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WORD COUNT 2057
TIME SUBMITTED 22-FEB-2022 05:15PM
PAPER ID 82860698

Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 74437

Manuscript Type: CASE REPORT

Development of plasma cell dyscrasias in a patient with chronic myeloid leukemia: A case report

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Abstract

BACKGROUND

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder. Plasma cell dyscrasias (PCD) are a rare heterogeneous group of hematological disorders. The co-occurce of CML and PCD in the same patient is an extremely rare incident and has been reported in several cases in the literature.

CASE SUMMARY

In the present report, we described a rare case of the co-occurrence of CML and PCD in a 48-year-old man and we discussed the reason why monoclonal gammopathy of undetermined significance (MGUS) progressed to smoldering multiple myeloma (SMM) and eventually to multiple myeloma (MM) while being treated with dasatinib for CML. The tyrosine kinase inhibitor (TKI) treatment and cytogenetic change may contribute to this phenomenon and clonal hematopoiesis of indeterminate potential may lead to both CML and MM cells in a patient. Future researches are warranted to further explain the hidden reasons.

CONCLUSION

This case highlights gene translocation may contribute to initiation and sustainability of clonal proliferation. Moreover, the treatment with TKI and cytogenetic change may contribute to progression from MGUS to SMM, and eventually to MM.

Key Words: Chronic myeloid leukemia; Plasma cell dyscrasias; Multiple myeloma; Tyrosine kinase inhibitor; Translocation; Case report

INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder, which is defined by the presence of Philadelphia chromosome (Ph) in a patient with a myeloproliferative neoplasm (MPN). Plasma cell dyscrasias are a rare heterogeneous group of hematological disorders, which include monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM), systemic AL amyloidosis, polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes (POEMS) syndrome and so on[1,2]. MGUS is an asymptomatic, pre-malignant disorder characterized by monoclonal plasma cell proliferation in the bone marrow and absence of end-organ damage such as osteolytic bone lesions, anemia, or renal failure[3]. It shows the risk of progression to MM and associated plasma cell neoplasms[4]. MM arises from the malignant transformation of post-germinal center plasma cells. The origin of the cells is distinctly different in CML and plasma cell dyscrasias (PCD). There were several cases of coexistence of CML and MM. However, there was few distinctive report about the evolution from MGUS to smoldering multiple myeloma (SMM) and to MM in patients with CML complicated with PCD. In this case report, we described a patient who developed MGUS which progressed to SMM and eventually to MM while being treated with dasatinib for CML. The tyrosine kinase inhibitor (TKI) treatment and cytogenetic change may contribute to this phenomenon.

CASE PRESENTATION

Chief complaints

A 48-year-old man who was admitted to our hospital was diagnosed with leukocytosis with white blood cell count of 25.2 × 10^9/L, hemoglobin level of 149 g/L, and platelet count of 330 × 10^9/L, eosinophils level of 0.99 × 10^9/L, basophil level of 1.38 × 10^9/L without any complaints during the health examination.

History of present illness

No special physical signs and symptoms were reported before. He did not appear to have a history of exposure to toxic agents or irradiation.

History of past illness

The patient did not have previous medical history.

Physical examination

No other special physical signs.

Laboratory examinations

At first, his serum creatinine was 110.18 μmol/L. His lactate dehydrogenase was 364.04 μ/L. His total protein and albumin were normal. His 24-h urine for total protein was 1.82 g/24 h. His serum immunofixation electrophoresis (SIFE) was weak positive. Quantitative reverse transcription polymerase chain reaction (qRT-PCR) using international scale for BCR/ABLP210 (blood) was 48.02%. The bone marrow plasma cells percentage was 1%. The diagnosis of CML was confirmed by qPCR analysis four months after he received dasatinib. In December 2020, Fluorescence *in situ* hybridization (FISH) for t(9;22) (q34;q11) was negative and BCR/ABL transcript has decreased from 48.02% to 0.25%. Then the percentage of bone marrow mature plasma cells was 4%. Serum free light chain (SFLC) ratio (κ/λ) was 85.62. In March 2021, his BCR/ABL transcript was 0.06% and rFLC (κ-FLC:λFLC) was 93.56%. SIFE and serum protein electrophoresis (SPEP) were negative. M1-protein in urine protein

electrophoresis (UPEP) was 89.99%. Urine immunofixation electrophoresis revealed the presence of monoclonal light chain κ. The percentage of plasma cells in bone marrow was about 11.5% (Figure 1). Whole-body low-dose computed tomography scan documented no osteolytic lesions. In April 2021, his BCR/ABL transcript was 0. At this time, SIFE showed monoclonal light chain κ, but SPEP was still negative, and rFLC (κ-FLC:λ-FLC) was 144.43. The 24-h urine for total protein rose to 3.84 g/24 h. M1-protein in UPEP 88.47%. Cytogenetic karyotyping results revealed normal male chromosome complement.

Imaging examinations

FISH analysis for the immunoglobulin heavy chain (IgH) locus on chromosome 14q32 was positive (Figure 2A and B). FISH analysis for RB-1/LAMP1 showed deletion of chromosome 13q14 (Figure 2C and D). Another FISH analysis showed normal for IgH partner genes arrangement, CKS1B/CDKN2C and P53/CEP17.

FINAL DIAGNOSIS

The final diagnosis for the present case is the coexistence of CML and MM.

TREATMENT

Now he is receiving bortezomib, lenalidomide, and dexamethasone (VRD) chemotherapy with simultaneously continued oral dasatinib. After 4 to 6 cycles of VRD treatment when he achieved complete response, he will experience allogeneic hematopoietic stem cell transplantation.

OUTCOME AND FOLLOW-UP

He has finished six cycles of chemotherapy with VRD, and he has already done a pretransplant match. One month later, he will receive an allogeneic transplant.

DISCUSSION

CML is a clonal myeloproliferative neoplasm derived from an abnormal multipotent hemopoietic stem cell that has acquired the BCR-ABL1 fusion gene, usually through t(9;22) (q34;q11), also known as the Ph chromosome. The derivation of this clonal population from a multipotent hematopoietic stem cell was supported by cytogenetic studies[5]. In rare cases, BCR-ABL1 has been described in essential thrombocytosis, myelodysplastic syndrome, MM, and malignant lymphoma.

MGUS is a clinically asymptomatic premalignant clonal plasma cell. Smoldering myeloma describes a stage of disease that has no symptoms and no related organ or tissue impairment.

In this case, the patient was diagnosed with CML initially and four months later was confirmed diagnosis of MGUS which progressed to MM ultimately. The hypothesis being that CML and MGUS should occurred simultaneously because of elevated serum light chain at the time of diagnosis of CML. Regrettably, no further examination was carried out at that time to verify the simultaneous occurrence of CML and MGUS.

The cause of co-existence of CML and PCD in one patient remains unclear. The paramount etiology may be what precursors commonly referred to as "clonal hematopoiesis of indeterminate potential (CHIP)" leads to both CML and MM cells in a patient[6]. Clonal hematopoiesis is often detected by next-generation sequencing, chromosomal analysis, FISH analysis, PCR, and other techniques. Dysplasia and blasts were not discovered in bone marrow in the early stage of the disease, which could not verify the pathogenesis. Meanwhile a new study also show us all patients with myeloma go through the stage of MGUS, but it is often unrecognized for some reason or it is subclinical[7].

Another hypothesis is secondary malignancies related to TKI treatment of CML. Gunnarsson *et al*[8] studied 868 patients diagnosed with CML in Sweden in 2002 and results indicated that CML patients had a high risk of developing a second malignancy in the TKI era. The common malignancies are as the following: gastrointestinal cancer, nose and throat cancer, prostate cancer, breast cancer except for hematological cancer. However, whether the cause leading to a secondary malignancy is associated with TKI

treatment or CML disease itself is uncertain. After all, multiple studies displayed that secondary cancers in CML were often found in early stage after the diagnosis of CML. The higher immunosuppressive effects and the DNA repair mechanisms of TKI may be involved in the phenomenon. For CML disease itself, BCR/ABL also participates in regulating cells apoptosis, proliferation and intercellular interactions, and promotes genomic instability and so on. Therefore, both the TKI treatment and CML disease itself may play an important role in the co-existence of CML and PCD in our case[8,9].

Studies show us the rate of progression from MGUS to MM is 1% per year, but approximately 10% per year for SMM[10]. We want to know more how this patient progressed from MGUS to SMM and then to MM under the circumstances of CML. Genes translocation may contribute to initiating and sustaining clonal proliferation. The common translocation at 14q32 and deletion of 13 in normal cells promote the genomic instability which results to the occurrence of MGUS/SMM. Finally, mutations in RAS genes, p16 methylation, abnormalities involving myc family of oncogenes, secondary translocations, p53 mutations and angiogenesis play an important role in promoting the development of MGUS/SMM into MM. In addition to that, recently, higher SFLC ratio has been shown to be an important risk factor for the progression[3]. In this case, translocations at 14q32, deletion of 13 in the patient was probably associated with the progression to MM.

CONCLUSION

Reports of the co-occurrence of CML and PCD in the same patient are rare. In the present report, we described a patient with CML. He received chemotherapy and oral dasatinib as therapy. During the follow-up, he developed MGUS and progressed to SMM and eventually to MM. Finally, the patient was diagnosed with CML and MM. Tyrosine kinase inhibitors and cytogenetic change are thought to potentially contribute to his disease progression. Further researches should be made to better understand the etiology of coexistence of CML and PCD.

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Figure Legends

Figure 1 Wright Giemsa stain. Bone marrow aspirate in the patient with multiple myeloma illustrated a preponderance of mostly mature-appearing plasma cells constituting 11.5% of the cells.

Figure 2 Interphase fluorescence *in situ* hybridization analysis. A: Interphase fluorescence *in situ* hybridization (FISH) analysis for the immunoglobulin heavy chain locus on chromosome 14q32. Normal reference; B: 14q32 deletion with only one red signal; C: Interphase FISH analysis. Normal reference; D: Monosomy of chromosome 13 with only one red and one green signal.

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