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CYTOTOXIC CHEMOTHERAPY INDUCED LIVER DAMAGE: THE ROLE OF DIAGNOSTIC IMAGING

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Abstract

Better comprehension of tumour mechanisms and diagnostic tool progress allowed physicians to increase the number of cancer diagnosis while providing useful early treatment lately. For this reason we are expecting to see an increased administration of common anti-neoplastic cytotoxic agents in developed countries. Meanwhile undergoing chemotherapy, patients should be regularly checked for potential side effects of such drugs which can arise suddenly and cause therapy interruption, slowing the healing process. Hereby we reported the latest finding about the cytotoxic drug side effects that affects the liver from a radiological point of view.

Keywords: *Chemotherapy, cytotoxic effects , liver damage, diagnostic imaging, duramycin*

Introduction

Today cancer is the second leading cause of decease around the globe, right after cardiovascular pathology [1] in a scenario where breast cancer has now overtaken lung cancer as the world's mostly commonly-diagnosed cancer [2, 3, 4]. While tumour diagnoses are skyrocketing worldwide, thanks to new diagnostic tools and general aging of the population, mortality and morbidity seem to decrease for almost every type of tumour. At this rate we expect to see more than 29 million new diagnoses of neoplasm each year by 2040 [5]. Despite the technologies fielded and the medical science progress, only a few of our patients will be provided with an early diagnosis that can strongly improve their outcome [6]. In this scenario, the role of neoadjuvant chemotherapy will be more and more consistent and cytotoxic drugs will spread widely, therefore, it is our duty to not underestimate the potential side effects of such agents we use today.

Background

Due to its role in activation and excretion of cytotoxic medications, liver is a key organ in their metabolism and is therefore subjected to numerous side effects involving both its function and its structure. Liver toxicity potentially affect any patient on cytotoxic drugs, even if the treatment is not directly aimed to a gastrointestinal tract tumour [7]. That is easily explained if we think about how poorly specific those molecules are, in fact, they can interact with almost every kind of replicating cell, causing potential damage through all the body. In most cases clinical examination and laboratory tests can't provide a certain diagnosis and only bring us little information before the disease has passed over its initial stage. Imaging diagnostic tool can be helpful if wisely used, allowing the radiologist to detect the pathological conditions before their clinical manifestation, in order to guide the multidisciplinary oncologic group to provide the most appropriate treatment for the patient according to his own liver modification.

Liver injuries from cytotoxic agents

Fatty liver

Hepatic steatosis, the fat accumulation inside the hepatocytes, it's the most common chemotherapy adverse effect involving the liver, even though the exact prevalence is not known [8]. Since our patients keep their chemotherapeutic regime for months or years, this condition tends to get worse, evolving in non-alcoholic steatohepatitis, a condition defined by cellular degeneration and ballooning [9]. Patients with steatohepatitis seem to have higher mortality rates when a liver segmentectomy is needed and have a general poorer income after surgery [10].

The blood of all the patients using cytotoxic agents should be monitored regularly and, as soon as an increase in their transaminase level is detected, a ultrasound should be performed. It's actually true that the exact subtype of steatosis is only assessed by pathological analysis [11], but a liver biopsy it's an invasive investigation that should be avoided whenever possible and, on the other hand, radiological imaging provides high-quality information with almost no effort from the patient other than a little compliance. Steatosis is visible on ultrasound as increased echogenicity of the liver parenchyma, often described as "blurred", while on CT the increased amount of cellular fat reduces the density of the liver [12], so the same pathological condition has two completely different manifestation according to which exam we decide to choose. Those procedures may allow the radiologist to detect a fatty liver but the MRI surely is more accurate, ensuring an early detection of the disease. Comparing T1w in- and out- of phase sequences on MRI, if one or more area of parenchymal signal loss (dropout) on T1w out of phase are detected, while on T1w in phase there are none, the diagnosis of liver steatosis is made [13].

Fatty liver should be addressed as soon as possible in order to avoid its evolution to cirrhosis, which may lead to hepatocellular cell carcinoma and portal hypertension. Up to date drug suspension is the only effective treatment if applied at a very initial stage, otherwise steatosis is not reversable.

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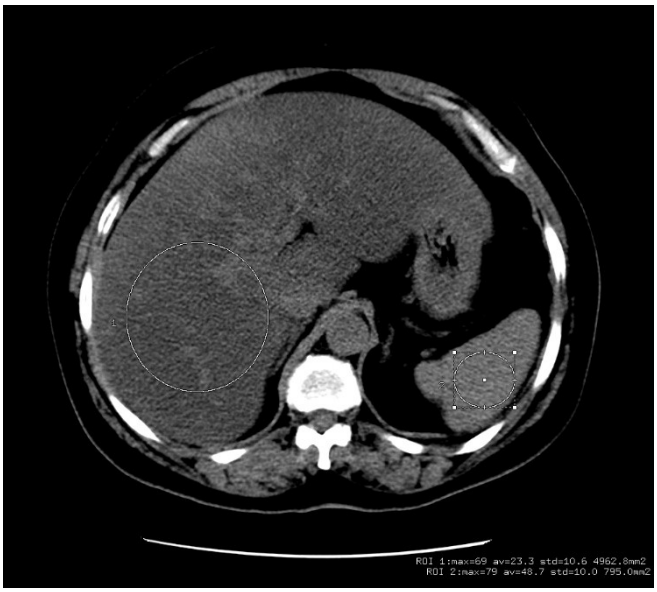
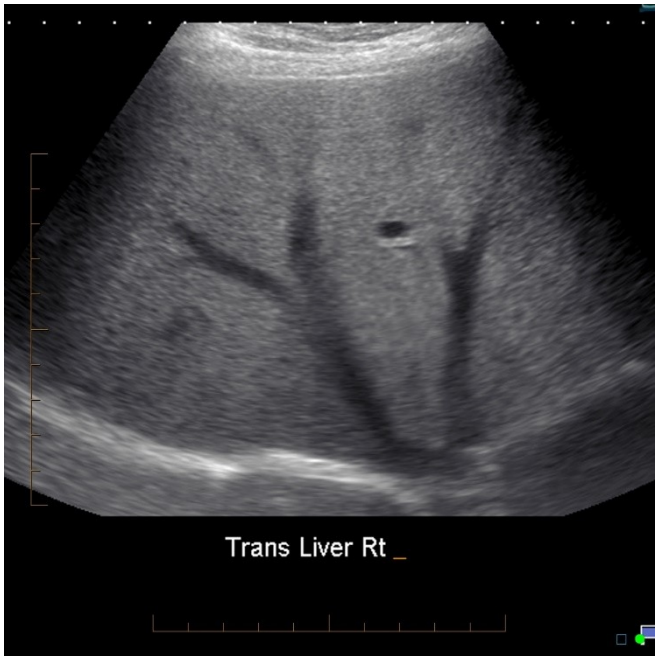


Pseudocirrhosis

Chemotherapy targeting liver secondary lesions often cause the onset of a cirrhosis-like pattern [14], known as pseudocirrhosis. The prevalence of pseudocirrhosis is higher in patients affected by breast cancer, up to 20%, and it's strongly related with a poorer life expectancy (69 vs 182 months) [15]. This condition is usually described as a perilesional capsular retraction due to nodular regenerative hyperplasia in metastatic sites with fast onset (1 – 3 months) and evolution [16], with a focal or extended involvement of the liver.



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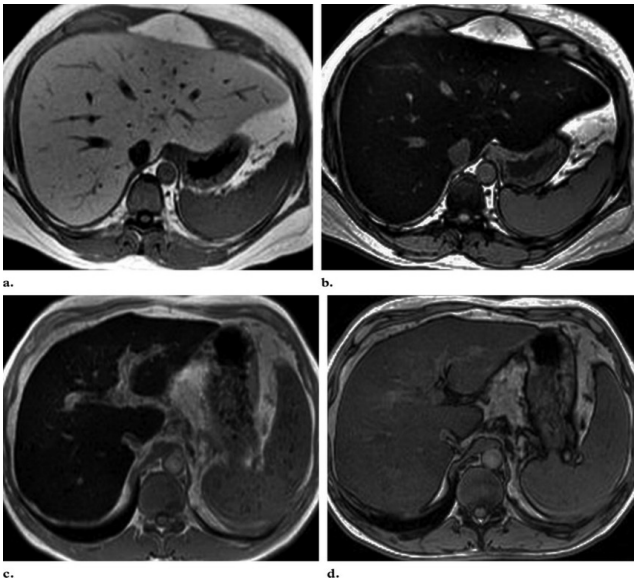
Those hyperplastic areas are often misdiagnosed as liver metastasis, this occurrence usually lead to unnecessary therapeutic interventions worsening the quality of life in both young and elder patients. As if it wasn't already similar enough to the common cirrhosis, the pseudocirrhosis can lead to portal hypertension, ascites and splenomegaly [17] mimicking the comorbidity of classical cirrhosis. During the early stages CT scan shows flattening of the liver's edges and capsular retraction, failing to identify the nodular hyperplastic areas. As the cytotoxic treatment goes on new findings are visible and liver scarring, fibrosis, ascites, hepatosplenomegaly, increased portal vein diameter appear [18] and caudate lobe enlargement. Even though the similarity with cirrhosis, the two conditions do not share the same biochemical effects on liver metabolism, that's why hepatic function is preserved in pseudocirrhosis [19]. Esophageal Varices bleeding, resulted from portal hypertension, is a common cause of sudden death in patient with liver cirrhosis or pseudocirrhosis which require immediate endoscopic therapy. Sometimes a cirrhosis-like pattern is seen before the treatment with cytotoxic drugs, in this scenario, the pseudocirrhosis

represent a desmoplastic reaction to tumour infiltration and is usually diagnosed thank to its fibrotic pattern on CT scan.



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Biliary Sclerosis

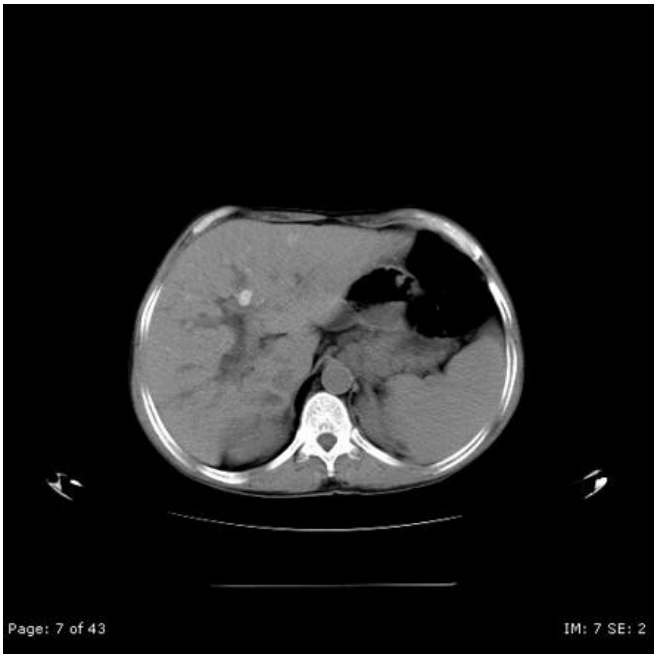
A chronic condition, known as biliary sclerosis, or secondary sclerosing cholangitis, is the result of direct (toxic agents) or indirect (ischemia due to pericholangitic vessel fibrosis) damage. Jaundice is often the only clinical appearance [20] and may be so severe to require stent placement and therapy discontinuation to be resolved [21], other common findings include gastrointestinal discomfort and stool problem like stypsis or diarrhoea. Ultrasound shows a brightly echogenic portal triad, biliary duct narrowing and a cirrhosis-like pattern when it comes to liver parenchyma, that's why sometimes this condition present with ascites. The CT findings are virtually not distinguishable from the ones of primary sclerosing cholangitis.[22] Bile ducts appear narrow with erratic caliber, in fact, the narrowed portions are almost invisible on CT and the dilatated ones are visible as linear hypodense areas with the common hepatic duct mainly involved and other bile ducts usually more preserved [23]. Fat stranding, periductal edema and thickened bile duct wall are common findings as well, particularly if associated with cholangitis [23]. In some cases the general reduction of liver size is accompanied by caudate lobe (or first segment) enlargement. MRI shows the same modifications of the biliary tree with higher resolution and it's able to detect biliary diverticula that are practically invisible on CT scan, moreover, almost 85% of all the patients with secondary sclerosing cholangitis will show intra- or extra- hepatic duct dilatation. Scientific community still doesn't have an agreement about if the secondary sclerosing cholangitis is a risk factor for gallbladder cancer, therefore, every gallbladder polyp found during ultrasound examination or magnetic resonance should be considered as a malignancy until proven otherwise.

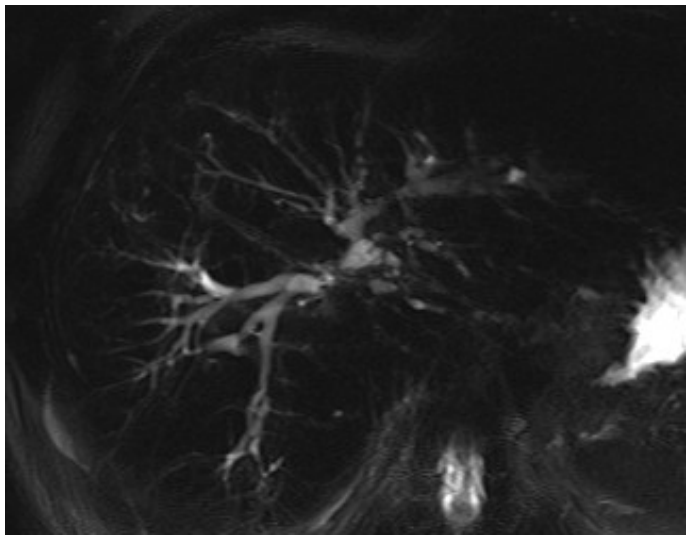
Sinusoidal obstruction syndrome (SOS)

SOS, formerly known as veno-occlusive disease, is a pattern of liver insults related to microvascular deposition of the remnants of hepatocytes necrotized by chemotherapy, especially oxaliplatin, with subsequent obliteration of small sublobular hepatic veins, vessel wall damage and red blood cells migration to the Disse's space. This can cause an immunological reaction with collagen deposition followed by intra-sinusoidal coagulation, perisinusoidal fibrosis and hepatocytes destruction [24]. The increasing sinusoidal pressure levels and the following hepatocytes death may cause regenerative hyperplasia areas [25]. Sometimes the veno-occlusive disease is due to bone marrow transplantation, in that case pathological modification are similar at cellular level but require a precocious involvement of the immune system cells. Common clinical manifestations may include: jaundice, ascites, hepatomegaly, abdominal pain, weight gain, splenomegaly and thrombocytopenia. Liver enzymes serum levels may be or may be not raised. SOS is also notable because it may be related to intraoperative bleeding [26] and liver insufficiency after surgery. According to the clinical condition of the different patients their very own diagnostic path will lead them first to ultrasound or to computer tomography. While CT scan is a better option, US is also able to detect the typical findings of the SOS, such as: ascites, gallbladder wall thickening, periportal edema, reduction of the right hepatic vein diameter (<0.45 cm) [27], augmented liver and spleen size, recanalization of the umbilical vein and periesophageal varices, just like in portal

hypertension. On Doppler mode decreased portal flow is usually seen and the flow direction is hepatofugal, meaning that, on the opposite of what usually happens, blood is leaving the liver throughout the portal vein. [28].

CT scan give us a deeper understanding of the liver changes thanks to the iodinated contrast media, in fact, post-contrast CT is able to detect a heterogeneous, patchy appearance of the liver parenchyma, this appearance is called nutmeg liver [29], mainly visible in arterial an portal phases. The nutmeg liver image appear as a result of ischemic area widespread trough the organ. Gadoxetic acid enhanced MRI shows a very specific reticular pattern during the hepatobiliary phase, which if the anamnestic data are consistent, is considered pathognomonic. On non-contrast enhanced sequences T2w shows increased intensity signal areas, corresponding to edema, those areas are isointense in T1w with ill-defined margin and non-spherical shape. [30, 31]. There's not a specific therapy for the SOS so the interruption of the chemotherapeutic regime is the first option. New protocols include antiplatelet agents and vasodilatators.





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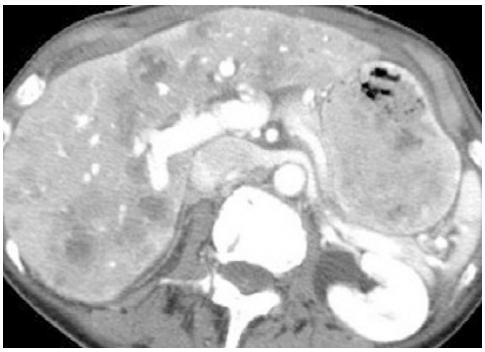
Hepatic necrosis

Regardless the etiology and the pathogenetic mechanism, most of the patients affected by the previously described disease will experience an evolving parenchymal liver damage followed by a progressive worsening of their clinical conditions. The point of no return is set early since the liver damage is self-increasing, nevertheless only few will have to deal with a necrotic liver. During the necrosis the enzymes formerly contained inside the cells will spread outside damaging the liver parenchyma and causing poor inflammatory response. [32] Macroscopically the liver become small and flaccid, the Glisson capsule wrinkle because of the sudden loss of parenchymal volume and the bile ducts will be destroyed, pouring out bile which will exasperate the parenchymal damage. This process does not occur simultaneously in every liver segment, that's why some people will overcome the damage. If one's lucky enough to survive, the liver will try to regenerate in a messy and chaotic pattern and we'll see a cirrhosis-like pattern again, only this time the regenerative nodules will be divided by huge fibrotic areas, mainly representing scars. CT findings include marked decrease parenchymal enhancement and cystic change. [33]



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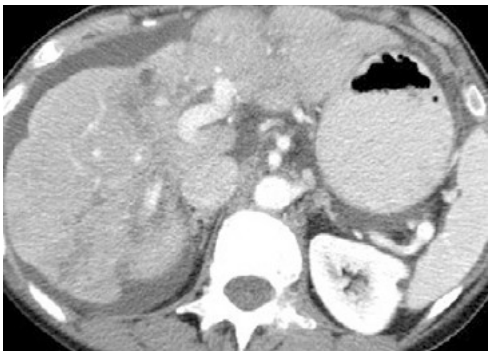

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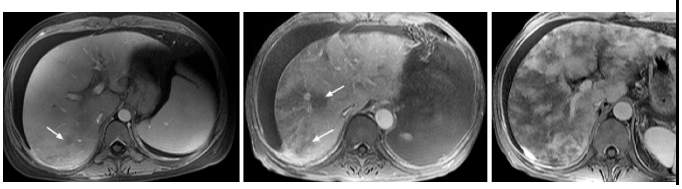
Clinical manifestations may include jaundice, encephalopathy, bleeding, coagulopathy and kidney failure. Most of the consequences of the hepatic necrosis are due to the liver failure that is easily spotted on blood analysis together with transaminase elevation. Specific treatment is not available. [34]



Functional and molecular imaging

Molecular imaging aims to extend current clinical imaging approaches by utilizing targeted agents to illuminate cellular and molecular processes of interest. [35-38] By complementing conventional "anatomical or physiological" imaging, molecular imaging enables early detection of disease, staging of disease, and quantitative assessment of therapeutic response. [39-41] In nuclear medicine imaging new non-invasive methods have been developed lately to early detect drug-induced damage. [42-44] Recent studies [45] have shown that Tc-99m labelled duramycin may be identify necrotic cells at SPECT after cytotoxic treatment in rats. PET provide higher sensitivity [45], so duramycin derivates suitable for this specific exam are seeing a general rising in their development. Labelling with Ga-68 seems to be the wisest choice since it's safe, cheap, and relatively fast to produced [46]. The main concern is the lower spatial resolution this molecule provides compared to others such as F-18 [47-48]. Addiction of NODAGA allows radiolabelling at room temperature, showing excellent results in vitro even tough its application in vivo may be limited due to duramycin potential nephrotoxic effects in patients with cisplatin-induced liver excretion reduction [49]. Duramycin derivates appear to be excreted trough kidney and bile and this should be considered when checking final images, even if NODAGA chelation provide lesser kidney and hepatobiliary accumulation. [68-Ga] NODAGA-duramycin was proven able to detect doxorubicin, cisplatin and busulfan liver damage on PET/CT, showing no higher cardiotoxic adverse effect rate if compared to the duramycin alone but seems to be more toxic when it comes to spleen and lungs [38]. Liver and kidney damage rate seemed to be not significantly higher. Lung damage secondary to Busulfan administration was early detected thanks to [68-Ga] NODAGA-duramycin PET/CT, less precocious was the detection of liver, spleen and heart damage, showing nonetheless a higher overall sensitivity if compared to

immunohistochemistry but that's probably due to PET's capacity to explore a whole organ at once while this is impossible on histology tests. Similar results were achieved investigating cisplatin- and doxorubicin-induced organ damage. Main application of this new discovery will be siding to immunohistochemistry and blood sampling allowing early detection of cytotoxic agents side effects. [50]

Conclusions

Fighting the battle against cancer, the well-being of the patients we meet day after day is our main concern, with that in mind we consider pivotal to choose shareable criteria to identify liver chemotherapy injuries [51,52]. Better diagnosis and a wiser approach to CT and MRI may improve both outcome and life quality of the patients, avoiding unnecessary invasive diagnostic procedure or unwanted surgery. Modern imaging should always hold in consideration before, and while, we embark on this journey with our patients.

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