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Review Article

Genetic Advances in Fibrolamellar Hepatocellular Carcinoma: Comparison with Focal Nodular Hyperplasia of the Liver

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ABSTRACT

Fibrolamellar Hepatocellular Carcinoma (FL-HCC) is more frequent in non-cirrhotic young adult populations and surgically complete resection is regarded as one of the only curative therapy options. Pathologically the central stellate scar and conspicuous fibrous tissue may be observed in up to 75% of FL-HCC, while characteristic central stellate scar with radiating fibrous septa is shown in Focal Nodular Hyperplasia (FNH) suggesting that the differential diagnosis of two entities is very important. The recent report described the trends in FNH along with oxaliplatin-induced this entity. In this article, the current knowledge and trends of genetic advances in FL-HCC along with comparison with FNH of the liver have been reviewed. Additionally, the author described the differential diagnosis of two entities emphasizing on the central stellate scar. It is plausible that patients with atypical FNH on radiological features should be examined at a specialized hepatobiliary center. The new technology, Super-Resolution Ultrasonography (US) without contrast agent may be a potential tool of detection of spoke wheel sign in FNH suggesting that this finding may contribute to the differential diagnosis of two entities. FL-HCC is associated with *DNAJB1-PRKACA* gene fusion having tumorigenesis, while unique endothelial cell expressed SOST of fibrous septa in FNH with no therapy may contribute to promote the fibrosis process through PDGFB/PDGFRB pathway suggesting the different genetic nature of two entities. For immunotherapy, based on the evidence, personalized *DNAJB1-PRKACA*-derived peptide vaccine may be an effective treatment in a single FL-HCC patient. Though further studies are needed to validate for immunotherapy in FL-HCC.

Key words: Fibrolamellar Hepatocellular Carcinoma (FL-HCC); *DNAJB1-PRKACA* gene fusion: Immunotherapy: Focal Nodular Hyperplasia (FNH); Central stellate scar

INTRODUCTION

Fibrolamellar Hepatocellular Carcinoma (FL-HCC) was first reported in 1956 by Edmondson [1]. It is known that this entity affects young adult populations without primary liver disease or cirrhosis [2]. Pathologically the central stellate scar and conspicuous fibrous tissue may be observed in up to 75% of FL-HCC, while characteristic central stellate scar with radiating fibrous septa is shown in FNH suggesting that the differential diagnosis of two entities is very important [3,4]. The recent report described the trends in FNH along with oxaliplatin- induced this entity [4]. Instead of hemodynamic procedure, the new technology, super-resolution US without contrast agent has been reported for detection of spoke wheel sign in FNH [5]. Genetically, the *DNAJB1-PRKACA* gene fusion may play a crucial role in tumorigenesis in FL-HCC [6]. In this article, the current knowledge and trends of genetic advances in FL-HCC along with comparison with focal nodular hyperplasia of the liver have been reviewed. In addition, the author described the differential diagnosis of two entities focusing on the central stellate scar.

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LITERATURE REVIEW

Clinical and pathological features in FL-HCC

Fibrolamellar Hepatocellular Carcinoma (FL-HCC) was first reported in 1956 by Edmondson [1]. It is known that this entity affects young adult populations without primary liver disease or cirrhosis without the identification of causative factors [2]. This disease pathologically showed large eosinophilic, hepatocyte-like polygonal cells with fibrotic bands of lamellae. The central stellate scar and conspicuous fibrous tissue may be observed in up to 75% of this entity [3]. FNH also represented pathologically characteristic central stellate scar with radiating fibrous septa suggesting that the differential diagnosis of two entities is very significant [4]. The previous report showed the pathologically typical stellate central scar and centrifugal filling to periphery, spoke wheel pattern on sonographic angiography in FNH [4]. Small focal calcifications may be observed in the central scar or radiating fibrous band in FL-HCC, while calcification is rare appearance in FNH [3]. Immunohistological analysis such as CK7 and CD68 have been used for the diagnosis of FL-HCC and genetically, *DNAJB1-PRKACA* fusion gene expression is detected in the most majority of patients with FL-HCC. Regarding therapeutic strategy, as chemotherapeutic agents using gemcitabine, cisplatin, 5-FU, interferon, and oxaliplatin for FL-HCC have been tried, this entity has been less chemo-responsive than the conventional HCC [7]. Operative resection is the only effective treatment. The previous report by Lemekhova et al. described that patients with atypical FNH on image features should be examined at a tertiary referral center to avoid fatal outcome [8]. As even after operation, aggressive manifestation with early relapse and recurrence rates have been reported indicating that this entity should be presented at a specialized hepatobiliary unit. They also suggested that thromboembolism might be an early paraneoplastic symptom [8].

Radiological and ultrasonographyic features in FL-HCC

FL-HCC is more frequent in non-cirrhotic young adult populations and surgically complete resection is regarded as one of the only curative therapy options [8]. The previous report described the differential diagnosis of hepatic tumor accompanied by central scar [9]. FL-HCC is regarded as heterogeneous hypervascular enhancement in arterial phase and irregular hyperattenuating or isoattenuating in the portal and late phases, whereas the central stellate scar represents hypoenhancement and calcifications in all phases [10]. On CT feature, the central stellate scar is typically observed in 65%-70% of cases, additionally presence of calcifications within the central scar is a promising diagnostic appearance [2]. On MRI appearance, FL-HCC showed hypointense on T1-weighted images and hyperintense on T2-weifgted images, while the central scar represented hypointense on both T1- and T2-weighted images. Meanwhile, central scar in FNH showed T2 hyperintense suggesting different features on T2-weighted image. FNH represents a central scar with small fine arteries radiating from the center toward the periphery along the fibrous septa, showing the spoke wheel pattern, characteristic sign of FNH enhancement [5]. It is known that the spoke wheel pattern is a useful diagnostic feature in FNH using CEUS [5]. The author previously experienced a case of FNH with central linear high echo on gray-scale US, showing the centrifugal filling pattern to the periphery, so-called spoke wheel sign on sonographic angiography (US angiography) [4,11]. With respect to the comparison between SonoVue (SV) and Sonazoid (SZ) contrast-enhanced ultrasound (CEUS), He et al. described that there was no significant difference in the depicting centrifugal filling, spoke wheel artery, or feeding artery between the contrast agents. Meanwhile they suggested that SZ CEUS may be significantly better than SV CEUS for the detection of a central scar appearance [12]. Super-resolution US using Doppler US modality can show real-time low-velocity blood flow within micro vessels without a contrast material [5]. Recent study revealed that compared to CEUS, super-resolution US showed a reliable incidence of depiction of the spoke wheel pattern in FNH patients [5]. Pathologically the central stellate scar and conspicuous fibrous tissue may be observed in up to 75% in FL-HCC, while central stellate scar with radiating fibrous septa is characteristically shown in FNH suggesting that differential diagnosis of two entities is very important. [3,4]. The hemodynamic image feature, namely, the spoke wheel pattern on CEUS has represented accurate diagnosis of FNH, while it is plausible that super-resolution US without contrast agent may be a potential tool of detection of spoke wheel sign. In addition, the presence of calcifications within the central scar on CT may be a useful finding in FL-HCC. Regarding MRI finding, the fibrous central scar in FL-HCC represented hypointense on T2-weighted images, while central scar in FNH showed hyperintense on T2-weighted images showing the difference feature on T2-weighted images of two entities.

Genetic advances in FL-HCC

The recent report provided the evidence for the progress including molecular mechanisms such as *DNAJB1-PRKACA* gene fusion and aberrant activation of PKA, development of disease models, immunotherapies, and clinical trials [13]. FL-HCC expressed characteristic gene fusion, *DNAJB1-PRKACA* is identified by Honeyman et al [6]. The chimeric transcript, *DNAJB1-PRKACA* is observed in 100% of patients with FL-HCC and has been recognized as the oncogenic driver in tumor pathogenesis [6]. It is known that DNAJB1 encodes a member of the HSP 40 family of heat shock proteins, whereas PRKACA encodes the α-isoform of the catalytic subunit (Cα) of protein kinase A (PKA) [13]. The previous study demonstrated that the *DNAJB1-PRKACA* gene fusion drives tumorigenesis in mice [14]. Another report identified that the *DNAJB1-PRKACA* gene fusion is sufficient to induce tumorigenesis and develops FL-HCC in the liver of mice by CRISPR/Cas9 engineering [15]. For the therapeutic targets, immunotherapeutic approaches have been performed using respective tumor antigens to induce an anti-tumor T cell response in patients with melanoma [16,17]. The previous report revealed that a gene fusion produces a neoantigen suggesting that neoepitopes have been indicated as an important category of tumor-specific antigens [18]. With respect to T cell immunity of COVID-19 peptide vaccine,

COVID-19 vaccination induce SARS-CoV-2 T cell immunity to combat COVID-19 showing that SARS-CoV-2-specific T cell responses were induced by multifunctional T helper 1 CD4+ and CD8+T cells, along with sustained IFNγT cell responses [19]. Regarding microRNA, the study by Dinh et al. demonstrated that the most down-regulated miRNA in FL-HCC is miR-375 showing that overexpression of miR-375 mitigated tumor cell growth and invasion of FL-HCC, suggesting that whether miR-375 expression has the potential targets in this entity [20]. *DNAJB1-PRKACA* fusion gene transcript has exhibited a target for the development of new treatments. Vyas et al. described that *DNAJB1-PRKACA* fusions occur in oncocytic pancreatic and biliary neoplasms and are not specific for FL-HCC suggesting that the caution should be paid in diagnosing hepatic masses with *DNAJB1-PRKACA* fusion as FL-HCC [21]. They also described that the upregulated protein kinase activity induced by *DNAJB1-PRKACA* fusion shows a crucial role in tumorigenesis of FL-HCC suggesting that protein kinase inhibition represents promising therapeutics for the pancreatobiliary tumors [21]. Meanwhile, recent report suggested whether FL-HCC is one cancer or a collection with similar phenotypes and also mentioned whether it is genetically inherited or the result of the somatic mutation [22]. The *DNAJB1-PRKACA* fusion gene derived HLA class 1 and HLA class II ligands induces *DNAJB1-PRKACA*-specific CD4+ and CD8+ T responses [23]. Regarding immunotherapy, *DNAJB1-PRKACA*-derived peptide vaccine induces persistent *DNAJB1-PRKACA*-specific T cell responses showing favorable clinical outcome in patients with FL-HCC [23]. The evidence provided the persistence of *DNAJB1-PRKACA*-specific T cell responses suggesting that these findings demonstrated the *DNAJB1-PRKACA* protein as a prime source for immunogenic neoepitopes and showed immunotherapeutic efficacy in a single FL-HCC patient [23]. Regarding FNH, previous study provided that unique endothelial cell expressed SOST of fibrous septa in FNH with no therapy may contribute to promote the fibrosis process through PDGFB/PDGFRB pathway using the integrated analysis [24,25]. Though further investigations are needed to elucidate the unique natures, especially in endothelial cell of fibrous septa in FNH [25]. Regarding microRNAs, the results provided that the decreased miR-18a, miR-195, and miR-210 expressions may differentiate FNH from cirrhosis [26].

DISCUSSION

In this article, the current knowledge and trends of genetic advances in FL-HCC along with comparison with focal nodular hyperplasia of the liver have been reviewed. Additionally, the differential diagnosis of two entities emphasizing on the central stellate scar has been described. It is plausible that patients with atypical FNH on image features should be examined at a tertiary referral center to avoid fatal outcome [8]. It is putative that differential diagnosis of two entities with central stellate scar is very important. The presence of calcifications within the central scar on CT may be a useful finding in FL-HCC [2,10]. Regarding MRI finding, the fibrous central scar in FL-HCC represented hypointense on T2-weighted images, while central scar in FNH showed hyperintense on T2-weighted images showing the difference feature on T2-weighted images of two entities [2]. The hemodynamic image finding using such as CEUS and sonographic angiography, namely spoke wheel sign has considered as a promising feature of accurate diagnosis in FNH [12]. Meanwhile it is putative that new modality, super-resolution US showing micro flow imaging without contrast agent is a useful tool of detection of spoke wheel sign suggesting that this result may also contribute to the differential diagnosis of two entity [5]. It is plausible that the *DNAJB1-PRKACA* gene fusion may play a crucial role in the development of FL-HCC [6,23]. Previous study described that *DNAJB1-PRKACA* fusions occur in oncocytic pancreatic and biliary neoplasms and are not specific for FL-HCC [21]. Meanwhile, recent report suggested whether FL-HCC is one cancer or a collection with similar phenotypes and also mentioned whether it is genetically inherited or the result of the somatic mutation [22]. Based on the evidence, FL-HCC is associated with *DNAJB1-PRKACA* gene fusion, while unique endothelial cell expressed SOST of fibrous septa in FNH with no therapy may contribute to promote the fibrosis process through PDGFB/PDGFRB pathway using the integrated analysis. These results may show the different genetic nature between FL-HCC and FNH [24,25]. For immunotherapy, recent study revealed the *DNAJB1-PRKACA* as a prime source for immunogenic neoepitopes and provided the immunotherapeutic efficacy in a single FL-HCC patient [23]. Though further investigations are needed to clarify for immunotherapy in FL-HCC.

CONCLUSION

It is plausible that patients with atypical FNH on image features should be examined at a tertiary referral center. The super-resolution US without contrast agent may be a promising tool of detection of spoke wheel sign in FNH suggesting that this finding may contribute to the differential diagnosis of two entities. FL-HCC is associated with *DNAJB1-PRKACA* fusion gene, while unique endothelial cell expressed SOST of fibrous septa in FNH with no therapy may contribute to promote the fibrosis process through PDGFB/PDGFRB pathway suggesting the different genetic nature of two entities. For immunotherapy, based on the evidence, personalized *DNAJB1-PRKACA* -derived peptide vaccine may be an effective therapy in a single FL-HCC patient. Though further studies are needed to validate for immunotherapy in FL-HCC.

CONFLICT OF INTEREST

Author declares that I have no conflicts of interest.

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None

REFERENCES

1. Edmondson HA. Differential diagnosis of tumors and tumor-like lesions of liver in infancy and childhood. AMA J Dis Child. 1956;91:168-186.
2. Ganeshan D, Szklaruk J, Kundra V, Kaseb A, Rashid A, Elsayes KM. Imaging features of fibrolamellar hepatocellular carcinoma. AJR. 2014; 202: 544-552.

3. Ichikawa T, Federle MP, Grazioli L, Madariaga J, Nalesnik M, Marsh W. Fibrolamellar hepatocellular carcinoma: imaging and pathologic findings in 31 recent cases. Radiology. 1999;213:352-361.
4. Fujioka K, Sanuki E, Kamata R, Yamamoto M. A case of focal nodular hyperplasia of the liver accompanied by a marginal hypoechoic zone in the ultrasonogram. Jpn J Med Ultrasonics. 1995;22:55-60.
5. Kang TW, Jeong WK, Kim YY, Min JH, Kim YK, Kim SH, et al. Comparison of super-resolution US and contrast material-enhanced US in detection of the spoke wheel sign in patients with foal nodular hyperplasia. Radiology. 2021;298:82-90.
6. Honeyman JN, Simon EP, Robine N, Chiaroni-Clarke R, Darcy DG, Lim IIP, et al. Detection of a recurrent *DNAJB1-PRKACA* chimeric transcript in fibrolamellar hepatocellular carcinoma. Science. 2014;343:1010-1014.
7. Abdelhamed W, El-Kassas M. Fibrolamellar hepatocellular carcinoma: a rare but unpleasant event. World J Gastrointest Oncol. 2022;14:1103-1114.
8. Lemekhova A, Hornuss D, Polychronidis G, Mayer P, Rupp C, Longerich T, et al. Clinical features and surgical outcomes of fibrolamellar hepatocellular carcinoma: retrospective analysis of a single-center experience. World J Surg Oncol. 2020;18(1):93.
9. Rudolphi-Solero T, Trivino-Ibanez EM, Medina-Benitez A, Fernandez-Fernandez J, Rivas-Navas DJ, Perez-Alonso AJ, et al. Differential diagnosis of hepatic mass with central scar: focal nodular hyperplasia mimicking fibrolamellar hepatocellular carcinoma. Diagnostics. 2022;12:44.
10. Ganeshan D, Szklaruk J, Kaseb A, Kattan A, Elsayes KM. Fibrolamellar hepatocellular carcinoma: multiphasic CT features of the primary tumor on pre-therapy CT and pattern of distant metastases. Abdom Radiol. 2018;43:3340-3348.
11. Kudo M, Tomita S, Tochio H, Mimura J, Okabe Y, Kashida H, et al. Sonography with intraarterial infusion of carbon dioxide microbubbles (sonographic angiography): value in differential diagnosis of hepatic tumors. AJR. 1992;158:65-74.
12. He M, Zhu L, Huang M, Zhong L, Ye Z, Jiang T. Comparison between SonoVue and Sonazoid contrast-enhanced ultrasound in characterization of focal nodular hyperplasia smaller than 3 cm. J Ultrasound Med. 2021;40:2095-2104.
13. Dinh TA, Utria AF, Barry K, Ma R, Abou-Alfa GK, Gordan JD, et al. A framework for fibrolamellar carcinoma research and clinical trials. Nat Rev Gastroenterol Hepatol. 2022;19:328-342.
14. Kastenhuber ER, Lalazar G, Houlihan SL, Tschaharganeh DF, Baslan T, Chen CC, et al. *DNAJB1-PRKACA* fusion kinase interacts with β-catenin and the liver regenerative response to drive fibrolamellar hepatocellular carcinoma. Proc Natl Acad Sci USA. 2017;114:13076-13084.
15. Engelholm LH, Riaz A, Serra D, Dagnaes-Hansen F, Johansen JV, Santori-Rugiu E, et al. CRISPR/Cas9 engineering of adult mouse liver demonstrates that the *Dnajb1-Prkaca* gene fusion is sufficient to induce tumors resembling fibrolamellar hepatocellular carcinoma. Gastroenterology. 2017;153:1662-1673.e10.
16. Ott PA, Hu Z, Keskin DB, Shukla SA, Sun J, Bozym D, et al. An immunogenic personal neoantigen vaccine for patients with melanoma. Nature. 2017;547:217-221.
17. Sahin U, Derhovanessian E, Miller M, Kloke BP, Simon P, Lower M, et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature. 2017;547;222-226.
18. Yang W, Lee KW, Srivastava RM, Kuo F, Krishna C, Chowell D, et al. Immunogenic neoantigens derived from gene fusions stimulate T cell responses. Nat Med. 2019;25:767-775.
19. Heitmann JS, Billich T, Tandler C, Nelde A, Maringer Y, Marconato M, et al. A COVID-19 peptide vaccine for the induction of SARS-CoV-2 T cell immunity. Nature. 2022;601:617-622.
20. Dinh TA, Jewell ML, Kanke M, Francisco A, Sritharan R, Turnham RE, et al. MicroRNA-375 suppresses the growth and invasion of fibrolamellar carcinoma. Cell Mol Gastroenterol Hepatol. 2019;7:803-817.
21. Vyas M, Hechtman JF, Zhang Y, Benayed R, Yavas A, Askan G, et al. *DNAJB1-PRKACA* fusions occur in oncocytic pancreatic and biliary neoplasms and are not specific for fibrolamellar hepatocellular carcinoma. Mod Pathol. 2020;33:648-656.
22. Simon SM. Fighting rare cancers: lessons from fibrolamellar hepatocellular carcinoma. Nat Rev Cancer. 2023; 23: 335-346.
23. Bauer J, Kohler N, Maringer Y, Bucher P, Bilich T, Zwick M, et al. The oncogenic fusion protein DNAJB1-PRKACA can be specifically targeted by peptide-based immunotherapy in fibrolamellar hepatocellular carcinoma. Nat Commun. 2022;13:6401.
24. Liu Y, Zhang J, Wang Z, Ma J, Wang K, Rao D, et al. Multi-omics characterization reveals the pathogenesis of liver focal nodular hyperplasia. iScience. 2022;25(9):104921.
25. Fujioka K. Trends in focal nodular hyperplasia of the liver along with oxaliplatin-induced this entity. J Carcinog Mutagen. 2023;14:1000414.
26. Lendvai G, Szekerczes T, Gyongyosi B, Schlachter K, Kontsek E, Pesti A, et al. MicroRNA expression in focal nodular hyperplasia in comparison with cirrhosis and hepatocellular carcinoma. Pathol Oncol Res. 2019;25(3):1103-1109.