Focal nodular hyperplasia after systemic chemotherapy: Pathological features of a series of 15 cases

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Abstract

Introduction: Chemotherapy, particularly oxaliplatin, has been associated with the development of focal nodular hyperplasia (FNH). Imaging diagnosis of FNH is well standardized, but it can be misdiagnosed as liver metastasis. The aim of this study was to describe the pathological features of FNH occurring after systemic chemotherapy.

Materials and methods: From our pathological files for 1990-2021, we retrieved 15 cases of resected newly developed FNH in adults with liver metastasis treated with systemic chemotherapy. Pathological features of FNH nodules and non-tumoral liver samples were reviewed.

Results: In 11/15 (73%) cases, FNH developed after an oxaliplatin-based regimen. The median interval from the beginning of chemotherapy to the FNH diagnosis was 15 months. FNH was unique in 11 (73%) cases, and the median size of nodules was 1.1 cm [range 0.5-2.5]. Histologically, 9 (60%), 11 (73%) and 11 (73%) cases exhibited fibrous central scar, dystrophic vessels and ductular proliferation, respectively, with all three criteria present in five (33%) cases. Eight (53%) cases showed intralesional steatosis and nine (60%) cases showed a glutamine synthetase immunostaining map-like pattern. In non-tumoral liver, eight (53%) cases exhibited sinusoidal obstruction syndrome and four (27%) nodular regenerative hyperplasia.

Conclusion: The occurrence of FNH after systemic chemotherapy is an emerging condition challenging the imaging diagnosis because typical morphological features are frequently missing. The presence of sinusoidal changes, including regenerative hyperplasia, in non-tumoral liver supports the potential role of chemotherapy in the pathogenesis of FNH.

KEYWORDS

chemotherapy, focal nodular hyperplasia, liver metastasis, oxaliplatin, sinusoidal obstruction syndrome

Abbreviations: FNH, focal nodular hyperplasia; GS, glutamine synthetase; HES, haematoxylin eosin and safran; MRI, magnetic resonance imaging; NRH, nodular regenerative hyperplasia; SOS, sinusoidal obstruction syndrome.
Focal nodular hyperplasia (FNH) is thought to be a hyperplastic response to a local-
ized vascular abnormality. Its pathogenesis implies dysregulated expression of angiopoietin 1 and 2, leading to the development of dysplastic vessels, seen in typical FNH. This local increased blood flow hyperperfuses the parenchyma, leading to focal hyperplasia.

In most cases, the diagnosis of FNH is incidental on imaging. On magnetic resonance imaging (MRI), FNH is a non-encapsulated, homogeneous nodule. The central scar present in two-thirds of cases is typically more intense on T1-weighted imaging and shows delayed enhancement. Because FNH presents a typical imaging appearance, liver biopsy is not required in most cases. If performed, biopsy of the presumed FNH has excellent diagnostic performance in typical cases. However, in atypical cases (lacking the central scar and some histopathological criteria), the diagnosis of FNH could be challenging, not only on imaging but also on biopsy. Because FNH cases are usually asymptomatic, with few complications, neither surgical resection nor follow-up is required. Therefore, an accurate diagnosis of FNH is mandatory.

FNH developing after systemic chemotherapy was first reported in children with malignant tumours treated with high-dose chemotherapy or undergoing chemotherapy before haematopoietic stem cell transplantation as well as more recently in adults with colorectal cancer after an oxaliplatin-based regimen. Observations are increasing of chemotherapeutic damage to the non-tumoral liver, particularly associated with oxaliplatin treatment, the main drug in colorectal cancer chemotherapeutic protocols. Reported liver injuries induced by oxaliplatin include sinusoidal obstruction syndrome (SOS) and nodular regenerative hyperplasia (NRH). In a few cases, such vascular changes can be so severe as to induce liver failure and increase morbidity after hepatectomy. SOS and NRH observed in patients receiving oxaliplatin may be because of a toxic effect of the drug on sinusoidal endothelial cells leading to disrupted sinusoidal wall integrity. Oxaliplatin-induced vascular liver injury is well described, but the association with FNH has been reported in only a limited number of cases including case reports (3 cases) and a series of 14 cases diagnosed by MRI.

The aim of the study was to report a series of surgically resected FNH cases occurring de novo after chemotherapy for liver metastasis and to describe their pathological features.
Breast adenocarcinomas not otherwise specified in two (13%) cases, and pancreatic mixed neuroendocrine non-neuroendocrine tumour in one (7%) case. All patients received adjuvant chemotherapy, and four received neoadjuvant chemotherapy. For 11 (73%) patients, chemotherapy was oxaliplatin-based for a median of 11.5 cycles (range 4-12). For the other patients, chemotherapy was 5-fluoracil for 3 (20%) patients and gemcitabine with trastuzumab for 1 (7%) patient. The median time from the beginning of chemotherapy to FNH pathological diagnosis was 15 months (range 3-61).

### 3.2 | Pathological features of FNH

Macroscopically, FNH was unique in 11 (73%) cases. Two FNH nodules were described in three (27%) cases. The median FNH size was 1.1 cm (range 0.5-2.5). Histology findings of FNH are summarized in Table 3. Nine (60%) cases exhibited a central fibrous scar. The FNH size with and without a central fibrous scar was similar (1.2 and 1.1 cm). Overall, 73% (n = 11) and 73% (n = 11) of cases exhibited ductular proliferation and dystrophic vessels respectively. Only five (33%) cases showed the three features simultaneously. Eleven (73%) cases exhibited lymphocytic infiltrates. Eight (53%) cases featured steatosis, with mild intensity (<33%) in five (33%) cases, moderate intensity (33%-66%) in two (13%) cases and severe intensity (>66%) in one (7%) case (Figure 1). For the eight steatotic FNH cases, three (38%) patients were overweight, one (13%) had a metabolic syndrome and one (13%) had high blood pressure.

In 60% (9/15) of cases, the GS immunostaining had the typical map-like expression pattern. Three (20%) cases showed a heterogeneous pattern, two (13%) cases moderate diffuse staining and one (7%) case no staining. In these cases, lesional hepatocytes exhibited neither SAA nor aberrant nuclear expression of β-catenin.

### 3.3 | Histological features in non-tumoral liver parenchyma

Thirteen (87%) cases exhibited liver parenchymal lesions (Figure 2). Eight (53%) cases exhibited SOS, which was more frequent with than with oxaliplatin-based chemotherapy [7/11 (63%) vs 1/4 (25%) cases]. After chemotherapy with oxaliplatin, marked sinusoidal dilatation was observed in two (13%) cases and NRH in four (27%) cases. Five (33%) cases exhibited steatosis, and in all of these cases, steatosis was also present in FNH. Among these five cases, two patients were overweight, one had high blood pressure and one had metabolic syndrome. No steato-hepatitis features were present. Seven (47%) cases exhibited parenchymal atrophy. The fibrosis stage was F0 in six (40%) cases, F1 in four (27%) cases, F2 in four (27%) cases and F3 in one (7%) case.

### 4 | DISCUSSION

We report 15 cases of FNH occurring after chemotherapy, 11 of these after oxaliplatin-based chemotherapy. To our knowledge,
TABLE 3 Pathological features of focal nodular hyperplasia cases after treatment with oxaliplatin (n = 15)

| Pathological features                      | Cases |
|--------------------------------------------|-------|
| Central fibrous scar                       | 9 (60%)|
| Central fibrous scar, size                 |       |
| Small                                       | 6 (40%)|
| Medium                                      | 2 (13%)|
| Large                                       | 1 (7%) |
| Dystrophic vessels                         | 11 (73%)|
| Ductular proliferation                      | 11 (73%)|
| Ductular proliferation, intensity          |       |
| Mild                                        | 8 (53%)|
| Moderate                                    | 3 (20%)|
| Marked                                      | 0 (0%) |
| Lymphocytic inflammation                   | 10 (71%)|
| Inflammation, intensity                    |       |
| Mild                                        | 7 (47%)|
| Moderate                                    | 4 (27%)|
| Marked                                      | 0 (0%) |
| Steatosis                                   | 8 (53%)|
| Steatosis, intensity                       |       |
| ≤33%                                        | 5 (33%)|
| 33%-66%                                     | 2 (13%)|
| >66%                                        | 1 (7%) |
| Glutamine synthase immunostaining pattern  |       |
| Geographical map-like pattern               | 9 (60%)|
| Other patterns                              | 6 (40%)|

This is the largest series focusing on pathological features of post-chemotherapy FNH. Indeed, in the Furlan et al series of 14 cases diagnosed on MRI, histological confirmation was available for seven cases. Three other cases were reported by Donadon et al and Jain et al. Despite the high accuracy of imaging in the diagnosis of FNH, some of these cases were misdiagnosed as colorectal cancer metastasis. Considering a mortality rate of liver resection of approximately 3% and a high rate of postoperative complications in the setting of preoperative chemotherapy, the diagnosis of FNH is important because FNH is a benign, polyclonal lesion that does not require surgical resection or follow-up.

In accordance with previous studies, the FNH lesions were small, with the median size of 1 cm. This is important because small FNH lesions are difficult to diagnose on imaging in that they usually do not display the cardinal features of FNH, especially the central scar, which may be absent in 65% to 88% of cases. In our study, a central scar was identified on microscopy in 60% of cases, not associated with FNH size. Only 33% (n = 5) of FNH lesions simultaneously showed a central scar, ductular proliferation and dystrophic vessels. Moreover, only 60% of cases exhibited a GS geographical-like expression pattern. In some cases, atypical FNH may be misdiagnosed as hepatocellular adenoma, especially the inflammatory subtype. Of note, in this series, all FNH cases with an atypical GS expression pattern were negative for inflammatory markers, including SAA. Overall, these atypical FNH lesions were morphologically very close to the FNH-like nodules reported in vascular liver diseases, which also may display an atypical GS expression pattern.

Another relevant finding is the high rate of intralobular steatosis (53%) in this context, which was frequently associated with steatosis in background liver (62%) and with at least one risk factor for metabolic syndrome. Indeed, in the literature, the rate of intralobular steatosis varies greatly (16.7%-52%). Ronot et al reported that steatotic FNH lesions are frequently atypical on MRI. Oxaliplatin is known to induce chemotherapy-associated liver injuries, particularly SOS lesions. Several histological lesions related to the use of oxaliplatin, from SOS to NRH, have been described. Eleven of our cases received an oxaliplatin-based chemotherapy, with a mean of 11 cycles, and half exhibited SOS lesions. These results were consistent with data reported by Rubbia-Brandt et al: 51% (44/87) of post-chemotherapy liver resections showed sinusoidal dilatation and these lesions were significantly associated with oxaliplatin-based chemotherapy. Among our patients, two received 5-fluoracil without oxaliplatin and one had SOS lesions. The induction of SOS lesions by 5-fluoracil has been reported. Moreover, FNH has been also reported in children after high-dose chemotherapy for cancer or haematopoietic stem cell transplantation. In these studies, the variety of cancers affecting patients is wide, and the occurrence of FNH is more likely linked to the nature of treatment received rather than the type of cancer.

Otherwise, the prime cause of FNH is thought to result from hyperarterialization as a result of portal vein injury, which leads to arterial proliferation and arteriovenous shunts. An association between FNH and the presence of SOS may lead to the development, in some cases, of NRH. The high rate of parenchymal lesions we observed, including SOS and NRH, could support this hypothesis, even though a control series is needed to confirm it.

The main limitations of our series include the monocentric retrospective study, which prevented us from reviewing imaging data in all cases and then performing a radiopathological correlation.

In conclusion, our series highlights that FNH occurring during the follow-up of patients after systemic chemotherapy (mostly based on oxaliplatin) is atypical on morphology and develops on a damaged background liver with SOS and NRH. Considering the wide use of oxaliplatin for colorectal carcinoma, a potential diagnosis of FNH should be systematically discussed in the follow-up of patients and not be misinterpreted as metastasis.

CONFLICT OF INTERESTS
The authors do not have any disclosures to report.
FIGURE 1  Histological features of focal nodular hyperplasia (FNH) occurring de novo after chemotherapy. A, At low magnification, FNH appears as non-encapsulated, multinodular with hyperplastic nodules separated by fibrous septa radiating from the central scar. B, Glutamine synthetase immunostaining showing a typical map-like pattern. C, The central scar contains numerous vessels, some thick wall arteries. D, Focal areas of steatosis are observed at high magnification.

FIGURE 2  Histological features of non-tumoral liver lesions observed in cases of focal nodular hyperplasia occurring de novo after chemotherapy. A, Haematoxylin eosin and safran HES and (B) (reticulin staining): nodular regenerative hyperplasia pattern of the liver parenchyma: small nodules of normal or hyperplastic plates of maximum two-cell-thick hepatocytes adjacent to strands of atrophic, compressed trabeculae. C, Sinusoidal obstruction syndrome (SOS) lesions with sinusoidal dilatation and subintimal haemorrhage of small hepatic venule. D, Moderate steatosis.

AUTHOR CONTRIBUTIONS
Study concept and design (A. Be., VP), acquisition of data (A. Be., A. Br); analysis and interpretation of data (A. Be., A. Br, VP); drafting of the manuscript (A. Be., A. Br, VP); study supervision (VP).

PATIENT CONSENT STATEMENT
Written consent was obtained for all patients. Permission to reproduce material from other sources.

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