EJCRIM
European Journal
of Case Reports
in Internal Medicine

A RARE CASE OF AN ELDERLY MALE WITH PROGRESSION TO CHRONIC MYELOID LEUKAEMIA SECONDARY TO CHRONIC LYMPHOCYTIC LEUKAEMIA

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Received: 12/01/2024 **Accepted:** 12/02/2024 **Published:** 04/03/2024

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

How to cite this article: Saowapa S, Pangkanon W, Adu Y, Chaisrimaneepan N, Olavarria Bernal D, Polpichai N, Siladech P, Sekhon J. A rare case of an elderly male with progression to chronic myeloid leukaemia secondary to chronic lymphocytic leukaemia. *EJCRIM* 2024;**11**:doi:10.12890/2024_004297.

ABSTRACT

Chronic lymphocytic leukaemia (CLL) is a lymphoproliferative disorder characterised by an accumulation of monoclonal B lymphocytes, with an increased risk of secondary cancers. The coexistence of CLL and chronic myeloid leukaemia (CML) is a rare phenomenon, with three main types being classified: CML preceding CLL, CLL preceding CML and simultaneous occurrence.

The coexistence of these chronic leukaemias poses a complex clinical challenge, with the underlying mechanisms of their association remaining enigmatic. Here, we present a report of an elderly male with a long history of CLL, who was subsequently diagnosed with secondary CML.

KEYWORDS

Coexisting CLL/CML, chronic lymphocytic leukaemia, chronic myeloid leukaemia, dasatinib

LEARNING POINTS

- The development of chronic myeloid leukaemia (CML) subsequent to chronic lymphocytic leukaemia (CLL) is an uncommon occurrence, challenging conventional expectations of disease evolution in chronic leukaemia.
- Extensive and appropriate testing is necessary to promptly identify secondary CML in CLL patients.
- Targeted therapy with dasatinib, a tyrosine kinase inhibitor, may demonstrate efficacy in reducing leukocytosis and *BCR-ABL1* levels in patients with coexisting CLL and CML.

EFIM
European Federation of Internal Medicine

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INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is a lymphoproliferative disorder characterised by a progressive accumulation of monoclonal B lymphocytes. Patients with CLL face an elevated risk of developing secondary solid or haematologic cancers following diagnosis. However, the progression from CLL to chronic myeloid leukaemia (CML) is rare. We present the case of an elderly male diagnosed with CML secondary to CLL.

CASE DESCRIPTION

An 82-year-old male with a past medical history significant for CLL presented to the oncology speciality clinic following concerns of elevated leukocyte levels from his primary oncologist. He was diagnosed approximately 21 years prior and underwent a period of 10 years of observation with limited symptoms. At that time, in response to escalating hyperleukocytosis, he was initiated on a four-month course of rituximab, followed by a subsequent one-year regimen of ABT-263 (a Bcl-2 inhibitor). A bone marrow (BM) biopsy was then conducted, revealing approximately 50% marrow cellularity with predominantly nodular infiltrates of CLL. Cytogenetic analysis showed 46, XY, t(6;11)(p21;q13){8}/46,XY[12], fluorescence in situ hybridisation (FISH) results indicated normal findings without the 17p deletion, and the immunoglobulin heavy-chain variable (IGHV) region gene was found to be mutated. Eleven years following the treatment, he was found to have leukocytosis with a white blood cell count of 92 K/µl.

While the initial peripheral blood smear at his current visit was consistent with CLL, additional involvement with CML was found. Further analysis revealed persistent nodular BM involvement with CLL of 5–10%. Additionally, he tested positive for *BCR-ABL1* in the chronic phase with <5% BM blasts and no circulating blasts. A focal (<5%) BM involvement of a B-cell lymphoproliferative disorder aligned with the established CLL. FISH revealed 46, XY, t(9;22)(q34;q11.2)[20], indicating *BCR-ABL1* positivity. Dasatinib 100 mg daily was started, resulting in a reduction of the white blood cell count from 85 K/µl to 5 K/µl and *BCR-ABL1* levels from 48% to 13% in a period of two months. The patient showed clinically satisfactory improvement and was transitioned to maintenance imatinib.

DISCUSSION

CLL is the most commonly diagnosed leukaemia in adults in Western countries, showing a higher incidence in men. Its prevalence increases with age, with an average age of diagnosis being approximately 70 years[1]. Individuals with CLL have an increased susceptibility to developing secondary malignancies as a result of their compromised immune system, or exposure to chemotherapy[2]. Although CLL and CML are frequently diagnosed in older individuals, it is rare for both of these diseases to be present in a patient simultaneously.

CML in CLL coexistence is primarily classified into three types: CML preceding CLL, CLL preceding CML and simultaneous occurrence. To date, there have been 18 cases documented of patients where CML was diagnosed following an initial diagnosis of CLL, with timeframes ranging from 6 to 96 months[3]. According to Laurenti et al., there were eight patients who developed CLL and CML simultaneously[4]. In our case, we report a patient who developed CML 21 years after the diagnosis of CLL, which is the most common type of coexistence[3].

Associations between these two chronic leukaemias have rarely been reported. The occurrence of both CLL and CML could be influenced by interactions between the lymphoid and myeloid cell lineages. Currently, several mechanisms have been proposed. A few studies indicate that the use of cytotoxic agents and B-cell receptor inhibitors in CLL may contribute to the development of myeloid neoplasms. Therefore, the cytotoxic agents frequently employed in CLL treatment might induce genetic changes that lead to the development of CML[5,6]. An alternative hypothesis proposes that *BCR-ABL* transformed cells have been observed to produce cytokines, such as interleukin-3, which enhance the proliferation of B-lymphoid progenitor cells. This mechanism could play a role in the emergence of CLL in individuals previously diagnosed with CML[7,8]. Few reports have retrospectively investigated patients with CLL who later progressed to CML, aiming to identify low levels of the *BCR-ABL* gene in the initial CLL diagnosis specimens. This exploration sought to uncover potential underlying causes of undiagnosed CML concurrent with CLL diagnosis. However, even with the sensitive method of reverse transcription polymerase chain reaction, the *BCR-ABL* gene was not detected in the initial specimens, suggesting that the development of CML may have occurred subsequently, possibly due to timing. The co-occurrence of both diseases could be associated with molecular genetic aberrations induced by cytokines and a weakened immune system, originating from either the lymphoid lineage (in CLL) or the myeloid lineage (in CML). This process may take some time to develop after one disease is established[9-12].

Immunochemotherapy with fludarabine, cyclophosphamide and rituximab remains a major first-line option for many CLL patients without the *TP53* gene mutation[10]. Conversely, those with either a 17p deletion or a *TP53* mutation often demonstrate resistance to chemotherapy and therefore should be managed with specialised targeted therapies[11]. The first-line treatment for CML involves using a tyrosine kinase inhibitor (TKI). In cases where patients with high white blood cell or platelet count experience symptoms, a brief hydroxyurea course may be considered while waiting for confirmation of a CML diagnosis through molecular and cytogenetic testing[12]. A major challenge in treating concurrent CLL and CML lies in balancing the efficacy and toxicity associated with using both a Bruton's tyrosine kinase (BTK) inhibitor and a TKI, which may result in combined cardiac toxicity and cytopenia. Additionally, concerns arise regarding drug interactions between these medications, as

imatinib (a TKI) inhibits CYP3A4 metabolism, potentially increasing the levels of ibrutinib (a BTK inhibitor) and predisposing the patient to adverse effects from the BTK inhibitor. Clinicians should carefully weigh the risks and benefits of administering both medications simultaneously[13].

CONCLUSION

The development of CML subsequent to CLL is uncommon. It is important for clinicians to recognise the inclusion of CML within the spectrum of disease progression, distinct from more prevalent secondary cancers such as lymphomas and solid tumours. Targeted therapy with dasatinib may provide favourable responses in this patient population.

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