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CASE REPORT

Two cases of chronic myelomonocytic leukemia combined with monoclonal gammopathy of undetermined significance and a literature review

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Abstract

To describe myelodysplastic syndrome (MDS)/myeloproliferative neoplasm (MPN) combined with monoclonal gammopathy of undetermined significance (MGUS) in order to investigate the potential association between these 2 diseases. Two cases of confirmed chronic myelomonocytic leukemia (CMML) combined with MGUS were reported. In addition, prior publications of cases with combined MDS or MPN with MGUS were reviewed. The first case was of a 77-year-old man whose routine blood tests showed abnormal hemogram results. The diagnosis was CMML combined with IgM monoclonal gammopathy, and the disease course was 4 years. The CMML gradually progressed and the patient presented with anemia, thrombocytopenia, autoimmune hemolysis, and an increase in the number of immature cells in the bone marrow. Although the MGUS caused fluctuations in the concentrations of IgM, no IgM-associated organ damage was observed. Eventually, this patient died from a lung infection. The second case was of a 78-year-old man who sought treatment because of fever and a cough. An increase in the number of monocytes was discovered in the peripheral blood. Bone marrow smear results suggested obvious active granulocytes and an increase in the percentages of promyelocytes, myelocytes, and metamyelocytes. Unhealthy granulocytes and immature monocytes could also be observed, and the percentage of monocytes was increased. In addition, serum IgG levels were increased, and immunofixation electrophoresis results showed IgG-κ type M proteins. The diagnosis was CMML combined with IgG monoclonal gammopathy. These diseases were stable and follow-up was conducted for 1 year after diagnosis. The cases in this study combined with those that were reviewed in the relevant literature indicate that the presence of these 2 diseases in the same patient might not be a coincidence. The development of the 2 diseases in case 1 was different, and we speculate that they might have had different clonal origins. Whether CMML is a risk factor for MGUS and the role of clonal plasma cells in the occurrence and development of MDS and MDS/MPN requires further studies on a larger number of cases.

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Chronic myelomonocytic leukemia (CMML) constitutes a group of clonal diseases that originate from committed hematopoietic myeloid stem cells or from pluripotent stem cells. Monoclonal gammopathy of undetermined significance (MGUS) is a common pre-malignant plasma cell disease. These diseases are both common neoplastic diseases in elderly people. Although these 2 neoplastic diseases originate from different types of committed hematopoietic stem cells, case reports of patients with both of these diseases are not rare. It is unclear if these 2 diseases present together coincidentally or are causally related. The current report describes 2 cases of CMML combined with MGUS and presents a review of the relevant literature.

Case report

Case 1

The patient in this case was a 77-year-old man. He was admitted to the hospital on July 15th, 2011 because of an increase in white blood cells (WBCs) for more than 1 year and gum bleeding for 3 days. The patient first sought

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treatment at a local health care institution in October 2010 because of an upper respiratory infection. Routine blood tests revealed WBC count: 11.4×10^9/L, hemoglobin (Hb): 132 g/L, and platelet (PLT) count: 71×10^9/L. The patient did not seem concerned at that time.

After admission in 2011, physical examination demonstrated that the patient was lucid and was in good spirits. No signs of anemia were present, the skin featured scattered petechiae and ecchymosis, there were no palpable superficial lymph nodes, and no abnormalities were found in the heart, lungs, or abdomen. A full abdominal computed tomography (CT) scan showed mild fatty liver, a cyst on the right kidney, and some pelvic fluid. Routine blood tests found a WBC count of 34.7×10^9/L with a differential count of 51.9% neutrophils, 10.8% lymphocytes, and 36.6% monocytes; Hb: 108 g/L; PLT: 26×10^9/L.

A blood smear showed metamyelocytes: 0.01%, rod neutrophils: 0.05, lobed neutrophils: 0.60, lymphocytes: 0.18, and monocytes: 0.16. Moreover, small clusters of platelets, but no eosinophils or basophils, were observed. Routine urine tests showed that protein was ±. Complete immunologic and serologic tests showed IgA: 1.9 g/L, IgG: 7.59 g/L, IgM: 48.44 g/L, IgE: 15 IU/ml, and the erythrocyte sedimentation rate (ESR) was 90 mm/hr. Blood biochemistry showed globulin: 48.1 g/L, total bilirubin concentration: 24.3 μmol/L, indirect bilirubin: 20.9 μmol/L, creatinine: 135 μmol/L, uric acid: 452 μmol/L, and the electrolyte concentrations were normal. Serum protein electrophoresis revealed the presence of immunoglobulin M protein.

A bone marrow smear showed clear active proliferation of nucleated cells and an increased granulocyte/erythrocyte ratio. The percentage of cells with a granulocyte lineage was 62%, of which myeloblasts, promyelocytes, myelocytes, metamyelocytes, rod neutrophils, lobed neutrophils, and eosinophils accounted for 0%, 1.2%, 12.4%, 13%, 21%, 12.4%, and 1.6%, respectively. Monocytes accounted for 12.4%, and among these, immature monocytes accounted for 6.4%, while mature monocytes accounted for 6%. A total of 16 megakaryocytes appeared on the whole smear, and the distribution of platelets was scattered. The percentage of lymphocytes was 13.4%. No abnormal cell morphology was observed. Iron staining showed that extracellular iron staining was positive (+). The intracellular iron positivity rate was 21%, the neutrophil alkaline phosphatase (NAP) positivity rate was 5%, and the NAP score was 5 points (the reference score in our laboratory is 7–63 points).

Bone marrow immunology typing showed that 0.7% of the immature cell population was of the myeloid lineage; in addition, 77% of cells of the granulocyte lineage had maturation defects. A bone marrow biopsy showed active bone marrow hyperplasia, active granulocyte lineage proliferation, scattered primitive immature cells, and an increased percentage of mature granulocytes. In addition, increased numbers of cells of plasma cell lineage were observed on histologic sections, and some regions contained aggregated clusters.

Quantitative polymerase chain reaction (qPCR) results for the BCR-ABL fusion gene were negative, tests for the *JAK2* V617F gene mutation returned negative results, and the karyotype of the chromosomes was normal. The diagnosis was 1. CMML combined with MGUS, 2. chronic renal insufficiency, and 3. hyperuricemia.

To alleviate his symptoms, the patient received treatment that included hemostasis, anti-inflammation, and renal protection; after his symptoms improved, he was discharged from the hospital. After that, the patient was admitted several more times because of recurrent dizziness and fatigue, coughing, asthma, and gum bleeding.

The results of a second exam showed that the patient's renal function was stable. The numbers of white blood cells and monocytes had increased, and the patient was anemic. The results of routine blood tests from February 2013 showed WBC: 10.57×10^9/L with a differential count of 28.9% neutrophils, 20.3% lymphocytes, and 47.8% monocytes; Hb: 69 g/L; and PLT: 31×10^9/L. Blood biochemistry showed globulin: 54.9 g/L, total bilirubin level: 52.1 μmol/L, and indirect bilirubin level: 49.3 mmol/L. A Coombs test returned positive results. The level of IgM was 68.51 g/L.

The results from the bone marrow puncture smear showed active proliferation. In addition, the percentage of immature monocytes had increased to 28%; in these cells, each had a large cell body with an irregular shape, the cytoplasm was abundant, the nuclei were irregular, the nuclear chromatin was fine and granular, and most of the cells did not have a nucleolus. Only 10.5% of the cells were mature monocytes. Proliferation of cells with a granulocyte lineage was clearly evident. Myeloblasts, promyelocytes, myelocytes, metamyelocytes, rod neutrophils, and lobed neutrophils accounted for 10%, 5%, 2.5%, 1.5%, 7.5%, and 22.5%, respectively. Abnormalities such as nuclear atypia and a decrease in the number of cytoplasmic granules could also be observed. Proliferation of cells of the erythrocyte lineage was decreased; the number of lymphocytes was also decreased and they accounted for only 7.5% of the cells. Thirty-nine megakaryocytes were present on the whole section, and the number of platelets was decreased.

A thoracic CT showed inflammation in the superior lobe of the left lung and in the inferior lobe of the right lung as well as emphysema. After the patient received oral hydroxyurea and prednisone as well as treatment for his symptoms (anti-infection, kidney protection, activating blood circulation to dissipate blood stasis,

blood perfusion, and improvement of myocardial blood supply), the patient's condition improved. However, the patient ultimately died in December 2014 of a lung infection combined with cardiopulmonary insufficiency.

Case 2

The patient was a 78-year-old man. He was admitted to the hospital on February 9, 2014 because of coughing for 10 days and fever for 2 days. Ten days before admission, the patient developed an upper respiratory infection and experienced a cough. He was treated with azithromycin and levofloxacin. The effects of these drugs were poor, and the patient then experienced fatigue and a fever of 39.4℃.

Physical examination upon presentation showed that the patient was lucid and in poor spirits. There were no obvious signs of anemia and both lungs exhibited coarse breath sounds and did not exhibit dry or wet rales; the heart rate was 90 beats/min, and atrial fibrillation without a murmur was detected. After admission, a thoracic X-ray showed bronchitis. Electrocardiography showed rapid atrial fibrillation, a complete right bundle branch block, and partial lead ST-T changes.

Routine blood tests found WBC: 7.93×10^9/L with a differential count of 58.9% neutrophils, 10.2% lymphocytes, and 29.6% monocytes; red blood cells (RBCs): 3.2×10^{12}/L; Hb: 108 g/L; and PLT: 137×10^9/L. Blood biochemistry results showed that the albumin, globulin, creatinine, and uric acid levels were 34.6 g/L, 44.5 g/L, 122 μmol/L, and 492 μmol/L, respectively. The ESR was 101 mm/h. A blood smear showed that the percentage of mature monocytes was significantly increased and accounted for 36% of the white blood cells. The ferritin concentration was 1203 ng/ml, and tests for serum folate and vitamin B12 revealed normal levels.

A bone marrow smear showed active bone marrow hyperplasia, proliferation of cells of the granulocyte lineage, and an increase in the percentage of promyelocytes, myelocytes, metamyelocytes, and monocytes. Additionally, unhealthy granulocytes could be observed; 0.4% of the total cells were immature monocytes, while 17.2% were mature monocytes. Complete serology showed IgA: 0.23 g/L, IgG: 27.8 g/L, and IgM: 0.26 g/L.

Immunofixation electrophoresis showed the presence of IgG-κ type M proteins; M proteins accounted for 28.2%, with levels of free light chain κ: 9.31 mg/L (range: 3.3–19.4 mg/L), λ: 11.7 mg/L (range: 5.7–26.3 mg/L), and κ/λ: 0.79 (range: 0.26–1.65).

The patient had a history of hypertension for more than 20 years and a history of coronary heart disease and atrial fibrillation. He had received a pacemaker and had a history of gallstone surgery. A review of the patient's routine blood tests from 2012 and 2013 showed that the patient had a normal white blood cell count and an increased percentage of monocytes, which fluctuated between 15%–35%.

The final diagnosis included the following: 1. CMML combined with MGUS, 2. bronchitis, and 3. hyperuricemia. The patient received anti-infection treatment, which was ineffective after 5 days, with the patient continuing to exhibit a high fever, poor appetite, and fatigue. The patient was then treated with an intravenous injection of methylprednisolone, and his body temperature returned to normal. However, the patient again exhibited signs of a fever 4 days later. After he received cyclophosphamide combined with methylprednisolone, the symptoms of fever and fatigue gradually disappeared. Treatment with these drugs was stopped after 2 months.

A clinical follow-up was performed recently. His disease was stable, and he did not complain of any discomfort. Routine blood tests, complete immunology tests, and immunofixation electrophoresis have been performed regularly, and the tests did not show any significant changes.

Discussion

MDS is composed of a group of clonal diseases that have the following clinical presentation: ineffective hematopoiesis in the bone marrow and a high-risk of transformation into acute myeloid leukemia. Before 2008, CMML had been classified as a subtype of MDS. In recent years, the World Health Organization (WHO) decided that the French-American-British (FAB) classification system did not adequately reflect the clinical prognosis and biological behaviors of patients; therefore, CMML was classified into an independent, larger disease group (MDS/MPN). In fact, according to the new classification system, CMML includes previous MDS-CMML (more emphasis on dyshematopoiesis) and MPN-CMML (more emphasis on bone marrow proliferative changes) [1]. MGUS is a common pre-malignant plasma cell disease. MGUS may be divided into 3 different subtypes: non-IgM type MGUS, IgM type MGUS, and light chain type MGUS. Non-IgM type MGUS is further divided into IgG, IgA, double clone, and the rare IgD and IgE types [2]. All types typically evolve into multiple myeloma (MM), AL amyloidosis, or other diseases at a rate of 1% per year.

Although the diseases mentioned above originate from different types of committed hematopoietic stem cells, case reports of the presence of these 2 diseases in a single patient are not rare. In 1986, the Spanish researcher Costa [3] first reported a case of CMML combined with lymphoma. Since then, researchers from different countries also reported cases of CMML combined with lymphoma [4–5]. A prospective study by Economopoulos [6] showed that 5 out of 61 patients with CMML had combined MGUS, 8.2%,

much higher than the 1–3% in the general population. However, Cesana[7] studied disease transformation of 1231 patients with either MGUS or smoldering MM and showed that only 0.4% of cases had combined MPN. This leads to the question of whether MGUS combined with MDS or MDS/MPN are coincidental or whether these 2 diseases are causally related.

Mailankody *et al* [8] retrospectively analyzed secondary hematological malignancies in 8740 cases of MM and 5652 cases of MGUS that occurred in Sweden between 1986 and 2005. In cases of MGUS, the risk of development of MPN/polycythemia vera (PV) was increased 5-fold. Compared with MGUS, the risk of development of AML/MDS in patients with MM was even higher, and patients with the IgG/IgA type were more prone to the development of acute myeloid leukemia (AML)/MDS than were patients with IgM type gammopathy. However, the incidence of MPN/PV was not increased significantly in patients with MM.

These results are not consistent with those of a study with a small sample size conducted by Duhrsen *et al* [9], which showed that the number of cases of plasma cell tumors combined with MPN/PV was significantly increased. The authors admitted that the high risk of incidence obtained in their study might have been because of detection bias. For example, the clinical data of patients with MGUS were obtained from the Swedish Inpatient Registry; therefore, they could not account for some patients who sought treatment for other diseases and who were diagnosed with MGUS after they underwent MGUS-related examinations. In addition, routine blood tests during the clinical follow-up of patients with MGUS might lead to the discovery of MDS at an early stage.

To exclude bias associated with targeted examinations for other diseases, Mayo Clinic [10] performed a survey on local healthy residents above the age of 50 years. Their results showed that the development of MDS in patients with MGUS was increased 2.4-fold compared with the control group; moreover, no patients with MGUS developed acute lymphoid leukemia (ALL). These results are consistent with the results of the Swedish report. Because the number of patients with AML in the cohort study was small, the study could not confirm whether MGUS was associated with AML. Compared with the Swedish study, which showed that the development of MDS in patients with MGUS was 8.1 times that in the controls, the number was significantly decreased. The researchers thought that the reason for this was that the subjects who were enrolled in the Swedish study were mostly patients who had clinical symptoms and went to the hospital for a serum protein electrophoresis examination; therefore, some patients who did not have clinical symptoms were missed.

The findings of the Mayo Clinic study, which differed from those of the Swedish study, did not show that patients with IgA/IgM MGUS were prone to the development of MDS or AML. Although conclusions from these 2 large studies had some differences, they both found that the incidence of MDS in patients with plasma cell diseases was significantly increased compared with that in the general healthy population.

It is unclear whether these 2 types of hematological tumors in the same individual arise from the same stem cells or have different cellular origins. The observation by Shvidel *et al* [11] was that the disease progression of CMML was different from the progression of lymphoma. Therefore, they thought that these tumor types did not arise from a common abnormal stem cell population. Zagaria [12] reported 1 case of MGUS in a patient who developed anemia and thrombocytosis after 2 years. The patient was diagnosed with MDS with a 5q deletion. After the first diagnosis of MGUS and before the development of MDS, the presence of a MYD88 mutation was discovered in the bone marrow. To clarify the origins of these 2 clones, allele-specific PCR combined with fluorescence in situ hybridization was used to detect the molecular cytogenetic changes in hematopoietic stem cells. All of the CD34+ hematopoietic stem cells had the 5q deletion; however, no mutations in the MYD88 gene were observed. At the cytogenetic and molecular levels, these results showed that these 2 tumors were independent of each other. Anelli [13] also reported that patients with polycythemia vera with the *JAK2* V617F mutation developed IgG type lymphoplasmacytic lymphoma (LPL) after several years. The detection of the *MYD*88 L265P mutation and the *JAK2* V617F mutation confirmed that these 2 diseases were two independent clonal diseases that co-existed in the same person.

However, some studies also reported that leukemia cells in patients with CMML expressed both monocyte and NK cell markers together; therefore, it is possible that these tumor cells might have originated from common progenitor monocyte and NK cells [14]. During treatment for a nose bleed following a respiratory infection, it was discovered that the first patient (case 1) in the current study had CMML combined with IgM MGUS. The disease course lasted more than 4 years, and the CMML gradually progressed; the clinical presentation included anemia, thrombocytopenia, autoimmune hemolysis, and an increase in immature cells in the bone marrow. Although MGUS is associated with fluctuations in IgM values, no IgM-associated organ damage was observed. For example, lymphadenopathy, hyperviscosity, hypercalcemia, and kidney and bone damage did not significantly worsen during disease transformation as compared with when the patient was first diagnosed. These results also suggest that these tumors had different clonal origins; if 2 types of tumor clones were present, CMML might have been the

dominant clone.

Because MGUS and MDS or MDS/MPN primarily occur in elderly people who typically do not exhibit clinical symptoms, MGUS is usually discovered incidentally when patients seek treatment for other diseases. The diagnosis of MDS or MPN/MDS is usually confirmed because of the presence of clinical symptoms induced by abnormal blood cells. Therefore, when a patient presents with these 2 diseases simultaneously, it is difficult to know which disease developed first. Malhotra *et al* [15] retrospectively analyzed 90 patients with MPN who were treated at their medical center within the past 5 years. Immunofixation electrophoresis results from the blood and urine of a total of 32 patients were examined. Out of these, 15 were diagnosed with MGUS/MM; however, the majority of patients were diagnosed with MPN at the same time or before the MGUS/MM was diagnosed, and only 3 patients were diagnosed first with MGUS/MM followed by MPN. None of these 3 cases featured an increase in the number of red blood cells or platelets, which indicates that the diagnosis was delayed relative to the actual course of disease development. The 2 elderly patients described in this article were discovered to have both CMML and MGUS during treatment for other diseases; therefore, no treatment-related factors were involved. Because immunoglobulin detection was not performed initially, this test could not confirm which disease developed first.

Studies have shown that monocytes and nurse-like cells derived from monocytes are important components of the tumor microenvironment that play important roles in the maintenance and protection of tumor cell growth in the blood [16]. Whether CMML may be a risk factor for MGUS and the function of clonal plasma cells in the occurrence and development of MDS or MDS/MPN requires further study.

Yoshida *et al* [17] reported 14 cases of MDS combined with MGUS at their medical center within the past decade; this article is currently the clinical report with the largest number of cases of MDS combined with MGUS. These cases accounted for 10.2% of MDS patients, significantly higher than the number of people of the same age in a control population with anemia. When the patients were diagnosed with MDS, the majority of them were also diagnosed with MGUS, which suggests that MGUS was not associated with treatment and that MGUS could be present in patients with any MDS WHO classification subtype. Among the 12 patients, 11 patients had low-risk chromosome karyotypes; combined with other risk factors, the clinical outcomes of the MDS combined with MGUS group were not significantly different from those in the MDS group, which suggests that MGUS did not influence the prognosis of the patients with MDS. Case 1 in this article had a 4-year-long disease course. The patient's disease did not transform into acute leukemia, and he eventually died from a lung infection. Compared with the median survival period of 20–40 months of patients with CMML without MGUS, the survival period was not decreased; therefore, this observation supports the idea that MGUS might not have an adverse effect on the prognosis of patients with CMML.

The elderly are susceptible to both MGUS and MDS/MPN. After a review of the relevant literature, a limited number of studies showed that the incidence of secondary MDS/MPN in patients with MGUS was higher than that in the general population. The association between these 2 diseases and the mutual influence on each of their prognoses require further studies of a larger number of clinical cases. In addition, these results suggested that in future work, routine blood tests should be the focus for patients with MGUS. Finally, an analysis of serum M protein should not be ignored in patients with MDS/MPN.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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