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SYNCHRONOUS HAIRY CELL LEUKEMIA AND HEPATOCELLULAR CARCINOMA: A CASE REPORT

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Multiple primary malignant tumors are characterized by independent occurrence and development of two or more malignant neoplasms in the same patient. We present an extremely rare case of synchronous double primary malignancies, hairy cell leukemia and hepatocellular carcinoma with lethal outcome. Diagnosis of hepatocellular carcinoma was difficult due to the presence of lymphoproliferative disease, which complicated the visualization of the process using ultrasonography. Carcinomatous emboli of hepatocellular carcinoma in small pulmonary arteries without the formation of metastatic foci have led to clinical manifestations typical of pulmonary embolism, pulmonary hypertension and severe respiratory failure. In lymphoproliferative diseases it is necessary to take into account the possibility of the development of another malignant neoplasm, which can be "buried" by tumor infiltration.
***Key Words*: multiple primary malignancies, diagnostic difficulties, pulmonary embolism.**

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In recent years, the incidence of multiple primary malignancies (MPMs), representing two or more independent primary malignancies of different histologies/origins in the same individual tends to increase. Both individual organs of various systems and paired organs as well as multiple sites of a single organ could be affected. A mandatory sign of MPMs is their true primacy, which is most reliably confirmed by their histological structure [1].

The incidence of MPMs ranges from 0.7% to 11.7% in various studies and different countries. In fact, second primary cancer predominantly occurs, whereas third and fourth primary tumors are relatively rare. MPMs may be synchronous (when the second primary cancer is diagnosed within 6 months of the primary neoplasm) and metachronous (when the second primary cancer is diagnosed more than 6 months after the diagnosis of the primary neoplasm); the latter are more frequent. Among different factors explaining the increased risk of a new malignancy in cancer patients are older age, antineoplastic therapy, long-term exposure to carcinogenic factors, obesity and family history of neoplasia. With improved survival of cancer patients and a longer lifespan of the general population the incidence of MPMs will likely increase. One of the reasons for the development of second primary tumors may be lymphoproliferative diseases, accompanied by severe immunodeficiency [2–4]. However, a recently published study suggests that the prevalence of MPMs in leukemia/lymphoma patients is significantly lower than that in the total patient population [5].

The current state of differential diagnosis of malignant neoplasms and their behavior includes the histological, immunohistochemical studies, immunophenotype assessment, molecular assays, enabling to reveal fundamental differences in the morphofunctional characteristics of tumors, including impaired regulation of oncogenes and DNA repair genes [6–9].

The patient was a 52-year-old female who was admitted to the emergency department of the Regional Hospital accompanied by an anesthesiologist in a serious condition with the diagnosis of pulmonary embolism. At hospitalization, the patient complained of the shortness of breath, a feeling of tightness in the chest, general weakness. She considered herself ill for about a week and did not seek medical help. Due to the deterioration of the condition, she called the emergency and was hospitalized at the district hospital. After treatment, the patient's condition did not improve.

Complete blood count: hemoglobin 122 g/L, red blood cells — $3.52 \cdot 10^{12}$/L, white blood cells — $8.0 \cdot 10^{9}$/L, platelets — $65 \cdot 10^{9}$/L, granulocytes — 20%, lymphocytes — 78%, prolymphocytes — 1%, plasmocytes — 1%, erythrocyte sedimentation rate — 39 mm/h, anisocytosis positive, anisochromia positive. Due to the alterations in the complete blood count, the patient was evaluated by a hematologist and diagnostic sternal puncture was performed. Bone marrow was hypocellular with the evidence of the inhibition of normal hematopoietic cell lineages due to infiltration of bone marrow by lymphoid cells, partially by lymphocytes with villous cytoplasm. Despite the changes in the hemogram and bone marrow puncture, the patient had no clinically manifested hemorrhagic syndrome.

Ultrasonography of the lower extremity vessels did not reveal blood clots in the veins. Chest computed tomography scan revealed polysegmental infiltrative changes in both lungs; no filling defects at the level of the main arterial pathways were found. Abdominal ultrasound revealed signs of spleen enlargement.

After clinical, laboratory and instrumental examinations a patient was diagnosed with primary hairy cell

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Abbreviations used: HCL – hairy cell leukemia; MPMs – multiple primary malignancies.

leukemia (HCL), severe community-acquired bilateral polysegmental subtotal pneumonia (clinical group IV), chronic obstructive pulmonary disease grade III, phase of infectious exacerbation (group C), diffuse pneumosclerosis, type II–III respiratory failure.

Despite the provided appropriate treatment, the patient's condition progressively worsened and she died on day 5.

Postmortem examination confirmed the presence of lifelong diagnosed HCL with lesions of the bone marrow, spleen, liver, lymph nodes of the thoracic and abdominal cavities. The main morphological feature for the diagnosis was the presence of tumor cells with fringed cytoplasm. Immunohistochemical study of tumor infiltrates in spleen and liver confirmed the diagnosis by detecting cells with CD20 overexpression (Fig. 1, *a*) and moderate expression of CD68 (Fig. 1, *b*) as well as by the negative expression of CD3 in cells with villous cytoplasm and a reduced population of $CD3^+$ cells in the spleen tissue.

Moreover, the morphological signs of hepatocellular carcinoma (Fig. 2, *a*) with diffuse form of growth, metastases to the spleen (Fig. 2, *b*), lymph nodes of the thoracic and abdominal cavities, multiple tumor emboli in small pulmonary vessels were detected (Fig. 2, *c*). Immunohistochemical study of the tumor revealed cytoplasmic expression of AFP in the trabecular structures of the tumor parenchyma and its absence in the cells that form solid and acinar structures (Fig. 2, *d*). The reaction for AFP was absent in groups of cells surrounded by a pronounced connective tissue stroma. In contrast, positive expression of CK20 was observed in cells of solid and acinar structures in its absence in the trabeculae-forming cells (Fig. 2, *e*). In metastatic foci in the spleen, mainly $CK20^+$ structures were detected.

Thus, taking into account the postmortem findings, the following pathoanatomical diagnosis was established. The underlying disease — HCL with damage to the bone marrow, spleen, liver, lymph nodes of the chest and abdominal cavities. Concurrent disease — hepatocellular carcinoma, diffuse form with metastases in the spleen, lymph nodes of the abdominal and chest cavities, multiple tumor emboli in the small vessels of the lungs, vessels of the spleen, and lymph nodes. Complications involved focal pulmonary edema with hemorrhagic component, bilateral focal pneumonia, parenchymal dystrophy of internal organs. Concomitant pathology revealed atherosclerotic cardiosclerosis, diffuse and small-focal pneumosclerosis, condition after uterine amputation, simple serous ovarian cysts.

Autopsy-revealed hepatocellular carcinoma with multiple metastases (not diagnosed during the patient's life) allowed considering HCL and hepatocellular carcinoma as synchronous double primary malignancies.

Carcinomatous emboli in small pulmonary arteries without the formation of metastatic foci have led to clinical manifestations typical of pulmonary embolism (Fig. 2, *c*), pulmonary hypertension and severe respiratory failure [10]. However, due to the predominant embolization of small vessels, this was not detected by chest computed tomography scan. The prognosis in patients with hepatocellular carcinoma is extremely unfavorable and they die within a week of developing respiratory failure [11]. In addition, a low survival rate in patients with chronic lymphocytic leukemia and HCL in combination with other primary malignancies is caused by infectious complications and errors in the interpretation of the findings of diagnostic procedures [12].

In this case, the direct cause of death was the development of respiratory distress. Diagnosis of hepatocellular carcinoma was difficult due to the general serious condition of the patient, which is explained by the presence of lymphoproliferative disease, as well as the diffuse growth of carcinoma, which complicated the visualization of the process using ultrasonography.

According to some data, the incidence of secondary malignancies in patients with HCL is about 22%, and its pathogenesis may be associated with dysregulation of *MYC* or other regulatory genes. Interestingly, secondary tumors are more common in patients who have not received any treatment for HCL. Death from secondary malignancies is the most common cause

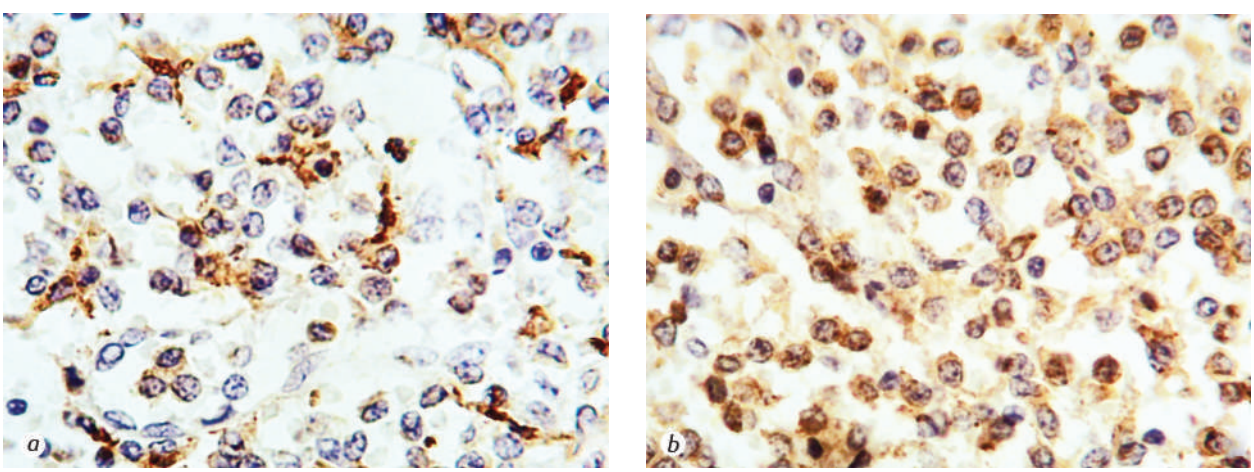

Fig. 1. Immunohistochemical examination of tumor cell infiltrates: immunostaining for CD20 (*a*) and CD68 (*b*), ×200

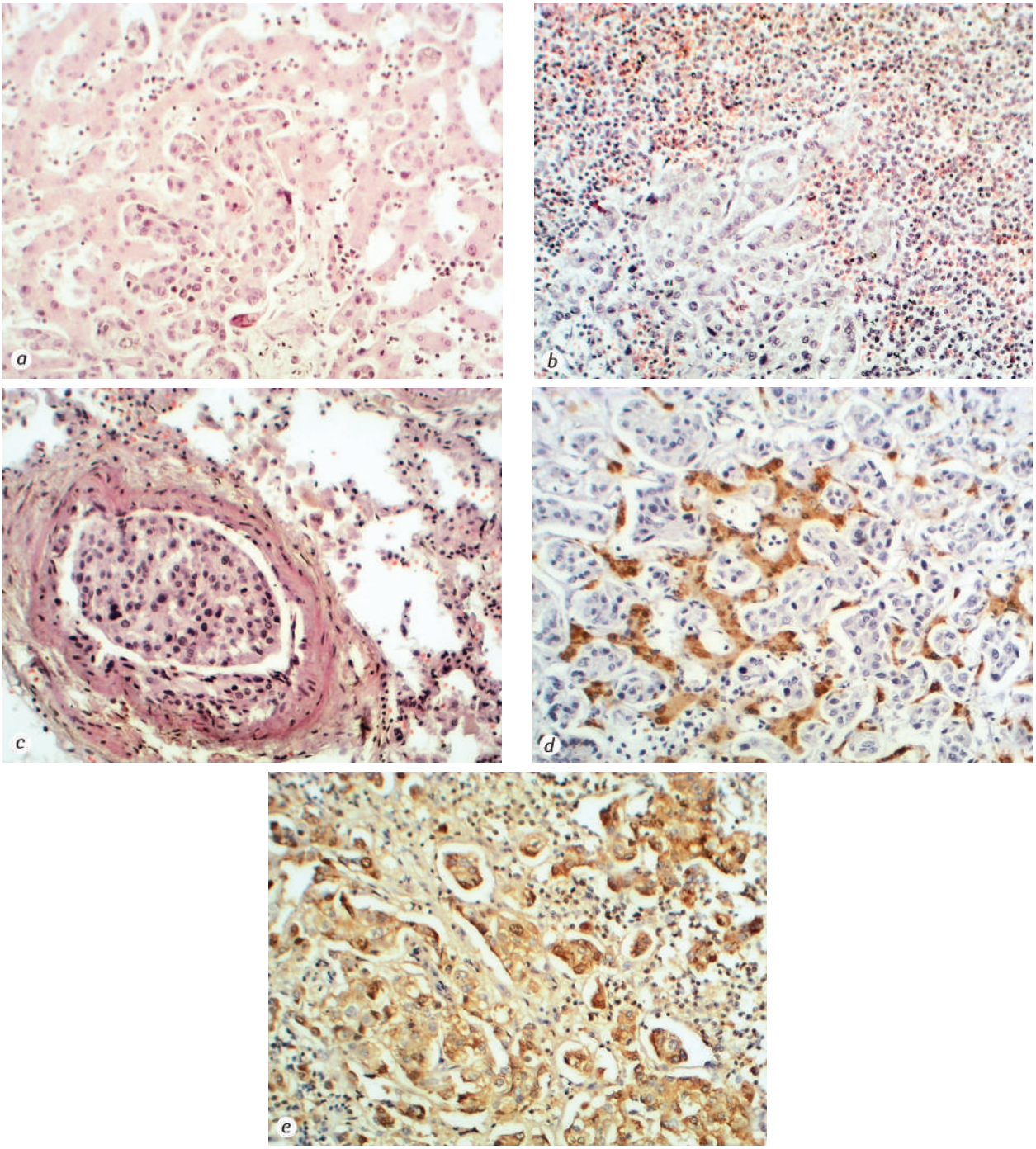

Fig. 2. Hepatocellular carcinoma: *a* — primary malignancy in liver; *b* — metastases to the spleen, *c* — tumor embolism of the small pulmonary artery (H&E, ×200); immunostaining for AFP (*d*) and CK20 (*e*),× 200

of death among HCL patients. It is hypothesized that immune disorders associated with HCL may be the cause of a greater predisposition to the development of other malignant tumors [13]. In recent years, there has been an improvement in the overall survival of HCL patients. However, notwithstanding therapeutic success, it is necessary to minimize the side effects of treatment and improve the quality of life of patients [14, 15].

Since secondary malignancies are an important cause of morbidity and mortality in HCL patients, the novel epidemiological, genetic, and clinical studies are needed to address the question of what causes the increased incidence of other malignancies in HCL patients. Thorough surveillance of the patients with this type of lymphoproliferative disease and implementation of all primary and secondary prevention of other cancers is crucial.

In conclusion, this case report detailed the case of a patient with synchronous HCL and hepatocellular carcinoma. To our knowledge, no similar case has been reported in the literature. This case indicates that in patients with lymphoproliferative diseases one need to consider the possibility of the occurrence of second, which can be “buried” by tumor infiltration. Further search for diagnostic criteria for tumor

embolism of small pulmonary arteries will be crucial in the diagnosis and treatment of symptoms of pulmonary hypertension and the development of respiratory distress syndrome, as well as improve the prognosis of survival of such patients.

CONFLICT OF INTERESTS

The authors have no existing or potential conflicts of interest to declare.

REFERENCES

1. **Parekh J D, Kukrety S, Thandra A, Valenta C.** Multiple primary malignant neoplasms in an elderly patient. Cureus 2018; **10**: e2384. doi: 10.7759/cureus.2384

2. **Lv M, Zhang X, Shen Y, *et al*.** Clinical analysis and prognosis of synchronous and metachronous multiple primary malignant tumors. Medicine (Baltimore) 2017; **96**: e6799. doi: 10.1097/MD.0000000000006799

3. **Nemes A, Todor N, Nagy V.** Follow-up protocol for oncological patients at risk of developing multiple primary neoplasms. JBUON 2020; **25**: 2117–22. PMID: 33099962

4. **Sovgirya SN, Starchenko II, Proskurnia SA, *et al*.** Clinical description of the rare case of polyneoplasia: B-cell lymphoma and bronhioloalveolar carcinoma. World Med Biol 2017; **2**: 113–6 (in Russian).

5. **Liu Z, Liu C, Guo W, *et al*.** Clinical analysis of 152 cases of multiple primary malignant tumors in 15,398 patients with malignant tumors. PLOS One 2015; **10**: e0125754. doi: 10.1371/journal.pone.0125754

6. **Radzishevska YB, Vasil'ev LY, Knigavko VG, Lykhovitskaya NI.** Relationships of nosological form of the primary and second neoplasms in oncological patients. Novosti Khirurgii 2017; **25**: 613–20. doi: 10.18484/2305-0047.2017.6.613

7. **Filenko BM, Roiko NV, Stepanchuk AP, *et al*.** Immunohistochemical description of proliferative activity and apoptosis of lung squamous cell carcinoma (literature review). Wiadomosci lekarskie 2016; **69**: 289–94. PMID: 27487551 (in Russian).

8. **Filenko BM, Starchenko II, Royko NV, *et al*.** Clinicomorphological observation of refractory hepatoblastoma: a case report. Exp Oncol 2020; **42**: 245–7. doi: 10.32471/exp-oncology.2312-8852.vol-42-no-3.14855

9. **Kryzhanivska AE, Dyakiv IB, Kyshakevych I.** Clinical and immunohistochemical features of primary breast cancer and metachronous ovarian and endometrial tumors. Exp Oncol 2018; **40**: 124–7. PMID: 29949531

10. **Price LC, Seckl MJ, Dorfmüller P, Wort SJ.** Tumoral pulmonary hypertension. Eur Respir Rev 2019; **28**: 180065. doi: 10.1183/16000617.0065-2018

11. **Morita S, Kamimura K, Abe H, *et al*.** Pulmonary tumor thrombotic microangiopathy of hepatocellular carcinoma: A case report and review of literature. World J Gastroenterol 2019; **25**: 6949–58. doi: 10.3748/wjg.v25.i48.6949

12. **Zheng G, Chattopadhyay S, Sud A, *et al*.** Types of second primary cancers influence survival in chronic lymphocytic and hairy cell leukemia patients. Blood Cancer J 2019; **9**: 40. doi: 10.1038/s41408-019-0201-0

13. **Murković M., Valković T.** Multiple malignant tumors in patient with hairy cell leukemia: case report. Medicina Flum 2018; **54**: 433–7. doi: 10.21860/medflum2018 207364 (in Croatian).

14. **Skrypnyk I, Maslova G, Lymanets T, *et al*.** How to improve quality of life in patients with acute leukemia and comorbid ischemic heart disease treated with anthracycline-based induction chemotherapy. Exp Oncol 2019; **41**: 353–6. doi: 10.32471/exp-oncology.2312-8852.vol-41-no-4.13906

15. **Skrypnyk I, Maslova G, Lymanets T, *et al*.** L-arginine is an effective medication for prevention of endothelial dysfunction, a predictor of anthracycline cardiotoxicity in patients with acute leukemia. Exp Oncol 2017; **39**: 308–11. PMID: 29284775

ПОЛІНЕОПЛАЗІЯ ВОЛОСКОВОКЛІТИННОГО ЛЕЙКОЗУ ТА ГЕПАТОЦЕЦЮЛЯРНОГО РАКУ: ВИПАДОК З ПРАКТИКИ

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Первинно-множинні злоякісні пухлини характеризуються незалежним виникненням і розвитком в одного хворого двох чи більше злоякісних новоутворень. Ми представляємо аналіз клінічного випадку комбінації волосковоклітинного лейкозу і гепатоцелюлярного раку з летальним наслідком з подальшою патоморфологічною верифікацією та виявленням неочікуваних ускладнень. Діагностика гепатоцелюлярної карциноми була ускладнена наявністю лімфопроліферативного захворювання, що перешкоджало адекватній візуалізації процесу за допомогою ультразвукового дослідження. Пухлинна емболія дрібних артерій легень без формування метастатичних вогнищ зумовила клінічні прояви, притаманні для тромбоемболії легеневої артерії, легеневу гіпертензію та виражену дихальну недостатність. При лімфопроліферативних захворюваннях необхідно враховувати можливість розвитку іншого злоякісного новоутворення, яке може бути замасковане пухлинною інфільтрацією.

***Ключові слова*:** множинні первинні злоякісні новоутворення, діагностичні труднощі, емболія легеневої артерії.