A Case of Newly Diagnosed Chronic Myelomonocytic Leukemia with Rheumatoid Arthritis Presentation

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Abstract

We describe a case of newly diagnosed chronic myelomonocytic leukemia that presented with predominantly rheumatologic symptoms. In addition to the deletion of chromosome 12p, marrow cytogenetics also revealed a unique translocation, t(x:4). This finding was not a constitutive abnormality. We report this unusual chromosomal abnormality and hypothesize about the potential immunogenicity of the gene product and its relation to the patient’s rheumatologic complaints.

Keywords: Chronic myelomonocytic leukemia (CMML); Rheumatoid arthritis; Immune suppression

Abbreviations: MDS: Myelo Dysplastic Syndrome; FISH: Fluorescence In situ Hybridization; RA: Rheumatoid Arthritis; ALL: Acute Lymphocytic Leukemia; AML: Acute Myelogenous Leukemia

Introduction

There are greater than 10,000 newly diagnosed cases of myelodysplastic syndromes in the United States each year [1]. Chronic myelomonocytic leukemia (CMML) is a myelodysplastic disease with myeloproliferative features. Not uncommonly, CMML presents with varying autoimmune phenomena. Vasculitis, polychondritis, and polyarthritis have been associated with myelodysplastic diseases such as CMML [2-5]. As many as 10% of patients diagnosed with myelodysplastic syndromes (MDS) have autoimmune manifestations which range from vasculitis to glomerulonephritis [2]. CMML diagnosis requires a peripheral monocytosis of greater than 1×10⁹/L for at least 3 months without presence of a Philadelphia chromosome or BCR-ABL mutation or PDGFRα/β rearrangement and less than 20% blasts in the peripheral blood and bone marrow. Additionally, there must be presence of dysplasia in at least one myeloid lineage. If dysplasia is not present, then diagnosis may be made using all of the previous requirements with either an acquired clonal cytogenetic, molecular genetic abnormality, or a monocytosis that has persisted for at least 2 months with exclusion of alternative causes [6].

CMML is typically diagnosed in patients aged 65-75 and with a 2:1 male predominance. Symptoms typically range from skin rash, to splenomegaly, to weight loss, but can be variable. CMML may be subcategorized into CMML-1 and CMML-2. CMML-1 has presence of less than 5% blasts in blood or less than 10% in bone marrow. CMML-2 is diagnosed with 5-19% blasts in the blood or 10-19% blasts in the bone marrow or Auer rod presence [6].

The molecular underpinning of the autoimmunity seen in CMML is not well understood. Chromosomal translocations play an important role in the varied manifestations of CMML. For example, a noted case of chronic inflammatory demyelinating polyeuropathy has been reported which was caused by a translocation t(3:8)(q26;q24). These autoimmune manifestations have been largely treated with immunosuppression by steroidal intervention for symptomatic relief [4].

CMML is associated with multiple translocations in 10% of cases. Of this group of translocations, 86% are balanced, and 14% are unbalanced. The chromosomes which are most commonly involved in descending order are 3, 1, 7, 2, 11, 5 and 12 [3] A unique feature of this case is the finding of a deletion of chromosome 12p resulting in the loss of the ETV6 gene and t(x:4)(q26:21) translocation. This translocation involves the region of DNA that has been associated with rheumatoid arthritis.

Case Report

A 61 year old Caucasian male initially presented with the complaint of malaise, arthragias, and lower extremity edema. He noted anorexia and energy loss accompanied by increasing dyspnea on exertion for the past few months. His review of systems was otherwise negative aside from a twenty pound weight loss over the last month.

On physical exam, the patient has significant lower extremity swelling and edema extending to the waist. Neck exam revealed tenderness over the right neck without lymphadenopathy or jugular venous distention or thyroid tenderness. Cardiac exam revealed only tachycardia. No ecchymosis was noted over the skin or mucous membranes. Joint exam revealed reduced range of motion of all joints without effusions. Initial labs showed the following abnormal results: WBC was 28.3×10⁹/L with hemoglobin of 10.4 mmol/L and platelet level of 33×10⁹/L. Total protein was decreased along with albumin (2.0 g/dL). Alkaline phosphatase was elevated (149 U/L). Haptoglobin was normal. The differential on the complete blood count revealed a monocytic hyperproliferation at 27% with (1%) band cell, (6%) lymphocytes, (13%) myelocytes, (1%) promyelocyte, (1%) blast cells, and (51%) segmented neutrophils. Erythrocyte sedimentation rate (ESR) was 90 mm/hr, prothrombin time (PT) was 15.1 s, international normalized ratio (INR) was 1.2, fibrinogen was (659 g/L) and d-dimer was (3.71 ng/ml). The patient underwent a battery of serological tests for rheumatologic and hematological abnormalities (Table 1).

Bone marrow biopsy pathology

The bone marrow biopsy showed hypercellular marrow (Figure 1).
with fibrosis. Dysplastic features were seen in megakaryocytes and myeloid cells. Marrow cellularity was estimated at approximately 70% with many increased myeloid cells of all stages. Dysplastic erythroid precursors were also demonstrated (Figure 2).

Bone Marrow flow cytometry: 78% mature granulocytes, 2% lymphocytes, 10% monocytes, 7% erythroid precursors and 3% blasts. 1% CD19-positive B cells present, 1% CD3-positive t cells.

FISH: There was rearrangement of ETV6 (TEL) (12p 13.2), No PDGFRA: 4q12 rearrangements noted. A deletion of (12p) containing the region encoding for ETv6 gene was noted. The bone marrow was also negative for BCR-ABL mutation.

Cytogenetics

Demonstrated the (t(x:4)) which was not constitutive based on subsequent buccal swab karyotyping.

Management

The patient was evaluated by a rheumatologist and appeared to have a constellation of autoimmune manifestations. The elevation in rheumatoid factor, ANA, anti-CCP, and decreased complement was felt to be consistent with rheumatoid arthritis. The patient was diagnosed with rheumatoid arthritis (RA) was placed on high dose methylprednisolone (125 mg/week). Upon further outpatient follow up, the patient maintained a monocytosis greater than 1×10^9/L for three months. He was diagnosed with CMML and offered the option between decitabine and azacitidine. After discussion of the options; the patient chose treatment with decitabine over azacitidine. He experienced a significant improvement of his symptoms, and has been transfusion independent with improving blood counts since discharge from the hospital.

Discussion

The autoimmune manifestations which this patient experienced initially may be explained by means of a positive rheumatoid factor and anti-cyclic citrullinated peptides (CCP). There have been reports that CD 14+ abnormal monocytes signal B cells to produce IgM-RF and thus play a role in pathogenesis of RA in addition to clinical and serological manifestations of RA. Increased bone marrow production of these monocytes may cause serological findings of RA [7]. However, this patient had normal CD14 on flow cytometry which makes this pathophysiology unlikely.

The translocation of (x:4) seems like a more plausible cause for the elevation in rheumatoid factor. Serological markers such as rheumatoid factor (RF) and anti-CCP in rheumatoid arthritis have been shown to have some association with the X chromosome genes (namely TIMP1, and IL9R genes) [8]. If these gene loci were part of the translocation, this may offer a credible reason that both anti-CCP and RF were elevated. These markers for rheumatoid arthritis have been reported with mutations in both TIMP1 and IL9R [8].

The combination of leukocytosis without infectious source, thrombocytopenia, and monocyte hyperproliferation, was suspicious for underlying bone marrow dysfunction. The decision to do a bone marrow biopsy should be done in this situation to elucidate the causative factor for the confounding serological findings. CMML was diagnosed based on the absence of Philadelphia chromosome, and absence of a PDGFRA rearrangement on FISH from bone marrow samples. There was a peripheral monocyte proliferation greater than

Table 1: Represents the pertinent positive and negative lab data.

<table>
<thead>
<tr>
<th>Anti CCP: 241 (normal &lt;20)</th>
<th>Rheumatoid Factor: 526 IU/ml (normal &lt;14 IU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Protein Electrophoresis: increased α immunoglobulin (0.4 g/dl) (normal 0.1-0.3 g/dl)</td>
<td>P-ANCA: negative; ANA: positive (1:80); Native DNA Ab: negative</td>
</tr>
<tr>
<td>Lupus Anticoagulant: negative</td>
<td>Cardiolipin IgG, IgM antibody: negative</td>
</tr>
<tr>
<td>Thyroid stimulating Immunoglobulin: 22 (normal &lt;140)</td>
<td>Anti SM-Abs: Negative</td>
</tr>
<tr>
<td>β2 glycoprotein IgM: 48 SAU (normal &lt;20 SAU)</td>
<td>Complement C3: 61 mg/dl (normal 82-185 mg/dl)</td>
</tr>
<tr>
<td></td>
<td>Complement C4: 12 mg/dl (normal 15-55 mg/dl)</td>
</tr>
<tr>
<td>H. pylori IgM, IgA: negative</td>
<td>CMV: Negative</td>
</tr>
<tr>
<td>Cryoglobulin: negative</td>
<td>HIV: Negative, Hepatitis C panel: negative</td>
</tr>
</tbody>
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Figure 1: A microscopic image of the bone marrow biopsy showing hypercellularity of granulocytes and megakaryocytes.

Figure 2: A microscopic image from bone marrow biopsy showing a dysplastic erythroid precursor cell present in the bone marrow consistent with myelodysplastic disease.
1x10^9/L documented for 3 months, less than 20% blasts, and bone marrow pathological findings consistent with both myeloproliferative and dysplastic features. Furthermore, the cytogenetic abnormalities appear clonal and confined to the bone marrow, thus confirming this is CMML. The presence of less than 5% blasts peripherally and less than 10% in marrow suggests this case was CMML-1.

The arthralgia’s and hypocomplementemia may be partially explained by the unique translocation of t(x;4). This translocation may be responsible for elevated transcription of an immunogenic protein which facilitates the fixation of complement and autoimmune reaction. This subsequently led to lowered complement level, positive ANA, and increased immunoglobulin. CMML has been noted to cause autoimmune manifestations in a variety of different presentations [1]. Additionally, it has been associated with various translocations in presentation. It may be possible that these varieties of translocations create a wide spectrum of autoimmune symptoms based on the translocation and resultant protein. The translocation found in this case is not typically seen with CMML cases.

Myeloid neoplasms and myelodysplastic syndromes have been associated with deletions of short arm of chromosome 12 [9]. Among the most commonly seen gene rearrangement on this chromosome associated with hematological malignancies is the ETV6 gene [10]. The ETV6 gene has the function of transcription repression and is expressed biologically in myeloid cells significantly more than other cells. It is required for hematopoiesis and development of vascular structures [9,11]. This gene sequence has been shown to be associated with CMML, fibrosarcoma, childhood ALL, and AML through translocations and rearrangements [5]. In this case, by virtue of deletion of 12p and thus ETV6 gene, there is potential loss of transcription regulation of monocyes and proliferation occurs.

The t(x;4) mutation was found to be isolated to the bone marrow and not consistent with a germline mutation. This segregation to the bone marrow strongly suggests that this translocation occurs in the bone marrow and not peripheral blood. The t(x:4) mutation was found to be isolated to the bone marrow and not consistent with a germline mutation. This segregation to the bone marrow strongly suggests that this translocation plays an important part in the expression of the disease in this case. We hypothesize that this protein is responsible for fixing complement in this patients’ blood and creating the rheumatologic manifestations seen clinically. The variability of translocations associated with CMML may be responsible for the varying clinical presentations of CMML.

Conclusion

In conclusion, more research is needed into the variety of translocations associated with myelodysplastic syndromes and the causative factors that are associated with the various autoimmune presentations of this disease. This case report shows that there are many unique presentations of serious hematological diseases which may manifest as other diseases. Most profoundly, this case outlines a unique and novel translocation and deletion of a chromosome which has not been described in CMML concurrently. Efforts are underway to identify the genes involved and the putative protein product of the t(x;4) demonstrated in this case.

References