Case Report

Histological Changes in Hepatocellular Carcinoma Post-locoregional Therapy

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Abstract

Locoregional therapies are widely practiced in treatment of primary hepatocellular carcinoma and metastatic carcinoma to the liver as they provide a more targeted treatment with lesser side effects. Transarterial chemo-embolisation and selective internal radiotherapy (SIRT) are a few examples. However, histopathological findings after locoregional therapy of hepatocellular carcinoma are rarely reported. We reported a case of a 61-year-old man with underlying Hepatitis B and subsequent hepatocellular carcinoma who was treated with SIRT followed by wedge liver resection. Macroscopically, the specimen showed a well-defined mass with areas of fibrosis and haemorrhage. Microscopic examination showed 70% tumour necrosis with numerous microspheres surrounded by multinucleated giant cells with histiocytes and chronic inflammatory cells. Currently, the patient is well with regular follow-up. The latest ultrasound findings showed no residual liver lesion in the background of liver cirrhosis. Although assessment of treatment response following locoregional therapy based on histopathological findings are not widely practiced, recognising histopathological changes such as tumour necrosis, provide valuable insight to a patient's prognosis. Minimal to absent tumour necrosis implies poor response, limiting further locoregional therapy option. Findings of numerous microspheres might pose a diagnostic challenge as they mimic fungal organisms. Hence, histological examination with aid of special stains like periodic acid Schiff (PAS) and Grocott's methenamine silver stain may be useful.

Keywords: Hepatocellular carcinoma; histopathological changes; locoregional therapy; microspheres; selective internal radiotherapy

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Introduction

Liver cancer or hepatocellular carcinoma is the fourth leading cause of cancer related death worldwide, with an estimation of 810,000 liver cancer-related deaths per year (1). Major risk factors for developing hepatocellular carcinoma (HCC) are hepatitis B infection followed by alcohol and Hepatitis C infection (1). According to European Society of Medical Oncology (ESMO) clinical practice guidelines of hepatocellular carcinoma, the treatment approach of hepatocellular carcinoma is based on Barcelona Clinic Liver Cancer (BCLC) staging, where the treatment choice depends on multiple variables such as tumour burden, liver function and patient's performance status (2). The treatment modalities includes resection, transplantation, locoregional therapy and systemic therapy.

Locoregional therapies are defined as minimally invasive image-guided liver tumour-directed procedures (3). The aim of locoregional therapy is to induce tumour necrosis by manipulating the formation of new blood vessels by tumour. Examples of locoregional are ablation therapy, transarterial chemo-embolisation (TACE) and selective internal radiotherapy (SIRT). There is parenchymal arterialisation, sinusoidal capillarisation and development of unpaired arteries during carcinogenesis of hepatocellular carcinoma. The objective of TACE, for example is to selectively deprive blood supply to the tumour, resulting in

ischemic necrosis (3). It is important to recognise the histological changes due to locoregional therapy, as part of treatment response assessment, as it will determine patient's prognosis. A study by Beal et al. (4) stated that patients who achieve transplant after locoregional therapies have excellent outcomes with good overall and recurrence-free survival, and well tolerated without high risk of morbidity. The aim of this article is to highlight the histological changes following locoregional therapy in hepatocellular carcinoma.

Case Report

A 61-year-old man with underlying Hepatitis B was diagnosed with HCC in mid-2021 at a private medical institution. Initial CT scan showed multinodular liver lesion at Segment VIII (8.2x6.3x7.8 cm), segment V (1.2 x1.4 cm) and segment VII (0.6x 0.5 cm). Patient was then referred to Gastroenterology team at our institution for further management. He was started on SIRT and TACE in August and December 2021 respectively. Reassessment CT scan showed smaller segment VIII (5.5x4.2x5.1 cm) liver lesion whilst segment V and VII lesions remained the same. Subsequently, wedge resection of segment VIII and cholecystectomy was sent for histological evaluation.

Macroscopically, the resection specimen showed a well-defined mass measuring 48 x 25 x 75mm. The mass exhibited tan to yellowish nodular surface with areas of fibrosis and hemorrhage. Microscopy showed mainly necrosis in 70% of tumour bed with remaining 30% viable tumour cells (Fig. 1A). The tumour were arranged in solid, trabeculae and pseudoglandular pattern in background. The tumour cells were polygonal in shape, enlarged in sized with moderate to marked nuclear pleomorphism, vesicular nuclei with single prominent nucleoli and eosinophilic cytoplasm (Fig. 1B). Numerous scattered round, purple microspheres were present, predominantly within and at the periphery of the tumour. Some of the microspheres were surrounded by multinucleated giant cells with histiocytes and chronic inflammatory cells (Fig. 1C). The microspheres were highlighted by periodic acid Schiff (PAS) stain (Fig. 1D) but not highlighted by Grocott-Gomori methenamine silver (GMS) stain (Fig. 1E). Both PAS and GMS were negative for fungal bodies. The patient is currently on regular gastroenterology clinic follow-up. His ultrasound 17 months post resection showed no recurrence or residual HCC in the background of liver cirrhosis.

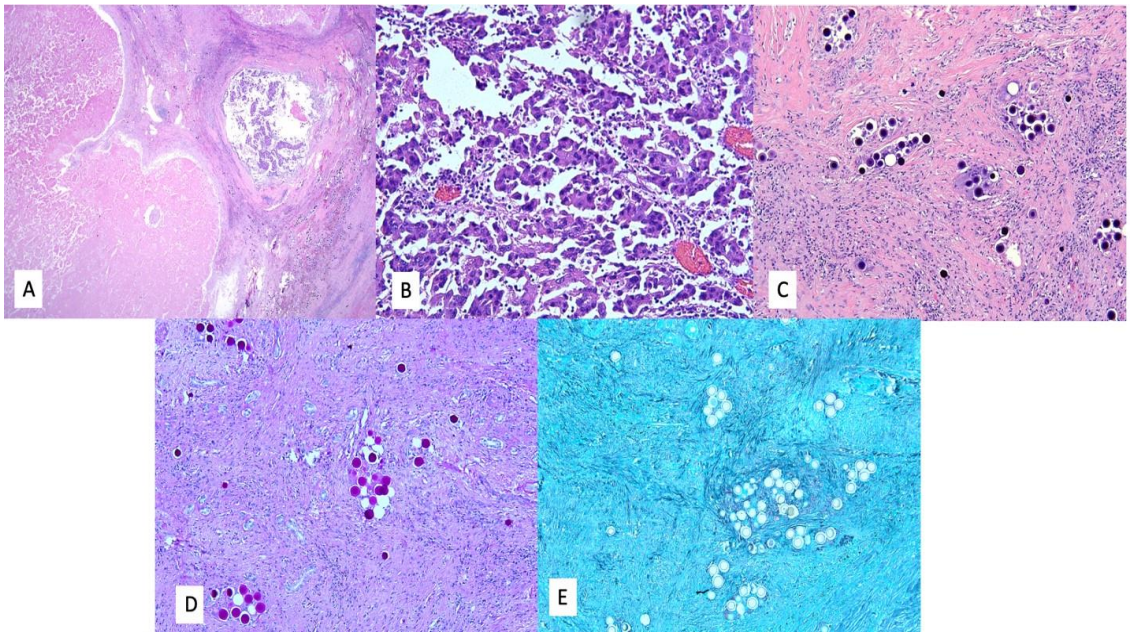

FIGURE 1: (A) Microscopic image from the tumour bed showing mainly necrosis (left side) with occasional cluster of viable tumour cells (right side) (H&E, 4x); (B) The tumour cells were polygonal in shaped with moderate to marked nuclear pleomorphism arranged in solid, trabeculae and pseudoglandular pattern (H&E, 40x); (C) Scattered microspheres noted, some were surrounded by histiocytes and multinucleated giant cells (H&E, 10x); (D) The microspheres were highlighted by periodic acid Schiff (PAS) stain (PAS, 10x); (E) Microspheres were not highlighted by Grocott-Gomori methenamine silver (GMS) stain (GMS, 10x). Both PAS and GMS were negative for fungal bodies

Liver transplantation and surgical resection are the only curative treatments for hepatocellular carcinoma, as it is not only removing the tumour but cures the underlying liver disease. However, these two treatments are limited by organ shortage.

Over the years, several hepatocellular carcinoma classification systems have been developed. For example, Okuda system, Cancer of the Liver Italian cancer score, Hong Kong Liver Cancer staging system and the BCLC classification system. These classifications were developed to stratify hepatocellular carcinoma patients based on disease extension, liver function and performance status, which later help to guide in the therapeutic modalities (3). Based on BCLC classification system, the treatment modalities includes liver resection and transplantation, locoregional therapy (e.g. radiotherapy and ablation therapy) and systemic therapy.

Locoregional therapies are defined as minimally invasive-guided liver tumour directed procedures that can be categorised into ablative therapy, transcatheter therapy and radiation therapy. The main role of these locoregional therapies in the management of hepatocellular carcinoma is to induce tumour necrosis.

TACE treatment is based on the occlusion of the arterial blood supply of the target neoplastic lesion by embolising microparticles combined with the injection of chemotherapeutic drugs in selective manner, sparing the adjacent healthy unaffected liver.

Meanwhile SIRT or also known as transarterial radio-embolisation uses a combination of chemotherapy and ischaemia, following injection and irradiation from Yttrium-90 (Y-90) bearing microspheres. Emission of the irradiation particles can deliver targeted radiation to the lesion, limiting radiation exposure to normal parenchyma while reducing the risk of radiation induced liver disease. As in this case, the patient had undergone both treatment modalities for his disease.

Assessment of treatment response is critical in determining prognosis and subsequent management. Based on the study by Patel et al. (5), assessment of response to therapy in hepatocellular carcinoma are by clinical examination, biochemical test (serum Alpha Fetoprotein, AFP), structural imaging as well as functional imaging (PET scan). The World Health Organisation (WHO) first developed the treatment response criteria by assessing tumour burden based on size. This response criteria was thereafter improvised by an international collaboration group, named the Response Evaluation Criteria in Solid Tumour (RECIST). RECIST establishes assessment by measuring the sum of the longest diameters of target measureable lesion based on one-dimensional measurement only. Newer criteria have since been developed, namely modified RECIST, EASL criteria and the Liver Imaging Reporting and Data system (LI-RADS) Treatment Response (LR-TR) algorithm (3).

However, there is not much study regarding histological changes in assessment of treatment

TABLE 1: Histopathological changes following locoregional therapy in hepatocellular carcinoma

Study	**Number of patients**	**Type of locoregional therapies**	**Histopathological changes**
Beal et al. 2016 (4)	63	Transarterial chemoembolisation / ablative therapy	• Tumour necrosis
Wang et al. 2013 (6)	3	Selective internal radiotherapy (SIRT)	• Microspheres • Tumour necrosis • Stromal fibrinous exudate • Paucicellular inflammatory response • Mucin • Foamy histiocytes • Calcification • Fibrosis • Ectatic vessels and vascular intimal alteration • Tumour mass effect • Steatosis
Yamashiki et al. 2003 (7)	4	Microwave coagulation therapy/ablative therapy	• Coagulative necrosis • Microvascular thrombosis • Presence of foamy histiocytes, multinucleated giant cells and fibrotic bands formation.
Chan et al. 2011 (8)	82	Transarterial chemoembolisation / ablative therapy	• Tumour necrosis

response. A few retrospective studies that had described the histopathological changes post locoregional therapy in hepatocellular carcinoma were shown in Table 1. Our patient showed similar morphological changes, which included numerous scattered microspheres, tumour necrosis with multinucleated giant cells, histiocytes and chronic inflammatory cells (4,6,7,8).

A study that correlated histological treatment response with prognosis is Beal et al. (4). They assessed the treatment response by assessing the percentage of tumour necrosis with viable tumour cells, and concluded that patient with complete tumour necrosis was associated with superior outcomes. This finding was concurred with Chan et al. (8), which showed tumour necrosis of more and equal to 60% by locoregional therapies gave a better outcomes for patient with hepatocellular carcinoma undergoing liver transplantation.

Conclusion

Locoregional therapies are widely practice in treatment of primary hepatocellular carcinoma as well as metastasis carcinoma to the liver. Although assessment of treatment response following locoregional therapy based on histopathological findings are not widely practiced, recognising these histopathological changes certainly provide valuable insight to a patient's prognosis. Minimal to absent tumour necrosis implies poor response, limiting further locoregional therapy option.

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