CORRESPONDENCE

De Novo Philadelphia Positive Acute Myeloid Leukemia with Extensive Basophilia: A Diagnostic Dilemma

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Abstract Basophilia in peripheral blood as well as bone marrow is an unusual finding, seen in certain reactive and neoplastic conditions. Amongst the malignant hematological diseases, it is a diagnostic hall mark of chronic myeloproliferative disorders, particularly, chronic myeloid leukemia. Basophilia may also be seen in cases acute myeloid leukemia, particularly FAB AML M2 and M4. Here we document an interesting case of de novo acute myeloid leukemia which had extensive peripheral blood and bone marrow basophilia. Molecular analysis revealed p190, bcr–abl fusion transcript. A short clinical course, absence of organomegaly and features suggestive of an underlying myeloproliferative disorder, aided in establishing a diagnosis of Philadelphia positive de novo acute myeloid leukemia.

Keywords Philadelphia positive · Acute myeloid leukemia · Basophilia

Dear Editor,

Basophilia is a diagnostic hallmark of chronic myeloid leukemia (CML). It is infrequently observed in acute leukemia and its relationship with the leukemic process, associated cytogenetic or molecular abnormalities predisposing to basophilia are poorly understood. The known morphological categories of acute myeloid leukemia associated with basophilia include AML M2, M4 and acute basophilic leukemia [1–5]. The presence of basophilia in AML is usually indicative of myeloid blast crisis in CML

(MBC-CML), and de novo a philadelphia positive AML (Ph + AML) with basophilia are rarely reported [6]. We document an unusual case of an elderly female who presented to hematology OPD with severe breathlessness and pruritis. Immunophenotyping and molecular analysis confirmed the diagnosis of Ph + AML.

A 42 years old female, known case of lymph nodal tuberculosis, presented to the hematology OPD with severe breathlessness and weakness of 20 days duration. She also complained of pruritus, facial puffiness and mild bilateral knee joint pain. She had received three units packed red blood cells in past 4 days. Physical examination showed pallor, bilateral pitting edema and mild diffuse facial swelling. There was no organomegaly or lymphadenopathy. Respiratory examination revealed crepitation over left lung. Sputum culture was positive for methicillin resistant staphylococcus aureus (MRSA). Hemogram showed hemoglobin of 91 g/l, total leucocyte count of 7.1×10^9 and 31×10^9 /l platelets. Approximately 30 % circulating blasts with moderate amount of granular cytoplasm and 10 % basophils were noted. Bone marrow smears were cellular with proliferation of approximately 45 % myeloperoxidase positive blasts and 50 % basophils including precursors (Fig. 1a and inset). Megakaryocytes were not seen. On flow cytometric evaluation, these cells were positive for CD34 (partly), CD38, CD13, CD33 and CD7; in addition on back gating distinct population of approximately 20 % basophils, was also identified, expressing CD11b, CD13, CD123 and were negative for CD117 (Fig. 2). Conventional cytogenetic analysis showed a normal female karyotype, however, a p190 bcr–abl fusion transcript (Fig. 1b) was detected by qualitative nested reverse transcriptase-polymerase chain reaction (RT-PCR). In the absence of a preceding history of chronic myeloid leukemia and organomegaly, the diagnosis of de novo

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Fig. 1 Panel of photographs showing, **a** presence of numerous blasts and basophils in the MGG stained bone marrow aspiration smears (o.m. $\times 1000$), *inset* shows presence of brown granular myeloperoxidase positive blasts along with the negatively stained basophils, and **b** image of the agarose gel electrophoresis showing presence of

381 bp product after nested PCR, corresponding to e1a2 fusion transcript in the patient in *lane 5*, *lanes 1* and *2* are showing 100 and 50 bp ladders, *lane 3* is a negative control and *lane 4* is positive control

Fig. 2 Flow cytometry *dot plots* showing gated blasts with low side scatter and dim CD45 expression. The blasts are positive for CD34, CD13, CD33, CD7 and negative for CD11b and CD123 (*arrow*). A distinct population of basophils is identified with low SSC, forming a

cluster just behind the lymphocytes in the CD45/SSC plot (*last plot*), which are positive for CD11b and CD123; the blast population being negative for these markers

Ph + acute myeloid leukemia (AML) was proposed. The patient was managed for severe bacterial pneumonia, with the plan to administer daunorubicin and cytarabine based chemotherapy protocol. However the patient succumbed to the disease, before the chemotherapy could be initiated.

Cytogenetic abnormalities commonly known to be associated with basophilia in acute leukemia include t(8;21)(q22;q22), t(6;9)(p23;q34) and inv 3(q21;26.2) [1, 7, 8]. Ph + AML constitute <1 % of newly diagnosed cases of AML [9, 10] and presence of basophilia in such cases

has rarely been reported. Igarashi et al. [6] reported a case with similar findings, where blasts harboring minor bcr-abl chimeric mRNA showed basophilic differentiation. Presence of such extensive basophilia in leukemia may lead to two potential differential diagnosis, namely, MBC-CML and acute basophilic leukemia (ABL). CML-MBC is indistinguishable from AML with basophilia, on the basis of morphology alone and the presence of Philadelphia chromosome positivity in AML further adds to the diagnostic dilemma. Though Soupir et al. [11] have shown that

basophilia is more striking a feature of MBC-CML, than Ph + AML; the index case exhibits features contrary to it. Another subtle morphological feature of CML-MBC, is the preservation of the megakaryocytic lineage, which are usually absent/markedly reduced in a de novo Ph + AML, as was seen in this patient. On the molecular front, MBC-CML more frequently shows presence of p210 bcr–abl transcript whereas de novo AML usually has a p190 breakpoint. [12]. Additional clonal cytogenetic abnormalities are more frequently observed in MBC-CML rather than in de novo Ph + AML. Thus in summary, a short duration of illness, absence of leucocytosis or splenomegaly and presence of p190 fusion transcript favored the diagnosis of a de novo AML over MBC-CML.

ABL, yet another morphological mimicker, shows blasts with primary differentiation towards basophils and immunophenotypically the blasts express CD9, CD13, CD33, CD22, CD36, CD123, CD34, HLA-DR and CD25 [13]. The current case showed a distinct population of mature basophils, expressing only CD11b, CD13 and CD123 along with myeloblasts, thus favoring a diagnosis of AML with basophilia over ABL.

To conclude, the relationship of Philadelphia chromosome with basophils is not limited to chronic myeloid leukemia. There is enough accumulating evidence, that Ph + AML is a distinct disorder with varied morphological presentations and poor prognosis [14]. The importance of identifying bcr–abl breakpoints lies in the use of tyrosine kinase inhibitors in their management and as a tumor-specific marker to monitor residual disease in follow-up marrow specimens.

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