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Plasmablastic crisis of Philadelphia chromosome-positive chronic myeloid leukemia

Kalliopi N. Manola, Despina Pantelidou, Maria Papaioannou

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Title: Plasmablastic crisis of Philadelphia chromosome positive Chronic Myeloid Leukemia

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Corresponding Author: Dr KALLIOPI MANOLA, Ph.D

Corresponding Author's Institution: NCSR "DEMOKRITOS"

First Author: Kalliopi Manola

Order of Authors: Kalliopi Manola; DESPINA PANTELIDOU; MARIA PAPAIOANNOU

Abstract: We report for the first time a rapidly fatal case of a Plasma Cell Leukemia crisis in a young patient with Ph chromosome positive CML. The patient, a 43-year-old male suffered from non diagnosed CML and presented at the time of blast crisis, which turned to be a plasmablastic leukemia. This hypothesis relies on the cytogenetic and immunophenotypic analysis of the leukemic cells. Two related clones were detected. The first clone was characterized only by t(9;22)(q34;q11.2). The evolutionary clone showed severe hypodiploidy, including monosomy 13 and chromosome aberrations different from that of the blast crisis of CML, in addition to t(9;22)(q34;q11.2). Severe hypodiploid karyotype and monosomy 13 are common cytogenetic features of plasma cell leukemia. Positivity for CD38 and cytoplasmic kappa light chain revealed by immunophenotypic analysis of the leukemic cells, confirmed the plasmacytic origin of blasts. Therefore, the most likely diagnosis of our patient is that of Plasmablastic crisis of Philadelphia chromosome positive CML.

Response to Reviewers: Dear Sirs,

The manuscript was revised according to the Reviewer's comments as follows:

- 1) "The pictures relating to karyotypes should be deleted, the information is already in the text".
- The pictures relating to karyotypes were deleted.
- 2) "Instead, a clear peripheral blood microphotograph (600-1000x) should document the presence of plasmablastic-type cells".
- A clear peripheral blood microphotograph (600x) was added to document the presence of plasmablastic-type cells.
- 3) "The immunophenotype study should report in detail the antisera used with respective percentages of positivity; this is especially important for CD45, CD20, CD56, CD30 and cytoplasmic/surface IgG and IgA (not reported in text)".
- The immunophenotype study is now reported in detail [CD45+ (79%), CD38+(77%), CD34+ (56%), surface κ (-), surface λ (-), cytoplasmic κ +(90%), cytoplasmic λ (-), CD20 (-)].
- 4) "Was kidney failure related to any degree of hypercalcemia or proteinuria? Were serum and urine free light chains quantified?"
- Neither hypercalcemia nor proteinuria was observed. Serum and urine free light chains were not quantified as the assay was not available.

Thank you very much for your suggestions.

I am looking forward to hearing from you soon.

Yours Sincerely,
Kalliopi N. Manola
Associate Researcher in the laboratory of Cytogenetics
NCSR "Demokritos"
Athens, Greece.
E-mail: pmanola@ipta.demokritos.gr

To: Tiziano Barbui
Associate Editor
Annals of Hematology

October 6, 2009

Dear Dr Tiziano Barbui,

Please accept the revised manuscript, entitled "Plasmablastic crisis of Philadelphia chromosome positive Chronic Myeloid Leukemia" by K.N. Manola et al., for consideration for publication as Letter in Annals of Hematology, containing the corrections according to the reviewer's recommendations.

The manuscript was revised according to the **Reviewer's** comments as follows:

1) *"The pictures relating to karyotypes should be deleted, the information is already in the text"*.

- The pictures relating to karyotypes were deleted.

2) *"Instead, a clear peripheral blood microphotograph (600-1000x) should document the presence of plasmablastic-type cells"*.

- A clear peripheral blood microphotograph (600x) was added to document the presence of plasmablastic-type cells.

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- The immunophenotype study is now reported in detail [CD45+ (79%), CD38+(77%), CD34+ (56%), surface κ (-), surface λ (-), cytoplasmic κ +(90%), cytoplasmic λ (-), CD20 (-)].

4) *"Was kidney failure related to any degree of hypercalcemia or proteinuria? Were serum and urine free light chains quantified?"*

- Neither hypercalcemia nor proteinuria was observed. Serum and urine free light chains were not quantified as the assay was not available.

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Yours Sincerely,

Kalliopi N. Manola
Associate Researcher in the laboratory of Cytogenetics
NCSR "Demokritos"
Athens, Greece.
E-mail: pmanola@ipta.demokritos.gr

Plasmablastic crisis of Philadelphia chromosome positive Chronic Myeloid

Leukemia

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7 The cytogenetic hallmark of Chronic Myeloid Leukemia (CML) is the Philadelphia
8 chromosome (Ph), the consequence of the reciprocal translocation t(9;22)(q34;q11.2)
9 that results in the BCR-ABL1 fusion gene, located in the Ph chromosome.¹ The
10 natural history of untreated CML is an initial indolent chronic phase which is
11 followed by a blast phase either suddenly or through an accelerated phase. Blast crisis
12 may be diagnosed when blast cells are $\geq 20\%$ of the peripheral blood WBC or the
13 nucleated cells of the bone marrow or when there is an extramedullary blast
14 proliferation.^{1,2} In approximately 70% of cases the blast lineage is myeloid while in
15 20-30% of cases the blasts are lymphoblasts.^{1,2} Progression is usually associated with
16 clonal evolution, and at the time of transformation to blast crisis, 80% of patients
17 demonstrate cytogenetic changes in addition to the Ph chromosome such as an extra
18 Ph chromosome, +8, i(17q) +19, t(3;21)(q26;q22), and very rarely t(7;11)(p15;p15).³
19
20 Plasma Cell Leukemia (PCL) is an aggressive and rare hematological malignancy
21 which is characterized by circulating plasma cells $>2 \times 10^9/l$ in peripheral blood or by a
22 plasmacytosis $>20\%$ of blood leukocytes and confers a poor prognosis. It originates
23 as a primary disease or as a secondary leukemic transformation of multiple myeloma.⁴
24
25 The most frequent features at diagnosis are asthenia, severe anemia,
26 thrombocytopenia, splenomegaly or hepatomegaly while CD38 and CD138 antigens
27 are excellent plasma cell markers.^{5,6} In the majority of the cases karyotypes are
28 complex and hypodiploid or pseudodiploid. Common chromosome abnormalities are
29 14q32 translocations such as t(11;14)(q13;q32), t(4;14)(p16.3;q32), t(14;16)(q32;q23),
30 deletions of the chromosomal regions 17p13, 13q, and 1p21, monosomies of
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1 chromosomes 13 and X (in women), trisomy 18, amplification of 1q21, and MYC
2 rearrangements.⁴⁻⁷
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4 Here, we report for the first time a rapidly fatal case of a Plasma Cell Leukemia crisis
5 in a young patient with Ph chromosome positive CML .
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7 The patient, a 43-year-old male with a 2-month history of persistent fatigue, weakness
8 and loss of weight was admitted to our department. On physical examination spleen
9 was remarkably enlarged and routine complete blood count revealed leukocytosis
10 with a WBC of $22 \times 10^9/l$, anemia with a Hb of 7 gr/dl, and thrombocytopenia with
11 platelet count (PLT) of $30 \times 10^9/l$. Neither hypercalcemia nor proteinuria was observed.
12

13 Blood smear showed 90% blasts with the appearance of plasma blasts (Figure 1).
14

15 Immunophenotyping of blast cells by flow cytometry showed CD45+ (79%),
16 CD38+(77%), CD34+ (56%), surface $\kappa(-)$, surface $\lambda(-)$, cytoplasmic $\kappa+(90\%)$,
17 cytoplasmic $\lambda(-)$, and CD20(-). The cytogenetic analysis of G-banded chromosomes
18 in peripheral blood cells revealed two evolutionary clones, which were positive for Ph
19 chromosome. The karyotype was described as: 46,XY,t(9;22)(q34;q11.2)[4]/
20 32,XY,-2,-3,-4,-5,t(9;22)(q34;q11.2),-10,-11,-12,-13,-15,-16,-17,-18,-20,-22[16].
21

22 Unfortunately, the patient developed acute renal failure on the second day after
23 admission and died two days later.
24

25 Ph chromosome and/or BCR-ABL1 fusion gene which are detected in 90-95% of
26 cases of CML is used as a major criterion for diagnosis of CML.^{1,2} Ph chromosome,
27 marked splenic enlargement, thrombocytopenia, and the high percentage of blasts are
28 compatible with the diagnosis of blast crisis of CML. It seems possible that our
29 patient suffered from non diagnosed CML and presented at the time of blast crisis,
30 which turned to be a plasmablastic leukemia. This hypothesis relies on the cytogenetic
31 and immunophenotypic analysis of the leukemic cells. Two related clones were
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1 detected in our patient. The first clone was characterized only by t(9;22)(q34;q11.2),
2 indicating that Ph chromosome was the primary aberration, possibly created in the
3
4 chronic phase of CML. The evolutionary clone showed severe hypodiploidy,
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6 including monosomy 13 and chromosome aberrations different from that of the blast
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8 crisis of CML, in addition to t(9;22)(q34;q11.2). Severe hypodiploid karyotype and
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10 monosomy 13 are common cytogenetic features of plasma cell leukemia. Positivity
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12 for CD38 and cytoplasmic kappa light chain revealed by immunophenotypic analysis
13
14 of the leukemic cells, confirmed the plasmacytic origin of blasts. Therefore, the most
15
16 likely diagnosis of our patient is that of Plasmablastic crisis of Philadelphia
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18 chromosome positive CML. To the best of our knowledge this case presents the first
19
20 reported case of Plasmablastic crisis of Ph chromosome positive CML.
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31 Kalliopi N Manola^{1*}, Despina Pantelidou², Maria Papaioannou²

32
33 ¹*Laboratory of Cytogenetics, National Center for Scientific Research (NCSR)*
34
35 *“Demokritos”, 15310 Aghia Paraskevi, Athens, Greece*

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37
38 ²*1st Department of Internal Medicine, Hematology department, Medical School*
39
40 *AUTH, Thessaloniki, Greece*

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43 *E-mail: pmanola@ipta.demokritos.gr
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Legend to figure

Figure 1. A peripheral blood microphotograph (600x) showing the presence of plasmablastic-type cells.

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Figure

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