Prevalence of monoclonal gammopathy of uncertain significance in chronic myeloid leukemia

A case report

Wanyan Ouyang, MD, Xiaohong Zhao, MD, Shiyun Lu, MD, Zhi Wang, MD

Abstract

Rationale: The abnormal cell types in chronic myeloid leukemia (CML) and monoclonal gammopathy of uncertain (MGUS) are quite different, being myeloid and plasma cells, respectively. The coexistence of CML and MGUS is an uncommon event, which is seldom reported in literature.

Patient concerns: A 52-year-old female was diagnosed with CML in April 2001. From November 2006, the patient started on imatinib mesylate and kept a complete hematologic and cytogenetic response for nearly 11 years. During her follow-up on July 7, 2017, thrombocytopenia (35×10^9/L) was found. Bone marrow aspiration revealed 6% plasma cell infiltration. Serum immunoelectrophoresis revealed 1.24 g/dL of serum monoclonal (M) protein of IgG-κ type.

Diagnosis: MGUS was diagnosed because of absence of anemia, hypercalcemia, lytic bone lesions, or renal failure. Immune thrombocytopenia (ITP) was also diagnosed in this patient following the detection of antiplatelet autoantibodies. Complex karyotype and missense mutation in PRDM1 were identified.

Interventions: Because of her obvious decrease of platelets, she started treatment with thalidomide and prednisone.

Outcomes: Three months later, bone marrow aspirate showed disappearance of plasma cells. There developed an abrupt decrease in IgG and the absence of M-spike in serum immunoelectrophoresis. The platelet count kept normal during 1 year follow-up.

Lessons: Karyotypic event and gene mutation found in this case may be the initiation of disease transformation. Administration of thalidomide and prednisone proved effective in this patient.

Abbreviations: CML = chronic myeloid leukemia, ITP = immune thrombocytopenia, MAIPA = monoclonal antibody-specific immobilization of platelet antigens, MGUS = monoclonal gammopathy of undetermined significance, MM = multiple myeloma.

Keywords: CML, ITP, MGUS, PRDM1 mutation, thalidomide

1. Introduction

Chronic myeloid leukemia (CML) is a hematological disorder of pluripotent hematopoietic stem cells, with the cytogenetic character of Philadelphia (Ph) chromosome. Monoclonal gammopathy of undetermined significance (MGUS), the most prevalent of the plasma cell disorders, is defined by increased proliferation of clonal plasma cells, resulting in a detectable monoclonal component or M-protein. It shows the risk of progression to multiple myeloma (MM) and associated plasma cell neoplasms. Thus, the abnormal cell types in CML and MGUS are quite different, being myeloid and plasma cells, respectively. There are several reports of the coexistence of CML and MM but no distinctive report of coexistence of CML and MGUS. Because MGUS are easily overlooked only if symptomatic events happen due to secreted monoclonal (M) proteins. In this case, we describe a patient who developed MGUS while being treated with imatinib for CML. Complex karyotype and missense mutation may contribute to this transformation. Immune thrombocytopenia (ITP) was also diagnosed following the decreased platelet count and detection of antiplatelet antibodies. Thalidomide and prednisone proved effective in our case. This study was approved by the institute’s Ethics Committee of our hospital. The patient provided her written informed consent for the publication of this report.

2. Case report

A 52-year-old female was diagnosed with CML in April 2001. She presented with leukocytosis on a routine complete blood count, with white blood cell count of 52.38×10^9/L, hemoglobin...
level of 12.4 g/dL and platelet count of $159 \times 10^9$/L. She did not appear to have a history of exposure to toxic agents or irradiation. A bone marrow aspirate and biopsy were typical of CML and cytogenetic analysis confirmed the diagnosis by revealing the presence of the Ph chromosome in all the 20 metaphases obtained from the bone marrow. Cytoreduction was initiated with hydroxyurea and then recombinant human interferon alpha injection was added. During the 6 years treatment of interferon and hydroxyurea, the patient had been kept in chronic phase CML based on bone marrow examination and Ph chromosome positivity. Cytogenetic analysis still revealed presence of the Ph chromosome in 10 of the 15 metaphases obtained from the bone marrow in November 2006. From then on, the patient started on imatinib mesylate at the standard dose of 400 mg per day and achieved a complete hematologic response at 3 months and a complete cytogenetic response at 6 months after treatment initiation. Then routine quantitative reverse-transcription polymerase chain reaction (QPCR) for the Bcr-abl transcript was followed every half a year. Bcr-abl copies were undetectable, and the patient was in complete molecular response according to the National Comprehensive Cancer Network (NCCN) clinical practice guidelines on Chronic Myeloid Leukemia. Her CML remained in complete molecular remission and no additional abnormalities were found on cytogenetic evaluation for nearly 10 years.

During her follow-up on July 7, 2017, thrombocytopenia ($35 \times 10^9$/L) was found. Bone marrow aspiration revealed 6% plasma cell infiltration. Plasma cells constituted 2.6% as assessed by flow cytometry. Serum immunoelectrophoresis revealed 1.24 g/dL of serum M protein of IgG-k type and no immuneparesis was documented. Urine studies showed a kappa light chain proteinuria. Serum free light chain ratio was 14.7. Extensive radiological investigations documented no osteolytic lesions. MGUS was diagnosed under the circumstance of CML. Cytogenetic karyotyping results showed $50-51; X-X, +X, +X, +X, +X, +8q, +9, +10, +14, +16; +17, +21, +mar[CP4]$ (Fig. 1) and the absence of the Ph chromosome. Fluorescence in situ hybridization (FISH) analysis revealed neither known myeloma-associated abnormalities nor the Ph chromosome. The patient was further studied with next-generation sequencing to characterize the genomic landscape on unsorted bone marrow at diagnosis. Missense mutation in PRDM1 was identified. Moreover, ITP was also diagnosed following the detection of antiplatelet antibody by the monoclonal antibody-specific immobilization of platelet antigens (MAIPA) assay. Autoantibodies were directed to GPIIb/IIIa. Megakaryocyte count in the bone marrow aspirate was normal.

Because of her obvious decrease of platelets, she started treatment with thalidomide (200 mg/day) and prednisone (50 mg/day), and at the same time imatinib treatment was continued. The platelet count reached $159 \times 10^9$/L a week later and prednisone was reduced in a manner similar to that seen in patients with ITP. Three months later, bone marrow aspirate showed disappearance of plasma cells. There developed a

Figure 1. Karyotype analysis at the diagnosis of MGUS showing $50-51; X-X, +X, +X, +3,4p, +8, +8q, +9, +10, +14, +16; +17, +21, +mar[CP4]$. MGUS = monoclonal gammopathy of undetermined significance.
decrease of the elevated serum IgG to 3.8 g/dL and absence of M-spike in serum immunoelectrophoresis.

3. Discussion
CML is associated with the BCR-ABL fusion gene located on the Ph chromosome and has a worldwide annual incidence of 1 to 2 cases per 100,000 individuals. In contrast, MGUS is the most common plasma cell dyscrasia, present in approximately 2% of the general population 50 years of age and 3% of those ≥70 years. MGUS is an asymptomatic premalignant plasma cell disorder. It would be symptomatic due to associated autoimmune manifestations.

Here we report the prevalence of ITP at MGUS diagnosis. It has been reported that ITP was determined in 6/228 cases accounting for a prevalence of 2630/100,000 (95% CI: 1210–5620) at MGUS diagnosis. Several observations indicate an association between ITP and MGUS. Compared with general population, the prevalence of ITP in MGUS is higher. The underlying reasons for the association between MGUS and ITP remain speculative. According to observations in MGUS-associated autoimmune diseases, the paraprotein in these patients may act as a platelet-reactive autoantibody. Serum immunoelectrophoresis in our patient proved to be IgGκ type. Antiplatelet antibody detected by MAIPA was also present to be IgG type.

MGUS is usually treated if it is causing substantial disease through deposition of secreted M proteins. Because of her obvious decrease in platelets, thalidomide and prednisone were started as a form of multi-platelet myeloma therapy. Prednisone quickly brought the platelet count to 159 × 10^9/L. When prednisone was suspended, the platelet count was stable on normal level. Thalidomide is being currently administered at lower dose (50 mg/d). Thalidomide displayed a definitive anti-MM and a possible concomitant anti-ITP activity. Secondary ITP benefits from the treatment of the underlying diseases. By reducing the IgG level secreted by plasma cells, thalidomide could have a secondary effect on platelet count. Its immunomodulatory effects on several autoimmune diseases have been revealed. ITP might be one of them.

As regard to the development of MGUS in this case, karyotypic event found may be the main cause in early stage of transformation, which may further lead to neoplastic transformation to MM. Similar to MM, MGUS is a genetically heterogeneous disorder, but overall cytogenetic instability is lower than in MM. According to Mikulasova’s study, hyperdiploidy is detected in 38.9% of MGUS cases which confirmed that genetic abnormalities may play a role in monoclonal gammopathies. Gene mutations are thought to be secondary events associated with tumor progression rather than initiation.

There is little data associated with mutations in oncogenes and tumor-suppressor genes in MGUS. In MM, clustered missense mutations are present in known driver oncogenes like KRAS, NRAS and BRAF, while truncating mutations are found in known tumor suppressors such as TP53, FAM46C, and SP140. PRDM1 has only recently been identified as a tumor suppressor gene in MM. B lymphocyte-induced maturation protein-1 (Blimp-1, PRDM1) ensures B-cell differentiation to the plasma cell stage. Differentiation of B cells into antibody secreting cells (ASCs), plasma blasts and plasma cells, is regulated by a network of transcription factors. Within this network factors, PAX5 and BCL6 prevent ASC differentiation and maintain the B cell phenotype, while PRDM1 promote plasma cell differentiation and induce immunoglobulin secretion. Its instability constitutes a crucial oncogenic element. Truncations and deletions in PRDM1 were previously described in lymphomas, which were regarded as poor prognosis. Recurrent mutations, often truncating, recently found in MM suggesting they may represent novel tumor suppressors in MM. Missense mutation in PRDM1 found in this case may render Blimp-1 protein instable and susceptible to degradation which seems to play a role in the development of monoclonal gammopathies. While this speculation seems reasonable, it still requires in vitro study and more cases with PRDM1 gene mutations to analyze in order to answer this question in a more comprehensive way.

There are also discussions about whether imatinib mesylate may promote the development of MGUS. It has been reported that imatinib mesylate has a small stimulatory effect on the proliferation of plasma cells through activation of the Erk1 and Erk2 mitogen-activated protein kinases (MAPKs). On the contrary, there are also studies that show inhibitory effect on MM cell lines in vitro. In the current patient, MGUS was detected 16 years after the diagnosis of CML and 11 years after the initiation of imatinib mesylate. At this point, the association of CML and MGUS has been considered coincidental, but it is possible that imatinib may induce changes in phenotype of plasma cells and advance to multiple myeloma. However, none of the cases in the literature have demonstrated this hypothesis, and there is no obvious evidence supporting it. To further understand the mechanism underlying the coexistence of CML and MGUS or MM, additional reports are needed.

Author contributions
Conceptualization: Wanyan Ouyang, Zhi Wang.
Writing – original draft: Wanyan Ouyang.
Data curation: Shiyun Lu, Xiaohong Zhao.
Methodology: Shiyun Lu.
Writing – review & editing: Zhi Wang.

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