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Case Report

Chronic Myeloid Leukemia in a Patient with Hepatitis B Virus Infection: A Case Report

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Keywords
Hepatitis B · Hepatitis B virus reactivation · Chronic myeloid leukemia · Imatinib · Tyrosine kinase inhibitor

Abstract
Chronic myeloid leukemia (CML) is a myeloproliferative disorder diagnosed by demonstrating the Philadelphia chromosome (Ph) or the BCR-ABL fusion gene. Tyrosine kinase inhibitors (TKIs) are the standard of therapy. There are increasing reports of hepatitis B virus reactivation (HBVr) in patients on this treatment. We report a case of a 46-year-old male patient diagnosed to have CML in the chronic phase and resolved hepatitis B infection. He was treated with imatinib as upfront therapy for CML and with lamivudine as prophylaxis against HBVr. The patient tolerated both treatments well with no adverse effects. The aim is to address the deficiencies in the literature in regard to managing these patients, prevention, and follow-up.

Introduction

Chronic myeloid leukemia (CML) is a malignant clonal disorder of hematopoietic stem cells and is one of the myeloproliferative disorders [1]. Revealing the Philadelphia chromosome (Ph) or the BCR-ABL fusion gene, by cytogenic or molecular analysis studies, is the standard diagnostic approach [2]. The management of Ph chromosome-positive and BCR-ABL1-positive CML has undergone a profound evolution with the tyrosine kinase inhibitors (TKIs) [3]. Currently, there are 5 TKIs approved by the FDA for the treatment of CML, including imatinib, dasatinib, nilotinib, bosutinib, and ponatinib [4].

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Table 1. Admission laboratory investigations showing marked leukocytosis

Lab test	Value	Normal range
WBC	96.3 × 10^3/μL	4.0–10.0
RBC	4.4 × 10^6/μL	4.5–5.5
Hgb	14.3 g/dL	13.0–17.0
Hct, %	44.6	40.0–50.0
MCV	101.6 fL	83.0–101.0
MCH	32.6 pg	27.0–32.0
MCHC	32.1 g/dL	31.5–34.5
RDW-CV, %	15.3	11.6–14.5
Platelet	203 × 10^3/μL	150–400
MPV	11.5 fL	7.4–10.4
Absolute neutrophil	49.1 × 10^3/μL	2.0–7.0
Lymphocyte#	9.6 × 10^3/μL	1.0–3.0
Monocyte	4.8 × 10^3/μL	0.2–1.0
Eosinophil	1.0 × 10^3/μL	0.0–0.5
Basophil	1.93 × 10^3/μL	0.02–0.10
Neutrophil, %	37.0	
Lymphocyte, %	10.0	
Monocyte, %	5.0	
Eosinophil, %	1.0	
Basophil, %	2.0	
Bands, %	14.0	
Metamyelocytes, %	4.0	
Myelocyte, %	24.0	
Promyelocytes, %	2.0	
Blasts, %	1.0	
Urea	4.9 mmol/L	2.8–8.1
Creatinine	77 μmol/L	62–106
Sodium	144 mmol/L	136–145
Potassium	4.3 mmol/L	3.5–5.1
Chloride	103 mmol/L	98–107
Bicarbonate	27 mmol/L	22–29
Calcium	2.43 mmol/L	2.15–2.50
Adjusted calcium	2.41 mmol/L	2.15–2.50
Bilirubin total	10 μmol/L	0–21
Total protein	76 g/L	66–87
Albumin	41 g/L	35–52
Alkaline phosphatase	65 U/L	40–129
ALT	19 U/L	0–41
AST	19 U/L	0–40
Glucose	3.9 mmol/L	3.3–5.5

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Table 2. Hepatitis B panel revealing a resolved/past HBV infection

Serology	Interpretation
Hepatitis B surface antibody	Reactive
Hepatitis B surface antigen	Nonreactive
Hepatitis B core antibody IgM	Nonreactive
Hepatitis B core antibody IgG	Nonreactive
Hepatitis B antibody titers	26.80

HBV, hepatitis B virus.

Hepatitis B virus (HBV) infection is a major public health problem worldwide; roughly 30% of the world's population show serological evidence of current or past infection [5]. It can cause both acute and chronic diseases. The WHO estimates that in 2015, 257 million people were living with chronic hepatitis B infection and that HBV resulted in an estimated 887,000 deaths [6]. We report a case of CML in a patient with a past hepatitis B infection to shed light on the rare association and nondecisive guideline recommendations regarding the prevention of flaring of hepatitis B infection.

Case Report/Case Presentation

A 46-year-old Filipino male patient was admitted for asymptomatic COVID-19 infection after he was tested positive for SARS-CoV-2 PCR as part of routine screening for contact of a known case of COVID-19. He had no significant past medical and surgical histories, no known allergies, and was not on chronic medications. Other than working as a cook and occasional alcohol intake, family and social histories were unremarkable. Aside from splenomegaly, which was also confirmed by ultrasound abdomen to be 16.2 cm, the rest of the physical examination was noncontributory.

On routine blood labs, CBC showed notable leukocytosis ($96.3 \times 10^3/\mu L$) with normal other parameters (shown in Table 1). Peripheral smear suggested CML. The diagnosis was confirmed by interphase fluorescence in situ hybridization showing BCR-ABL1, *t*(9; 22)(q34; q11.2) positivity. More detailed testing revealed a BCR-ABL1 to ABL1 percentage ratio of 84% international scale (IS), and characterization was positive for an e14a2 BCR-ABL1 gene fusion by single-step reverse transcription-polymerase chain reaction. At this stage, the diagnosis was confirmed to be CML in the chronic phase.

Before starting the TKI, the patient was screened for HBV infection. Serologic markers were going with past HBV infection (reactive anti-HBc IgG and reactive anti-HBs) (shown in Table 2).

Initially, the patient was put on preventive measures against tumor lysis until confirmation of the diagnosis. Then, the patient was started on imatinib for CML chronic phase as well as on lamivudine as a prophylactic against flaring of the HBV infection.

Blood cells were closely monitored during the initial period of treatment, and the latest results are shown in Table 3. BCR-ABL1 levels were also monitored at diagnosis (84% IS), 3 months (92% IS), and 6 months (3% IS). By the newest results, it was evident that the response to treatment is optimal, and the decision is to continue the same regimen with further follow-up of BCR-ABL1 levels at 12 months. The patient is doing well and did not experience side effects from the medications.

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Table 3. Follow-up laboratory investigations at 6 months

Lab test	Value	Normal range
WBC	3.8 × 10^3/μL	4.0–10.0
RBC	3.0 × 10^6/μL	4.5–5.5
Hgb	11.3 g/dL	13.0–17.0
Hct, %	31.5	40.0–50.0
MCV	104.0 fL	83.0–101.0
MCH	37.3 pg	27.0–32.0
MCHC	35.9 g/dL	31.5–34.5
RDW-CV, %	14.6	11.6–14.5
Platelet	63 × 10^3/μL	150–400
MPV	9.6 fL	7.4–10.4
Absolute neutrophil	2.1 × 10^3/μL	2.0–7.0
Lymphocyte#	1.4 × 10^3/μL	1.0–3.0
Monocyte	0.2 × 10^3/μL	0.2–1.0
Eosinophil	0.1 × 10^3/μL	0.0–0.5
Basophil	0.02 × 10^3/μL	0.02–0.10
Neutrophil, %	54.5	
Lymphocyte, %	36.9	
Monocyte, %	6.0	
Eosinophils, %	2.1	
Basophil %	0.5	
Urea	3.6 mmol/L	2.8–8.1
Creatinine	86 μmol/L	62–106
Sodium	141 mmol/L	136–145
Potassium	3.2 mmol/L	3.5–5.1
Chloride	106 mmol/L	98–107
Bicarbonate	26 mmol/L	22–29
Calcium	2.21 mmol/L	2.15–2.50
Adjusted calcium	2.27 mmol/L	2.15–2.50
Bilirubin total	8 μmol/L	0–21
Total protein	70 g/L	66–87
Albumin	37 g/L	35–52
Alkaline phosphatase	85 U/L	40–129
ALT	44 U/L	0–41
AST	48 U/L	0–40

Discussion/Conclusion

TKIs, since their introduction, have become a cornerstone in the treatment of CML in the chronic phase, and the initial choice is imatinib (branded or generic), dasatinib, and notilinib [7–9]. Imatinib was first used in 1998, and its effect is primarily through inhibition of proliferation and induction of apoptosis of the BCR-ABL1 oncoprotein [8, 10, 11]. It is widely available and economically cheaper in comparison with the other options.

Hepatic toxicity is one among other reported side effects of imatinib and other TKIs in general. It can be self-limited and reversible upon discontinuation of the inducing agent, and it can be serious and fatal. HBV reactivation (HBVr) is increasingly recognized as an important adverse effect with an incidence approaching 10.8 per 100 person-years in a retrospective cohort study [4]. Most of the reported cases are triggered by the use of imatinib [12–16]. It remains unclear whether imatinib alone causes HBVr or other TKIs are underreported.

Several definitions have been proposed for HBVr based on virologic, serologic, or both criteria; a simple definition would be an increase in HBV replication usually associated with a rise in serum aminotransferase levels [4, 17, 18]. Although there are recommendations to screen for HBV infection before starting immune-suppressing medications, however, guidelines about the prevention of HBVr in the context of TKIs remain uncertain. Given a growing number of reports about HBVr among patients taking these medications, our patient was started on lamivudine based on physician preference as there is no consensus upon it.

A recent publication addressed the issue of follow-up in such a population, and we agree with the authors [4]. Baseline liver function tests were established before starting treatment and followed at 1 month, 3 months, and 6 months. Further monitoring is planned at 1 year. However, infections and reactivation of infections like hepatitis and tuberculosis [19] remain important unmet needs that require further studies. The weight of this case report is to boost awareness about deficiencies in the current literature and to open a discussion in addressing the risk of HBVr and the lack of guidance in terms of prophylaxis and monitoring.

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Statement of Ethics

The case was approved by the Hamad Medical Corporation Research Center with Reference No. MRC-04-21-232. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Yousef Mohammed Ali Hailan and Mohamed A. Yassin performed writing and editing and gave final approval of the concept. Deena Mudawi performed editing and approved of the final version.

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