 µg/l)	260		
Vitamin A	(300 – 650 µg/l)	40		
Vitamin E	(5 – 20 mg/l)	1.8		
Zink	(80 – 120 µg/dl)	39		
Magnesium	(1.58 – 2.55 mg/dl)	1.54		
Cupper	(80 – 140 µg/dl)	103		
Ceruloplasmin	(0.22 – 0.58 g/l)	0.3		
Endomysium Ig A		Negative		
Gliadine Ig A	(< 20 U)	>100		
Gliadine Ig G	(< 20 U)	48		
HLA typing		A1A3B8BxDR3DR15		

ammonia level was elevated and the liver tests were indicative of mixed cholestastic and hepatocellular damage. Anti-endomysial antibodies were negative, antigliadin antibodies positive.

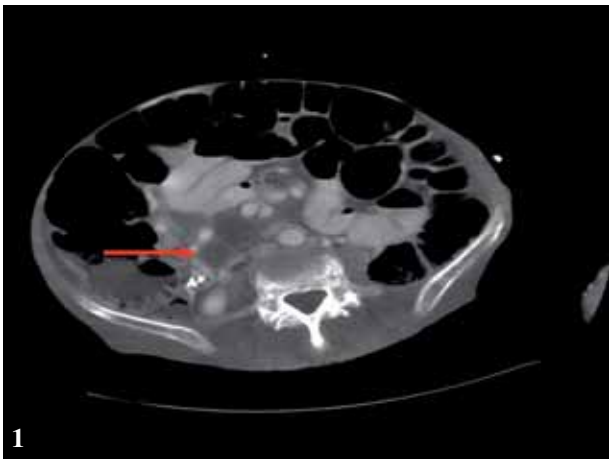
CT of the abdomen confirmed the ascites and showed a nodular appearance of the liver, the known multiple mesenteric cysts and a cystic lesion in the pancreas (Fig. 1). Remarkably, no spleen could be visualized (Fig. 2). Hepatic vein catheterization was performed and a transjugular liver biopsy was taken. Portosystemic pressure gradient was 14 mmHg and indicative of portal hypertension. Liver biopsy showed no signs of cirrhosis but a subacute necrotizing cholestatic hepatitis (Fig. 3). Active viral hepatitis A, B and C were excluded and auto-antibodies (Anti Nuclear Factor ANF, AntiNeutrophil Cytoplasmic Antigen ANCA, Anti Smooth Muscle, Anti-Mitochondrial antibodies and Anti Liver Kidney Microsomes) tested negative. Gastroduodenoscopy showed no varices or hypertensive gastropathy but diffuse scalloping and a nodular aspect of the duodenum. Pathology showed active chronic duodenitis, but no signs of celiac disease as villus atrophy or intra-epithelial lymphocytes and no pathological or molecular evidence of (T-cell) lymphoma.

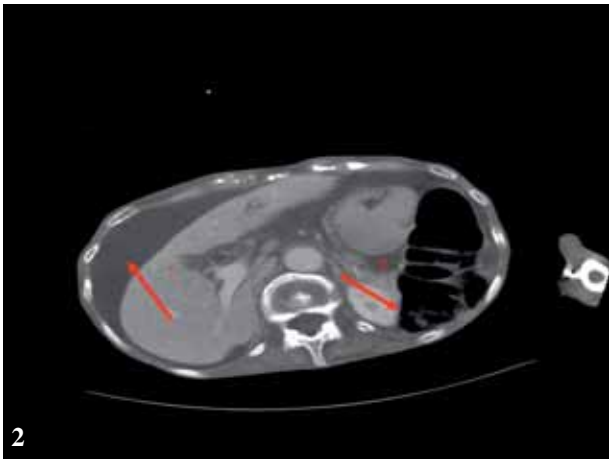
It was concluded at that stage that the patient suffered from celiac disease complicated with severe fat malabsorption, associated with splenic atrophy and mesenteric cystic lesions. Moreover, a cryptogenic necrotizing hepatitis was found. A gluten free diet was restarted and the patient was treated with vitamin supplements, total parenteral nutrition and methylprednisolon and ursodeoxycholic acid for the necrotizing hepatitis. Control of the ascites required diuretics and large volume paracentesis. Under this therapy she recovered clinically and biochemically and her general condition improved. 1 year after the initial admission in April 2004 she was still doing remarkably well, her weight did increase under total parenteral nutrition and she was still living alone. In April 2006 however, she was readmitted due to severe jaundice and on liver biopsy the diagnosis of anaplastic large cell lymphoma was made (Fig. 4, 5). Short after chemotherapy was started, she deceased. An autopsy was not performed.

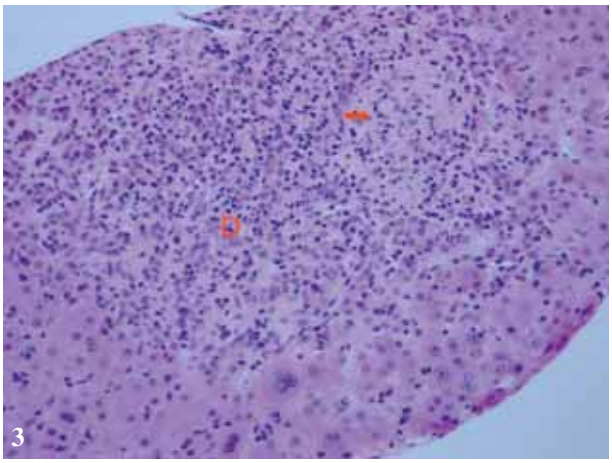
Discussion

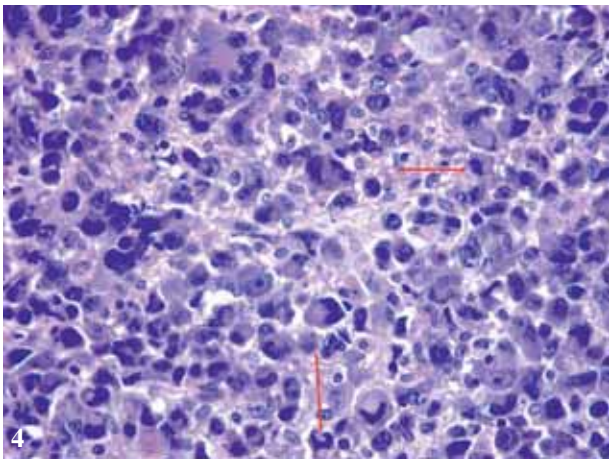
This case illustrates the combination of celiac disease (albeit absence of typical pathologic findings on duodenum biopsy does not exclude the diagnosis (4)), mesenteric lymph node cavitation (complicated with lymphatic obstruction and chylous ascites) and splenic atrophy which is a rare and poorly understood triad (5).

Mesenteric lymph node cavitation is a rare complication of celiac disease that is most often associated with splenic atrophy. Since 1952 only 26 cases with this triad were reported in literature. The pathogenesis is unknown. Holmes hypothesized that the damaged intestinal mucosa elicits an extreme immune response which,









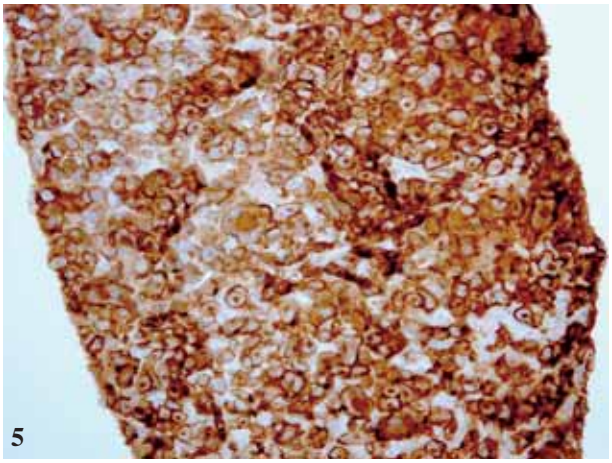


Fig. 1 revealing mesenterial cysts (arrow), Fig. 2 revealing ascites (arrow 1) and absence of spleen (arrow 2) on Computerized Tomography, Fig. 3 showing periportal ductular reaction (D) and mixed infiltrate with a lot of lymphocytes, and lymphocytes infiltrating between the biliary epithelium (arrow) (hematoxylin-eosin, original magnification $\times 200$), Fig. 4 showing tumor cells (atypical cells with eosinophilic cytoplasm with large irregular nuclei) (hematoxylin-eosin, original magnification $\times 400$) and Fig. 5 showing positive CD30 immunohistochemic stain of tumor cells (original magnification $\times 200$).

in turn, results in depletion of cellular components of lymph nodes, and hence involution or cavitation. Possibly immune complexes derived from small bowel mucosal lesions induce endothelial lesions in mesenteric lymph nodes which in turn induce complement activation, resulting in localized intravascular coagulation and bleeding in mesenteric lymph nodes. It can be speculated that lymph node cavitation is the next sequence of this necrosis process after the hemorrhagic necrosis (5).

Twenty-five to 75 percent of celiac disease patients have hyposplenism. Two forms of hyposplenism have been described, a reversible (responsive to gluten free diet) and an irreversible form. The irreversible form is caused by real splenic atrophy. Increased levels of immune complexes have been claimed to functionally block the splenic reticulo-endothelial system (6).

The clinical implications of the cavitated mesenteric lymph nodes are unclear. The implications of splenic atrophy mimic those of post-splenectomy patients, which holds an increased risk for infections with capsulated bacteria and the need for adequate pneumococcal, meningococcal and influenza vaccination on one hand and the administration of prophylactic antibiotics on the other hand.

Based on our case, we add to this triad the occurrence of necrotizing hepatitis. The association of celiac disease with liver disease was documented many years ago (7), but only recently these associations have been more clearly defined (8-11). Liver involvement shows a clinical spectrum varying from nonspecific reactive hepatitis, chronic active hepatitis, steatohepatitis to frank cirrhosis. Associations with autoimmune hepatitis, autoimmune cholangitis, primary biliary cirrhosis (12) and primary sclerosing cholangitis (13) have been described. The majority of these patients with celiac disease and elevated serum liver enzyme tests have a complete normalization following one year of gluten free diet (14). Mechanisms to explain the elevated liver tests in patients with celiac disease remain unclear. Several hypotheses have been presented. The first is that liver damage is the consequence of increased intestinal permeability for antigens and toxins that reach the liver through the portal system (15). The second hypothesis suggests that chronic intestinal mucosal inflammation may be the primary trigger (16). In our patient, we found no obvious cause for the necrotizing hepatitis and the negative autoantibodies made it impossible to firmly establish the diagnosis of autoimmune hepatitis (17). Patient was restarted on a gluten free diet and given the severity of the liver inflammation, she was treated with a low dose of methylprednisolone and ursodeoxycholic acid (UDCA). Under this treatment a relevant improvement of the liver tests was found after 2 and 4 months (Table 1). However, the causal relationship of this necrotic hepatitis with celiac disease, if any, remains unproven. We do not believe that the later diagnosed lymphoma contributed to the liver problem in 2004 since the absence of lymphoma on the liver biopsy and because of the significant improvement of the liver tests after a gluten free diet was restarted and after the treatment with UDCA was installed.

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