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Review Article

Trends in Focal Nodular Hyperplasia of the Liver along with Oxaliplatin-Induced this Entity

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ABSTRACT

It is known that Focal Nodular Hyperplasia (FNH) of the liver is the second common benign liver tumor following hemangioma. Recently, it is Probable that the Senescence-Associated Secretory Phenotype (SASP) plays a crucial role for fibrosis, inflammation, and reduced apoptotic cell death, leading to the increased tissue volume observed in FNH. Regarding microRNAs (miRNA), the results provided that the decreased miR-18a, miR-195, and miR-210 expressions may differentiate FNH from cirrhosis suggesting the different pathogenesis of two entities. In this article, current knowledge and trends of FNH along with oxaliplatin-induced this entity have been reviewed in detail. Additionally, the author described previously treated two cases of FNH showing peculiar image features and clinical presentation. Results provided that unique endothelial cell expressed SOST of fibrous septa in FNH with no therapy contributes to promote the fibrosis process through Platelet-Derived Growth Factor β/ Platelet-Derived Growth Factor Receptor β (PDGFB/PDGFRB) pathway using the integrated analysis. Further investigations are needed to elucidate the unique natures, especially in endothelial cell of fibrous septa in FNH. As it is known that FNH lesions also develop after treatment using oxaliplatin in adult population, the accurate diagnosis in FNH using comprehensive image modalities such as MRI and Contrast-Enhanced Ultrasonography (CEUS), along with the consideration of the interval between the completion of oxaliplatin therapy and the detection of new lesion may avoid unnecessary surgery.

Keywords: FNH; Central stellate scar; Oxaliplatin-induced FNH; Sinusoidal obstruction syndrome; PDGFB/PDGFRB pathway.

INTRODUCTION

It is known that FNH of the liver is the second common benign liver tumor following hemangioma [1]. Pathologically FNH represents characteristic central stellate scar with radiating fibrous septa. Recently, it is suggested that the Senescence-Associated Secretory Phenotype (SASP) plays a crucial role for fibrosis, inflammation, and decreased apoptotic cell death, leading to the increased tissue mass and tumor-like feature of FNH [2]. Regarding microRNAs (miRNA), the results provided that the decreased miR-18a, miR-195, and miR-210 expressions may differentiate FNH from cirrhosis suggesting the different pathogenesis of two entities [3]. With respect to the multi-omics characterization, the results provided the confirmation of expressing of SOST in vascular endothelial cells of fibrous septa in FNH and PDGFRB fibroblasts were found proximal to PDGFB endothelial cells in FNH with no therapy [4]. Meanwhile, oxaliplatin-induced this entity has been reported [5-7]. In this article, current knowledge and trends of FNH along with oxaliplatin-induced FNH have been reviewed in detail. In addition, the author described the previously treated two cases of FNH showing unique image appearances and clinical manifestation [8-10].

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LITERATURE REVIEW

Unique nature in FNH

This entity is well demarcated lesion without capsule, showing lobulated, firm parenchyma, and characteristic central stellate scars on cut sections. Histological appearances look like a focal cirrhosis due to fibrous bands encompassing tissues of benign hepatocytes [1]. Previous report suggested that this disease is regarded as a hyperplastic, regenerative response to arterial hyperperfusion and shunting associated with anomalous arteries in the center [11]. Recent study indicated that proposed mechanism of FNH occurrence showed the local hyperoxygenation and oxidative stress leading to cellular senescence in hepatocytes and cholangiocytes. Furthermore it may be plausible that transdifferentiation of hepatocytes to cholangiocytes develops in combination with K7 expression and ductular metaplasia. The SASP may play a crucial role for fibrosis, inflammation, and reduced apoptotic cell death, leading to the increased tissue mass and tumor-like feature of FNH [2]. With respect to the microRNAs (miRNA), they are short regulating noncoding RNA molecules that negatively modulate gene expression at the posttranscriptional level [12]. Though this entity develops in non-cirrhotic liver, the pathological feature of FNH may look similar to a part of cirrhosis. The results provided that the decreased miR-18a, miR-195, and miR-210 expressions may differentiate FNH from cirrhosis suggesting the different pathogenesis of two entities [3]. Though previous studies have been investigated by single molecule such as overexpression of GLUL, the map-like distribution of glutamine synthetase, and the upregulation of angiopoietin-1 and CD34, the recent study recommended a data-driven analysis for the development and progression in FNH. Genetically, it is known that FNH had low mutation with low variant allele frequencies and recurrently genomic outcomes were not observed. Results provided the confirmation of expressing of SOST in vascular endothelial cells in fibrous septa of FNH by RNA in situ hybridization and PDGFRB fibroblasts were found proximal to PDGFB endothelial cells in FNH without chemotherapy, radiotherapy, interventional therapy, and drug therapy before surgery [4]. The study showed that most FNH shows benign behavior, however specific endothelial cell expressed SOST in FNH leads to promote the fibrosis process through PDGFB/PDGFRB pathway using the integrated analysis by whole exome sequencing, RNA-seq, and single cell RNA-seq data [4].

Oxaliplatin-induced FNH

It is known that chemotherapy-induced hepatopathies include steatosis, steatohepatitis, and Sinusoidal Obstruction Syndrome (SOS) [13]. Meanwhile, previous studies have reported benign regenerative nodules as pseudometastatc liver tumors as a late presentation of SOS in children with malignant tumors after high-dose chemotherapy or undergoing hematopoietic stem cell transplantation [14, 15]. Regarding the adult population, Furlan et al. have reported FNH after treatment with oxaliplatin, suggesting that the mean interval between the completion of oxaliplatin therapy and the detection of new FNH lesion at MRI image was 47.6 months [16]. Whereas they strengthened that the interval for occurrence of liver metastasis from colorectal cancer is much shorter [16]. Though the detection and growing of new lesions at follow-up study tend to raise the concern for new metastasis, they suggested that the recognition of the possible development of FNH along with the diagnosis of typical MRI features may contribute to decrease the risk of misdiagnosing as metastatic nodules. They concluded that FNH lesions develop after treatment using oxaliplatin in the adult population, suggesting that the identification of the possible FNH development and the typical features of this entity on MRI may avoid unnecessary surgery [16]. Generally, it is well-known that a vascular malformation and increased arterial hepatic inflow can contribute to the occurrence of FNH [17]. The use of oxaliplatin in patients with colorectal cancer has been associated with the occurrence of the vascular hepatic lesions such as SOS and FNH [17]. Previous literatures of the relationship between oxaliplatin chemotherapy and FNH development have been reported [5-7]. It is known that pathophysiology of SOS is induced by toxic injury to the endothelium of the liver sinusoids [18, 19]. Previous report described that chemotherapy contribute to cause loss of sinusoidal wall integrity with the extravasation of erythrocytes within the Disse space and endothelial cell exfoliation. In result, portal hypertension, liver dysfunction, and destruction of the liver parenchyma with nodular regeneration were observed [20]. Though the pathogenesis of development of FNH after oxaliplatin chemotherapy remains unknown, previous report described that the changes of SOS and related local disturbance in hepatic perfusion may cause the occurrence of nodular regenerative hyperplasia suggesting that this disturbance may also lead to the development of FNH [16]. In comparison to the short interval for occurrence of liver metastasis from colorectal cancer, as FNH may also develop in the condition of chemotherapy-induced SOS, it is plausible that the interval between the completion of oxaliplatin and detection of new lesions may be long.

Peculiar image appearances and clinical presentations in FNH from our experiences

The author previously has reported a case of FNH of the liver accompanied by a marginal hypoechoic zone in the US, based on the comparison of the US and pathological appearances presuming that the halo was caused by proliferative vessels surrounding the nodule [8]. The author also treated another case of FNH surrounded hemangioma like lesion, accompanied by leiomyosarcoma on the back of the left hand of a 21-year-old man [9, 10]. Interesting pathological features were observed, thereby presuming that this lesion was in an early stage of development [9, 10]. After receiving chemotherapy including CPA and VCR at the first therapy and CDDP and ADR at the second therapy, the hand lesion was resected and hepatic lesion was also removed later [9, 10]. This case is accompanied by leiomyosarcoma on the back of the left hand of a 21-year-okd man without colorectal cancer, showing that peripheral hypoechoic zone on US is strongly suggestive of metastasis from leiomyosarcoma. The interval between the completion of chemotherapy and the detection of new FNH occurrence was short in our case. Characteristics image appearances of FNH

have been provided including US, CT, MRI. The new modality by CEUS study using Sonazoid as the agent has showed that the central artery vascularity, stellate vascularity, and centrifugal enhancement pattern are typical appearances [21]. Regarding the occurrence of this entity after oxilaplatin, the ring enhancement pattern on hepatobiliary phase images was detected in five of 10 cases on enhanced MRI, thereby differential diagnosis between FNH and liver metastatic tumors is important for treatment strategy [16]. Meanwhile, Fibrolamellar Hepatocellular Carcinoma (FLHCC) is more frequent in non-cirrhotic young adult populations and surgically complete resection is regarded as one of the only curative methods [22]. This entity also showed a solitary, lobulated mas with characteristic central scar on US. The previous study suggested the promising role PET/CT in the differential diagnosis of hepatic tumor accompanied by central scar [23]. From our experiences, the author emphasizes that the accurate diagnosis of FNH using comprehensive modalities including US, CEUS, CT, MRI, and PET/CT is important, especially in patients after oxaliplatin treatment.

DISCUSSION

FNH shows pathologically characteristic central stellate scar with radiating fibrous septa. Recently it is suggested that the SASP plays a role for fibrosis, inflammation, and decreased apoptotic cell death, leading to the increased tissue volume in FNH. In addition, it is putative that the decreased miR-18a, miR-195, and miR-210 expression may differentiate FNH from cirrhosis suggesting the different pathogenesis of two entities. With respect to the fibrosis septa, results provided the confirmation of expressing of SOST of vascular endothelial cells of fibrous septa in FNH by RNA in situ hybridization and PDGFRB fibroblasts were found proximal to PDGFB endothelial cells in FNH with no therapy. Though the study showed that most FNH are benign behavior, specific endothelial cell expressed SOST in FNH leads to promote the fibrosis process through PDGFB/PDGFRB pathway using the integrated analysis by whole exome sequencing, RNA-seq, and single cell RNA-seq data. Peculiar nature in FNH was shown and further investigations are needed to elucidate this unique behavior, especially in endothelial cell of fibrous septa in FNH. Regarding oxaliplatin-induced FNH, the previous report suggested that the recognition of the possible development of FNH along with the diagnosis of typical MRI features may contribute to decrease the risk of misdiagnosing as metastatic nodules. Furlan et al. concluded that FNH lesions develop after treatment using oxaliplatin in adult population, suggesting that the knowledge of the typical MRI features of this entity may avoid unnecessary surgery [16]. In comparison to the short interval for occurrence of liver metastasis from colorectal cancer, as FNH may also develop in the condition of chemotherapy-induced SOS, it is plausible that the interval between the completion of oxaliplatin and detection of new lesions may be long. Based on the evidence, the consideration of the interval between the completion of oxaliplatin and detection of new FNH may avoid unnecessary surgery. From our experience, the author also emphasizes that the accurate diagnosis of FNH using comprehensive modalities including US, CEUS, CT, MRI, and PET/CT is important, especially in patients with receiving oxilaplatin treatment.

CONCLUSION

It is plausible that the specific endothelial cell expressed SOST of fibrous septa in FNH with no therapy contributes to promote the fibrosis process through PDGFB/PDGFRB pathway using the integrated analysis. Unique trends in FNH have been revealed and further researches are needed to elucidate the peculiar natures, especially in endothelial cell of fibrous septa in FNH.

As it is known that FNH lesions also develop after oxaliplatin treatment in adult population, the accurate diagnosis of FNH using comprehensive images features along with the consideration of the interval between the completion of oxaliplatin therapy and the detection of new lesion may avoid unnecessary surgery.

CONFLICT OF INTEREST

Author declares that I have no conflicts of interest.

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