

A Mosaic of Malignancy: Multicentric Hepatocellular Carcinoma in Medicolegal Autopsy

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and is strongly associated with chronic liver disease and cirrhosis. Multicentric HCC is characterized by the presence of multiple primary tumor nodules arising independently within the liver and is commonly observed in chronically diseased hepatic tissue. We report the case of a 46-year-old man who underwent medicolegal autopsy following sudden deterioration and death. External examination revealed no evidence of trauma. The liver was enlarged and had a nodular external surface. On cut section, multiple tumor nodules of varying sizes were distributed throughout both hepatic lobes, with areas of hemorrhage and necrosis. Histopathological examination demonstrated HCC, with malignant hepatocytes arranged predominantly in trabecular and pseudoglandular patterns, together with cirrhosis and steatohepatitis in the surrounding liver parenchyma. Metastatic deposits of HCC were identified in the mesentery and omentum. No evidence of poisoning or external injury was identified. The cause of death was attributed to complications of advanced multicentric HCC. This case highlights the diagnostic and medicolegal importance of comprehensive postmortem examination in patients with previously undiagnosed hepatic malignancy, particularly when death occurs suddenly or without an established cause.

Keywords: Hepatocellular carcinoma; Multicentric hepatocellular carcinoma; Medicolegal autopsy; Cirrhosis; Liver malignan

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Introduction

Hepatocellular carcinoma (HCC) is the predominant primary malignancy of the liver and a major cause of cancer-related mortality worldwide. It most commonly develops in the setting of chronic liver disease and cirrhosis [1]. Major risk factors include chronic hepatitis B and C virus infection, alcohol-related liver disease, and metabolic dysfunction-associated steatotic liver disease, while male sex and increasing age further contribute to risk [1, 2]. Although surveillance programs have improved the early detection of HCC in high-risk populations, some patients remain undiagnosed until advanced disease or death.

Multicentric hepatocellular carcinoma is characterized by the presence of multiple tumor nodules arising within the liver, which may represent independently developing primary tumors rather than intrahepatic metastases from a dominant lesion [3]. This pattern is particularly associated with chronically injured and cirrhotic livers.

The development of multiple primary tumors has been linked to widespread carcinogenic changes within diseased hepatic tissue, often described as a field-effect or field cancerization phenomenon. Molecular studies have further demonstrated genetic heterogeneity among separate HCC nodules, supporting the possibility of independent clonal evolution [4, 5].

From a medicolegal perspective, the identification of previously unsuspected HCC at autopsy may be critical in determining the cause of death, particularly when death occurs suddenly or without a clear clinical diagnosis. Comprehensive examination of the liver, other abdominal organs, and relevant lymphatic and metastatic sites, together with histopathological confirmation, is essential for distinguishing primary hepatic malignancy from metastatic disease and other potential causes of death.

We present a case of extensive multicentric HCC identified during medicolegal autopsy in a 46-year-old

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man who died following sudden clinical deterioration. The case emphasizes the importance of meticulous gross and microscopic examination in establishing the natural cause of death in individuals with previously undiagnosed advanced liver malignancy.

Case Presentation

A 46-year-old man was brought to the hospital in an unconscious state and was declared dead shortly after admission. A medicolegal autopsy was performed to determine the cause of death. The available clinical history was limited. There was no documented previous diagnosis of chronic liver disease, and no records of prior imaging, liver biopsy, or tumor marker evaluation were available. A history of chronic alcohol consumption or exposure to viral hepatitis could not be reliably established because of incomplete medical documentation and follow-up.

At autopsy, the liver was markedly enlarged and irregular, with a nodular external surface. On cut section, multiple non-encapsulated, tan-yellow tumor nodules of varying sizes were distributed throughout both hepatic lobes, without a clearly identifiable dominant mass. Several nodules showed focal areas of hemorrhage and necrosis. The multifocal distribution of the lesions raised the possibility of multicentric tumor development (Figure 1).

Microscopic examination demonstrated malignant hepatocellular proliferation arranged predominantly in trabecular and pseudoglandular patterns. The tumor cells showed marked pleomorphism, an increased nuclear-to-cytoplasmic ratio, prominent nucleoli, and frequent mitotic figures (Figure 2). Focal areas demonstrated tumor nodules surrounded by desmoplastic stroma. The surrounding non-neoplastic liver parenchyma showed architectural distortion, fibrosis, regenerative nodules, steatosis, and areas of neutrophil-rich lobular inflammation, consistent with cirrhosis with steatohepatitis. Masson's trichrome and reticulin staining further demonstrated established fibrosis and architectural distortion, supporting the diagnosis of cirrhosis.

The presence of multiple tumor nodules with variable histological differentiation and the absence of a single dominant mass favored a multicentric pattern of hepatocellular carcinoma rather than simple intrahepatic metastatic spread from a dominant primary lesion. However, the distinction between multicentric primary tumors and intrahepatic metastases can be challenging on morphological grounds alone.

Examination of the mesentery (Figure 3) and omentum (Figure 4) revealed metastatic deposits of hepatocellular carcinoma. No definitive metastatic lesions were identified in the heart, lungs, kidneys, spleen, or brain. The remaining autopsy findings were compatible with terminal hypoxia and systemic deterioration.

Based on the gross and histopathological findings, the cause of death was attributed to advanced multicentric hepatocellular carcinoma with intra-abdominal metastases, occurring in a background of previously undiagnosed cirrhosis with steatohepatitis. The extensive hepatic



Figure 1. Gross Examination of the Liver Showing Multiple Non-encapsulated, Tan-yellow Nodules of Varying Sizes with Focal Areas of Hemorrhage and Necrosis.

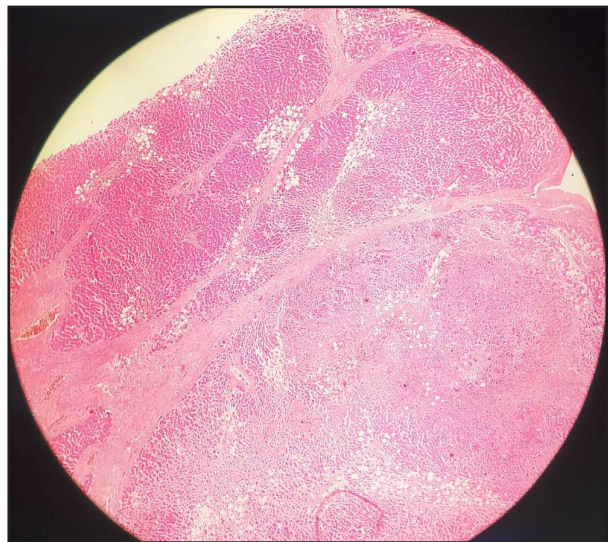


Figure 2. Histopathological Examination Showing Malignant Hepatocellular Proliferation Arranged in Trabecular and Pseudoglandular Patterns. The tumor cells demonstrate marked pleomorphism, an increased nuclear-to-cytoplasmic ratio, prominent nucleoli, and frequent mitotic figures (H&E, $\times 10$).

tumor burden was considered likely to have resulted in progressive hepatic dysfunction and systemic deterioration. This case highlights the importance of comprehensive gross and histopathological examination during medicolegal autopsy, particularly in sudden or unexplained deaths involving previously undiagnosed chronic liver disease and advanced malignancy.

Discussion

Multicentric hepatocellular carcinoma (HCC) represents a distinct pattern of hepatocarcinogenesis characterized by the synchronous or metachronous development of multiple primary tumor nodules within the liver [3, 6]. It occurs predominantly in patients with chronic liver disease, particularly cirrhosis associated with

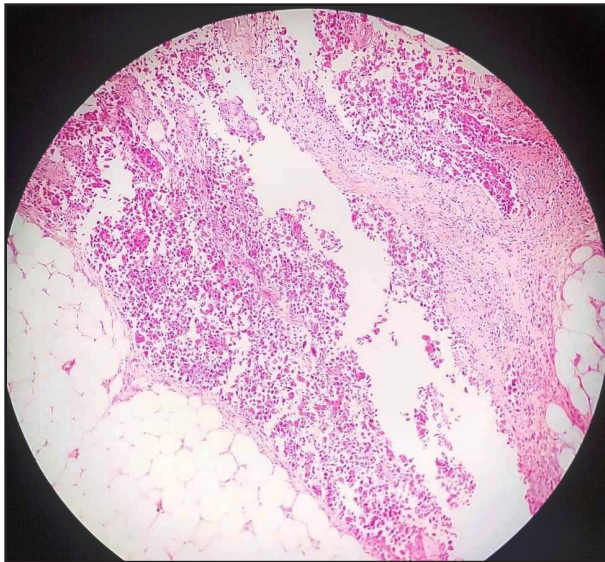


Figure 3. Histopathological Examination Showing Metastatic Hepatocellular Carcinoma in the Mesentery (H&E, ×4).

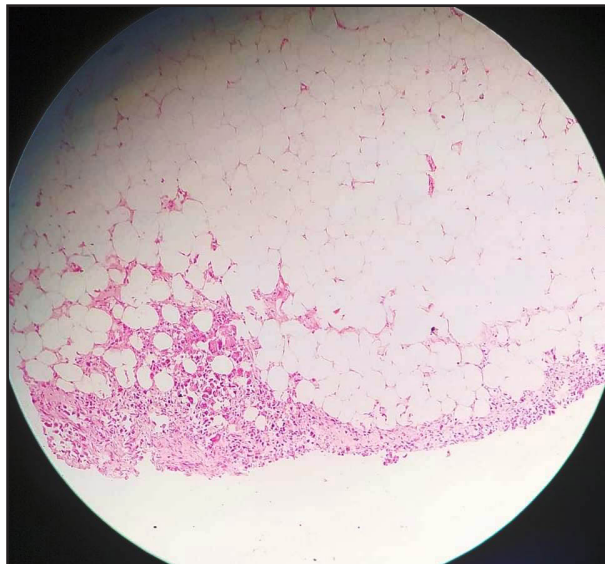


Figure 4. Histopathological Examination Showing Metastatic Hepatocellular Carcinoma in the Omentum (H&E, ×4).

chronic hepatitis B or C infection, alcohol-related liver disease, or steatohepatitis [7, 8]. Persistent hepatic injury and inflammation promote repeated cycles of hepatocyte necrosis, regeneration, and fibrosis, creating a carcinogenic field in which multiple genetically altered hepatocyte clones may develop independently [4, 5, 9]. Progressive accumulation of genetic and epigenetic abnormalities can lead to malignant transformation at multiple sites, accounting for the coexistence of tumors with different sizes, morphologic characteristics, and degrees of differentiation [7].

In the present case, a 46-year-old man died shortly after being brought to the hospital in an unconscious state, with no established prior diagnosis of chronic liver disease or hepatic malignancy. Autopsy revealed a markedly enlarged, nodular liver containing multiple hemorrhagic

and necrotic tumor nodules distributed throughout both lobes. The surrounding hepatic parenchyma showed established cirrhosis with steatohepatitis, providing a plausible background for multifocal hepatocarcinogenesis. Histopathological examination demonstrated malignant hepatocytes arranged in trabecular and pseudoglandular patterns, with marked cytological atypia and frequent mitotic activity, confirming HCC.

The differential diagnosis of multiple hepatic nodules includes intrahepatic metastatic carcinoma, cholangiocarcinoma, combined hepatocellular-cholangiocarcinoma, and benign hepatocellular nodules. Metastatic tumors may present as multiple hepatic lesions but generally require correlation with the morphology and immunophenotype of the primary tumor. Cholangiocarcinoma typically demonstrates malignant glandular structures and prominent desmoplastic stroma, whereas combined hepatocellular-cholangiocarcinoma contains both hepatocellular and biliary components. Regenerative nodules and focal nodular hyperplasia generally lack the marked cytological atypia and malignant growth patterns observed in HCC [3]. In the present case, the distribution of multiple nodules throughout both lobes, the absence of a dominant hepatic mass, the variable histological differentiation among tumor nodules, and the presence of cirrhosis favored a multicentric pattern. Nevertheless, definitive distinction between independently arising primary tumors and intrahepatic metastases may require molecular or clonality analysis.

Molecular studies have provided important evidence for distinguishing multicentric occurrence from intrahepatic metastatic spread [4, 5, 9-11]. Loss-of-heterozygosity analysis, comparative genomic hybridization, hepatitis B virus integration-site analysis, and next-generation sequencing have demonstrated distinct molecular alterations in some anatomically separate HCC nodules, supporting independent clonal origins [4, 5, 9-11]. Conversely, intrahepatic metastatic lesions generally demonstrate substantial genetic similarity to the dominant primary tumor. Alterations involving pathways such as Wnt/ β -catenin signaling, TERT promoter activity, TP53, and oxidative stress and inflammatory signaling have been implicated in hepatocarcinogenesis [4, 5, 11]. The molecular heterogeneity observed among multifocal HCCs may also contribute to differences in histological differentiation and biological behavior [10].

Although molecular analysis was not performed in the present case, the gross and histopathological findings were strongly supportive of multicentric HCC in a cirrhotic liver. The identification of metastatic deposits in the mesentery and omentum further established the advanced nature of the disease. Importantly, no definitive metastatic lesions were identified in the other major organs examined at autopsy. The extensive hepatic tumor burden, together with the underlying cirrhosis, provided a plausible pathological basis for progressive hepatic dysfunction and systemic deterioration.

The medicolegal significance of this case lies in the identification of an advanced, previously undiagnosed

malignancy in an individual who presented with sudden and unexplained death. In such circumstances, the absence of external trauma or a known medical history does not exclude a fatal natural disease process. Detailed examination of the liver and other abdominal structures, followed by appropriate histopathological evaluation, is therefore essential for establishing the cause of death. Autopsy examination also permits assessment of the overall tumor burden and identification of metastatic disease that may not have been recognized clinically.

This case emphasizes that multicentric HCC may remain clinically occult until advanced disease develops and that medicolegal autopsy can play a critical role in recognizing previously undiagnosed hepatic malignancy. Careful correlation of gross findings, histopathology, and the distribution of tumor and metastatic deposits is essential for accurate diagnosis and determination of the cause of death.

From both pathological and clinical perspectives, recognition of multicentric HCC has important diagnostic and prognostic implications. The biological behavior of multicentric tumors may differ from that of intrahepatic metastatic disease, although prognosis is influenced by both tumor burden and the severity of the underlying liver disease [6, 9]. Detailed histopathological assessment, supplemented by molecular profiling when available, can improve the distinction between independent primary tumors and intrahepatic metastases and provide further insight into the mechanisms of hepatocarcinogenesis. Continued surveillance of patients with chronic liver disease remains essential for early detection of HCC. Autopsy examination is also valuable for documenting the full extent of disease, identifying previously unrecognized metastatic involvement, and contributing to a better understanding of the natural history and pathological heterogeneity of multicentric HCC.

In conclusion, this case demonstrates extensive multicentric hepatocellular carcinoma in a relatively young 46-year-old man with previously undiagnosed cirrhosis and steatohepatitis. Comprehensive gross and histopathological examination was essential for establishing the diagnosis, determining the extent of tumor involvement, and identifying metastatic disease. The case also emphasizes the medicolegal importance of recognizing natural disease processes that may present as sudden or unexplained death. Thorough autopsy examination, supported by appropriate histopathological evaluation, remains essential for establishing the cause of death and identifying occult malignancies in medicolegal practice.

Acknowledgments

Statement of Transparency and Principles

- The authors declare no conflict of interest.
- The study was approved by the Research Ethics Committee of the authors' affiliated institution.
- The study data are available upon reasonable request.
- All authors contributed to the implementation of this research.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. 2024 05;74(3):229-263. <https://doi.org/10.3322/caac.21834>
2. Mauro E, De Castro T, Zeitlhofer M, Sung MW, Villanueva A, Mazzaferro V, Llovet JM. Hepatocellular carcinoma: Epidemiology, diagnosis and treatment. *JHEP Reports*. 2025 Dec;7(12):101571. <https://doi.org/10.1016/j.jhepr.2025.101571>
3. Matsumoto Y, Fujii H, Matsuda M, Kono H. Multicentric occurrence of hepatocellular carcinoma: diagnosis and clinical significance. *Journal of Hepato-Biliary-Pancreatic Surgery*. 2001 Oct 01;8(5):435-440. <https://doi.org/10.1007/s005340100006>
4. Tang X, Xiang L, Li Q, Shao Y, Wan L, Zhao D, Li X, et al. Molecular evolution in different subtypes of multifocal hepatocellular carcinoma. *Hepatology International*. 2023 Dec;17(6):1429-1443. <https://doi.org/10.1007/s12072-023-10551-8>
5. Ren F, Wang D, Zhang X, Zhao N, Wang X, Zhang Y, Li L. Cross Analysis of Genomic-Pathologic Features on Multiple Primary Hepatocellular Carcinoma. *Frontiers in Genetics*. 2022 06 20;13:846517. <https://doi.org/10.3389/fgene.2022.846517>
6. Feo F, Pascale RM. Multifocal hepatocellular carcinoma: Intrahepatic metastasis or multicentric carcinogenesis? *Ann Transl Med*. 2015;3(1):4. <https://doi.org/10.3978/j.issn.2305-5839.2014.12.08>
7. Oikawa T, Ojima H, Yamasaki S, Takayama T, Hirohashi S, Sakamoto M. Multistep and multicentric development of hepatocellular carcinoma: histological analysis of 980 resected nodules. *Journal of Hepatology*. 2005 02;42(2):225-229. <https://doi.org/10.1016/j.jhep.2004.10.024>
8. Kubo S, Nishiguchi S, Hirohashi K, Shuto T, Kuroki T, Minamitani S, Ikebe T, et al. Clinicopathological Criteria for Multicentricity of Hepatocellular Carcinoma and Risk Factors for Such Carcinogenesis. *Japanese Journal of Cancer Research*. 1998 04;89(4):419-426. <https://doi.org/10.1111/j.1349-7006.1998.tb00580.x>
9. Chang Y, Chou Y, Chung C, Lee Y, Yen J, Jeng L, Chang J. Molecular Classification of Hepatocellular Carcinoma Using Wnt-Hippo Signaling Pathway-Related Genes. *Cancers*. 2022 09 21;14(19):4580. <https://doi.org/10.3390/cancers14194580>
10. Da BL, He AR, Shetty K, Suchman KI, Yu H, Lau L, Wong LL, et al. Pathogenesis to management of hepatocellular carcinoma. *Genes & Cancer*. 2022 Dec 13;13:72-87. <https://doi.org/10.18632/genesandcancer.226>
11. Zucman-Rossi J, Villanueva A, Nault J, Llovet JM. Genetic Landscape and Biomarkers of Hepatocellular Carcinoma. *Gastroenterology*. 2015 Oct;149(5):1226-1239.e4. <https://doi.org/10.1053/j.gastro.2015.05.061>



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