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CORRESPONDENCE

Neoplastic Pseudocirrhosis Pathophysiological Deepening

Antonio Manenti[1] · Stefania Caramaschi[2] · Gianrocco Manco[1] · Luca Reggiani Bonetti[2]

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Dear Editor,

Neoplastic pseudocirrhosis (NPC), the clinical aspects of which have been comprehensively reported by Sadlik et al., deserves to be studied in depth from a pathophysiological point of view to understand it better and learn from it, given its increasing relevance in the current era of long-term anti-neoplastic chemotherapy and precise diagnostic imaging [1]. It usually represents the most advanced stage of a liver metastatic disease, the diagnosis of which is essentially clinical-radiological, rarely needing to be supported by histopathological data. We investigated its pathophysiology by correlating specific clinical-radiological signs with inherent histopathological observations, validated in the light of known features of common metastatic liver diseases. Neoplastic cells can reach the liver parenchyma by various routes, mainly vascular, represented by branches of the hepatic artery or portal vein, easily 'capillarise' or directly obstruct the hepatic sinusoids [2, 3]. This process, typical but not exclusive of hematological neoplasms, can also complicate carcinomas of various organs, especially if highly aggressive and undifferentiated [4]. Its widespread diffusion may increase intrahepatic portal resistance, leading to a general portal hypertension with secondary porto-systemic collaterals, splenomegaly and ascites. This abnormal hemodynamics may be mitigated by efficient collaterals developed between portal branches and hepatic vein roots within the liver parenchyma or sub-glissonian space, or by directing part of portal blood to the caudate lobe and its retro-hepatic veins, which inflow directly into the inferior vena cava [5–8]. Alternatively, portal hypertension may be pre-sinusoidal when intrahepatic portal branches are subject to neoplastic thrombosis or external compression by metastatic masses. Finally, neoplastic cells can reach the liver parenchyma, transported by blood flow refluxing from the superior or inferior vena cava into the hepatic veins and downstream into the central lobular veins. Hemodynamic damage is proportional to the area of congested liver parenchyma and ranges from a 'limited' Budd-Chiari syndrome with little or no effect on overall portal hemodynamics in the case of a single hepatic vein involvement, to a zone of congested liver lobules. This may complicate with an accelerated necro-apoptosis, followed by an interstitial fibrosis. The diagnostic contribution of radiological imaging is essential in all cases.

Other lesions affect the liver parenchyma architecture through an abnormal interstitial fibrosis and lobular regeneration. The first corresponds radiologically to a retracted hepatic capsule, pronounced hepatic lobulation and narrowing of one lobe, usually the right, and correlates histologically with thickened interlobular septa, however thinner than in cirrhosis and lacking portal bridging bands. This may be the result of long-term chemotherapy or multifactorial necrosis of hepatocytes, in turn releasing cytokines and growth factors that activate fibroblasts through autocrine or paracrine mechanisms without altering the extracellular matrix substance. Regeneration of liver parenchyma, could be better considered a "nodular hyperplasia", different from the often dysmorphic and distorted creation of neolobules in cirrhosis.

In NPC, other fine structures, when involved, can play an essential role. The intrahepatic lymphatic system may undergo two opposing processes: a first of distortion/compression of lymphatic channels by neo-generated fibrous bands or metastatic masses, and a second of neo-lympho-angiogenesis promoted by vascular growth factors released by the tumor tissue through para-neoplastic mechanisms [9–11]. In the first case, lymph stagnation favors colonization and replication of neoplastic cells and their diffusion along the lymphatic channels surrounding the larger intrahepatic bile ducts, leading to their obstruction, and mimicking

✉ Antonio Manenti
antonio.manenti_2024@libero.it

[1] Department of Surgery, University of Modena and Reggio Emilia, Polyclinic Hospital, Via Del Pozzo,, 41124 Modena, Italy

[2] Department of Pathology, University of Modena and Reggio Emilia, Polyclinic Hospital, Via Del Pozzo, 41124 Modena, Italy

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primary sclerosing cholangitis [12–14]. In the second case, small newly formed subcapsular lymphatic channels, mainly if congested, facilitate spillage of neoplastic cells into the peritoneum, transforming ascites into peritoneal carcinomatosis. In both cases, metastases to regional lymph nodes are facilitated. In addition, the small intrahepatic bile ducts, particularly the cholangioles, may be infiltrated by neoplastic cells: this results in obstructive jaundice without dilatation of the intra- and extrahepatic bile ducts on cross-sectional imaging. In conclusion, PNC is a complex disease with some basic features: damage to hepatic venous, biliary and lymphatic structures, increased hepatocyte necrosis, abundant fibrous tissue proliferation in the perilobular spaces and nodular regenerative hyperplasia. Clinically, this can lead to portal hypertension, hepatomegaly and progressive liver failure [15, 16]. In contrast, NPC lacks the dysmorphic hepatic nodular regeneration and thickened fibrotic septa with bridging portal tracts typical of cirrhosis.

Author's contributions A.M: conceptualization; S.C.: provided references; G.M.: discussed radiological data; L.R. and A.M.: writing. All authors reviewed the manuscript.

Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors disclose no conflict of interest, grant, financial arrangements or support related to the research or assistance with manuscript preparation.

References

1. Sadlik G, Anderson RC, Lei X, Cen SY, Duddalwar VA, Fong TL. Pseudocirrhosis: A case series with clinical and radiographic correlation and review of the literature. *Dig Dis Sci.* 2024;69:1004–1014. https://doi.org/10.1007/s10620-023-08226-3.
2. Yang M, Zhang C. The role of liver sinusoidal endothelial cells in cancer liver metastasis. *Am J Cancer Res.* 2021;11:1845–1860 (**PMID: 34094657**).
3. Gibert-Ramos A, Sanfeliu-Redondo D, Aristu-Zabalza P et al. The hepatic sinusoid in chronic liver disease: the optimal milieu for cancer. *Cancers (Basel).* 2021;13:5719. https://doi.org/10.3390/cancers13225719.
4. Parikh R, Bansal N, Sen R. Liver histopathology in scope of hematological disorders. *Indian J Pathol Microbiol.* 2023;66:683–693. https://doi.org/10.4103/ijpm.ijpm_85622.
5. Shi B, Bian C, Li Z et al. Imaging findings of hepatocellular carcinoma with portal vein tumor thrombosis secondary to hepatic portal vein collateral circulation: a cross-sectional study. *J Gastrointest Oncol.* 2023;14:334–351. https://doi.org/10.21037/jgo-23-45.
6. Barbier L, Ronot M, Monsinjon M et al. Development of collateral pathways in tumor obstruction of confluence of the hepatic veins: neither fortuitous nor innocuous. *J Am Coll Surg.* 2016;223:595–601. https://doi.org/10.1016/j.jamcollsurg.2016.06.013.
7. Sharma A, Keshava SN, Eapen A, Elias E, Eapen CE. An update on the management of Budd-Chiari syndrome. *Dig Dis Sci.* 2021;66:1780–1790. https://doi.org/10.1007/s10620-020-06485-y.
8. Rizzetto F, Rutanni D, Carbonaro LA, Vanzulli A. Focal liver lesions in Budd-Chiari syndrome: spectrum of imaging findings. *Diagnostics* 2023;13:2346. https://doi.org/10.3390/diagnostics13142346.
9. Roncati L, Manenti A, Zizzo M, Farinetti A. Re: Anatomy of hepatic lymphatics and its implications in hepatic malignancies. *ANZ J Surg.* 2017;87:103–104. https://doi.org/10.1111/ans.13829.
10. Pupulim LF, Vilgrain V, Ronot M, Becker CD, Breguet R, Terraz S. Hepatic lymphatics: anatomy and related diseases. *Abdom Imaging.* 2015;40:1997–2011. https://doi.org/10.1007/s00261-015-0350-y.
11. Umemura K, Shimoda H, Ishido K et al. Microanatomical organization of hepatic venous lymphatic system in humans. *PLoS One.* 2023;18:e0286316. https://doi.org/10.1371/journal.pone.0286316.
12. Vernuccio F, Dioguardi Burgio M, Barbiera F et al. CT and MR imaging of chemotherapy-induced hepatopathy. *Abdom Radiol* 2019;44:3312–3324. https://doi.org/10.1007/s00261-019-02193-y.
13. Pope MC, Olson MC, Flicek KT et al. Chemotherapy-associated liver morphological changes in hepatic metastases (CALM-CHeM). *Diagn Interv Radiol.* 2023;29:571–578. https://doi.org/10.4274/dir.2023.232299.
14. Roehlen N, Crouchet E, Baumert TF. Liver fibrosis: mechanistic concepts and therapeutic perspectives. *Cells.* 2020;9:875. https://doi.org/10.3390/cells9040875.
15. Rich NE, Sanders C, Hughes RS et al. Malignant infiltration of the liver presenting as acute liver failure. *Clin Gastroenterol Hepatol.* 2015;13:1025–1028. https://doi.org/10.1016/j.cgh.2014.09.040.
16. González Grande R, Bravo Aranda A, Santaella Leiva I et al. Acute liver failure secondary to malignant infiltration: a single center experience. *Semin Oncol.* 2023;50:71–75. https://doi.org/10.1053/j.seminoncol.2023.05.003.