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Case Report

A Case of Advanced Liver Steatosis in an Apparent Lack of Evident Risk Factors: A Lesson to Learn

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is a silent pathological accumulation of lipids inside hepatocyte and represent one of the most common diseases in developed countries. This illness, when progresses to the advanced stage of non-alcoholic hepatitis (NASH) or hepatocellular carcinoma (HCC) represents the most common cause of liver transplant in USA (1) . Most common risk factors are obesity, overweight, metabolic syndrome, a highly processed western-type diet rich in carbohydrates, especially if of high glycaemic index) and saturated fatty foods as well as sedentarity. Such life- dietary and environmental-feature have recently triggered the discussion on how to redefine the shift of NAFLD/MAFLD (2) as Metabolic dysfunction-associated steatotic liver disease (MASLD) (3), the latter being recognized as a leading cause of liver-related in at least 30% of all-cause morbidity and mortality. On the other hand, as occurred in our below presented patient, a part of the NAFLD patient population has a normal BMI index (4). Indeed, a very recent autoptic analysis has confirmed the very high prevalence of MASLD and steatohepatitis within the general adult population (5).

Case report

Mrs D.G., female, age 57, BMI: 24, family history of diabetes ad overweight (mother) and coronary artery disease (father). She is in uncomplicated menopause since the age of 49, no hormonal replacemente therapy, but used a birth control pill beforehand for years. Works as an accountant in an industrial polluted area, overall sedentary life-style, no physical activity and 10-15 cigarettes smoker. She refers a long standing history of Irritable Bowel Syndrome with tendency to loose stools and bloating, normal stool tests and recent colonoscopy showing multiple small-medium uninflamed diverticula I the left colon. For past heartburn, she was found to have a 2cm hiatal hernia but no oesophagitis not helycobater pilory. Nonetheless, by her own decision she is daily taking PPI (pantoprazole 40mg) for the past 17 years. Her diet at work is based mostly on a cheese sandwich. a fruit, a soft beverage and some fructose-sweetened snacks in the afternoon. At home she cooks for the whole family of three a diet based on starch (pasta, rice), dairy products (although she was aware to have some lactose itolerance), meat (poultry, veal), some little salad and only in the weekends a glass of wine. From November throughout March for the past 10 years she is used to overtreat upper respiratory tract infection, no matter if of viral origin or just a common cold, with courses of antibiotics (amoxicillin, clarythromicin, All blood tests were within normal limits except a mild dyslipidemia (LDL cholesterol 144mg/dl, HDL 41mg/dl) hypertransaminasemia (AST/ALT: 49/54) and fasting blood sugar (118 mg/7dl), Homa test was normal and HBA1 value was 5.9%. A liver ultrasound revealed an extensive steatosis (fig 1). Further tests revealed negativity of viral hepatitis markers and for hemochromatosis. Suspecting a form of inherite liver metabolic disease, she underwent liver biopsy (fig 2) which showed a typical fat-storing steatosis. Further studies showed abnormal zonulin (74 ng/ml; normal range: <38 ng/ml) and breath test strongly positive for Small Intestinal Bowel Overgrowth (SIBO). The patient, who had undergone all prior tests on a private basis, was unwilling to spend further money to do a NGS gut microbiota testing.

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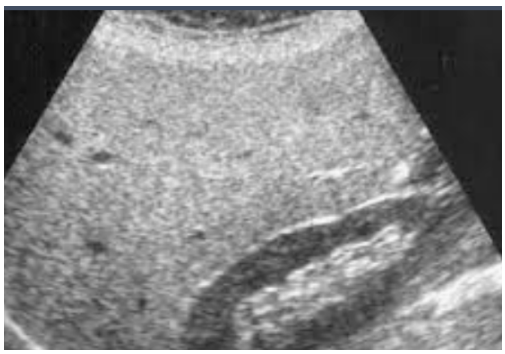

Figure 1. *Ultrasonography: severe steatosis*

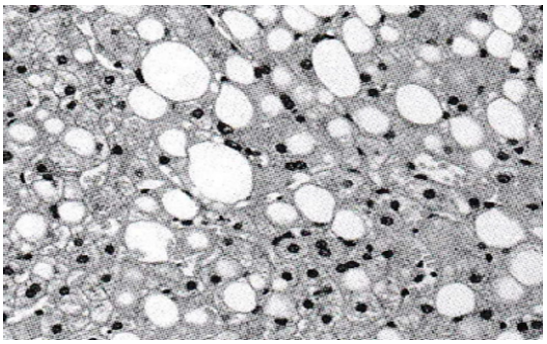

Figure 2. *Biopsy: diffuse fatty liver transformation*

Conclusion

This case gave us some opportunities to explore further viewangles to tentatively understand the multifaceted pathophysiological mechanisms behind NAFLD/MAFLD/MASLD in the lack of gross abnormalities of canonical biochemistry. First, we have to note that the unnecessary and very prolonged PPI therapy may be one of the reasons of high plasma zonulin, i.e. abnormal gut permeability (6). Although an increased prevalence of gastroesophaal reflux with NAFLD has been reported (7), the prolonged full dose use of PPI is condemnable and potentially altering upper gastrointestinal physiology in middle age/elderly subjects (8). Enhanced translocation into splancnic circulation of gut moieties such as endotoxin is known to negatively affect the liver (9). Several studies have in recent years pointed this out an either an experimental and a clinical study that PPI may increase liver fibrosis (10-13). Smoking and a likely environmental industrial exposure may have represented further detrimental liver burden (14-16). As a matter of fact, a number of clinical surveys has unveiled a direct correlation between environmentaL pollutants and NAFLD while warning its still neglected attention from medical community (17-21). This is mostly affecting the redox system which with aging, as tested also in vitro (12) that is hampered in all organs. This has been shown experimentally and clinically to be partly counteracted by antioxidants, probiotics and phytochemicals (22-27).

One more evident abnormality was the finding of a significant SIBO which is usually termed as an bacterial overgrowth in the small intestine above 100000 cells per mL of luminal content. Interestingly, it has been reported that PPI therapy is a significant risk factor for SIBO, increasing already after one year of continuous treatment and increasig up 90% with age expecially if associated to lactose malabsorption, irritable bowel syndrome with diarrhea and to diverticular disease (28-31). A further factor detrimental for liver steatosis and potentially synergizing with the dysbiosis and the use of fructose may have been played by the frequent antibiotics use along the years (32-34).

Mild dyslipidemia and fructose consumptions were probably of minor ancillary pathogenetic significance.

Finally, our study lacked a detailed gut microbiota analysis as well of the study of an, albeit still limited contribution of genetic factors (PNPLA3 rs738409 risk genotype-GG) to NAFLD and the reported Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis linking policystic ovary syndrome to NAFLD and dysbiosis (35, 36), both worth an investigation by the clinician. Nonetheless, this case report may serve to alert the physician to deepen his/her investigation with also a detailed analysis of macronutrient and micronutrient intake and gut microbiota gene analysis whenever coming across mild hypertransamiasemia without overt causes.

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