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Clinical Aspects of Pathomorphological Diagnosis of Hepatocellular Cacinoma in Practical Oncology

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ABSTRACT

In modern clinical oncology, pathomorphological verification of the tumor substrate is key, the purpose of which is to determine the type and genotypic affiliation of the tumor process, which in turn determines further treatment tactics, the sequence of existing treatment methods, determination of sensitivity to treatment, and also determines the prognosis of the disease. Some nosologies known to oncology require not only a standard set of cytological and histological tests for malignant neoplasms, but also additional immunohistochemical and molecular genetic profiling, performed through biopsy, excisional biopsy, or diagnostic surgery. Furthermore, definitive diagnosis based on radiological examination (CT, MRI, PET/CT) and tumor marker titers in peripheral blood remains clinically relevant. Currently, liver cancer hepatocellular carcinoma and/or cholangiocarcinoma is of greatest interest and complexity in the aforementioned verification. HCC ranks eighth in the oncological morbidity structure, with the number of newly diagnosed cases worldwide ranging from 820,000 to 850,000, with a consistent mortality rate of approximately 700,000 to 720,000 patients annually. This confirms the high mortality rate due to late staging of this pathology and the late onset of symptoms. This, in turn, determines the need for the introduction and application in clinical practice of periodic diagnostic and treatment protocols, the essence of which comes down to the existing algorithms for both diagnosis and treatment, according to which, in the case of widespread hepatocellular carcinoma/cholangiocarcinoma, when it is impossible to take biopsy material with the remaining risk of bleeding, CT/MRI confirmation of the characteristic pathognomonic signs of HCC/CCC with an increased titer level of the inherent tumor marker - AFP, CEA is sufficient. In clinical oncology, discrepancies between clinical and radiological confirmation of the tumor's progression are common during specialized treatment. This raises the question of repeat biopsy followed by histological review. This issue is particularly relevant in the case of HCC dissemination into brain structures, skeletal bones, and other anatomical sites, which are not typically associated with hematogenous and lymphogenous dissemination of this pathology, according to various literature data. We have described several cases of the aforementioned types of metastases and the specifics of their pathomorphological diagnosis.

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The Aim of the Study

Was to assess the error of quantitative and qualitative indicators of the possibility of pathomorphological diagnosis of hepatocellular carcinoma from a practical point of view.

Materials and Methods

Thirty-five patients aged 55 to 70 years underwent morphological and histological verification (including those after radical surgeries with postoperative verification) in 2022-2024. All patients had locally advanced or metastatic stage III-III and IV disease (T3NxM0 - T4N1M1). At the time of initial presentation, all patients had a diagnosis of hepatocellular carcinoma confirmed by histological verification, as well as based on the AFP index and CT scan of the abdominal organs with contrast. In 5 cases (14.3%), morpho-verification revealed hepatocellular carcinoma, while undifferentiated carcinoma was identified in 25 cases (71.4%). All 35 patients underwent specialized treatment. Of these, 29 patients underwent surgical intervention involving right or left hemihepatectomy, and 6 patients underwent transarterial chemoembolization (TACE) in combination with targeted therapy. In all cases of operated patients, relapse occurred no earlier than 6-8 months later, and 40% of cases involved mts lung and skeletal lesions. For the purpose of morphological verification, a biopsy of the formation was performed; in 24 cases, the morphology of the relapse was described as undifferentiated carcinoma; in 2 cases, the nature of the course of the disease and the response to the combined therapy (transarterial chemoembolization + immunotargeted therapy) did not correspond to the classical descriptive course of the disease, which initiated additional immunohistochemical

clarification caused by doubts about the reliability of the previously established clinical diagnosis. Upon further clarification and review of the biopsy specimen, an undifferentiated carcinoma was diagnosed, which in turn corresponds to various types of malignant disease. Only by obtaining IHC data was it possible to confirm the tumor's conformity with hepatocellular carcinoma. Depending on the level of histological differentiation, four grades of malignancy were distinguished. Hepatocellular carcinoma cells stained for alpha-fetoprotein in 70-90% of cases, allowing for the exclusion of cholangiocarcinoma and liver metastases. However, the staining was usually partial or focal, and the sensitivity did not exceed 10%, although according to various authors it varies between 15-70% [1-4]. In addition, according to the same authors, small amounts of Alpha-Fetoprotein (AFP) can be detected in regenerating hepatocytes in hepatitis and cirrhosis, as well as in normal cells located around hepatomas and metastatic nodes. Nevertheless, determination of the alpha-fetoprotein content in the blood serum is currently the most reliable marker of HCC, although the sensitivity and specificity of the method, respectively, are 39-64 and 76-91% [5,6]. The specificity of AFP determination depends, in particular, on the etiology of the process and is higher (78%) in HBsAg-positive patients compared to HBsAg-negative patients (50%). An alpha-fetoprotein concentration greater than 20 ng/ml or lower values with a tendency to slowly increase are considered indicative of tumor involvement. However, a weak correlation has been established between the serum alpha-fetoprotein level and tumor nodule size, both according to our observations and those of a number of scientists [7-9]. Another marker of hepatoid differentiation is considered to be Hep Par-1, diffuse granular expression of which is found in the cytoplasm of normal hepatocytes, as well as tumor cells in 80-90% of HCC observations, however, this technique was not applied by us in practice.

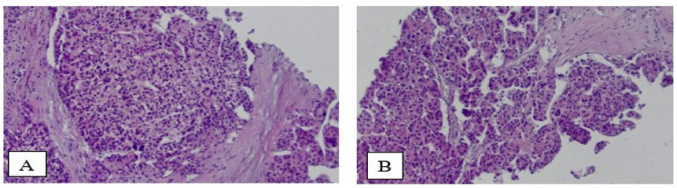

Figure 1: Morphological Picture of Hepatocellular Carcinoma G II (A, B)
(The material contains liver tumor tissue in which tumor complexes of medium and
large cells with broad cytoplasm, hyperchromic nuclei form a trabecular structure. Individual fragments of necrotic masses up to 20%)

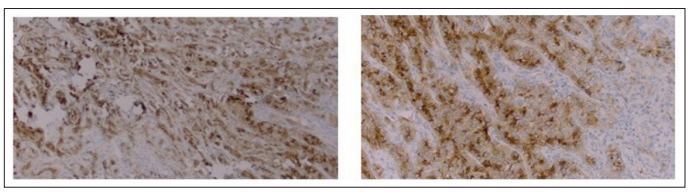

Figure 2: Morphological Picture of Hepatocellular Carcinoma G II (A, B)
(Immunohistochemical study of liver cancer, in the biopsy metastasis of poorly differentiated carcinoma, Glypikan 3 is positive, TTF is negative, NapsinA is negative)

Results and Discussion

Based on the analysis, the morphology of the relapse was described as undifferentiated carcinoma in 24 cases. In two cases, the course of the disease and the response to combination therapy (transarterial chemoembolization + immunotargeted therapy) did not correspond to the classic descriptive course of the disease, which prompted additional immunohistochemical clarification due to doubts about the reliability of the previously established clinical diagnosis. Upon further clarification and review of the biopsy specimen, an undifferentiated carcinoma was diagnosed, which in turn corresponds to various types of malignant disease. Only after obtaining IHC data was it possible to confirm the tumor's conformity with hepatocellular carcinoma. Meanwhile, other authors have observed a high degree of positive correlation between mitotic activity, vascular invasion, and high nuclear activity in studies of poorly differentiated hepatocellular carcinomas. The mitotic index is significantly higher in the periphery of anaplastic HCC complexes than in the central portions of the tumor. The above observations have also been confirmed in a number of other clinical cases involving hepatocellular carcinoma [10]. It is becoming clear that the approaches previously recommended in many clinical protocols for rebiopsy of lesions in breast and lung cancer with repeat morphological examination, using the same analogy, are also relevant for hepatocellular carcinoma for subsequent study of the above observations. Only repeated, confirmed morphological verification allowed us to confirm the correctness of the previously established diagnosis and continue treatment according to the clinical protocol for hepatocellular carcinoma. It was established that of the 24 previously described cases, all 24 were confirmed as undifferentiated hepatocellular carcinoma, the type of which was described above, allowing for continued treatment in 22 cases (91.6%) and achieving a statistically significant median survival of 12 months or more.

Conclusions

Morphological verification of the oncological process remains the main diagnostic technique and does not lose its relevance. In addition, the existing primary histological verification requires additional detailed revision and clarification, which in turn reliably and clinically significantly affects the therapeutic treatment option by increasing the frequency of the overall response, the median survival and demonstrating an improvement in the quality of life of patients.

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