



Focal Nodular Hyperplasia-Like Lesions after Chemotherapy with Oxaliplatin or Cyclophosphamide in Cancer Survivors: along with Differentiation from Liver Metastases

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ABSTRACT

Recently the development of Focal Nodular Hyperplasia (FNH)-like lesions after chemotherapy with oxaliplatin or cyclophosphamide in patients with cancers has emerged. Meanwhile, the role of gadoteric acid (Gd-EOB-DTPA) MRI in the differential diagnosis of chemotherapy-induced FNH-like lesions and liver metastases has been established. In this article, the current knowledge and trends of FNH-like lesions after chemotherapy with oxaliplatin or cyclophosphamide along with the differentiation from liver metastases using Gd-EOB-DTPA MRI in cancer survivors have been reviewed. Cyclophosphamide-based chemotherapy in patients with breast cancer should be regarded as a probable factor for the development of FNH-like lesions due to Sinusoidal Obstruction Syndrome (SOS) involvement. Based on the evidence, compared to oxaliplatin-based chemotherapy group, the shorter interval between the completion of chemotherapy and the development of FNH-like lesion may be suggested in the cyclophosphamide-based chemotherapy group. The characteristic appearance of FNH-like lesion may exhibit a ring hyperintense on Hepatobiliary Phase (HBP) of Gd-EOB-DTPA MRI in patients with oxaliplatin-based chemotherapy. FNH-like lesions may also tend to increase the nodules in size and number at late-term follow-up in patients with oxaliplatin-based chemotherapy. Many FNH-like nodules are diagnosed based on highly typical MRI features by Gd-EOB-DTPA MRI and exhibit varying changes during follow-up, therefore, diagnostic confirmation is extremely significant in differentiating from liver metastases in patients with oxaliplatin- or cyclophosphamide-based chemotherapy.

Keywords: Chemotherapy-induced FNH-like lesion; Oxaliplatin- or Cyclophosphamide-based chemotherapy; Colorectal cancer; Breast cancer; Pediatric cancer; Gd-EOB-DTPA MRI

INTRODUCTION

Focal Nodular Hyperplasia (FNH) arises in a normal liver, while FNH-like lesions are associated with liver abnormalities including hepatic inflow and outflow and hepatic microvascular disturbances such as cirrhosis, Nodular Regenerative Hyperplasia (NRH), and chemotherapy-induced Sinusoidal Obstruction Syndrome (SOS) by chemotherapeutic agents such as oxaliplatin and cyclophosphamide [1]. A case of FNH in the normal liver and a case of FNH after chemotherapy with cyclophosphamide have been previously reported [2-4]. Recently the development of

FNH after chemotherapy with oxaliplatin or cyclophosphamide in patients with cancers has emerged [5-8]. Meanwhile, the role of Gd-EOB-DTPA MRI in the differential diagnosis of chemotherapy-induced FNH-like lesions and liver metastases has been revealed [5-8]. In this review, the current knowledge and trends of FNH after chemotherapy with oxaliplatin or cyclophosphamide in cancer survivors have been summarized. Additionally, the author has described the characteristic features of chemotherapy-induced FNH-like lesions on Gd-EOB-DTPA MRI using Hepatocyte-Specific Contrast Agent (HSCA) in differentiating from liver metastasis.

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LITERATURE REVIEW

Comparison between FNH and FNH-like lesions

FNH is the second most common benign lesion that arises in a normal liver, meanwhile FNH-like lesions associated with liver abnormalities including hepatic inflow and outflow and hepatic microvascular disturbances are observed [1]. In addition, hepatic microvascular disturbances include cirrhosis, Nodular Regenerative Hyperplasia (NRH), and chemotherapy-induced SOS using oxaliplatin and cyclophosphamide agents [1]. A case of FNH of the liver accompanied by a marginal hypoechoic zone in the US in a normal liver has been previously described [2]. While a case of FNH accompanied by a hemangioma like lesion in the ultrasonogram with leiomyosarcoma on the left hand has been reported after chemotherapy including cyclophosphamide [3,4]. The patient was treated with chemotherapy including Cyclophosphamide (CPA) and Vincristine (VCR) as previously described [3,4]. From our experiences, the author emphasized that the accurate diagnosis of FNH using comprehensive modalities including US, CEUS, CT, MRI, and PET/CT is important [5]. Recently, several studies have demonstrated that Gd-EOB-DTPA enhanced MRI on Hepatobiliary (HB) phase are sensitive and specific for diagnosing accurate diagnosis of FNH-like lesion in patients with chemotherapy such as oxaliplatin or cyclophosphamide of chemotherapeutic agents [6-8].

Mechanism of the FNH-like lesion following cyclophosphamide-based chemotherapy

Chemotherapy can induce acute hepatocellular injury, steatosis and steatohepatitis, SOS, NRH, and FNH-like lesion [1]. The author described a thorough review of the literature on oxaliplatin-induced hepatic complications focusing on SOS, NRH, and FNH in patients with colorectal cancer and colorectal liver metastasis emphasizing the Liver Stiffness Measurement (LSM) as a novel predictor by elastography and updated biological pathway analysis in patients with SOS [9,10]. Recent report also described the mechanism of oxaliplatin-induced SOS along with therapeutic strategy describing that oxaliplatin causes increased porosity of the sinusoidal endothelium, increased cellular fenestrations, stimulated release of free radical and depletion of glutathione transferase, and increased MMP 2-9 [11]. The previous report described that the changes of SOS and related local disturbance in hepatic perfusion may cause the occurrence of NRH suggesting that this disturbance may also lead to the development of FNH [5,6,9]. To decrease the tumor size, neoadjuvant chemotherapy has been increased, leading to radical or conservative surgical therapeutics in breast cancer. The combination of cyclophosphamide, anthracycline, and taxane is the most common neoadjuvant chemotherapeutic strategy [12]. Cyclophosphamide, alkylating agent, has been reported to induce SOS in a synergistic effect with total body irradiation suggesting that the potent mechanism might be depletion of decreased glutathione in sinusoidal endothelial cells as previously reported [12,13]. The underlying mechanism by cyclophosphamide has been suggested that depletion of decreased glutathione in liver sinusoidal endothelial cells may be related to the development of FNH-like

lesion due to the SOS [12,13]. While previous study suggested that the depletion of decreased glutathione in hepatic sinusoidal endothelial cells may be related to the development of FNH in patients administered with alkylating agent chemotherapy such as cyclophosphamide [8,13]. Based on the evidence, it is plausible that in addition to the use of oxaliplatin-based chemotherapy in patients with colorectal cancer, cyclophosphamide-based agents in patients with breast cancer should be regarded as a probable factor for the development of FNH-like lesions due to SOS involvement.

Correlation between OATP8 expression and signal intensity on HBP

The previous study indicated that immunohistochemical expression showed Organic Anion Transporting Peptidase (OATP) 8 in the hepatocytes in the peripheral areas of the nodule [14]. Gadoxetic acid (Gd-EOB-DTPA), HSCA can estimate not only the vascularity but also the function of hepatocyte [15]. The study provided that an association between signal intensity on Hepatobiliary Phase (HBP) by Gd-EOB-DTPA and OATP8 expression [15]. OATP1B3 is strongly expressed in the peripheral hepatocytes of FNH while negative or weak expression has been exhibited in the central scar suggesting that these findings lead to the concept of ring-like enhancement on HBP [7,15]. Regarding pediatric cancer patients, the most common HBP enhancement pattern was homogeneous hyperintense/isointense, followed by ring-like enhancement, and heterogeneous hypointense. It has been suggested that FNH-like nodules in pediatric cancer survivors exhibit several temporal changes in the size and number during follow-up [7]. While another study showed the central scar in 12.5% of the patients, the ring enhancement pattern probably reflecting OATP8 in 37.5% of the patients on Hepatobiliary (HB) Phase, and the increased size and number at follow-up [16].

FNH-like lesions after treatment protocols including cyclophosphamide in pediatric cancer survivors

Previous studies described that hepatic FNH can develop in pediatric cancer survivors following chemotherapy or hematopoietic stem cell transplantation [8,16]. Due to the liver development in childhood, chemotherapy may more likely damage normal liver formation leading to occurrence of FNH [8,17]. It is known that vascular injury with the resultant thrombosis and recanalization of vessels leads to the development of FNH-like lesions in pediatric cancer survivors. Treatment history of chemotherapy, either for therapy of primary tumors or for myeloablation has been regarded as a possible risk factor. In addition, radiotherapy has also been considered a risk factor for the development of FNH-like lesions in pediatric patients [7]. Meanwhile, the previous study demonstrated that neuroblastoma was the most common diagnosis, describing that the treatment protocols composed of vincristine, cisplatin, and cyclophosphamide were used [16]. The patient with ganglioneuroma was also treated with chemotherapy including cyclophosphamide agent [16,18]. Meanwhile, the use of Gd-EOB-DTPA for pediatric patients has been approved by US Food and Drug Administration (FDA)

from 2015 [7]. Ozcan, et al. studied liver Gd-EOB-DTPA MRI using a HSCA in cancer survivors describing hyperintensity or isointensity on HBP for the diagnosis of FNH-like lesions and increased size and number of the lesions at follow-up [16]. The studies indicated that in comparison with FNH in general pediatric population, FNH-like nodules in pediatric patients treated with chemotherapy have characteristic features of multiplicity, small size, and lack of a central scar [7,19]. FNH-like lesions with a central scar have been shown in 943% of pediatric cancer survivors on MRI [19,20]. The recent study described that FNH in pediatric patients with malignancy receiving therapy showed a smaller size compared to those without malignancy [21]. Gu, et al. described the presence of low central scar due to the smaller size of the nodule. Three different HBP enhancement patterns have been reported showing that the most common was homogeneous hyperintense/isointense, followed by ring-like enhancement, and heterogeneous hyperintense. They also indicated that MRI features exhibited different temporal alterations in the size and number of the lesions during follow-up [7].

FNH-like lesions after cyclophosphamide-based chemotherapy in patients with breast cancer

Previous studies have described oxaliplatin-related SOS, NRH, and FNH in patients with colorectal cancer and colorectal liver metastasis. Meanwhile, a case of FNH diagnosed by typical CT and MRI features after cyclophosphamide-based chemotherapy has been reported in a patient with breast cancer [12]. Recently, Yang, et al. have investigated case series of FNH during follow-up of patients including 18 patients with breast cancer treated by cyclophosphamide-based chemotherapy and 17 patients with colorectal cancer administered with oxaliplatin-based chemotherapy [8]. They studied a series of FNH diagnosed by either pathology or typical MRI features and follow-up [8]. While ring hyperintensity on HB images was defined as a ring of high signal surrounding a central area of relatively low or isointense signal in comparison with the surrounding normal liver tissues reflecting OATP8 expression as previously mentioned [8]. Previous study suggested that the special expression pattern of OATP8 may be the pathological mechanism underlying the ring hyperintensity on HBP [8,14]. Yang, et al. demonstrated multiple nodules, the presence of low central scar, small size of the nodule, and a ring hyper-intense in 57.6% of all target lesions on HBP [8]. In cyclophosphamide-based chemotherapy group, the increased size of the nodule was shown in six out of nine patients. In comparison with oxaliplatin-based chemotherapy group, younger population, a greater proportion of female, and a shorter time of the detection of FNH have been significantly shown in cyclophosphamide-based group. The author previously treated a case of FNH accompanied by hemangioma like lesion with leiomyosarcoma after treatment including cyclophosphamide on the back of the left hand of a 21-year-old man suggesting that pathological features showed an early stage of FNH development [3, 4]. The patient was treated with chemotherapy including Cyclophosphamide (CPA) and Vincristine (VCR) and later received chemotherapy with Cisplatin (CDDP) and Adriamycin (ADR). Meanwhile diagnostic confirmation was pathologically made as FNH, 15 mm in diameter.

The characteristics features included the peripheral hypoechoic zone at the US, small size and lack of a central scar, and shorter interval for discovery of FNH in our case [3,4]. The peripheral hypoechoic zone (halo) at the US was strongly suggestive of metastasis from leiomyosarcoma. The pathological features of early stage of FNH and the short interval between the completion of chemotherapy and the detection of new FNH occurrence might be in part attributed to use of the cyclophosphamide chemotherapeutic agent.

Differential diagnosis between FNH-like lesions and liver metastasis on Gd-EOB-DTPA enhanced MRI

Regarding Gd-EOB-DTPA MRI features, Suh, et al. by using a meta-analysis also demonstrated that iso- or hyperintensity on HBP of Gd-EOB-DTPA MRI was a characteristic finding of FNH having a pooled sensitivity of 94% and a pooled specificity of 95% respectively [22]. The signal intensity on HBP using Gd-EOB-DTPA is associated with the expression of Organic Anion-Transporting Polypeptide 1B3 (OATP1B3), a hepatocyte uptake transporter. It is known that FNH exhibited ring-like enhancement on HBP in 941% of the general adult population [7,23]. The smaller size of the nodules tended to be related to ring-like enhancement, speculating to reflect the grade of OATP1B3 expression [7,23]. Meanwhile, the previous study revealed that peripheral ring-like enhancement with hypointense or hyperintense central core was highly specific for accurate diagnosis of FNH [24]. Furlan et al. described that the ring enhancement pattern on HBP images was detected in 5 of 10 cases on enhanced MRI, thereby this finding is important for differentiating between FNH and liver metastatic tumors [5,6]. In contrast, metastatic lesions showed hypointense on HBP without contrast materials [6]. Meanwhile, the reticular hypointensity of HBP on Gd-EOB-DTPA enhanced MRI is a characteristic feature for the diagnosing SOS in patients administered with oxaliplatin-based chemotherapy [9,25]. With regards to the detection of tiny metastatic live tumors measuring less than 1 cm, Gd-EOB-DTPA-enhanced MRI test may be a single modality achieving a diagnostic level [26]. Previous study showed that all liver metastases were hypointense on HBP [27]. Hyperintensity on DWI, hypo-vascular with irregular rim enhancement on post-contrast images, and hypointensity on HBP were regarded as typical imaging appearances of liver metastases [28]. Metastatic liver tumors treated with oxaliplatin regimens are usually hypoenhancing at MRI, while typical FNH-like features exhibit Arterial Phase Hyperenhancement (APHE) and hyperintense or isointense uptake of HSCA during the HBP indicating that HSCA-enhanced MRI is reliable for differentiating between liver metastasis and FNH-like lesions [1]. Additionally, previous study also suggested that the normal level of CEA is important for the diagnosis of FNH-like lesions [27].

FNH-like lesions after oxaliplatin-based chemotherapy in patients with CRC

The lesion growth or new lesion was shown in 75% of patients and the mean interval from cessation of therapy and development of the FNH-like lesion was 47.6 months at follow-

up in patients treated with oxaliplatin as previously reported [6]. Whereas the time interval for liver metastasis from colorectal cancer is much shorter [5,6]. Yang, et al. showed ring hyperintense on HBP in 57% of patients and increased size of the nodule in five out of seven patients in oxaliplatin-based chemotherapy group [8]. Recently, Chen, et al. studied the Gd-enhanced MRI features and follow-up of FNH-like lesions after oxaliplatin-based chemotherapy in patients with CRC describing ring-like enhancement in 73% on HBP and 31 months for mean interval between the completions of chemotherapy and detection of FNH [27]. They showed that the FNH-like lesions exhibited three enhancement patterns on HBP and at follow-up varying status of nodules including stability, growth, reduction, and disappearance in size and number [27]. While Wang, et al. also demonstrated that a ring enhancement on HBP was detected in 56% of nodules and median 34 months for detection of FNH-like lesion during late-term follow-up in patients with almost gastrointestinal cancers [28]. Changes at follow-up showed that early-term focal observations tended to resolve due to chemotherapy-induced hepatopathy, while FNH-like lesions exhibited the increased nodules in size and number at late-term follow-ups [28]. Based on Gd-enhanced MRI features and temporal alterations, chemotherapy-related hepatic observations can be differentiated from liver metastases [28]. According to the published studies, many FNH-like nodules were not confirmed pathologically but were diagnosed based on highly typical MRI features and follow-up suggesting that diagnostic confirmation by Gd-enhanced MRI were extremely significant in differentiating from liver metastases in patients with CRC using oxaliplatin-based chemotherapy. Further it may be a potential procedure in patients with breast cancer using cyclophosphamide-based chemotherapy.

DISCUSSION

Previous studies described that hepatic FNH can develop in pediatric cancer survivors after chemotherapy or hematopoietic stem cell transplantation [8,16]. Based on the evidence, chemotherapy-induced FNH-like lesion in pediatric cancer survivors may exhibit the characteristic findings of small size, lack of a central scar, and multiplicity of the nodules in comparison with FNH features in general pediatric population [7,19]. Recent report described the mechanism of oxaliplatin-induced SOS along with therapeutic strategy [11]. The previous report described that the changes of SOS and related local disturbance in hepatic perfusion may cause the occurrence of NRH suggesting that this disturbance may also lead to the development of FNH [5,6,9]. Cyclophosphamide has been reported to induce SOS in a synergistic effect with total body irradiation suggesting that the potential mechanism might be depletion of decreased glutathione in sinusoidal endothelial cells [12,13]. Based on the evidence, it is plausible that in addition to the use of oxaliplatin-based chemotherapy in patients with Colorectal Cancer (CRC), cyclophosphamide-based chemotherapy in patients with breast cancer should be regarded as a probable factor for the development of FNH-like

lesions due to SOS involvement. Compared to the oxaliplatin-based chemotherapy group, younger population, a greater proportion of female, and a shorter time of the detection of new FNH have been significantly shown in cyclophosphamide-based chemotherapy group [8]. In our case, the pathological features of early stage of FNH and the short interval between the completion of chemotherapy and the development of FNH-like lesions may be in part attributed to the use of cyclophosphamide agent [3,4]. It is putative that the cyclophosphamide-based chemotherapy group may show a shorter time than the oxaliplatin-based chemotherapy group [28]. A ring hyperintense on HBP at Gd-EOB-DTPA MRI reflecting OATP8 expression has been demonstrated, indicating the potential feature of FNH-like lesion in differentiating from metastatic liver tumors in patients with oxaliplatin-based chemotherapy. FNH-like lesions may also tend to increase the nodules in size and number at late-term follow-up in patients with CRC and almost gastrointestinal cancer treated with oxaliplatin chemotherapy. According to the published studies, many FNH-like nodules were diagnosed based on highly typical MRI features and follow-up suggesting that diagnostic confirmation by Gd-EOB-DTPA MRI were extremely significant in differentiating from liver metastases in patients with oxaliplatin chemotherapy. Further it may be a potential procedure for diagnostic value in patients with breast cancer with cyclophosphamide-based chemotherapy.

CONCLUSION

Chemotherapy-induced FNH-like lesion in pediatric cancer survivors may exhibit the characteristic findings of small size, lack of a central scar, and multiplicity of the nodules. Cyclophosphamide-based chemotherapy in patients with breast cancer should be regarded as a probable factor for the development of FNH-like lesions due to SOS involvement. Based on the evidence, it is plausible that the cyclophosphamide-based chemotherapy group may show a shorter time between the completion of chemotherapy and the development of FNH-like lesion than the oxaliplatin-based chemotherapy group. The characteristic appearance of FNH-like lesions in differentiating from liver metastasis may exhibit a ring hyperintense on HBP at Gd-EOB-DTPA MRI and FNH-like lesions may also tend to increase the nodules in size and number at late-term follow-up in patients with oxaliplatin-based chemotherapy. The most of FNH-like nodules are diagnosed based on highly typical MRI features by Gd-EOB-DTPA MRI and exhibit varying changes during follow-up, therefore, diagnostic confirmation is extremely significant in differentiating from liver metastases in patients with oxaliplatin- or cyclophosphamide-based chemotherapy.

CONFLICT OF INTEREST

Author declares that I have no conflicts of interest.

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None

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