Case Report

Multiple Myeloma and Chronic Myelogenous Leukemia; an Uncommon Coexistence in 2 Patients, with Literature Review


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Abstract

The coexistence of Multiple Myeloma (MM) and Chronic Myelogenous Leukemia (CML) is an extremely uncommon event that has only been reported in very few cases. Here, we present 2 new cases of concurrent MM and CML. The case of a 63 year old woman with CML, who was treated with imatinib mesylate and subsequently developed MM 6 years after the diagnosis of CML, and the case of a 68 year old man with MM, who was treated with radiation therapy and chemotherapy and subsequently developed CML 4 years and 7 months after the diagnosis of MM. The relationship between CML and MM, is also discussed.

Keywords: Multiple myeloma; Chronic myeloid leukemia; Cell transformation

Introduction

Multiple Myeloma (MM) is a malignancy of lymphoid origin, characterized by monoclonal proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in serum and/or urine and associated organ dysfunction [1]. The diagnosis is based on the presence of at least 10% bone marrow infiltration by clonal plasma cells that are usually secreting a monoclonal immunoglobulin in addition with or without end organ damage manifestations [1–3]. Chronic Myeloid Leukemia (CML) is a clonal disorder of myeloid origin characterized by a chromosomal reciprocal t(9;22) (q34;q11) translocation, the Philadelphia (Ph) chromosome [4]. The crucial pathogenetic consequence of this translocation is the creation of a chimeric BCR-ABL fusion protein, resulting in a constitutively active tyrosine kinase with high proliferative potential [5,6].

Therefore, the respective malignant cells in MM and CML are completely different, being lymphoplasmacytic and myeloid cells, accordingly. The occurrence of MM and CML in the same patient, either at diagnosis or with one or the other disease pre-existing, is a rare event that has previously been reported in a limited number of case reports in the literature [7–25], and the question of the origin of these 2 malignancies in such patients, remains unanswered.

In this report, we reviewed previously published cases, and presented 2 more patients with concurrent MM and CML.

Patient 1

A 63 year old woman was referred to our hospital in October 2002 because of leukocytosis. She had a history of hepatitis A, hysterectomy for benign fibroids (1996), and colon cancer (1999) in complete molecular CML remission, her karyotype presented restricted plasma cell infiltration, while a small M-spike was present under imatinib treatment, qRT-PCR became positive for BCR-ABL transcripts, and BM karyotype revealed Ph chromosome in 1 out of 20 metaphases; BM biopsy showed additionally 5-8% κ light chain restricted plasma cell infiltration, while a small M-spike was present on serum protein electrophoresis, serum immunofixation showed an IgGκ monoclonality and quantitative Immunoglobulin (Ig) measurements were within normal range; Monoclonal Gammopathy of Undetermined Significance (MGUS) was diagnosed. Imatinib mesylate dosage was increased to 600mg/day, resulting again in a complete molecular response.

While under follow-up and regular CML evaluation with BM karyotypes and BCR-ABL quantification, and although she remained in complete molecular CML remission, her karyotype presented in 2005 an additional abnormality del (7)(q32) and two more in 2006 [t(1;7)(q32;q21) and t(2;7)(q33-35q21)]. At that time BM examination showed 12% infiltration by clonal plasma cells (Table 1). As she had no MM-related symptoms, the diagnosis of asymptomatic MM (AMM) was made.

In October 2012, BM biopsy revealed 80% monoclonal plasma cell infiltration, IgG and serum FLC-K quantification were steadily increasing (Table 1) and 6 months later she presented severe bone
pains with spontaneous lumbar fractures. Her MM was Symptomatic (SyMM) and she received treatment with Velcade (bortezomib) and Dexamethazone, while imatinib continued. After 4 cycles, MM was in very good partial response but treatment had to be stopped due to severe peripheral neuropathy. The patient deteriorated 3 months after, and 2nd line treatment with Revlimid (lenalidomide) and Dexamethazone was started, additional radiation therapy was also performed for a new fracture. The patient is stable since then. With regard to combined treatment toxicities, it should be reported that after six months of treatment with lenalidomide 25 mg per day and imatinib, the patient presented neutropenia and lenalidomide dosage was reduced to 15 mg per day, while she still sporadically needs granulocyte colony stimulating factor injections in order to keep safe her neutrophils counts.

**Patient 2**

In April 2008, a 68 year old man with history of hypertension (2003), diabetes (2003), hypothyroidism (2007), and diverticulosis (2005), presented with mild anaemia and spinal bone pains and an elevated monoclonal spike on serum protein electrophoresis. Serum immunofixation showed IgGκ monoclonality, Urine total protein was 1005mg/24h. IgG and serum FLC- λ levels were increased (2400mg/dl and 97mg/L respectively). BM biopsy revealed 40-45% plasma cell infiltration, with λ light chain monoclonality. Fluorescence In Situ Hybridization (FISH) analysis was negative for IgH rearrangements, chromosome 13q and 17p deletion. Lytic lesions and a L5 bone plasmacytoma were present in lumbar spine. The patient had IgGκ λ light chain MM, He was treated with radiation therapy followed by VAD (vincristine, doxorubicin and dexamethazone) resulting in very good partial response.

From September 2008 until October 2012, the disease remained in plateau. He was re-evaluated in October 2012 because of a slight paraprotein increase. BM trephine biopsy and smears revealed limited 10% plasma cell infiltration; however BM karyotype detected the presence of Philadelphia chromosome in 24 of 28 metaphases. BCR-ABL transcripts were also detected confirming the diagnosis of CML. At that time, blood analysis exhibited white blood cell count of 11810x10⁹/l (78% neutrophils, 2% myelocytes, 12% lymphocytes, 5% monocytes, 3% basophils). Haemoglobin level was 11.3gr/dl, and platelet count 417x10⁹/l.

The patient was placed on imatinib mesylate at standard dose, and achieved major molecular response at 9 months after treatment initiation. He is thereafter asymptomatic and clinically stable as concerning both diseases. It should however be mentioned that at the time of imatinib mesylate administration, the patient was still under zoledronic acid bi-monthly adjuvant administration for the prevention of bony manifestations but as serum creatinine increased, we were obliged to discontinue zoledronic acid and renal function returned to normal thereafter.

**Literature Review**

There are only 19 cases in the literature, in which coexisting MM
and CML have been reported (Table 2) [7-25]. In 7 of the 20 cases, MM and CML were diagnosed simultaneously [7-13]. In 5 of the 20 cases, MM diagnosis preceded that of CML [14-18], while in the rest 7, CML diagnosis preceded that of MM [19-25]. Regarding the interval between the diagnosis of each disease, MM preceded CML from 17 to 33 months, while CML preceded MM from 3 to 113 months. As for treatment after diagnosis of the first disease, anti-neoplastic therapy or radiotherapy was performed in 3 out of 5 and in 7 out of 7 cases, in the MM preceding CML group and in the CML preceding MM group, respectively. No particular disease characteristics were found in literature that could be connected somehow with increased or decreased possibility of these 2 diseases coexisting.

**Discussion**

The coexistence of MM and CML is an extremely uncommon event. However, there are reports of MM coexisting with a variety of myeloproliferative disorders, including polycythemia vera [26-28], myelofibrosis [28,29], essential thrombocytosis [30,31], and chronic neutrophilic leukemia (CNL) [32-35]. In addition MGUS, a pre-neoplastic plasma cell disorder, has also been reported to develop in pre-existing myeloproliferative neoplasms, while myeloid malignancies have been reported to develop in MGUS patients with accumulative incidence risk of <2% [36-38]. As for CML, in most cases the patient’s chronic disease eventually changes to a more aggressive disease, usually towards acute myelogenous leukemia or acute lymphoblastic leukemia [39]. In addition, lymphoma [40-42], monoclonal gammopathy [34,43], or Waldenström macroglobulinemia [44] could also occur in association with CML.

All the above suggest the existence of a common malignant pluripotent progenitor stem cell, capable of differentiating into both myeloid and lymphoid cell lineages that could lead to the development of CML and MM in the same patient [15,18,33,34]. In favour of this theory, it has been shown that Ph+ B lymphoblastoid cells may be observed in patients with CML even during the chronic phase, and they may arise from the CML stem cell alone [45]. Furthermore, despite the fact that MM unlike leukemias and lymphomas, typically has no specific chromosomal abnormalities and is characterized by genomic instability [46,47], there have been cases of MM patients with a Philadelphia chromosome [48-50].

Another potential theory is that when CML develops before MM and vice versa, the secondary disease may be caused by the cytotoxic drugs or irradiation used to treat the first disease. In the literature several clinical observations suggest that Imatinib mesylate treatment for CML, could promote the development of MM [18,21-24]. This is further supported by a study in which Imatinib was shown to stimulate MM cell proliferation through activation of the Erk1 and Erk2 Mitogen-Activated Protein Kinases (MAPKs) [51]. Nevertheless, Imatinib has also been shown to inhibit proliferation of MM cells in vitro by arresting cell-cycle progression [51]. Therefore, development

<table>
<thead>
<tr>
<th>Patient</th>
<th>Reference</th>
<th>Year</th>
<th>Age/Sex</th>
<th>Diagnosis</th>
<th>MM</th>
<th>CML</th>
<th>MM/+/CML</th>
<th>CML/+/MM</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Boots MA et al. [7]</td>
<td>1982</td>
<td>58/M</td>
<td>IgG-k</td>
<td>numerous</td>
<td>yes</td>
<td>140</td>
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<td>2</td>
<td>Tanaka M et al. [8]</td>
<td>1998</td>
<td>72/F</td>
<td>IgG-k</td>
<td>3%</td>
<td>yes</td>
<td>162.4</td>
<td>yes yes</td>
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<tr>
<td>3</td>
<td>Alvarez-Larrain A et al. [9]</td>
<td>2001</td>
<td>81/M</td>
<td>IgA-k</td>
<td>25%</td>
<td>yes</td>
<td>28.7</td>
<td>NS yes</td>
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<tr>
<td>4</td>
<td>Schwarzenberger JD et al. [10]</td>
<td>2003</td>
<td>66/M</td>
<td>IgG-k</td>
<td>3%</td>
<td>yes</td>
<td>171</td>
<td>yes yes</td>
</tr>
<tr>
<td>5</td>
<td>Wakayama T et al. [11]</td>
<td>2005</td>
<td>85/F</td>
<td>IgG-λ</td>
<td>32.8%</td>
<td>NS</td>
<td>8.1</td>
<td>no yes</td>
</tr>
<tr>
<td>6</td>
<td>Offiah C et al. [12]</td>
<td>2012</td>
<td>71/F</td>
<td>IgG-k</td>
<td>30%</td>
<td>no</td>
<td>12.7</td>
<td>no yes</td>
</tr>
<tr>
<td>7</td>
<td>Romanenko NA et al. [13]</td>
<td>2013</td>
<td>64/F</td>
<td>IgA-κ</td>
<td>12.4%</td>
<td>no</td>
<td>27.2</td>
<td>NS yes</td>
</tr>
<tr>
<td>8</td>
<td>Macsween JM et al. [14]</td>
<td>1972</td>
<td>77/M</td>
<td>no BJP</td>
<td>9-12%</td>
<td>no</td>
<td>145</td>
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<tr>
<td>9</td>
<td>Klenn PJ et al. [15]</td>
<td>1993</td>
<td>71/M</td>
<td>yes IgG-k cluster</td>
<td>yes</td>
<td>40.8</td>
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<tr>
<td>10</td>
<td>Nitta M et al. [16]</td>
<td>1999</td>
<td>70/M</td>
<td>33 months</td>
<td>no IgG-k</td>
<td>25%</td>
<td>no</td>
<td>25.2 yes</td>
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<tr>
<td>11</td>
<td>Nakagawa M et al. [17]</td>
<td>2003</td>
<td>47/M</td>
<td>yes BJP-k</td>
<td>9.8%</td>
<td>yes</td>
<td>23.9</td>
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<tr>
<td>12</td>
<td>Raghupathi L et al. [18]</td>
<td>2013</td>
<td>62/F</td>
<td>yes IgG-k</td>
<td>70%</td>
<td>no</td>
<td>yes yes</td>
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<td>13</td>
<td>Derghazarian C et al. [19]</td>
<td>1974</td>
<td>65/F</td>
<td>113 months</td>
<td>yes IgG-k</td>
<td>9%</td>
<td>yes</td>
<td>43. NS yes</td>
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<tr>
<td>14</td>
<td>Zumbo BNC et al. [20]</td>
<td>1987</td>
<td>57/M</td>
<td>yes light-k</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS no</td>
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<tr>
<td>15</td>
<td>Yokota A et al. [21]</td>
<td>2005</td>
<td>71/M</td>
<td>yes BJP-A</td>
<td>74.4%</td>
<td>NS</td>
<td>NS</td>
<td>NS yes</td>
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<tr>
<td>16</td>
<td>Garipidou V et al. [22]</td>
<td>2005</td>
<td>68/M</td>
<td>yes IgG-A</td>
<td>25%</td>
<td>no</td>
<td>NS</td>
<td>NS yes</td>
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<tr>
<td>17</td>
<td>Galanopoulos A et al. [23]</td>
<td>2009</td>
<td>75/M</td>
<td>yes IgA-κ</td>
<td>60%</td>
<td>no</td>
<td>NS</td>
<td>NS yes</td>
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<tr>
<td>18</td>
<td>Michael M et al. [24]</td>
<td>2009</td>
<td>57/F</td>
<td>yes IgA-k</td>
<td>95%</td>
<td>NS</td>
<td>52.38</td>
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<tr>
<td>19</td>
<td>Ise M et al. [25]</td>
<td>2010</td>
<td>72/F</td>
<td>yes IgG-k</td>
<td>21.6%</td>
<td>no</td>
<td>31.3</td>
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</tr>
</tbody>
</table>

**Table 2**: Coexisting MM and CML cases.

**MM**: Multiple Myeloma; **CML**: Chronic Myeloid Leukemia; **Marrow PC**: Marrow Plasma Cells; **Ph+**: Philadelphia Positive; **WBC**: White Blood Cells
of MM in Imatinib treated CML backround can neither be ruled out, nor can be taken for granted, and since there are only a few reports on this issue, long-term studies are needed. Furthermore, exposure to radiation has been reported to induce t(9;22) translocation [52]. Therefore, CML development as a secondary disease in MM patients having received radiation therapy in the past also cannot be excluded.

Regarding MM patients, the chronic immunological deficiency of the disease, could lead to the formation of secondary malignancies including CML [53].

Lastly, it is notable that despite allogeneic stem cell transplantation is the only potentially curative treatment both for CML and MM separately, no report could be found in the literature in the setting of these two entities coexisting. This is probably due to the fact that most coexisting CML and MM cases seen in the literature are patients older than 65 years old.

In conclusion, coexistence of MM and CML suggests either a different clonal evolution from a common pluripotent malignant stem cell, or exposure to previous chemotherapy and radiation, or existence of a pro-carcinogenic environment, or a coincidence, or every each one of the above possible factors. Further investigation of associated possible causes is needed to get to definitive conclusions.

References


7. Boots MA, Kyle RA. Coexisting CML and MM cases seen in the literature are patients older than 65 years old.


