

Reticular T1 hypointensity at hepatocellular phase Gd-EOB-DTPA enhanced MR imaging: a non-invasive sign of oxaliplatin induced hepatic toxicity

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Introduction Chemotherapy induced liver toxicity is well recognized in oncology and can result in significant morbidity. In patients with colorectal liver metastases, oxaliplatin based chemotherapy is known to cause sinusoidal congestion that can lead to perisinusoidal fibrosis with increased morbidity. Sinusoidal congestion cannot be identified on conventional MR imaging. However, sinusoidal congestion may be identified on the delayed hepatocellular phase of Gd-EOB-DTPA (Eovist/Primovist, Bayer Healthcare, Berlin) enhanced MR as reticular low signal intensity T1 changes within the liver [Khan MA et al. 2011] However, the prevalence and associated diagnostic features have not been reported in the at risk population. Confident non-invasive identification of this entity can alert the managing physician of developing liver toxicity, presenting the opportunity to dose modify to reduce possible morbidity and mortality.

Purpose The aim of this study was to determine the prevalence of reticular low T1 signal intensity on hepatocellular phase Gd-EOB-DTPA enhanced MR imaging, and describe associated changes on conventional T1-weighted, T2-weighted and diffusion-weighted MR imaging (DWI) in patients receiving neoadjuvant chemotherapy for colorectal liver metastases.

Materials and Methods The MR imaging of patients with colorectal liver metastases who received neoadjuvant chemotherapy treatment were retrospectively reviewed. The *inclusion criteria* were: (1) Patients with pathological proven colorectal cancer and (2) Gd-EOB-DTPA enhanced MR imaging performed after neoadjuvant chemotherapy. Patients with contraindications to MR imaging and not receiving Gd-EOB-DTPA contrast medium were excluded. Imaging was performed on a 1.5T MR system (Siemens' Avanto, Erlangen). An expert radiologist with more than 15 years experience reviewed all images. The in-oppose phase T1-weighted imaging, T2-weighted imaging, dynamic contrast enhanced T1-weighted imaging (arterial, portovenous and interstitial phases) and delayed hepatocellular phase T1-weighted images were classified as normal or abnormal. For all abnormal scans, the radiological abnormality was recorded. The occurrence of abnormality seen on MR imaging was corroborated with patient's chemotherapy history, serum liver function tests and histopathological findings where available. The frequency of low T1 reticular signal intensity on delayed hepatocellular phase Gd-EOB-DTPA imaging in different chemotherapy regimes were compared by Chi-square test. A p-value of <0.05 was accepted as statistically significant.

Results Over the period of 2008 to 2011, 92 patients fulfilled the inclusion criteria; none were excluded. Of these 92 patients, 64 received oxaliplatin based chemotherapy, while 28 received other treatment regimes. 11/92 (12%) developed reticular low T1-signal intensity on hepatocellular phase Gd-EOB-DTPA enhanced MR imaging (**Figure 1D**), of which 3 were pathologically confirmed to show sinusoidal congestion at histology. The pattern of involvement was diffuse in 6/11 and segmental in 5/11 (in segments VII, VIII and/or VI of right lobe). All 11 cases were associated with abnormal serum liver function tests, with elevated serum alanine transferase (10/11), alkaline phosphatase (8/11) and/or gamma-glutamyltransferase (10/11). All cases showed changes within 3 months of chemotherapy and follow-up MR imaging at 6 months in 2 patients showed persistence of abnormalities. 2/11 patients revealed concomitant liver steatosis on in/oppose phase T1-weighted MRI. In all cases, the dynamic contrast enhanced MR imaging and DWI demonstrated no significant liver abnormality. The reticular T1-weighted changes were observed in 11/64 (17%) patients who received oxaliplatin-based chemotherapy and 0/28 (0%) patients treated with other chemotherapeutic regimes (Pearson chi-square, p=0.019).

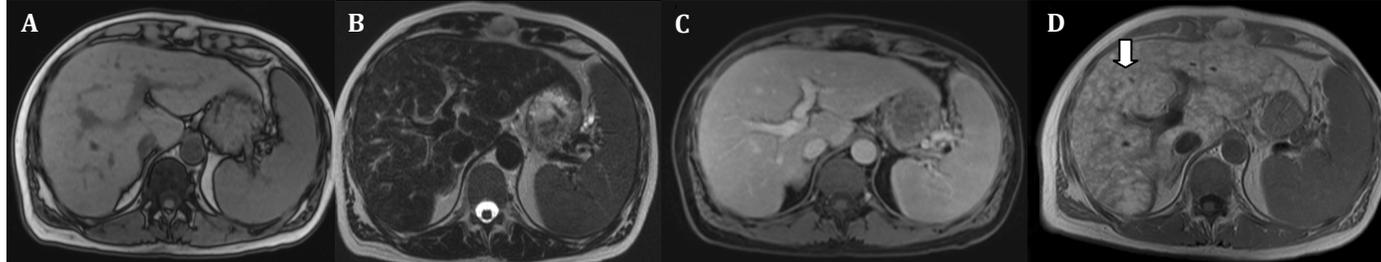


Figure 1. 46 year-old man who received capecitabine and oxaliplatin chemotherapy for metastatic liver disease. Normal appearance of the liver on conventional imaging with oppose phase T1-weighted imaging (A.), T2-weighted imaging (TE = 240 ms) (B.) and portovenous phase Gd-EOB-DTPA enhanced T1-weighted VIBE imaging (C.). However, the hepatocellular phase of T1-weighted Gd-EOB-DTPA enhanced imaging showed a diffused pattern of reticular hypointensity (D.; arrow). Histology confirmed sinusoidal congestion following surgical resection.

Discussion Oxaliplatin is a platinum-based cytotoxic agent used for the treatment of colorectal liver metastases. It is usually combined with other anti-tumour drugs such as capecitabine and bevacizumab. Oxaliplatin is known to cause sinusoidal obstruction, leading to the appearance of the 'blue liver syndrome' at surgery, with increased risk of surgical complications and morbidity. In one series (Rubbia-Brandt L et al. 2010), sinusoidal obstruction was observed in 51% of post-surgical specimens in patients who received oxaliplatin-based chemotherapy. However, prior to Gd-EOB-DTPA enhanced MR imaging, there was no radiological method of establishing the diagnosis. Interestingly, the reticular T1 appearance of the liver parenchyma was only visible in the hepatocellular phase, with normal appearances during unenhanced and dynamic contrast enhanced imaging (**Figure 1 A, B and C**). Furthermore, the imaging appearances on DWI were normal. The mechanism for the reticular MR appearance remains unclear, but may relate to perisinusoidal hepatocyte dysfunction, leading to reticular hypointensity at delayed hepatocellular phase imaging. In our series, this appearance, either segmental or diffuse, was only observed in patients who received oxaliplatin and sinusoidal dilatation was confirmed pathologically in 3 patients who underwent surgery. The small number of pathological proven cases limits our current study but the clinical findings supported the diagnosis of sinusoidal obstruction in the patients identified by imaging.

Conclusions Reticular T1 hypointensity on Gd-EB-DTPA enhanced hepatocellular phase imaging is only observed in patients who receive oxaliplatin chemotherapy and is shown to be related to sinusoidal obstruction.

Clinical implications This is to our knowledge, the first series describing the imaging findings of oxaliplatin induced hepatic toxicity in a patient cohort. Our findings have implication for the non-invasive identification of patients developing sinusoidal congestion related to oxaliplatin chemotherapy, thereby presenting an opportunity to reduce associated morbidity as a result of the complication.

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