



Case Report

Giant Hepatic Regenerative Nodule in a Patient With Hepatitis B Virus-related Cirrhosis

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Received: 4 July 2021 | Revised: 18 September 2021 | Accepted: 22 October 2021 | Published: 4 January 2022

Abstract

Hepatic regenerative nodules are reactive hepatocellular proliferations that develop in response to liver injury. Giant hepatic regenerative nodules of 10 cm or more are extremely rare and have only been reported in patients with biliary atresia or Alagille syndrome. A 50-year-old man presented with a pathologically confirmed giant 11.3×9.4×11.2 cm hepatic regenerative nodule and hepatitis B virus-related cirrhosis. Imaging of intrahepatic nodule included mild hyperenhancement in the portal phase of contrast-enhanced CT and the hepatobiliary phase in the gadoteric acid-enhanced MRI scan, as well as the portal vein crossing through sign in the setting of liver cirrhosis. This case highlights the imaging characteristics of giant hepatic regenerative nodules in hepatitis cirrhosis.

Citation of this article: Li L, Feng J. Giant Hepatic Regenerative Nodule in a Patient With Hepatitis B Virus-related Cirrhosis. *J Clin Transl Hepatol* 2022;10(4):778–782. doi: 10.14218/JCTH.2021.00266.

Introduction

Histopathological, regenerative nodules are hyperplastic proliferations of hepatocytes in response to necrosis, altered circulations, or other stimuli.¹ They usually occur in patients with hepatitis or alcoholic cirrhosis, vascular liver diseases such as Budd-Chiari syndrome,² or cholangiopathic disorders such as biliary atresia³ or Alagille syndrome.^{4,5} Regenerative nodules are classified by size as micronodules (<3 mm) or macronodules (≥3 mm).^{1,6} Large regenerative nodules are usually 5 to 15 mm in diameter, but they can be

5 cm or larger.^{1,6} Giant nodules as large as 5 cm have been reported in patients with liver cirrhosis,⁷ Budd-Chiari syndrome,⁸ biliary atresia,³ or Alagille syndrome.^{4,5} Giant nodules of 10 cm in diameter or more have only been reported in patients with biliary atresia³ or Alagille syndrome.^{4,5} We report a rare and unique case who presented with a giant hepatic regenerative nodule more than 10 cm in size and associated with hepatitis B virus (HBV)-related cirrhosis.

Case report

A 50 year-old man was found to have a hepatic mass suspected to be liver cancer by ultrasonography. He denied any clinical symptoms. Physical examination revealed an enlarged non-tender liver with a firm and uneven surface. The lower edge of the liver extended to the right iliac crest. The spleen was not palpable. A routine blood workup found a white blood cell count of $5.3 \times 10^9/L$, a red blood cell count of $4.5 \times 10^{12}/L$, a hemoglobin level of 141 g/L, and a platelet count of $80 \times 10^9/L$. Liver function tests showed increased levels of alanine aminotransferase (ALT) 107.8 IU/L (reference range, 0–40 IU/L), aspartate aminotransferase (AST) 69.4 IU/L (reference range, 0–38 IU/L), alkaline phosphatase 171.3 IU/L (reference range, 30–150 IU/L), and gamma-glutamyl transferase 452.4 IU/L (reference range, 0–47 IU/L), normal serum total bilirubin, albumin, plasma prothrombin time, international normalized ratio, and ammonia. Hepatitis virus tests were positive for hepatitis B surface antigen (HBsAg), HB e antigen, HB e antibody, and HB core antibody, and negative for HB surface antibody, hepatitis C virus antibody, and hepatitis C antigen. Alpha-fetoprotein and carcinoembryonic antigen assays were negative.

A CT scan showed pronounced nodular irregularity of the liver surface, enlargement of the interlobar fissure, hypertrophy of the left lobe, and dilatation of the portal vein, with a diameter of 21.0 mm (Fig. 1). Diffuse multiple nodules of <1 cm diameter in the liver parenchyma showed slight hyperdensity on precontrast CT images and became isodense in post-contrast phases (Fig. 1). Precontrast CT showed a well-circumscribed 11.3×9.4×11.2 cm oval hypodense mass in segment VI of the liver, including a focal hypodense area extending downward to the right iliac fossa (Fig. 2A, A'). Contrast-enhanced CT showed iso-enhancement in the arterial phase (Fig. 2B, B') with slight hyperenhancement, a portal vein branch crossing through the lesion in the portal phase (Fig. 2C, C'), and slight hypo-enhancement in the de-

Keywords: Regenerative nodules; Cirrhosis; Hepatitis B virus; Computed tomography; Magnetic resonance imaging.

Abbreviations: ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; CT, computed tomography; FIB-4, fibrosis-4 score; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HU, Hounsfield units; IU, international unit; MRI, magnetic resonance imaging.

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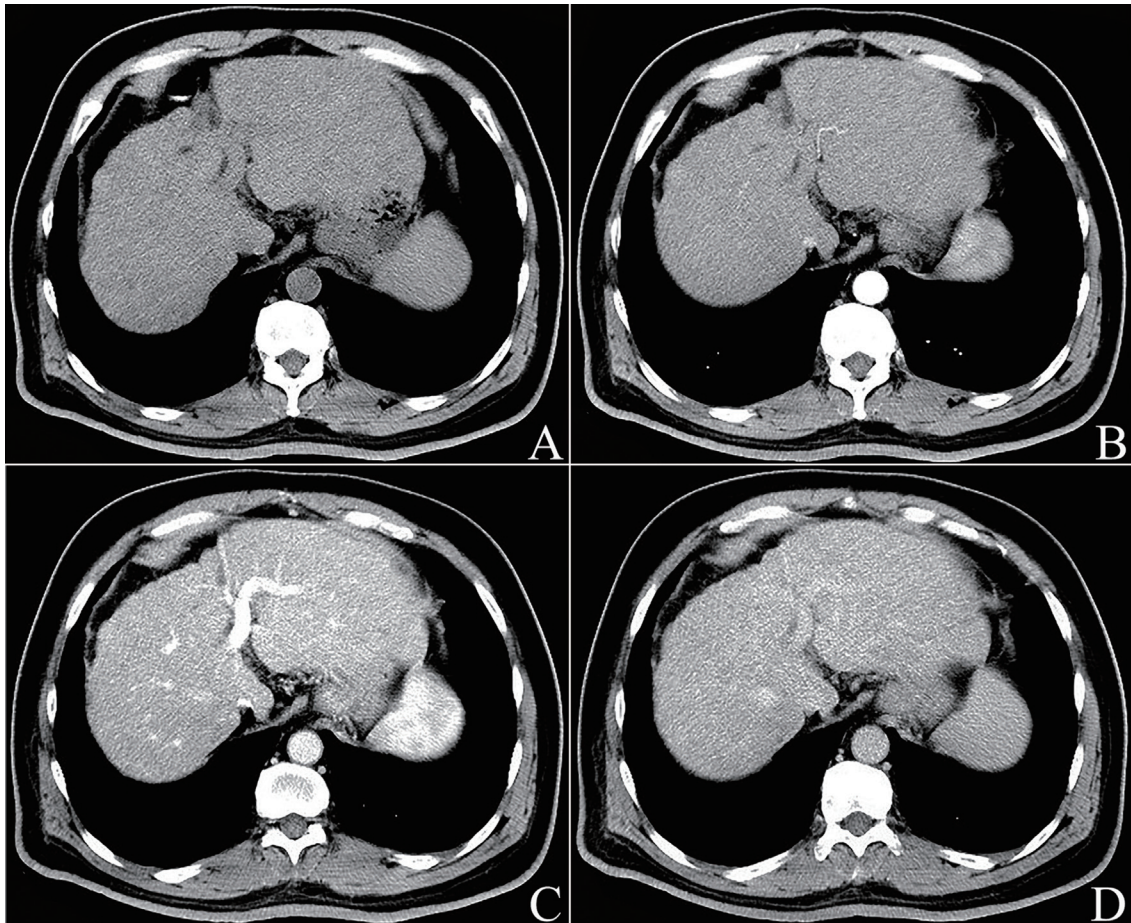


Fig. 1. CT images of liver cirrhosis. Axial CT images show dysmorphia of the liver, including pronounced nodular irregularity of the liver surface, enlargement of the interlobar fissure, and hypertrophy of the left lobe (A–D). A precontrast CT image shows diffuse multiple nodules of <1 cm diameter and slight hyperdensity in the liver parenchyma (A), and contrast-enhanced isodense CT images in liver during the arterial (B), portal (C), and delayed phases (D). CT, computed tomography.

layed phase (Fig. 2D, D'). The focal hypodense area within the lesion was not enhanced from the arterial phase to the delayed phase.

A follow-up contrast-enhanced MRI with gadoxetic acid at 6 months found no significant differences in the size, shape, margin, internal characteristics, and three-phase contrast-enhancement patterns compared with the original CT images, except for slight hyperenhancement in the delayed 20 and 30 m hepatobiliary phases (Fig. 3). At 10.5 months after the first hospital admission, a CT-guided percutaneous biopsy resulted in pathological confirmation of a hepatic regenerative nodule (Fig. 4).

Discussion

When assessing a patient with a liver mass, noninvasive diagnosis of HBV-related cirrhosis and the imaging characteristics of hepatic regenerative nodules are important. Non-invasive diagnosis of HBV-related cirrhosis depends on calculation of the AST-to-platelet ratio index (APRI) and the fibrosis-4 score (FIB-4) using indirect markers of fibrosis such as ALT, AST and platelet count.⁹ $APRI = [(AST/AST_{ULN}) / \text{platelet count}] \times 100$ and the Fib-4 score = $(\text{age in years} \times AST) / (\text{platelet count} \times \sqrt{ALT})$. In clinical practice, liver biopsy has been replaced by noninvasive methods as APRI and FIB-4 scores and imaging.⁹ An APRI score >2 is recom-

mended as the preferred noninvasive threshold to determine the presence of cirrhosis in resource-limited settings by the World Health Organization HBV guidelines. A FIB-4 >3.25 has a 97% specificity and a 65% positive predictive value for advanced fibrosis.⁹ Conventional ultrasound, CT, and MRI can detect morphologic changes in the liver related to advanced fibrosis, but the methods have a limited ability to identify early-stage fibrosis.^{10,11} Our patient was positive for HBV, with an APRI of 2.283 and a FIB-4 of 4.18. CT scan showed morphological changes in the liver and the dilation of portal veins. We diagnosed HBV-related cirrhosis based on the findings.

During imaging evaluation, predominant portal perfusion was visible in dynamic contrast-enhanced imaging, including CT, MRI, and ultrasound. The vascular supply of regenerative nodules is similar to the surrounding hepatic parenchyma,^{3-5,7,12} unlike hepatocellular carcinoma (HCC), which usually shows arterial wash-in and late washout, regenerative nodules are usually isointense during the arterial and portal venous phases and become more isointense or hypointense during the equilibrium and delayed phases.^{7,12} In the hepatobiliary phase of gadoxetic acid-enhanced MRI, regenerative nodules commonly appear as isointense or mildly hyperintense signals, and not hypointense, relative to the surrounding liver parenchyma because of the preserved hepatocellular function.¹³ In addition to the contrast-enhancement pattern, the image of the portal vein crossing through the mass is re-

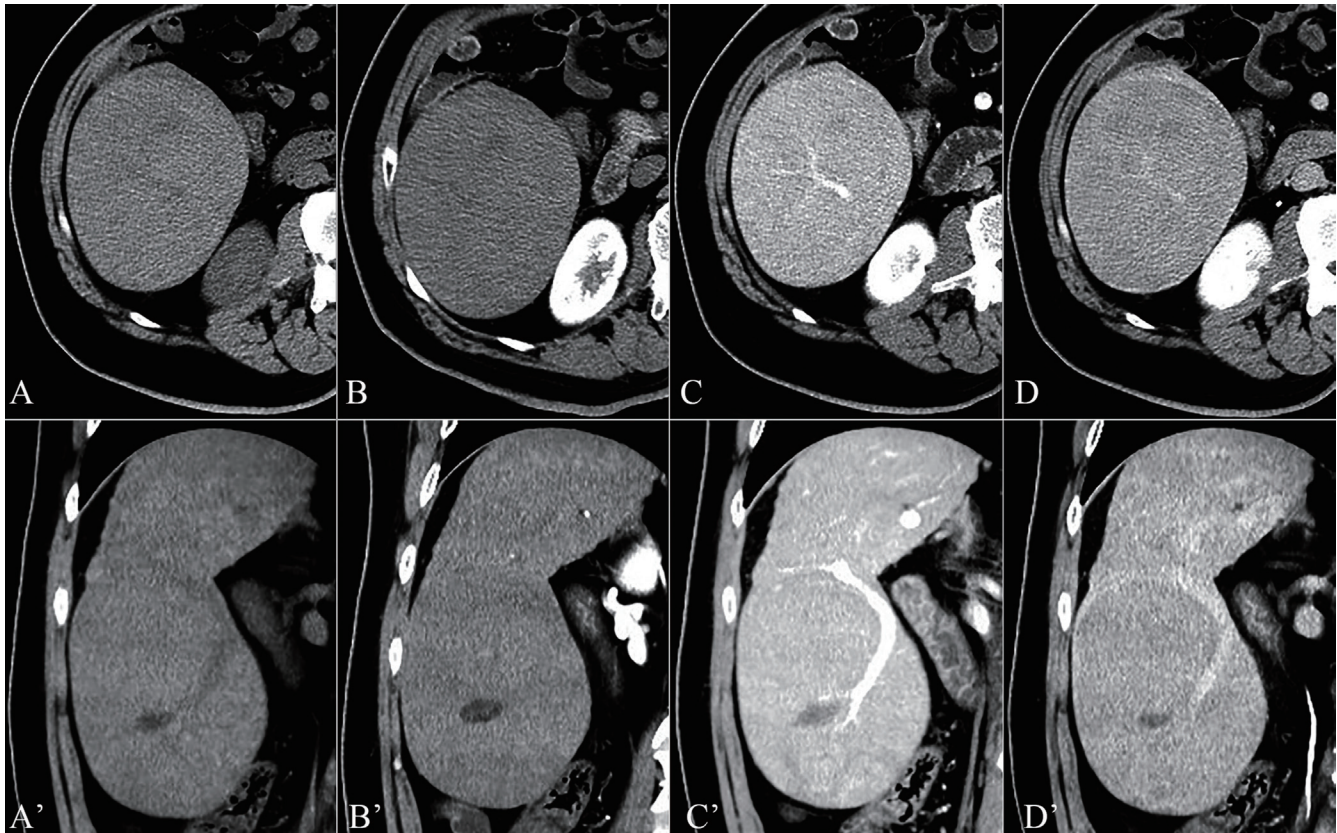


Fig. 2. CT images of a giant hepatic mass. (A and A') Precontrast CT scan shows a well-circumscribed oval hypodense mass with an average attenuation of 50.5 HU in segment VI of the liver, including a focal hypodense area (18.5 HU) and extending downward to the right iliac fossa. (B and B') Contrast-enhanced CT scan in the arterial phase showing a nodule (53.5 HU) with a density similar to that of the surrounding liver cirrhosis (52.0 HU). (C and C') The portal phase shows that the mass density (91.3 HU) was slightly greater than that of the surrounding liver cirrhosis (83.0 HU), with a portal vein branch crossing through the lesion. (D and D') The delayed phase shows a mass density (77.3 HU) that is slightly lower than that of the surrounding liver cirrhosis (81.0 HU). The focal hypodense area within the lesion was not enhanced from the arterial phase to the delayed phase. A–D, axial images; A'–D', coronal reformation images. CT, computed tomography; HU, Hounsfield units.

ported to be characteristic of giant hepatic regenerative nodules in the portal phase images^{3–5} because the nodules have normal portal tracts at the center.^{1–5,7,12} Therefore, hepatic regenerative nodules of various sizes should be categorized as Liver Imaging and Reporting Data System category 2, as they did not have the major and ancillary imaging features of HCC and other malignancies.^{14,15}

Current international guidelines recommend that all HBsAg-positive patients with cirrhosis should be routinely monitoring for disease activity and progression to HCC.⁹ Recent clinical practice guidelines include gadoteric acid-enhanced liver MRI as the first-line diagnostic and monitoring tool for hepatic nodules instead of biopsy. A single dynamic CT or MRI study rather than two dynamic imaging modalities is recommended for the diagnosis of HCC lesions of < 2 cm.¹³ Huge lesions should be considered as focal malignant transformations if major and/or ancillary imaging features of Liver Imaging and Reporting Data System category to assess HCC or other malignancies have developed.¹⁶ Percutaneous needle biopsies may be difficult to obtain in cases of focal malignant transformation. During the initial stage of tumor initiation, HCC may retain hepatocellular function and isointense or mildly hyperintense signals similar to regenerative nodules.¹⁷ For early HCC in cirrhotic livers, patients should be evaluated with multiparametric imaging, including T₁ hypointensity, T₂ hyperintensity, diffusion-weighted imaging hyperintensity, arterial enhancement, late wash-out, and hepatobiliary hypointensity at a size threshold

of ≥ 1.5 cm on gadoteric acid-enhanced MRI. The findings should be interpreted with care.^{18–20} Finally, if imaging features and laboratory results still cannot support a definitive diagnosis, a multidisciplinary team may discuss the atypical features to help to develop an appropriate approach for the patient.¹⁹ In conclusion, giant hepatic regenerative nodules in the background of liver cirrhosis have characteristic imaging features that can help guide clinical management and avoid unnecessary medical interventions.

Funding

None to declare.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Both authors, LL and FJ, contributed to the design and implementation of the study and to the analysis of the results and to the writing of the manuscript.

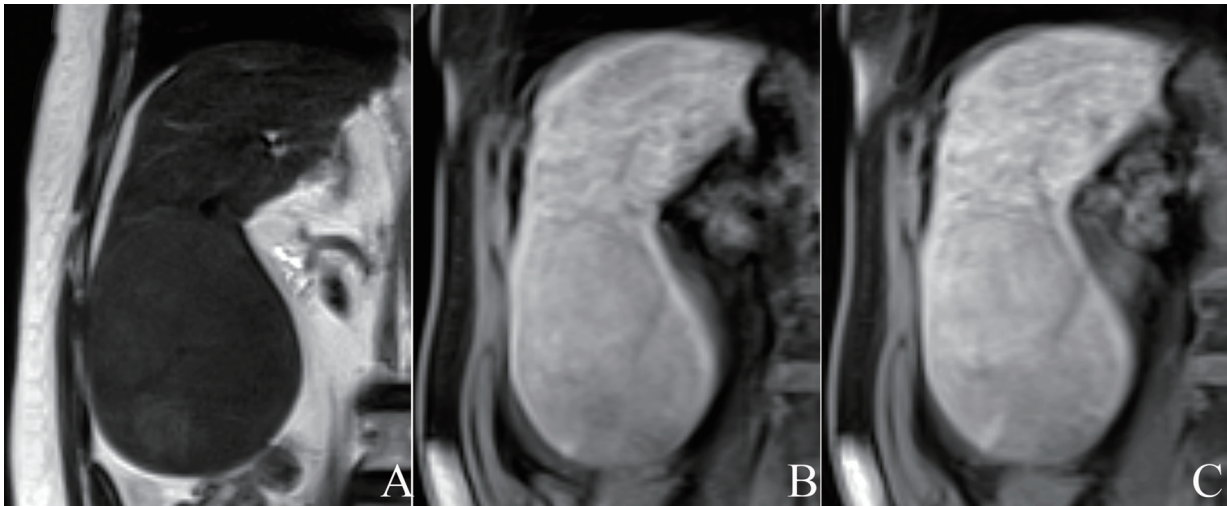


Fig. 3. Follow-up contrast-enhanced MRI with gadoxetic acid. (A) Precontrast coronal T2-weighted image shows an oval, well-circumscribed iso-signal mass in segment VI of the liver. (B) Delayed 20 m hepatobiliary phase in the gadoxetic acid-enhanced MRI shows a slightly hyperenhanced mass and surrounding liver cirrhosis with heterogeneous. (C) Delayed 30 m hepatobiliary phase in the gadoxetic acid-enhanced MRI shows a persistent slightly hyperenhanced mass. MRI, magnetic resonance imaging.

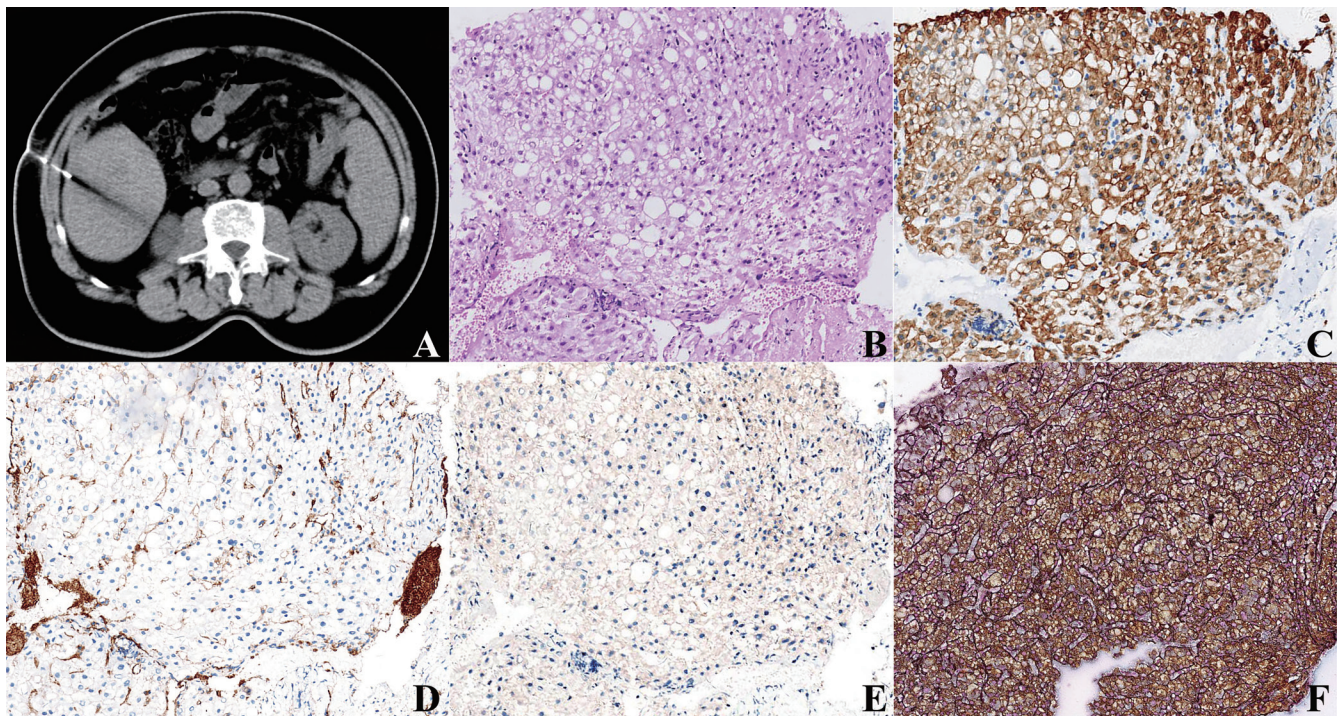


Fig. 4. CT-guided percutaneous biopsy and pathological findings of a giant mass in segment VI of the liver (A) CT image showing a biopsy needle inserted into the margin of the mass in segment VI of the liver. (B) Hematoxylin and eosin staining indicates vacuolar degeneration in the cytoplasm of most hepatocytes, bilirubin deposition in cytoplasm of some hepatocytes, and interstitial fibrous proliferation with focal lymphocytic infiltration of portal areas. 100× magnification. (C) Anti-cytokeratin 8 immunostaining is strongly positive in hepatocytes, indicating normal and mature differentiation. 100× magnification. (D) Anti-cluster of differentiation 34 immunostaining is positive in vascular endothelial cells in portal areas and hepatic sinusoid endotheliocytes. 100× magnification. (E) Anti- alpha-fetoprotein immunostaining is negative in hepatocytes. 100× magnification. (F) Gordon and Sweet silver staining (black) shows a reticular fiber network in the subendothelial spaces of the hepatic sinusoids. 200× magnification. CT, computed tomography.

Patient consent

The patient provided written informed consent and gave permission for publication of this case report and any accompanying images.

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