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Case Report

A Case of Hepatocellular Carcinoma after Treatment for Chronic Myeloid Leukemia in a Patient without Liver Disease

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Keywords
Carcinoma · Hepatocellular carcinoma · Leukemia · Myelogenous leukemia · Chronic myeloid leukemia · BCR-ABL positive

Abstract
Introduction: Chronic myeloid leukemia (CML) is a myeloproliferative disease caused by the reciprocal translocation of chromosomes 9 and 22, which leads to a chimeric gene product known as BCR-ABL. Some studies have shown a higher incidence of secondary malignancies than the one seen in the general population in patients with CML. Hepatocellular carcinoma (HCC) is rarely reported in association with CML and/or CML-related treatment. ***Case Presentation:*** We describe a case of a patient with no history of liver disease and CML on imatinib for 10 years, who presented with worsening right upper quadrant abdominal pain. Imaging revealed a large hepatic mass highly suspicious of malignancy that later was confirmed to be HCC after biopsy. The patient was bracketed with advanced stage HCC (BCLC stage C) and given her advanced age and poor performance status; palliative care was offered. ***Conclusion:*** Patients with CML have a common association with secondary malignancies. This is the first case report based on our extensive review of available literature that HCC was diagnosed in a patient with CML on treatment with imatinib without any clear or usual underlying cause.

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Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by a reciprocal translocation t(9;22)(q34;q11) causing a gene fusion between BCR (chromosome 22) and ABL1 (chromosome 9) which results in the BCR::ABL1 fusion gene and an abnormal small chromosome 22 called the Philadelphia chromosome. This new gene results in the production of BCR::ABL1 fusion protein, a tyrosine kinase (TK) enzyme responsible for the uncontrolled proliferation of granulocytes in the bone marrow. CML has 3 phases: an initial chronic phase (common at time of diagnosis, 85% of patients), an intermediate accelerated phase (impaired neutrophil differentiation), and a terminal blast crisis phase (uncontrolled proliferation) [1]. While CML mainly affects the bone marrow, peripheral blood, and spleen, there are infrequent occurrences, particularly during the progression to blast crisis, where the proliferation of CML cells can extend to unusual locations such as lymph nodes, liver, skin, and the central nervous system [1]. An association between CML and solid tumors has been documented in four distinct scenarios: myeloid sarcoma (MS), secondary CML after treatment for solid tumors, CML after organ transplant usually kidney transplant, and secondary solid tumors after CML treatment [2]. There are very rare cases reported of hepatocellular carcinoma (HCC) after CML treatment. Here, we present an unusual occurrence of HCC in an 80-year-old female patient with no history of liver disease who was on treatment for CML with a tyrosine kinase inhibitor (TKI) for more than 10 years.

Case Presentation

An 80-year-old female with a past medical history of CML in chronic phase on imatinib for more than 10 years, hypertension, and type 2 diabetes mellitus on metformin presented to the emergency room complaining of nausea for the last few months associated with new episodes of non-bloody emesis and worsening right upper quadrant abdominal pain for 2 weeks. She denied fever, chills, night sweats, weight loss, headaches, respiratory symptoms, chest pain, melena, hematochezia, or urinary symptoms. She has no history of alcohol, tobacco, or drug use.

Her initial vital signs were afebrile, heart rate 88 bpm, blood pressure 117/84 mm Hg, respiratory rate 19 bpm, no hypoxia on room air. On physical examination, she was in mild distress due to pain. There was no palpable lymphadenopathy. Heart with normal S1 and S2, and no rub or murmur. The lung auscultation was unremarkable. Her abdomen was tender to palpation in the right upper quadrant, no guarding or rebound, no palpable splenomegaly. The rest of her physical examination was normal.

She received symptomatic treatment with antiemetics. Her initial laboratory evaluation was remarkable for hemoglobin 13.4 g/dL, white blood cell count 6.5 × 10^9/L with normal differential, platelet count 130 × 10^9/L. Rest of laboratory workup is summarized in Table 1. A CT abdomen and pelvis with contrast revealed a noncirrhotic liver morphology with a large right hepatic lobe centrally necrotic mass in the inferior aspect of segments 5/6 measuring 7.3 × 8.4 × 8.2 cm with adjacent infiltrative component extending superiorly in segment 5 and into several right anterior portal vein branches concerning for malignancy (Fig. 1).

MR abdomen without and with IV contrast showed two large lesions (8.8 cm and 4.9 cm) within the right hepatic lobe suspicious for multifocal HCC, with tumor invasion of the right portal vein branches (Fig. 2). Oncology recommended ultrasound-guided needle biopsy for diagnosis and additional imaging to complete staging. CT chest with contrast and NM bone scan showed no evidence of metastatic disease. Ultrasound-guided right lobe liver mass core

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Table 1. Summary of laboratory evaluation

	Initial admission (day 0)	Time of discharge (day 6)	Second admission (day 12)	Time of discharge (day 15)
White blood cell count, $\times 10^9$/L	6.5	4.9	6.9	5.4
Hemoglobin, g/dL	13.4	13.4	14.0	12.6
Platelet count, $\times 10^9$/L	**130**	173	169	**141**
Creatinine, mg/dL	0.81	0.78	0.75	0.67
Alanine aminotransferase, U/L	**51**	–	**97**	**60**
Serum tumor markers	**Alpha-fetoprotein 25 ng/mL**, carcinoembryogenic antigen 1.6 ng/mL, carbohydrate 19-9 antigen 22 U/mL			
Additional laboratory studies on initial admission (day 0)	Lactic acid 0.8 mmol/L, sodium 136 mEq/L, bicarbonate 28 mmol/L, glucose 152 mg/dL, total bilirubin 0.7 mg/dL, AST 51 U/L, **alkaline phosphatase 118 U/L**, albumin 3.7 g/dL, lipase 58 U/L, PT 12.4 s, INR 1.1, aPTT 25 s, hepatitis A and C antibodies negative, HB surface antibody positive, HB surface antigen and HBc total antibody negative, SARS-CoV-2 PCR negative, normal urinalysis			

Abnormal values are in bold.

Reference values: white blood cell count 3.4–9.6 × 10^9/L; hemoglobin 11.6–15.0 g/dL; platelet count 157–371 × 10^9/L; creatinine 0.59–1.04 mg/dL; alanine aminotransferase 8–43 U/L; alpha-fetoprotein <8.4 ng/mL; carcinoembryogenic antigen ≤3.0; carbohydrate 19–9 antigen <35 U/mL; total bilirubin <1.2 mg/dL; alkaline phosphatase 35–104 U/L; albumin 3.5–5.0 g/dL; PT 9.4–12.5 s; INR 0.9–1.1; aPTT 25–37 s.

HB, hepatitis B.

biopsy was completed, and the patient was discharged on day 5 from the hospital with a plan to follow oncology as outpatient with biopsy results.

Unfortunately, her nausea and emesis recurred, and her right upper quadrant abdominal pain worsened despite analgesics, so she presented again to the emergency room 6 days after hospital discharge. Her vital signs were stable without tachycardia, hypotension, or hypoxia. At physical examination, her abdomen was significantly tender in right quadrants with no guarding or rebound. There were no other new positive physical exam findings from initial hospital admission. Liver biopsy results were available at this time which revealed HCC. Immunohistochemistry stains showed tumor cells positive for cytokeratin 20, glypican, arginase, and Hep Par-1 (weak), and negative for CK7, CDX2, and TTF1. New laboratory evaluation showed increasing ALT (shown in Table 1). A repeat CT of the abdomen and pelvis with IV contrast revealed interval development of fluid collection (6.6 × 4.3 cm) within dominant mass in the inferior aspect of the right hepatic lobe (biopsied area) with associated rupture of the liver capsule (Fig. 3), additional enlarging hepatic masses from prior imaging, and irregular thickening of the gallbladder wall adjacent to liver masses concerning for tumor invasion.

Oncology suggested staging as advanced stage HCC (Child-Pugh A, ALBI grade 1, BCLC stage C). She was not considered a candidate for surgical resection or Y90 radioembolization due to her performance status. Poor prognosis and options for systemic palliative treatment were explained to the patient. The patient's symptoms improved with symptomatic management, and she was discharged home on day 3 with a plan to continue multidisciplinary team evaluation as outpatient. Further evaluation deemed her not a candidate for additional interventions such as immunotherapy given her significant worsening functional status. The patient decided to enroll in hospice care.

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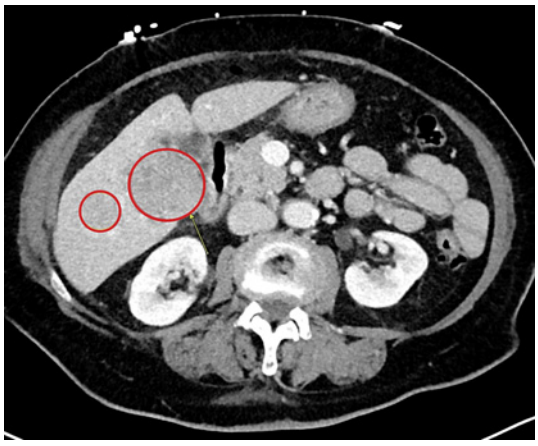

Fig. 1. CT abdomen and pelvis with contrast revealed a noncirrhotic liver morphology with a large right hepatic lobe centrally necrotic mass in the inferior aspect of segments 5/6 measuring 7.3 × 8.4 × 8.2 cm with adjacent infiltrative component extending superiorly in segment 5 and into several right anterior portal vein branches.

Discussion

CML is a myeloproliferative neoplasm characterized by uncontrolled myeloid cell lineage proliferation in the peripheral blood. CML is a result of a reciprocal translocation between chromosomes 9 and 22 t(9:22)(q34;q11) which generates BCR-ABL1 fusion gene responsible for the deregulated activity of TK. CML represents 15% of the adult leukemias. Its incidence increases with age, and its median age of presentation is 67 years. Ionizing radiation exposure is the only recognized risk factor. Most patients are asymptomatic, and the disorder is found incidentally on routine blood tests. If symptoms are present, these are usually fatigue, malaise, weight loss, and left upper quadrant discomfort or pain which are mostly related to anemia and splenomegaly [1, 3]. CML occurs in 3 phases: chronic, accelerated, and blast phase. Most patients (90–95%) are diagnosed in the chronic phase which if untreated will eventually progress to accelerated or blast phase in approximately 3–5 years [4]. During the chronic phase, different TKIs are used for treatment based on patient's risk score, specific TKI toxicity profile, patient age, comorbid conditions, and BCR-ABL1 mutation profile. In our case, the patient was in a chronic phase of her disease and on treatment with imatinib for more than 10 years. Decision about treatment discontinuation must be individualized and based on possibility of proper monitoring given an overall risk of a molecular relapse in 61% of the patients [3]. The most common causes of death in patients with CML on chronic phase while on treatment with a TKI are progression to advance staging (23%), development of secondary malignancies (17%), and cardiovascular events (17%) [5].

There is an established relation between CML and solid tumors which has been documented mainly in four specific scenarios [2] being the latest scenario described below the one related to our case. The first scenario describes patients with CML who have developed MS, an extremely rare tumor made of myeloid blasts which can be located at any extramedullary location but has a predilection for skin, bone, and soft tissues of head and lymph nodes. This scenario is mostly seen during CML progression to blast crisis phase. However, less often MS could also precede or be the first manifestation of CML [6].

The second scenario pertains to the development of secondary CML after systemic cytotoxic and/or radiation therapy of solid tumors which has mainly been seen in ovary and breast cancer and may be related to the increasing number of patients being treated with intensive chemotherapy regimens [7]. On the other hand, the specific duration and dose of radiation exposure to promote BCR-ABL translocation have not been determined despite observation of patients surviving atomic bomb exposures. Another significant exposure in this

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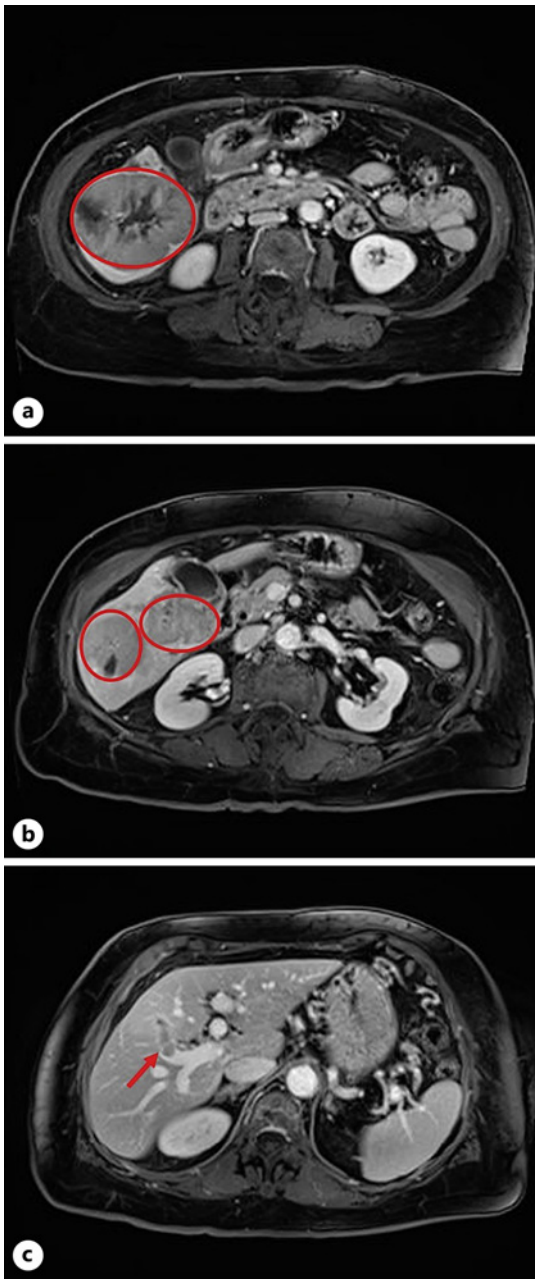

Fig. 2. An 8.8-cm well-circumscribed mass is seen arising from the inferior right hepatic lobe. This mass demonstrates heterogeneous arterial enhancement, washout, and pseudocapsule with central necrosis (**a**). An adjacent 4.9-cm lesion is seen within hepatic segment V with similar imaging characteristics (**b**). There is tumor invasion into the adjacent hepatic segment V portal vein, extending into the anterior right portal vein and segment IV portal vein branches (**c**).

scenario is a very rare occurrence of secondary CML reported on patients who have received radioactive iodine for thyroid carcinoma [8].

The third scenario involves the occurrence of CML following solid organ transplantation and concurrent immunosuppression, with most cases emerging after kidney transplant but also seen after liver and heart transplant. This scenario seems potentially linked to immunosuppression following organ transplantation which may be related to primary toxicity, compromised immune surveillance, and intrinsic mutagenic potential [9].

The fourth scenario, one of the interests in our presented case, encompasses the development of secondary solid tumors after treatment for CML. The exact mechanisms underlying these occurrences remain unclear; however, they could be linked to multiple genetic changes, DNA damage induced by chemotherapy, and increased vulnerability to oncogenic

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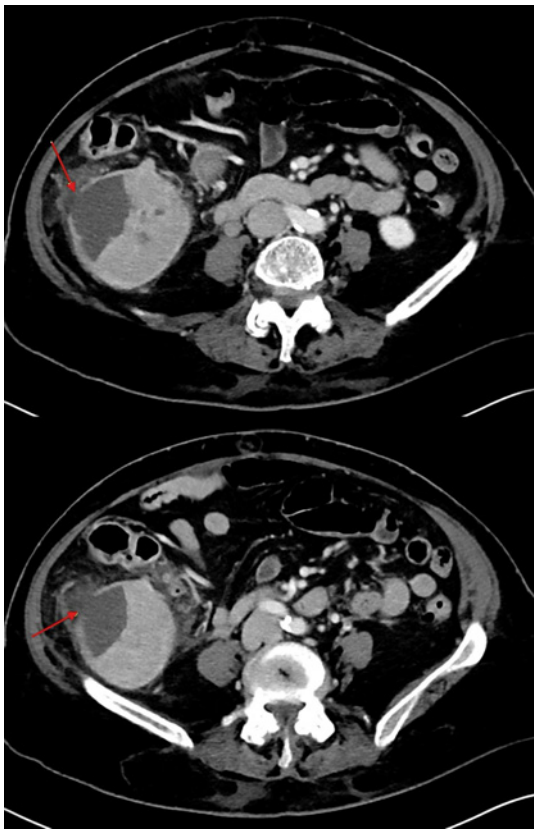

Fig. 3. Interval development of fluid collection within the dominant mass in the inferior aspect of the right hepatic lobe (biopsy-proven HCC) with associated rupture of the liver capsule. Inflammation and small amount of ill-defined fluid at the site of capsular rupture.

viruses due to the weakening of the immune system [10–12]. A study evaluated the incidence and type of secondary malignancies in patients with CML in the era of TKIs using US-based Surveillance, Epidemiology, and End Results database to select 14,897 patients diagnosed with CML from 2001 to 2014 excluding mainly patients with prior malignancies and patients with malignancies on the same year of CML diagnosis. This study revealed an incidence of 4.5% (597 patients) of secondary malignancies in patients with CML which was approximately 20% higher than the average risk of second malignancies of the US 2,000 general population. The 3 most common systems involved in secondary malignancies were male genital system (130 patients), digestive system (129 patients), and respiratory system (92 patients). In the group who developed secondary malignancies of the digestive system, there were only 14 cases of HCC found [5]. This study was not able to identify how many of these patients were on treatment with a TKI but suggested that TKIs may not contribute to the development of secondary malignancies. It also did not describe if any specific risk factor for liver disease was present in the patients who developed HCC as a secondary malignancy while on treatment for CML.

A systematic review of gastrointestinal manifestations in CML in 2021 found 3 cases of HCC in patients already being treated for CML. Other GI malignancies in patients with CML found in this study from the most common to the less common included colorectal cancer (5 out of 11 cases have cancer before CML) and pancreatic adenocarcinoma (3 cases) [13].

A Swedish study where most of the CML patients were treated with a TKI showed no difference in the incidence of secondary malignancies before and after initiation of TKI 2 years since diagnoses of CML which suggested that the increased number of secondary malignancies in CML could be related to CML itself rather than to TKI treatment [14]. An Italian study in a cohort of 514 patients with CML with imatinib as the first-line treatment showed an incidence of 5.8% of

secondary malignancies (2 cases of HCC) which was not above the incidence of the age- and sex-matched Italian population. Therefore, this study suggested that there is a lack of correlation between imatinib and secondary malignancies in patients with CML [15].

In our case, the patient experienced the development of HCC while undergoing treatment with imatinib for CML. Given the absence of any substance abuse such as alcohol consumption or exposure to harmful substances, along with well-managed diabetes and no evidence of hepatic infections or other conditions affecting the liver, the occurrence of HCC in a liver without cirrhosis could potentially be associated with CML itself or linked to the treatment administered for CML.

Interestingly, imatinib, one of the TKIs used to treat CML, seems to have therapeutic implications in HCC through inhibition of the growth of HCC cells by downregulation of proteins related to tumor cell cycle [16] and inhibition of autophagy in HCC cells in vitro and in vivo [17]. This may support the inclusion of imatinib as a future therapeutic agent for the treatment of HCC. However, further research is needed to clarify the effects of imatinib and other TKIs in HCC malignancy.

Miranda et al. [18] conducted an analysis using data from the CML study phase IV to investigate the occurrence of secondary malignancies as a potential result of long-term toxicity associated with TKIs. Among a total of 1,525 chronic phase CML patients, 64 individuals (n = 61 on TKI, n = 3 on interferon-α) developed secondary malignancies. The most frequently observed secondary malignancies included prostate, colorectal, and lung cancers, as well as non-Hodgkin's lymphoma, malignant melanoma, non-melanoma skin tumors, and breast cancer.

To date, only a small number of cases have been documented involving the simultaneous presence of CML and HCC [2, 5, 10, 15]. From the available data of all these cases, one had untreated hepatitis B (HB), another one had been an alcoholic for 30 years, and others had reactivation of HB. There were no data of preexisting liver disease or risk factors for liver disease in the large database studies [5, 15]. Our case is the first case reported with no history of liver disease. The precise underlying mechanisms for this co-occurrence remain ambiguous and continue to be an area of ongoing research.

Conclusion

Secondary malignancies are the second most common cause of death in patients with CML on chronic phase in the era of TKIs. CML has an unclear association with secondary malignancies. Among them, HCC is very rare. CML is treated with a revolutionary medicine, imatinib, known to inhibit TK-1. Furthermore, imatinib has been shown to promote antitumor effects of HCC in vitro and in vivo. Patients with concurrent HCC in CML are rarely reported and, those too, are in light of either reactivation of HB virus or with a background of prolonged heavy alcohol use in one of the cases. Our case, thus, describes the only patient in known literature where there was no known or usual causal agent or factor for HCC. More research is needed to clarify the relation between CML, TKIs, and HCC. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000540260).

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent to publish the details of this case report and any accompanying images was obtained from the patient.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors attest that they meet the current ICMJE criteria for authorship. L.R.P. wrote manuscript with input from D.R., R.P., and S.B. formatted images.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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