CASE STUDY

Chronic myeloid leukaemia presenting in blast phase - a case study

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ABSTRACT

Chronic myeloid leukaemia (CML), *BCR-ABL1* positive is a myeloproliferative neoplasm characterised by a chromosomal translocation t(9;22), the Philadelphia (Ph) chromosome resulting in the *BCR-ABL1* fusion gene which manifests as uncontrolled proliferation of myeloid cells. CML is a triphasic neoplasm with a chronic phase (CP), an accelerated phase (AP), and a blast phase (BP). The majority of patients present in chronic phase. Treatment of CML in chronic phase is extremely successful with patients having a life expectancy of that of the general population. Presentation of CML in accelerated or blast phase is rare and occurs in approximately 5% of cases. We report a rare case of CML presenting in blast phase with over 20% blasts found in the peripheral blood and bone marrow.

Keywords: chronic myeloid leukaemia; blast phase, WDF scattergram

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INTRODUCTION

Chronic myeloid leukaemia (CML), *BCR-ABL1* positive is a myeloproliferative neoplasm characterised by the reciprocal translocation of chromosomes 9 and 22. This translocation results in the *BCR* gene found on chromosome 22 fusing with the *ABL1* gene found on chromosome 9 and the formation of the Philadelphia (Ph) chromosome containing the *BCR-ABL1* fusion gene (1). The resultant *BCR-ABL1* gene has dysregulated tyrosine kinase activity that causes uncontrolled proliferation of myeloid cells (2). CML follows a triphasic course with an initial indolent chronic phase followed by a more aggressive accelerated phase and blast phase (1).

Most patients, approximately 95% of cases, present in chronic phase while presentation in the accelerated or blast phase is rare (3,4). Patients with CML may present with fatigue, weight loss, fever, night sweats, abdominal fullness, signs and symptoms of anaemia, infection, or bleeding (5). Splenomegaly is present in up to 50% of cases (6). However, nearly half of patients diagnosed with CML-CP are asymptomatic and the diagnosis is made from routine blood work (6).

The complete blood count in patients with CML typically shows a leucocytosis with neutrophil and myelocyte peaks and an accompanying eosinophilia and basophilia. The presence of either leucocytosis, neutrophilia, immature granulocytes, eosinophilia, or basophilia should all trigger blood film review depending on user defined ranges set by the laboratory (7). The presence of immature granulocytes is detected by haematology automated analysers and depending on the technology used will either generate a suspect flag or enumerate the immature granulocytes. Sysmex XN automated analysers (Sysmex Corporation, Japan) use fluorescence flow cytometry principles to classify and quantify white blood cells, including immature granulocytes, according to their size, structure, and cellular complexity. The cell volume is indicated by the intensity of the forward scattered light, the internal cell structure and content is indicated by the side scatter and the amount of nucleic acids present in the cell are indicated by the intensity of the side fluorescence, which are all then expressed in a graph known as a scattergram (8) as shown in Figure 1.

The diagnosis of CML requires the detection of the Philadelphia chromosome and/or the *BCR-ABL1* gene rearrangement by molecular techniques (1). According to the WHO classification in CML-CP there are usually less than 2% blasts in the peripheral blood, in accelerated phase 10-19%, and blast phase ≥20% (1). Tyrosine kinase inhibitors (TKIs) are used for the treatment of CML and act by inhibiting the *BCR-ABL1* fusion gene (9). The use of TKI's has dramatically reduced the number of cases that progress from chronic phase to accelerated or blast phase disease (4). Patients with CML-CP that are treated with TKIs respond extremely well to treatment and have a near normal life expectancy (10), whereas patients with CML-BP often have an extremely poor outcome (11). In this case report we present a novel case of CML presenting in blast crisis with an atypical presentation and response to treatment.

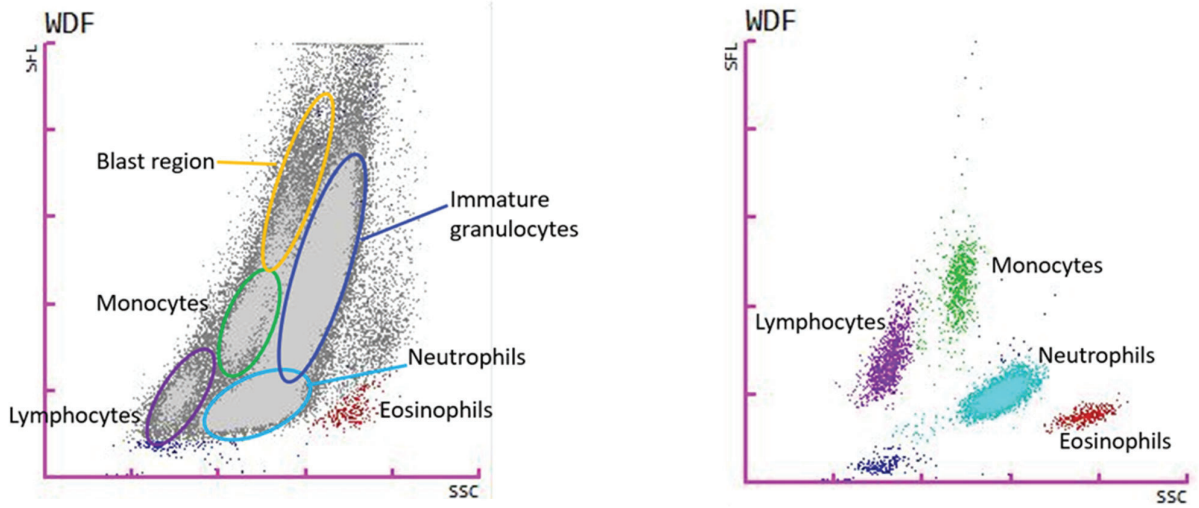

Figure 1. An example of the patient's white cell differential scattergram (WDF) on the left showing the region where the immature granulocytes are found (dark blue), one of the regions where blasts are found (yellow) and eosinophils identified shown in red. A normal white cell differential scattergram is shown on the right for comparison.

CASE REPORT

A 47-year-old male presented to the emergency department with chest pain. He had a two-day history of increasing left rib pain/chest pain on a background of heart disease with hypertension and previous ST-elevation myocardial infarction (STEMI). He denied any fevers or hot/cold flushes but did describe night sweats in the preceding six months with some unintentional weight loss noted. No bleeding, evidence of infection, headache, or blurred vision were present. On examination he was found to have no lymphadenopathy but an enlarged spleen (4 finger breadths below the costal margin) with no tenderness.

The patient's CBC revealed a markedly high WBC of 252.64 x 10^9/L, haemoglobin 132 g/L, RBC 4.95 x 10^{12}/L, and platelets of 262 x 10^9/L. Early information could be derived from the white cell differential scattergram generated by the analyser. The scattergram in this case showed a heterogeneous population with a large number of cells sitting in the immature granulocyte region and blast region found above the monocytes (Figure 1). A clear eosinophilia can also be seen. The lack of distinct separation between cell clusters caused the analyser to 'grey out' the usually coloured scattergram as it was unable to clearly classify the cells, resulting in an abnormal scattergram flag.

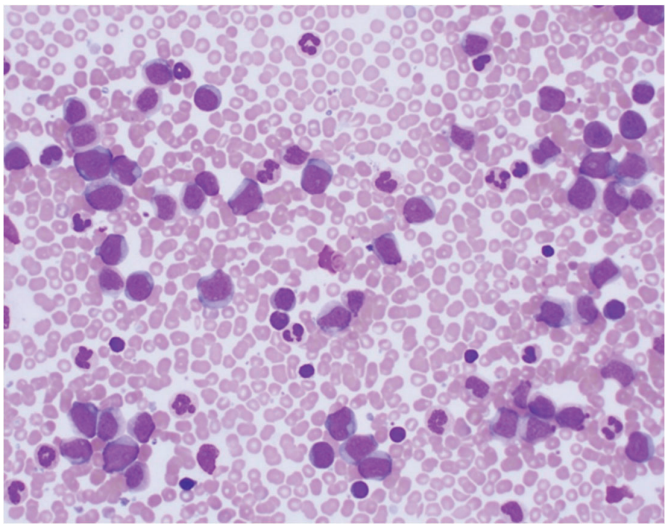

Figure 2. Peripheral blood smear at x50 magnification with many blast cells present.

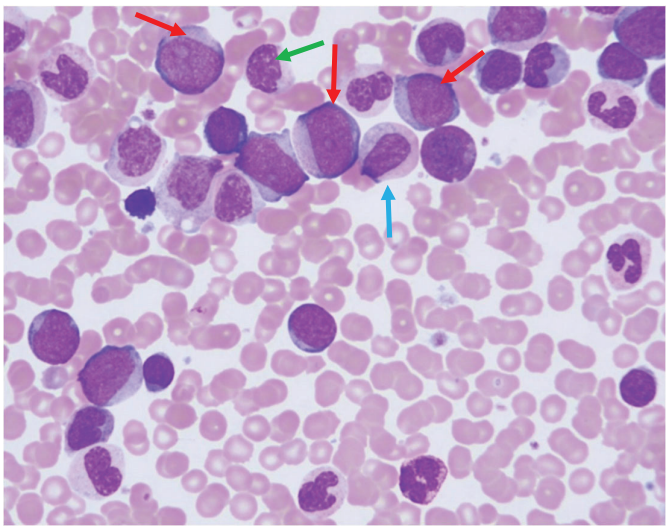

Figure 3. Peripheral blood smear at x100 magnification. Red arrows indicating blasts, blue arrows myelocytes and green arrow a metamyelocyte.

The blood film confirmed the presence of a marked leucocytosis with many immature granulocytes as well as a large number of blast cells (Figures 2 and 3). Blasts cells were large with 1-2 large nucleoli and deeply basophilic cytoplasm. No Auer rods were present. There was a myelocyte and neutrophil peak with an associated eosinophilia and basophilia.

The features seen on the blood film were consistent with CML; however, a bone marrow was required to confirm blast phase disease given the high number of blast cells present in the peripheral blood (26% of total white cells). Cytogenetic testing was performed on the peripheral blood which revealed the presence of the *BCR-ABL1* gene rearrangement, confirming the diagnosis of CML. The bone marrow aspirate mirrored the peripheral blood findings. A marked eosinophilia was noted; however, basophils were significantly less prominent. Blast cells were increased at 23% of nucleated cells. A diagnosis of CML-BP was made.

DISCUSSION

The hallmark laboratory features of CML are an increased WBC and immature granulocytes with a peak in myelocytes and neutrophils. There is often an associated eosinophilia and basophilia (1). Laboratory scientists are trained to recognise these features as potential flags for the disease. Blood film review should be triggered by these CBC findings. User defined ranges for blood film review for all CBC parameters are established by each laboratory in accordance with ISCH guidelines and clinical correlation with laboratory haematologists (7). In our laboratory we use a cut off of > 3% immature granulocytes for blood film review.

The patient in this case had a history of heart disease with previous CBCs taken at the time of each acute presentation. There is some overlap with CML, and a reactive picture caused by infection and inflammation which has the potential to make identification more difficult. A leukaemoid reaction with a marked leucocytosis is a haematological abnormality that may be confused with leukaemia (12). Features that suggest a leukaemoid reaction include toxic changes such as granulation, Dohle bodies and vacuolation due to infection, and a predominance of more mature myeloid cells. Toxic features are usually absent in patients with CML (12). The presence of a persistent thrombocytosis with large or giant platelets may support a diagnosis of CML (13). The WBC in patients with CML can range anywhere from 12-1000 x10^9/L (1,5). The platelet count is either normal or increased and in chronic phase marked thrombocytopenia is uncommon (1,5). CML-chronic phase is associated with a hypercellular bone marrow with leucocytosis with an increase in myelocyte and neutrophil fractions. There is no significant dysplasia seen (1). Blasts are usually <5 % in the marrow and <2 % in the blood. Like the peripheral blood eosinophils and basophils are increased. In the bone marrow megakaryocytes are smaller than normal and have hyposegmented nuclei. These are not true micromegakaryocytes like those seen in myelodysplastic syndromes called dwarf megakaryocytes (1).

According to the WHO criteria accelerated phase disease is defined by one or more of the following criteria: 10-19 % blasts in the peripheral blood and/or bone marrow, ≥ 20% basophils in the peripheral blood, platelets <100 x10^9/L not treatment related or platelets >1000 x10^9/L unresponsive to treatment, additional chromosomal abnormalities occurring on treatment, white cell count and spleen size increasing and uncontrolled on treatment (1). Response to treatment is also considered. Blast phase is defined as ≥ 20% blasts in the peripheral blood or bone marrow or extramedullary blast proliferation (1). Our patient had 23% blasts in the bone marrow and 26% in the peripheral blood therefore meeting the WHO criteria for blast phase disease.

Early information in this case was able to be obtained from the WDF scattergram from the automated haematology analysers. As the patient's WBC was markedly increased the results were flagged for validation and phoning by a scientist as per laboratory protocol.

Whilst awaiting blood film review, we were able to review the white cell differential scattergram for any information regarding a likely diagnosis. The presence of a large number of cells in the neutrophil and immature granulocyte region, the clear eosinophilia, the patient's markedly increased WBC and preserved indices somewhat suggested a potential CML.

However, the large population of cells sitting in the blast region is not typical of a scattergram seen in patients with CML-chronic phase. The scattergram shown on the left in Figure 4 is typical, but not exclusive to that seen in a patient with CML-chronic phase. Distinct populations can be seen as shown in colour with a large number of cells in the region of neutrophils (light blue) and immature granulocytes (dark blue) as well as an eosinophilia (red). Unlike our patient there are no cells found in the blast region as would normally be the case in a patient with CML-chronic phase. The heterogenous population of cells seen in the scattergram of our patient (shown on the right in Figure 4) and the presence of abnormal cells in the blast region may give an early indication of CML-blast phase. This was confirmed by the presence of a large numbers of blasts seen in the patient's blood film.

Upon review of the patient's previous CBC results, note was made of a mild persistent thrombocytosis and neutrophilia. An eosinophilia and raised red cell count were present intermittently. This raises the possibility that the patient's blast phase may have arisen from a previously undiagnosed CML-chronic phase. It is of note that in this case our patient previously demonstrated a borderline basophilia that was not overt. It was, however, higher than his previous counts and was at the upper range of normal. His eosinophilia was also intermittent.

This case highlights the importance of early detection and treatment of CML in chronic phase. With the use of TKIs treatment of CML-chronic phase has excellent response rates and overall survival rates. Patients who are treated in chronic phase have an overall survival similar to those of the general population (10). Some patients can achieve deep molecular remission and can discontinue treatment. The majority of patients, however, remain on TKIs indefinitely (10). Lack of efficacy and intolerance in some patients may lead to discontinuation of treatment (10). Progression to accelerated or blast phase occurs in approximately 5-10% of cases even with treatment (4,14). Patients with CML-blast phase are treated with TKIs with or without chemotherapy (15). Those with *de novo* accelerated phase disease should be treated with a second generation TKI. The patient presented in this case was treated with Dasatinib. Dasatinib is a second generation TKI which targets both *BCR-ABL1* and SRC- family kinases and has the ability to bind to active and inactive forms of *ABL* kinase (2,4). Dasatinib has been shown to be more effective than Imatinib against *BCR-ABL1* and is effective against most *BCR-ABL1* mutations (2,4). In patients that achieve a haematological response, subsequent allogenic stem cell transplant (SCT) should then be considered (15). Studies have shown patients with CML-BP who have undergone allogenic SCT following TKI therapy had a significantly higher overall survival than those treated with TKI alone (4). Relapse and resistance to TKIs is common in CML-blast phase and long-term overall survival rates remain low. The main goal for management and treatment of CML is to prevent the development of CML-blast phase from occurring in the first instance (16,17).

Very few patients present in blast phase disease and typically present with a more severe clinical picture than was seen in our case. Patients in accelerated or blast phase disease present with a clinical picture similar to an acute leukaemia with constitutional symptoms, such as fever and weight loss or symptoms related to anaemia or thrombocytopenia (1,6). Our patient presented to the emergency department with unrelated clinical issues and neither anaemia nor thrombocytopenia were present. He was, however, noted to have splenomegaly on examination and on reflection some night sweats and unintentional weight loss. The patient has had a good response to treatment which is unexpected in patients with accelerated or blast phase disease as they are more likely to be resistant to treatment and have a poorer outcome (4,11). The patient has shown an early molecular response with his *BCR-ABL* transcriptase levels reducing well over time however the patient's overall survival remains to be seen.

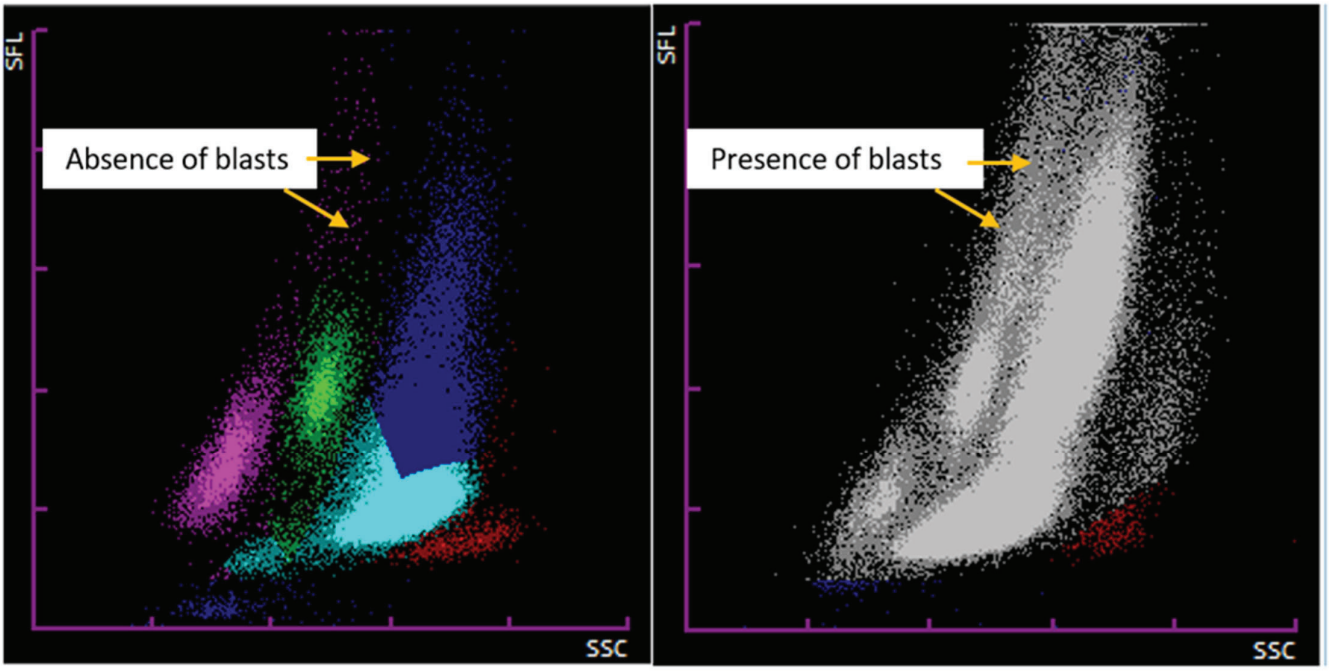

Figure 4. An example of a white cell differential scattergram seen in a patient with CML-CP on the left with an absence of blasts. An example of our patient's WDF scattergram on the right with increased numbers of blasts present and heterogeneous 'greyed out' population.

CONCLUSIONS

Nearly all patients diagnosed with CML present in chronic phase disease. Our patient was one of the rare cases that presented and was diagnosed in blast phase disease. Up to half of patients with CML are asymptomatic and diagnosis may be an incidental finding from routine blood work. This places importance on the role the laboratory scientist plays in the diagnosis of CML. As treatment in CML-chronic phase is extremely effective it is important to detect cases early in the course of the disease to ensure prompt treatment and a more favourable outcome. Even when presenting in situations where the picture can be explained by an acute setting there may be potential flags for an underlying myeloproliferative neoplasm, such as persistence of neutrophilia and immature granulocytes or accompanying abnormalities such as eosinophilia or basophilia. Recommendations for repeat CBC testing when patients are well with review of all previous CBC results would be appropriate in these instances to detect potential myeloproliferative neoplasms that have a chronic clinical picture.

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