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Are there cancer risks in individuals with the metabolic syndrome and imaging condition of splanchnic inflammatory syndrome?

Abstract

In this opinion article we postulate that conditions that result in prolonged inflammation of the organs in the splanchnic system, specifically the Metabolic Syndrome and Splanchnic Inflammatory Syndrome, not only predispose sufferers to Hepatocellular Carcinoma, but also to malignancies of other organs in the splanchnic system. Discussion of individual splanchnic organs and malignant disease are described.

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Introduction

Chronic inflammation is a common underlying cause for the development of malignancy.[1-6] It has been well established in recent years that Metabolic Dysfunction-associated Steatohepatitis (MASH, formerly termed NASH) has become a primary cause for the development of Hepatocellular Carcinoma (HCC) because of the increasing incidence of hepatosteatosis.[7-10] Over a similar recent time frame the Metabolic Syndrome (we prefer the term Splanchnic Metabolic Syndrome as it is more precise) as a common cause of hepatosteatosis is progressively becoming a more important cause of HCC.

The Splanchnic Inflammatory Syndrome (SIS) is a term devised to describe the imaging findings of the combination of upper digestive tract inflammation coupled with the resultant hepatosteatosis.[10,11] It has also been observed that all organs within the splanchnic system experience this pan-splanchnic inflammation, which mani fest in different responses in the various organs.[12]

Clinical reports over recent years have expanded the knowledge that the clinical entity Splanchnic Metabolic Syndrome, not only shows hepatosteatosis, but also upper digestive tract inflammation (12), mesenteric panniculitis,[13] and pancreatosteatosis.[14] All of these findings of other organ systems in the splanchnic system being affected by pan-splanchnic inflammation, have been reported in the imaging condition Splanchnic Inflammatory Syndrome (SIS).[6,10,11,13,14] An even greater array of abnormal findings has been observed in SIS, than has been described to date in the MS. The explanation is that on imaging studies it is more evident the extent of inflammation, than appreciated clinically. For example, our current opinion is that the majority of cases of acalculous acute cholecystitis actually represent primary duodenal inflammation in the SIS with secondary sympathetic inflammation of the gallbladder wall.[12,15]

The combination of upper digestive tract inflammation and hepatic steatosis has also been observed on MRI in the clinical conditions of leaky gut and irritable bowel syndrome, hence also reflecting the imaging condition of SIS. As yet unestablished is what the relationship is between the clinical conditions of leaky gut, irritable bowel syndrome, and the MS. Are these all the same disease with progressive severity of disease and symptoms? Are they all distinctly different entities? If they are all distinctly different entities, how many different disease processes (either based of underlying pathophysiology or based on causative entity) are there?

The SIS describes imaging findings the full spectrum of which are not observable on CT or ultrasound, but only evident on modern MRI that also necessarily includes T1 gradient echo imaging at 5 minutes post Gadolinium- Based Contrast Agent (GBCA) injection. This time frame later post contrast is typically not performed at most centers, but at this time point the appreciation of greater enhancement of inflammation of upper digestive tract structures is best achieved.

The description of malignancies potentially, or already, established, associated with the MS/ SIS are described below:

Results

Liver

The link between MASH and HCC is well established (1-6). Therefore, the link between MS/SIS and HCC is beyond question.[11] What is interesting to conjecture are what about additional disease processes/focal lesions in the liver, how many of these are related to MS/SIS. It has been reported that Focal Nodular Hyperplasia (FNH) is commonly seen in the setting of hepatosteatosis. FNH we opine may represent a response of the liver to ongoing inflammation. To the extent that other lesions are caused by chronic inflammation has yet to be established. This includes whether intrahepatic cholangiocarcinoma may also result from the chronic inflammation present with these conditions of MS/SIS.

Upper digestive tract

Esophagus

Inflammatory enhancement of the distal esophagus is reported in > 90% of individuals with the SIS[11,12] and is the commonest segment of the upper GI tract described as affected. Clinical descriptions of the MS also describe frequent occurrence of distal esophageal inflammation.[12]

Chronic inflammation is well recognized as a cause for esophageal cancer.[16,17] It is early in the recognition of esophageal inflammation both in the MS and SIS, so no reports clearly linking esophageal

cancer to these conditions have not been established. Nonetheless empirically it is clear that these conditions can result in esophageal cancer.

Stomach

The same hypothesis appliesto the stomach. Chronic inflammation is established as a cause of gastric cancer,[18,19] hence underlying MS/ SIS is a likely cause.

Duodenum, jejunum, and ileum

The duodenum, jejunum and ileum all experience inflammatory findings in SIS, so our hypothesis is that these organs are susceptible for cancer development in MS/SIS.

Pancreas

Pancreatosteatosis has been reported in the MS.[20,21] A recent report has described the frequent presence of pancreatosteatosis in the setting of SIS.[14] This recent article though also described the frequent occurrence of pancreatic cysts and Intraductal Papillary Mucinous Neoplasms (IPMNs) with SIS (14). Our hypothesis is that pancreatic cancer may arise also in MS/ SIS, due to prolonged organ inflammation.[14]

Gallbladder and biliary tree

Acalculous cholecystitis has been described in the SIS[22] and shown to arise as a sympathetic inflammatory response to adjacent duodenal inflammation. Although, not previously described, we conjecture that the development of calculi in calculous cholecystitis, and both acute and chronic inflammation, may have contributions from the general pan-splanchnic inflammation. We postulate that gallbladder cancer and cholangiocarcinoma, both associated with chronic inflammation[6,10,12,23-25] may arise secondary to MS/SIS.

Discussion

The links between cancer and underlying inflammation, which is present with MS/ SIS, is well established for HCC in the liver. In other organs, because chronic inflammation has already been clearly ascertained to be causative for cancer, our hypothesis is that MS/SIS causes these entities. This especially applies to upper digestive tract cancers, and perhaps most clearly with esophageal cancer.

The links are not as firmly established between pancreatic cancer and cancer in the setting of acalculous cholecystitis and MS/SIS, but our hypothesis is that we suspect these chronic inflammatory entities play a role. The association between calculous cholecystitis and MS/ SIS itself are not firmly established, so although the combination of cholelithiasis and chronic gallbladder inflammation with cancer development has been ascertained, the association between MS/SIS and gallbladder cancer are at present a hypothesis. As inflammation of the biliary tract is observed in SIS, and chronic inflammation is recognized to cause cholangiocarcinoma, the link between SIS and cholangiocarcinoma is more clear.

It is important to emphasize that detection of the SIS can only be made on modern MRI. Conventional sequences such as fat suppressed 3D gradient echo are the mainstay and are the most commonly employed T1 weighted sequence pre- and post-GBCA injection. But the time point of acquiring post contrast images at 5 minutes post injection may not be generally employed. In the desire to limit imaging time, many centers stop acquiring T1 sequences at approximately 3 minutes post contrast. At this earlier postcontrast time point, mild chronic inflammation, as typically is observed with SIS in the upper digestive tract, may not be readily apparent, as enhancement on mild inflammation progresses in intensity and becomes more evident at 5 minutes. The major limitation at present is that few radiologists have the experience to recognize inflammation of the upper digestive tract on MRI, so even though the findings may be quite obvious, for example increased enhancement of the distal esophagus, since it is at present not widely taught, radiologists generally overlook it, unless it is very severe. Most cases of inflammation of the upper digestive tract are mild in the SIS.

Neither ultrasound or CT can detect the full range of pathologies in the SIS. In brief, ultrasound does not see tiny pancreatic cysts well, does not see bowel inflammation, and cannot visualize the mesentery adequately. The main limitation of CT is that it cannot appreciate mild inflammatory enhancement of the upper digestive tract, because of the lesser sensitivity of CT to identify mild enhancement with iodine-based contrast agents, compared to the greater sensitivity of MR to GBCAs. The lesser ability of CT to detect small pancreatic cysts compared to MRI is real, however this does not necessarily impact the ability to detect SIS per se. It is primarily the inability on CT to demonstrate mild-moderate inflammation of the upper GI tract, and by extension the inability to recognize that inflammation of the gallbladder wall secondary to adjacent inflammation of the duodenal wall, that limits CT in showing SIS.

One cautionary note is worth mentioning. Attention should be paid to individuals undergoing GBCA enhanced MRI to observe for the development of Gadolinium Deposition Disease following injection of GBCA. In some people substitution of Diffusion Weighted Imaging (DWI) for GBCA injection may be merited. This sequence is able to show findings of distal esophageal and duodenal inflammation, but not with the resolution of post-GBCA images, and is not so successful at showing changes in the stomach, jejunum, and ileum.

Regarding management and treatment, the most important approach is with prevention. Dietary change may be the most affordable, practical, and straightforward management approach. Elimination of the most common pro-inflammatory foods is the most critical first step. In particular ultra processed foods. Empirical limiting intake of other foods associated with dietary intolerance is wise; limiting dairy and gluten in most individuals. In some individuals more careful analysis of food intolerances may be needed under the guidance of dieticians, such as red meat (alpha Gal) or lecithin containing foods (tomatoes). Restoration of the normal microbiome is also an important step. This may be the starting point. This is especially true for individuals who have experienced a lifetime of taking antibiotics.

We do not describe in this report the possibility of malignancy development beyond the splanchnic system?. Current medical investigations describe the links between the digestive tract and the skin, CNS, and by extension all other bodily systems. Inflammation that has origin in the splanchnic system does extend throughout the body, and hence our opinion is that there is impetus for cancer development beyond the splanchnic system.

In summary, the chronic inflammation of the splanchnic system, as observed in MS/ SIS, is a definite cause of some splanchnic system malignancies, such as HCC. Our opinion is that as these conditions cause chronic inflammation, and chronic inflammation is a common precursor for malignancy, MS/ SIS is a likely underlying cause for many malignancies throughout the splanchnic system.

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Conflict of interest

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