Case Report

Chronic Myelomonocytic Leukemia Presenting With Polyserositis and Seropositivity for Rheumatoid Arthritis

Anthony Kunnumpurath, MBBS, Sai Prasad Desikan, MD, Charles McClain, MD, and Raman Desikan, MD

Abstract

Chronic myelomonocytic leukemia (CMML) is a rare clonal stem cell disorder associated with clinical and pathologic of myelodysplasia and myeloproliferation. Systemic autoimmune/inflammatory disorders (SAID) and polyserositis have been associated with CMML. These manifestations can be observed concomitantly, shortly before diagnosis or anytime along the course of illness. We report a case of myeloproliferative CMML who presented with polyserositis and positive serology for rheumatoid arthritis. Retrospective studies of myelodysplasia/CMML have reported 15% to 25% incidence of SAID. The most commonly observed disorders include systemic vasculitis, connective tissue diseases, polychondritis, seronegative arthritis, and immune thrombocytopenia. SAID does not confer adverse prognosis in retrospective studies. Polyserositis is less common; this may result from leukemic infiltrate or result from autoimmunity. Treatment of serositis includes steroids and cytoreductive agents. Serositis may confer poor prognosis and hypomethylating therapy may improve the outcome.

Keywords

CMML, polyserositis, autoimmunity

Introduction

Chronic myelomonocytic leukemia (CMML) is a clonal stem cell disorder characterized by persistent monocytosis along with myelodysplasia (MDS) and/or myeloproliferation, and hence is classified as MDS/myeloproliferation in the World Health Organization classification. Diagnostic criteria include persistent monocytosis (≥1 × 10⁹/L), monocyte count of ≥10% of white blood cells count (WCC) in peripheral blood, absence of other myeloproliferative syndrome, and acute leukemia. CMML is classified as myeloproliferative when the total WCC is >13 × 10⁹ L. CMML is further stratified based on peripheral blood (PB) and bone marrow (BM) blast percentage—CMML-0 (<2% in PB and <5% in BM), CMML-1 (<5% in PB and BM <10%), and CMML-2 (PB 5% to 19% and BM 10% to 19%). CMML is associated with high risk of transformation to acute myeloid leukemia (AML; 15% to 30%). The 5-year risk of transformation to AML in CMML-2 was as high as 63% in CMML-2 compared with 18% in CMML-1. Prognosis worsens with increasing blast count even in less aggressive disease. Overall survival in CMML-0 was significantly better than CMML-1 (31 months vs 19 months). Clinical findings may include incidental finding of monocytosis, symptoms from cytopenias, constitutional symptoms, splenomegaly, extramedullary myelomonocytic infiltrates, and symptoms from associated autoimmune and inflammatory disorders. Systemic inflammation and/or autoimmune disorders are frequently observed in patients with MDS/CMML (10% to 30%). Patients with autoimmune disorders also carry a higher risk of myeloid disorders including MDS/AML, and this can be increased by use of immunosuppressive therapy with azathioprine. There is no clear association between SIADs (syndrome of inappropriate antidiuretic hormones) and other prognostic indicators. Presence of SIADs have no impact on survival. Polyserositis is much less common and presence of serositis may be associated with adverse prognosis. Occurrence of both of these may also influence choice of therapy.

1White River Health Systems, Batesville, AR, USA

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Corresponding Author:
Anthony Kunnumpurath, MBBS, White River Medical Center, 1710 Harrison Street, Batesville, AR 72501, USA.
Email: akunnumpurath@wrmc.com
Case Report

A 65-year-old female was initially evaluated in the emergency room for right upper quadrant pain; imaging studies did not confirm cholecystitis. She was treated with parenteral narcotics in short stay. WCC was elevated at $12.4 \times 10^9$/L. Absolute monocyte count was also elevated at $3.6 \times 10^9$/L, hemoglobin was 11.8gm/dL, and platelets were adequate at $392 \times 10^9$/L. She was admitted 2 weeks later with dyspnea and chest discomfort. Cardiac workup, including coronary angiogram, was negative. Computed tomography scan revealed bilateral pleural effusions and pericardial effusion (Figure 1). WCC was further elevated at $33.4 \times 10^9$/L. Rheumatoid factor was positive (54.9 IU) and anti-CCP antibody was also positive. Pleural fluid was exudative and showed monocytic infiltrate. Flow cytometry of pleural fluid could not be performed due to lack of fresh specimen. Peripheral smear confirmed monocytosis, and bone marrow biopsy was consistent with CMMML-2. Janus Kinase 2 mutation and BCR/ABL translocation and fluorescence in situ hybridization analysis did not reveal CHIC2 (cysteine rich hydrophobic domain) or FIP1L1 translocation with PDGFRA (platelet-derived growth factor-α) at 4q12. Cytogenetic analysis revealed normal karyotype (46,XX; Figures 2 and 3). Symptoms from polyserositis including chest discomfort, dyspnea, and abdominal pain subsided spontaneously and the patient was discharged with minimal nausea on tapering dose of prednisone. On evaluation, 2 weeks later, the patient’s WCC was significantly elevated at $140 \times 10^9$/L with 78% monocytes. Hemoglobin was reduced at 7.2 mg/dL, and platelet count low at $36 \times 10^9$/L. After initiation of azacitidine, the patient’s WCC and platelet count normalized and hemoglobin improved to 11 mg/dL. Despite the observed improvement in hematologic parameters, bone marrow evaluation after 5 cycles revealed transformation to AML. Cytogenetic evaluation revealed 46XX deletion (9 q13-q 22) in 20 cells (Figure 4). Molecular studies revealed mutated nucleophosmin gene. The patient underwent remission induction, following which she was maintained on decitabine. Allogenic stem cell transplant was performed as a curative treatment; she continues in excellent remission. Posttransplant course was complicated by GVHD, which is presently well controlled off the immunosuppressants. The patient did not have any recurrence of serositis-related symptoms. Positive serology for rheumatoid arthritis was not associated with joint or extra-articular manifestations of rheumatoid arthritis.
Discussion

Polyserositis in conjunction with monocytosis could result from a large number of disorders including malignancies (hematopoietic and nonhematopoietic), rheumatoid arthritis, systemic lupus erythematosus, chronic infections, and vasculitides. Peripheral smear evaluation is the first step in distinguishing reactive monocytosis from monocytic malignancies. Morphologic evaluation of maturity should distinguish monocytes from promonocytes, which are considered to be blast equivalents (Figure 5). Dysplasia should be assessed in neutrophils, as dyserythropoiesis may be observed in rheumatoid arthritis and other collagen vascular disorders. Flow cytometry does not reliably distinguish reactive monocytes from promonocytes. However, flow cytometry can differentiate reactive monocytosis characterized by aggregation of intermediate (CD14+/CD16+; MO2), nonclassical (CD14−/CD16+; MO3) from classical (CD14+/CD16−) monocytes (MO1). Classical monocyte (≥94%) reliably differentiates CMML from reactive monocytosis of monocytes in healthy individuals and predominates in CMML. Bone marrow biopsy is indicated for unexplained persistent monocytosis to rule out myeloid malignancies (AML, CMML). Cytogenetics and molecular genetics are integral parts of bone marrow evaluation.14-20

Retrospective studies have established a greater incidence of SIADs in patients with MDS/CMML compared with the general population and, in one study, compared with patients with chronic myeloid leukemia. Patients with autoimmune disease are at higher risk for development of myelodysplastic syndrome and AML; odds ratio of 1.5 increasing to 2.1 for patients who have autoimmune disease for 10 years or longer. In a large population of patients with autoimmune disorders, exposure to azathioprine was associated with 7-fold risk of myeloid neoplasm. Serologic abnormalities of rheumatoid arthritis were not associated with any articular or extra-articular manifestation of the disease in our patient. Serologic abnormalities of autoimmunity may be as high as 65% in MDS/CMML. Incidence of clinically apparent inflammatory/autoimmune disorders is 10% to 30%; autoimmune disorders can be observed concomitantly, precede the diagnosis, or occur anytime during the course of MDS/CMML. SIADs may exhibit all the classification criteria in the majority of patients, but complete criteria may be missing in a significant minority of patients. The most commonly observed disorders include systemic vasculitis, connective tissue diseases, polychondritis, seronegative arthritis, and immune thrombocytopenia. CMML was significantly associated with systemic vasculitis. Association between SIAD and other prognostic indicators is unclear; however, SIADs do not confer adverse prognosis in retrospective studies.1-9 The relationship between CMML and SIADs is not fully understood. Autoimmune/inflammatory disorders–associated chronic inflammation may be a contributing factor to the development of myeloid malignancies. Chronic inflammation is thought to lead to oncogenesis through recruitment of inflammatory cells with resultant production of reactive oxygen species, cytokines, chemokines, growth factors. Continual exposure to these inflammatory cells is thought to cause mutations, thus leading to activation of prosurvival and anti-apoptotic pathways. Chronic inflammation thus drives clonal selection, dominance, and independence, resulting in myeloid malignancies. Marrow failure is probably mediated by autoimmunity in some MDS subtypes, wherein immunosuppressive therapy has been successfully employed. Conversely, CMML may predispose patients to SIADS, through cytokine production by monocytes (interleukin (IL)-6, tumor necrosis factor-α, interferon regulatory factor-1) or by abnormality of immune...
cytokine production by macrophages. In contrast to auto-

demonstrate upregulation of multiple inflammatory path-

may be indicated for remission induction prior to stem cell

cures. Reduced intensity conditioning enables the

demethylating agents may enable dose reduction or discontinuation of ste-

therapy. In conclusion, serositis and SIADs are significant complications affecting the life of patients with MDS/CMML. In addition to symptom load from SIADs and serositis, they may affect choice of therapy as well.

Authors’ Note

This case has been presented as a poster presentation at the American College of Physicians Arkansas chapter in September 2017 at Little Rock, Arkansas, and also at the American College of Physicians National Conference in April 2018 at New Orleans, Louisiana.

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal consent was obtained from the patient regarding publication of the case report.

ORCID iDs

Anthony Kunnumpurath https://orcid.org/0000-0001-5091-3463

Sai Prasad Desikan https://orcid.org/0000-0003-1157-6489

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