

Focal nodules in chronic Budd-Chiari, what are they and why do they develop?

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Aim of this presentation: To describe the imaging features, differential diagnosis, pathology and possible aetiology of focal hepatic nodules in patients with Budd Chiari Syndrome (BCS).



- Nodules of various types, including large regenerative nodules, focal nodular hyperplasia-like nodules and hepatocellular carcinoma (HCC) have been described on imaging of patients with chronic BCS.
- BCS presentation varies from fulminant signs and symptoms to an asymptomatic condition depending on the temporal nature of the disease (acute, sub-acute, or chronic).
- BCS can be classified into primary or secondary types. The primary type is caused by hepatic venous outflow obstruction originating from an endoluminal venous obstruction and secondary when the obstruction is not originating from the endoluminal system.



- It is reported that a spectrum of benign nodules of greater than 5mm develop in 60-80% of patients with Budd-Chiari syndrome.
- Hepatocellular carcinoma can also occur in patients with chronic Budd-Chiari syndrome and therefore it is important to distinguish benign nodules from HCC on imaging follow-up.
- Both benign and HCC nodules are hypervascular on arterial phase imaging, but other features can help distinguish these conditions, as will be illustrated.



Background



Characteristic CT appearance of acute Budd-Chiari syndrome with mottled and heterogeneous enhancement of the liver parenchyma. There is relatively normal enhancement of the caudate lobe. No focal discrete



Gross pathological specimen of an explanted liver demonstrating marked caudate lobe hypertrophy. A recent thrombus is seen within a hepatic vein (top right). The parenchyma has a nutmeg appearance, as seen on contrast enhanced CT (previous slide).

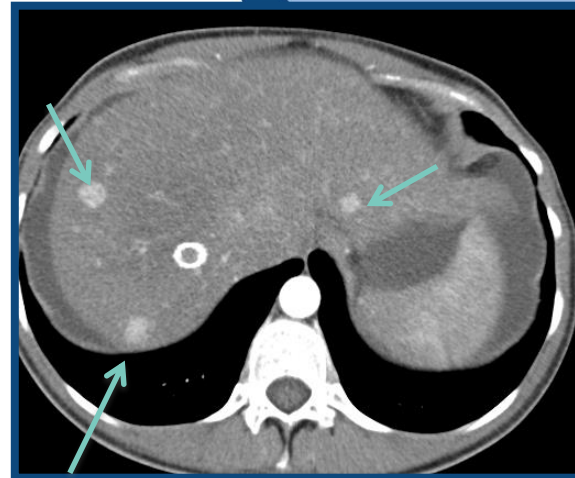
Imaging Findings / Procedure de



- We reviewed imaging from 26 patients with BCS. 10/26 patients developed new liver nodules on follow-up imaging and 7 of these 10 patients underwent Transjugular Intrahepatic Portosystemic Shunt Procedure (TIPS) prior to development of the nodules. One patient developed multifocal HCC and the other 9 are presumed to have benign nodules on the basis of follow-up to date.
- The 10 patients who developed nodules were imaged with multiphase CT and/or Gadolinium-enhanced MRI with / without gadoxetic acid enhanced MRI.
- Selected imaging features of these nodules are described and illustrated, with pathological correlation where available. Late dynamic phase contrast washout is a key distinguishing feature of HCC. Most of the nodules in our series developed in patients who had TIPS insertion, suggesting that alteration in portal flow is important in aetiology and the relevant literature, including animal studies of portal occlusion, will be reviewed.



36 year old male with BCS. Figure 1 Arterial phase CT with classic nutmeg attenuation of Budd-Chiari. Follow-up arterial phase CT in Figure 2 post TIPS insertion demonstrating new hyperenhancing nodules in segments 2,7,8 (blue arrows), which did not wash out on subsequent phases. Arterial phase enhancement is a typical feature on benign and malignant nodules in BCS and the goal of imaging is to distinguish benign from malignant nodules



36 year old male with BCS. Figure 1. is a histological specimen from this patient showing complete occlusion of the lumen by occlusion with fibrous connective tissue representing an old thrombus. Figure 2, is a small lumen in a recanalised thrombosed vein seen in Budd-Chiari

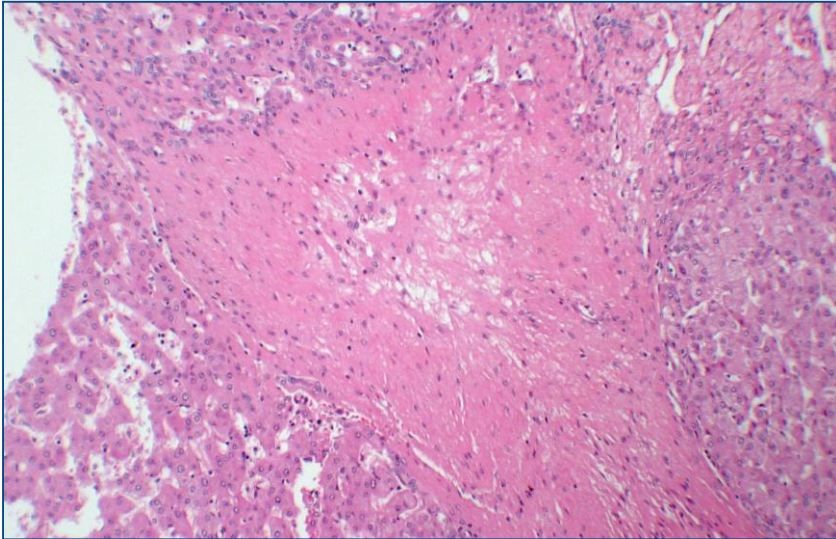


Figure 1

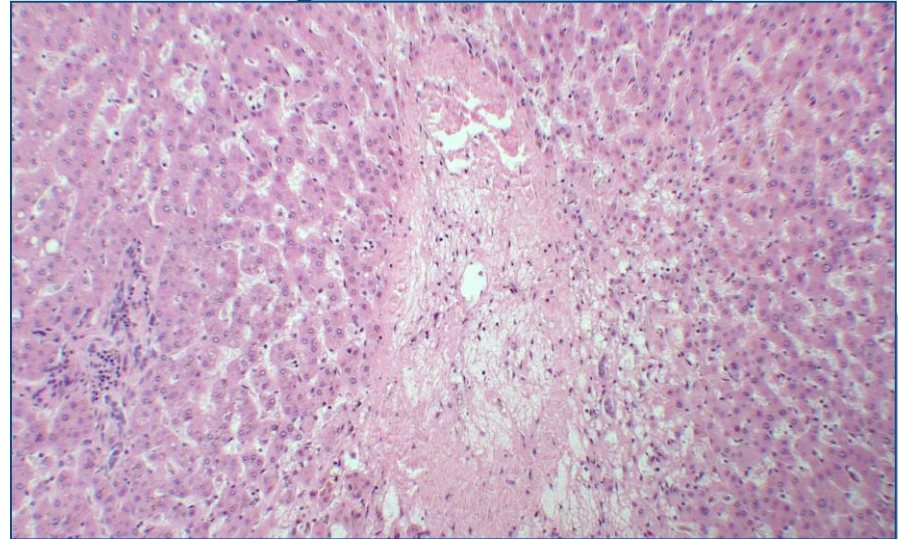
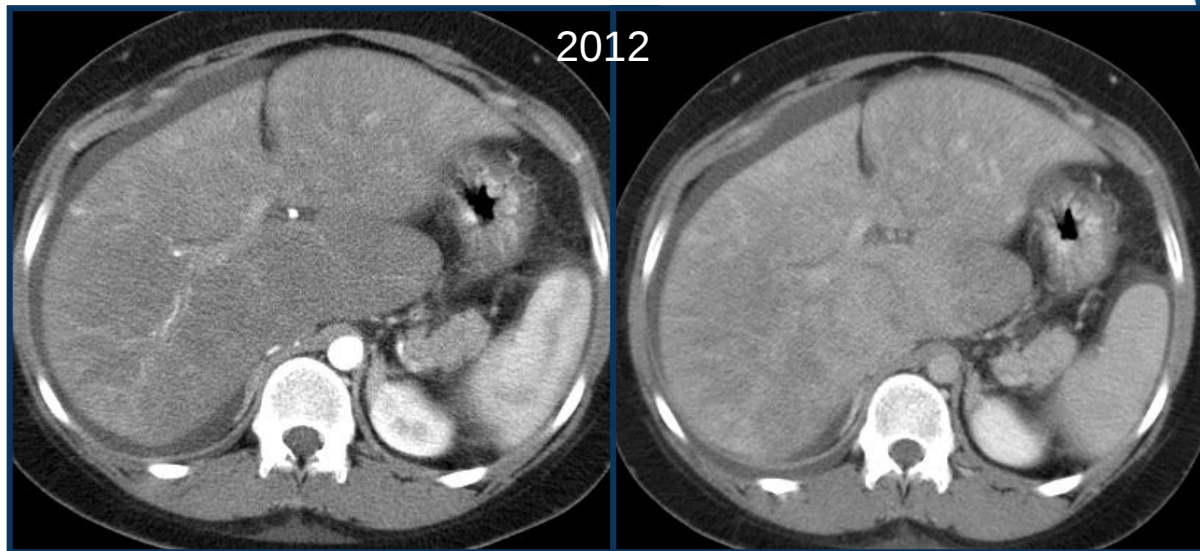


Figure 2

24 year old female with BCS. CT demonstrating features of BCS, with hypertrophy of the caudate and heterogenous enhancement of the liver parenchyma.

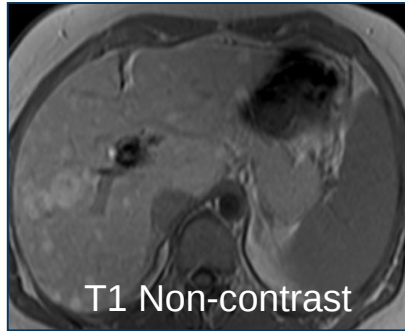


Contrast enhanced CT abdomen in arterial and portal venous phases demonstrating BCS with preservation of the caudate lobe and without liver nodules.

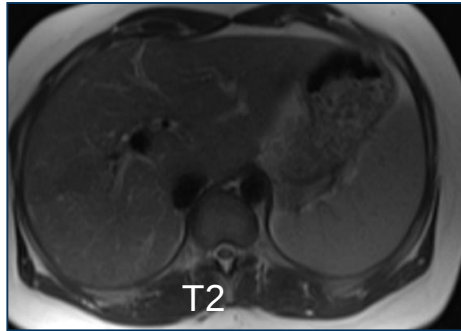


The patient had a TIPS inserted in 2013 and follow-up imaging is shown on the

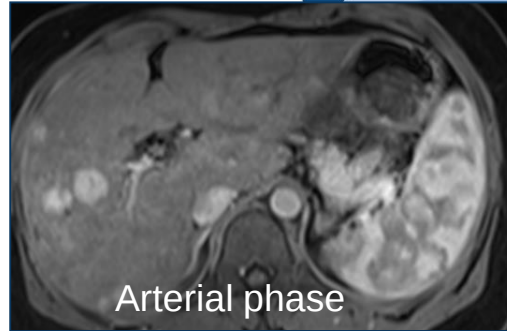
24 year old female with Budd-Chiari. MRI (2016) demonstrating the longitudinal progression of the liver disease post insertion of TIPS. Images are from liver MRI with gadoxetic acid enhancement



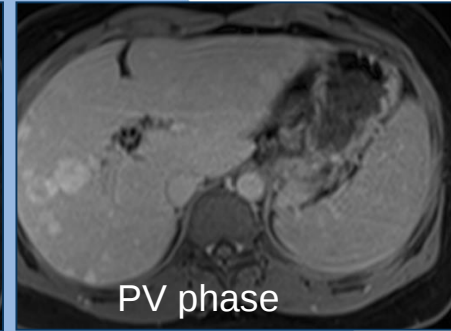
T1 Non-contrast



T2



Arterial phase



PV phase



Hepatocyte phase

MRI characteristics of the new nodules include T1 hyper-intensity, T2 hypo-intensity, arterial and portal venous enhancement without washout and peripheral concentration of gadoxetic acid in the hepatocyte phase. These features are typical of benign nodules that arise in chronic BCS (Brancatelli). Many of these features are similar to those of focal nodular hyperplasia in patients without BCS, although nodules are not significantly hyperintense on unenhanced T1w imaging.

Nodules in Budd Chiari Syndrome



- Alteration of hepatic venous blood flow in patients with chronic BCS is thought ultimately to lead to a reduction in portal flow and a compensatory increase in arterial flow to the liver. This has been postulated as a potential causative mechanism of nodules in chronic BCS¹.
- A recent study in a rat model has shown that portal deprivation by ligation or portocaval shunting induces a sustained increase in intrahepatic markers of inflammation, angiogenesis, fibrosis and proliferation².
- The apparent increased occurrence of these nodules in our patients with BCS who underwent a TIPS shunt would support the important aetiological role of portal deprivation in these nodules, as this shunt reduces portal flow to the liver parenchyma.
- Functioning hepatocytes can now be demonstrated in these large regenerative nodules, as enhanced uptake in the hepatocyte phase of gadoxetate-enhanced MRI. This feature is shared with FNH, a condition in which local vascular alteration has also been postulated as a causative mechanism.



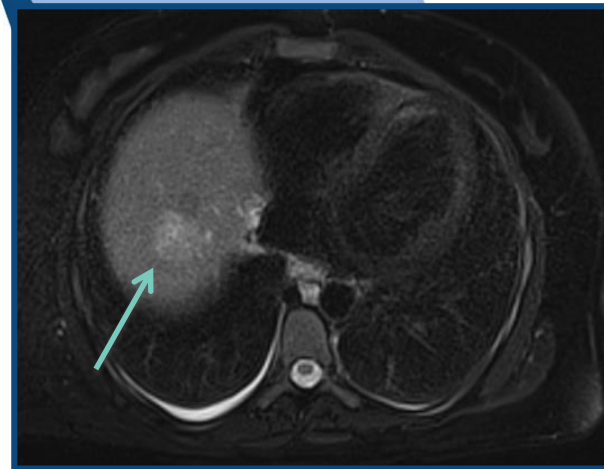
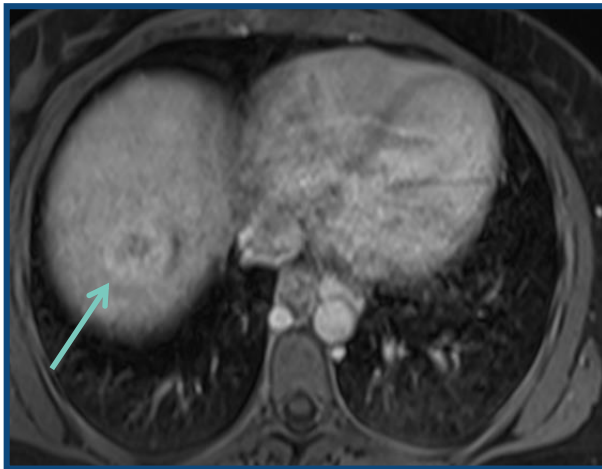
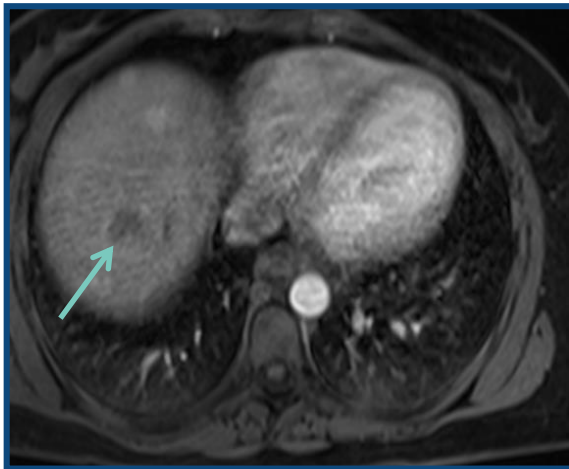
Nodule nomenclature in BCS



- Different nomenclature has been used in relation to these nodules, with large regenerative nodules being the most appropriate name pathologically.
- Nodular regenerative hyperplasia is used by pathologists to refer to nodules that are typically much smaller (about 1mm) and occur in non-cirrhotic livers in patients with myeloproliferative disease, organ transplantation and autoimmune conditions^{3,4}. They are typically not visible on imaging and this term should not be used for the nodules that are seen in BCS.



29 year old female with Budd-Chiari. The patient was followed with serial MRI Liver imaging. 3 years from diagnosis she developed a peripherally hyperenhancing and T2 hyperintense nodule in segment 8, with progressive enhancement in the portal venous phase (arrows). Histology of this nodule is shown on the following slide.



Case 3

29 year old female with Budd-Chiari. The patient had a resection of the nodule, with images of the histology specimens demonstrated below. Figure 1 is a H+E stain on low power showing an ill-defined parenchymal nodule composed of mature hepatocytes, which explains the characteristic hepatocyte phase uptake of gadoxetic acid in many of these nodules (not available for this case). Figure 2 is a reticulin specimen highlighting the smooth nodule without a capsule and Figure 3 is on high power demonstrating no loss of reticulin within the lesion. All features are consistent with a benign large regenerative nodule.

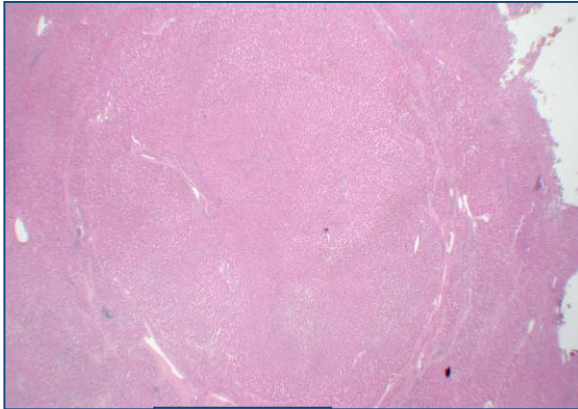


Figure 1

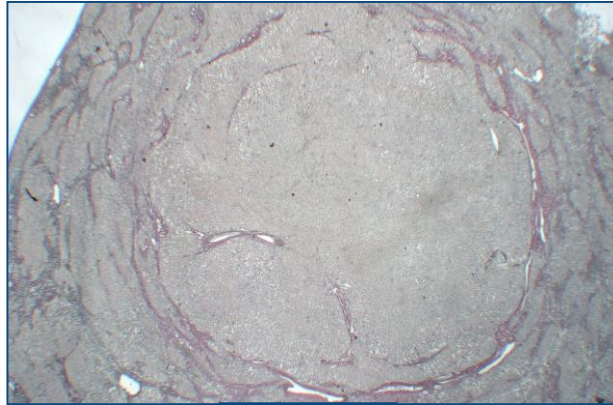


Figure 2

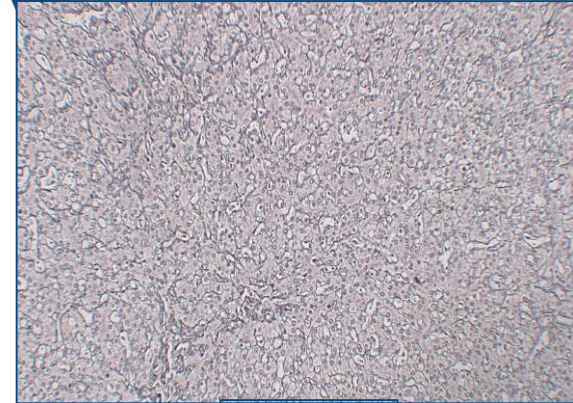
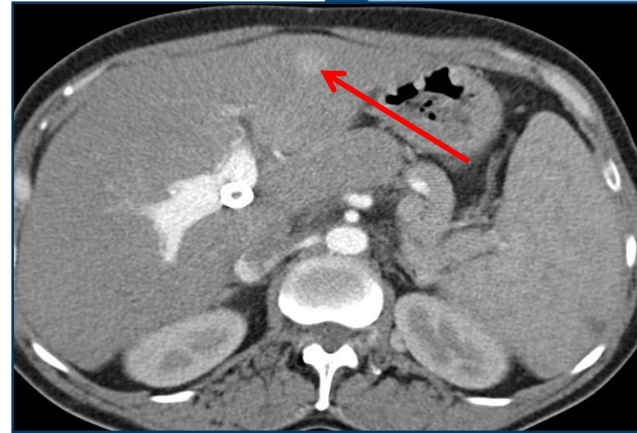


Figure 3

56 year old male with Budd-Chiari. Axial CT images of the liver show a TIPS insitu. The patient developed a new arterially enhancing nodule 2 years post insertion of the TIPS.



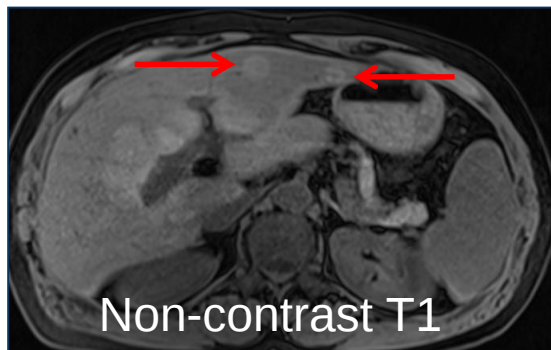
2006 -
Contrast
enhanced
CT with a
TIPs in-
situ. No
liver
lesion.



2008 -
Contrast
enhanced
CT with new
enhancing
liver lesion in
segment 2
(arrow).

56 year old male with Budd-Chiari. Axial MRI images of the liver

2008 – There are two focal lesions in segment 2 of the liver (red arrows). Both are hyperintense on native T1w images, making it difficult to assess arterial enhancement, although this had already been shown on CT. There is unequivocal delayed phase washout in both lesions, which is a feature that increases suspicion of hepatocellular carcinoma. These nodules were resected and were confirmed to represent HCC.



Since 1834



Hepatocellular carcinoma in BCS



- A study from 2012 compared the imaging features of benign regenerative nodules in BCS with those of HCC in BCS⁵.
- Both types of nodules showed arterial phase enhancement
 - Benign nodules showed either centre-to-periphery arterial phase hyperenhancement (70%) or homogenous arterial phase enhancement (30%)
 - Malignant nodules typically showed more heterogenous arterial phase hyperenhancement.
- Delayed phase appearances differed significantly
 - The majority of benign nodules were homogeneously hyperenhanced in portal and delayed phases, with a few showing isoenhancement, but none showing hypoenhancement (0/23).
 - All HCCs (9/9) were hypoenhanced in the delayed phase
- **Therefore in summary, as in nodule evaluation in patients with cirrhosis, washout in the portal or delayed phase is the key feature to look for nodules in BCS and it should lead to a high suspicion of HCC.**



Hypervascular nodules are common in patients with BCS, particularly post-TIPS. Most are benign and are likely due to increased inflammation, angiogenesis, fibrosis and proliferation caused by portal deprivation. These should be termed large regenerative nodules. Hepatocellular carcinoma is less common in BCS, but can also cause hypervascular nodules. As with imaging in cirrhosis, washout in the portal venous or delayed phase is a feature that suggests malignancy.

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2. Guérin F, Wagner M, Liné A, Zappa M, Fasseu M, Paradis V, et al. Hepatic proliferation and angiogenesis markers are increased after portal deprivation in rats: a study of molecular, histological and radiological changes. Avila MA, editor. PLoS ONE. 2015;10(5):e0125493.
3. Brancatelli G, Federle MP, Grazioli L, Golfieri R, Lencioni R. Benign regenerative nodules in Budd-Chiari syndrome and other vascular disorders of the liver: radiologic-pathologic and clinical correlation. Radiographics. 2002 Jul;22(4):847–62.
4. Ames JT, Federle MP, Chopra K. Distinguishing clinical and imaging features of nodular regenerative hyperplasia and large regenerative nodules of the liver. Clin Radiol. 2009 Dec;64(12):1190–5.
5. Zhang R, Qin S, Zhou Y, Song Y, Sun L. Comparison of imaging characteristics between hepatic benign regenerative nodules and hepatocellular carcinomas associated with Budd-Chiari syndrome by contrast enhanced ultrasound. Eur J Radiol. 2012 Nov;81(11):2984–9.

