Case Report
Myeloid Disease with the CSF3R T618I Mutation after CLL

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1. Introduction

Chronic lymphocytic leukemia (CLL) is a very common and usually indolent lymphoid malignancy. Most patients remain in surveillance for a long time. CLL increases the risk of secondary malignancies, mainly in the skin and digestive tract, by diminishing the humoral and cellular responses of the immune system.

A Chronic Neutrophilic Leukemia (CNL) is defined by \( \text{CSF3R} \) persistent neutrophilic proliferation (mainly mature forms), hyperplasia of the bone marrow granulocyte lineage, and usually splenomegaly.\[1\] It is a BCR-ABL negative myeloproliferative neoplasm, named in 1964 for the first time. It is a rare event typically found in elderly people, more frequently males \[1\]. Patients are usually asymptomatic, but there is a hemorrhagic tendency probably caused by the neutrophilia and vascular infiltration by the disease \[1\]. The recent finding of the activating mutations of the gene \( \text{CSF3R} \), the T618I (found in 80% of the cases), revolutionized the understanding of the pathogenesis of this disease, nowadays being an important diagnosis criterion \[1–6\]. However, CNL still is an exclusion diagnosis.

The diagnosis of a chronic myeloid neoplasia as CNL in a patient with a chronic lymphoid neoplasia is a rare phenomenon, mainly when the first diagnosis is CLL \[7–8\]. As far as we know, there is only one case report describing a CLL after a CNL, published in 1998 \[7\].

2. Case Report

A 58-year-old male was diagnosed with CLL Rai 1 in 2012, remaining in regular surveillance. He had a past medical history of hyperuricemia, hypertension, hypothyroidism,
prostate benign hyperplasia, biliary calculus, and clear cells carcinoma of the right kidney (submitted to partial nephrectomy).

In 2014, the CLL progressed with anemia, growing adenopathy, and fast doubling of the leucocyte count. Rituximab, fludarabine, and cyclophosphamide were prescribed for 6 cycles, and the patient achieved a partial response, remaining in surveillance afterwards.

One year later, he was hospitalized for febrile neutropenia caused by right base pneumonia, in septic shock and multiorgan failure (being admitted in the ICU). This episode was followed by another admittance for febrile neutropenia with respiratory symptoms in 6 months.

In 2016, the patient developed autoimmune hemolytic anemia. Prednisolone 1 mg/kg and folic acid were prescribed, being stopped in 3 months with a fast relapse of the hemolysis. A second treatment course was performed for 7 months, with stabilization of the hemoglobin levels around 11-12 g/dL.

Suddenly in the end of 2018, there was a significant increase in the leucocyte count, mainly caused by a neutrophilia (Table 1). The previous kidney cancer had no signs of relapse, and there was no infectious process in the course. There was a soft decrease in the hemoglobin level, but the increase in the leucocyte and neutrophil counts persisted, with the identification of immature myeloid forms in the peripheral blood smear and 0.31 × 10⁹/L of blast cells. A leukemic reaction was suspected. In three months, the hemolytic anemia relapsed, preceded by a dental abscess. The patient complained about asthenia, loss of weight (5 kg in 5 months), bone pain, and nausea. He denied other symptoms. The leukocytosis and neutrophilia became even more evident, as well as the thrombocytopenia. The direct coombs test was positive for complement and IgG (1 : 30). An abdominal echography showed homogeneous splenomegaly (15.8 cm). The flow cytometry of the peripheral blood showed polyclonal B lymphocytes circulating. The bone marrow aspirate was morphologically suggestive of a chronic myeloproliferative disease without dysplasia. The del17p was found by FISH (fluorescence in situ hybridization) in the bone marrow aspirate (fluorescence in situ hybridization) in the bone marrow aspirate. The flow cytometry of the bone marrow aspirate identified a major population of the neutrophilic lineage in different stages of maturation, without blasts. The search for the activating mutation T618I of the CSF3R gene is essential for the final diagnosis of CNL. This gene is related to other disorders apart from CNL, such as CMML, severe congenital neutropenia, hereditary chronic neutrophilia, and rarely myeloid leukemia, and recently, it was described in the literature also in atypical CML [10]. However, the specific T618I mutation was never described in CMML [11]. CNL is not associated with lymphoproliferative neoplasms other than CLL (there is only one case report of a CLL after a CNL, but not the opposite) [7].

CMML should be considered too. Apart from the neutrophilia, this patient also had a monocytosis count in the upper limit of normal values (absolute counts regularly between 0.94 and 1.94 × 10⁹/L, having one episode with 0.39 × 10⁹/L), a persistent monocytosis. CMML is a more common diagnosis compared with CNL.

The loss of the short arm of chromosome 17 (where the TP53 gene is located) identified in the bone marrow aspirate is a genetic abnormality typically found in CLL (as well as the hemolytic events) but not in myeloproliferative diseases. However, there were no signs of CLL in the flow cytometry at the myeloid diagnosis time. The archival cytogenetic sample did not have sufficient quality to allow the study for the CSF3R mutation or p53 mutation.

In what refers to the therapeutic approach, a cyteduction with hydroxyurea is usually successful in the leukocytosis control and splenomegaly (25% of the patients are refractory) for both CNL and CMML [3, 11].
Table 1: Blood counts obtained in a temporal line (from the left to the right; time 0 is the moment of the myeloid diagnosis and the beginning of hydroxyurea).

<table>
<thead>
<tr>
<th></th>
<th>17 months before</th>
<th>16 months before</th>
<th>12 months before</th>
<th>7 months before</th>
<th>5 months before</th>
<th>3 months before</th>
<th>2 months before</th>
<th>1 month before</th>
<th>Time 0 (HU started)</th>
<th>1 month later</th>
<th>2 months later</th>
<th>3 months later</th>
<th>4 months later</th>
<th>6 months later</th>
<th>12 months later</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin g/dl</td>
<td>10.7</td>
<td>11.6</td>
<td>12.1</td>
<td>11.4</td>
<td>11.4</td>
<td>9.4</td>
<td>8.9</td>
<td>11.3</td>
<td>9.5</td>
<td>12.4</td>
<td>11.1</td>
<td>11.4</td>
<td>9.4</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Leucocytes x 10^9/L</td>
<td>9.96</td>
<td>8.33</td>
<td>11.59</td>
<td>13.81</td>
<td>24.82</td>
<td>62.71</td>
<td>77.8</td>
<td>81.7</td>
<td>84.01</td>
<td>21.15</td>
<td>36.61</td>
<td>14.91</td>
<td>61.48</td>
<td>71.77</td>
<td>117.01</td>
</tr>
<tr>
<td>Neutrophils x 10^9/L</td>
<td>5.94</td>
<td>5.08</td>
<td>7.74</td>
<td>10.21</td>
<td>19.94</td>
<td>56.23</td>
<td>63.8</td>
<td>69.48</td>
<td>72.67</td>
<td>15.89</td>
<td>34.77</td>
<td>13.08</td>
<td>53.96</td>
<td>63.02</td>
<td>94.78</td>
</tr>
<tr>
<td>Eosinophils x 10^9/L</td>
<td>0.34</td>
<td>0.18</td>
<td>0.20</td>
<td>0.18</td>
<td>0.22</td>
<td>0.63</td>
<td>0.78</td>
<td>0.03</td>
<td>0</td>
<td>0.03</td>
<td>0.02</td>
<td>0.03</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Basophils x 10^9/L</td>
<td>0.05</td>
<td>0.05</td>
<td>0.1</td>
<td>0.07</td>
<td>0.18</td>
<td>0.63</td>
<td>0</td>
<td>0.05</td>
<td>0.34</td>
<td>0.08</td>
<td>0.12</td>
<td>0.04</td>
<td>0.03</td>
<td>0</td>
<td>0.59</td>
</tr>
<tr>
<td>Lymphocytes x 10^9/L</td>
<td>2.3</td>
<td>2</td>
<td>2.24</td>
<td>2.09</td>
<td>1.96</td>
<td>2.76</td>
<td>3.11</td>
<td>2.01</td>
<td>1.08</td>
<td>1.11</td>
<td>1.96</td>
<td>1.11</td>
<td>1.98</td>
<td>6.68</td>
<td>2.34</td>
</tr>
<tr>
<td>Monocytes x 10^9/L</td>
<td>1.23</td>
<td>1.02</td>
<td>1.07</td>
<td>1.12</td>
<td>1.23</td>
<td>0.94</td>
<td>0.39</td>
<td>1.94</td>
<td>1.09</td>
<td>2.65</td>
<td>0.53</td>
<td>0.45</td>
<td>1.03</td>
<td>1.09</td>
<td>9.95</td>
</tr>
<tr>
<td>Immature granulocytes x 10^9/L</td>
<td>0.1</td>
<td>0.05</td>
<td>0.16</td>
<td>0.18</td>
<td>1.29</td>
<td>0.94</td>
<td>0.39</td>
<td>1.94</td>
<td>1.09</td>
<td>2.65</td>
<td>0.53</td>
<td>0.45</td>
<td>1.03</td>
<td>1.09</td>
<td>9.95</td>
</tr>
<tr>
<td>Metamielocytes 2.76 x 10^9/L, mielocytes 2.20 x 10^9/L, promielocytes 1.23 x 10^9/L</td>
<td>0.1</td>
<td>0.05</td>
<td>0.16</td>
<td>0.18</td>
<td>1.29</td>
<td>0.94</td>
<td>0.39</td>
<td>1.94</td>
<td>1.09</td>
<td>2.65</td>
<td>0.53</td>
<td>0.45</td>
<td>1.03</td>
<td>1.09</td>
<td>9.95</td>
</tr>
<tr>
<td>Platelets x 10^9/L</td>
<td>263</td>
<td>189</td>
<td>228</td>
<td>211</td>
<td>193</td>
<td>147</td>
<td>117</td>
<td>77</td>
<td>90</td>
<td>66</td>
<td>67</td>
<td>86</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blast x 10^9/L</td>
<td>0.31</td>
<td>0.31</td>
<td>0.31</td>
<td>0.31</td>
<td>0.31</td>
<td>0.31</td>
<td>0.31</td>
<td>0.31</td>
<td>0.31</td>
<td>0.31</td>
<td>0.31</td>
<td>0.31</td>
<td>0.31</td>
<td>0.31</td>
<td>0.31</td>
</tr>
<tr>
<td>Sedimentation velocity</td>
<td>20/45</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Legend: HU - hydroxyurea.
The main therapeutic options for CNL are interferon, hypomethylating agents, ruxolitinib, thalidomide, and cladribine [3]. TKI therapy was experimented successfully in a CNL patient for the first time in 2004, for the CSF3R mutation [12]. Treatment with the SRC kinase inhibitor dasatinib and the JAK1/2 kinase inhibitor ruxolitinib also have shown efficacy for CNL with membrane proximal mutations and truncation mutations, respectively [3, 12, 13]. Most of the agents proposed for CNL treatment are palliative, not achieving remission of the disease. There is little role for bone marrow transplantation (the only curative option) or induction regimens, given the bad results obtained [1]. The prognosis of CNL is not favorable nowadays: between 20–30 months of median survival and a transformation rate to AML between 10 and 21.2% in a median time of 21 months. Due to the rarity of the disease, there is no prognostic scoring system approved to guide treatment options and follow-up [1, 3, 8].

The main treatment options for CMML are hypomethylating agents (such as 5-azacitidine or decitabine), with an overall response rate of ∼30–40% and complete remission rate of ∼7–17%, with no impact on mutational allele burdens. Allogeneic stem cell transplantation is the only potentially curative option, but it is associated with significant morbidity and mortality [11].

The authors emphasize the importance of the T618I mutation in the CNL diagnosis, and they wonder whether it is enough to exclude the CMML diagnosis. A wider targeted genotyping could be appropriate to better clarify the etiology of this disease. Future investigations should address the T618I mutation presence in a broad group of CMML patients, in order to strengthen its specificity. Furthermore, the impact of this mutation in selecting treatment options for CNL should also be better understood.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

References