CASE REPORT

Atypical CML with massive splenic infarct: an extremely rare presentation

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SUMMARY

We report a case of a 47-year-old man who presented with hepatosplenomegaly, anaemia and massive splenic infarct. A series of investigations led us to a diagnosis of atypical chronic myeloid leukaemia, a rare variety of a mixed myelodysplastic/myeloproliferative neoplasm. This is the first case of atypical CML presenting with massive splenic infarction.

BACKGROUND

Atypical chronic myeloid leukaemia (aCML) presents similarly to CML, but has a more aggressive course with bone marrow failure occurring within 2 years of presentation.¹ It is negative for Philadelphia chromosome (Ph-chr.) and BCR/ABL transcript. In the WHO classification, aCML has been considered a new distinct clinical entity, and included in the category of 'MPS/MDS'. The MPS/MDS group includes chronic myelomonocytic leukaemia (CMML), juvenile myelomonocytic leukaemia (JMML), refractory anaemia with ring sideroblasts with marked thrombocytosis (RARS-T), atypical chronic myeloid leukaemia (aCML) and myelodysplastic/myeloproliferative neoplasm (MPN), unclassifiable (MDS/MPN-U).² "Within this category, the diagnostic criteria for CMML, JMML, and refractory RARS-T, are well defined and easy to follow, but criteria for aCML and MDS/MPN-U are less well defined."³

CASE PRESENTATION

A 47-year-old non-diabetic, non-hypertensive man, with no history of addiction, presented with an insidious onset abdominal swelling, which started from the left hypochondrium and progressed up to the umbilicus over the past 2 years. This was associated with a dragging sensation and early satiety. There was a localised sharp pain over the left hypochondrium for the last 4 days. He also had a history of (H/O) anorexia, significant weight loss and easy fatigability. There was no H/O haematemesis, melena, jaundice, blood transfusion, night sweats, fever or bleeding manifestations.

On examination, the patient had moderate anaemia, massive tender splenomegaly with splenic rub, hepatomegaly and sternal tenderness. There was no lymphadenopathy or features of portal hypertension.

INVESTIGATIONS

Investigations revealed: haemoglobin 7.4 g%, total leucocyte count (TLC) 67 000/mm³, with a

differential count of neutrophil 86%, lymphocyte 1%, monocyte 0%, eosinophil 1%, basophil 0%, myelocyte and metamyelocyte 12% (figure 1). Platelet count was 113 000/mm³ and reticulocyte count was 1% with normocytic normochromic red blood cells.

Liver function tests, electrolytes, urea and creatinine were normal. Other blood tests revealed a serum vitamin B₁₂ >1000 pg/mL (range 279–996 pg/mL), serum LDH 1275 U/L (range 115–221 U/L), uric acid 8.9 mg%, red cell folic acid 150 ng/mL (range 150–450 ng/mL) and serum ferritin 128 ng/mL (range 29–248). Ultrasonography of the abdomen with Doppler study showed a massively enlarged spleen >20 cm with normal splenic artery but without any flow in splenic parenchyma. Contrast-enhanced CT scan of the abdomen showed massive ischaemic insult of the whole spleen except the splenic capsule and some heterogeneous areas in the lower pole (figure 2). Upper gastro-oesophageal endoscopy was normal. Blood culture was negative. Echocardiography was normal.

Bone marrow aspiration cytology showed hypercellular marrow with a myeloid:erythroid ratio of 24:1, predominantly normoblastic erythropoiesis. A trephine biopsy of bone, performed later, showed hypercellular marrow with evidence of myelodysplasia and suppressed erythropoiesis, a fair number of megakaryocytes, normal blast population and grade 4 myelofibrosis on reticulin stain (figure 3).

The G-banded metaphase preparation failed to detect the Ph-chr. and PCR detected no BCR/ABL transcript. Additional investigations showed a neutrophil alkaline phosphatase score of 35 (range 38–100) and the presence of SETBP1 mutation, and no BCR/PDGFR FIP fusion gene or JAK2 V617F mutation was detected by RT-PCR.

Figure 1 Peripheral blood picture showing many mature neutrophils, RBCs show mild anisocytosis. RBCs, red blood cells.

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Figure 2 Contrast-enhanced CT scan of the abdomen showing massive splenic infarct except the splenic capsule.

TREATMENT

The patient was put on hydroxyurea (500 mg twice daily). Non-steroidal anti-inflammatory drugs and narcotic analgesics were given for severe abdominal pain due to splenic infarction. The patient did not agree to bone marrow transplantation.

OUTCOME AND FOLLOW-UP

Follow-up blood examinations showed a TLC of $16\,000/\text{mm}^3$ and the patient had minimal symptoms with improved satiety and weight gain. But he died of septicaemia and bleeding leading to shock after 12 months of diagnosis.

DISCUSSION

Persistent leucocytosis with massive splenomegaly without any obvious underlying infective or inflammatory cause, as seen in this patient, suggests a MPN, until proved otherwise.⁴ According to WHO classification, MPNs are composed of several groups of disorders including CML, PV, essential thrombocythaemia (ET), primary myelofibrosis or myelofibrosis with myeloid metaplasia (MMM), chronic neutrophilic leukaemia (CNL) and a few uncommon others.

In this patient, as the BCR-ABL transcript was absent, CML or neutrophilic CML⁵ were excluded and MPNs without BCR-ABL transcript were considered in the differential diagnosis. These are ET, polycythaemia vera (PV), myelofibrosis with MMM or primary myelofibrosis, and CNL.

Among these, ET was ruled out, as the platelet count of this patient was never too high. The PV may present rarely without an elevated red cell mass, but absence of JK2V617F mutation makes it very unlikely in this patient.⁶ MMM generally presents in the sixth decade of life and is characterised by anaemia, splenomegaly, mild neutrophilia, thrombocytosis, extensive marrow fibrosis and extramedullary haematopoiesis.⁷ Episodic

left upper abdominal pain may occur secondary to splenic infarction, and palpable hepatomegaly is found in the majority of cases. The classic blood picture of MMM shows teardrop red cells, leucoerythroblastosis and large platelets. Elevation of serum lactate dehydrogenase (LDH), vitamin B₁₂ and alkaline phosphatase level is seen in MMM. JAK 2 mutation is positive in >50% of patients.⁸ The bone marrow shows increased reticulin fibre and, at a later stage, collagen fibrosis with numerous abnormal megakaryocytes. Our patient had no leucoerythroblastosis or tear drop red cells in the peripheral blood, and no large megakaryocyte in bone marrow, in spite of fibrosis. So MMM was excluded from the diagnosis.

CNL is a rare myeloproliferative disease that presents with a clinical picture similar to what this patient had, with increased leukocyte alkaline phosphatase (LAP) activity and elevated serum vitamin B₁₂ level and absent Ph-chr. and BCR-ABL transcripts.⁹ But the presence of dysgranulopoiesis and stage 4 myelofibrosis in the bone marrow and low LAP score, as found in this patient, went against a diagnosis of CNL.

The bone marrow trephine biopsy from this patient showed myelodysplasia and grade 4 myelofibrosis. So, at that point, we expanded our differential diagnosis to include myelodysplastic/MPNs (MDS/MPNs), which include CMML, JMML, atypical chronic myeloid leukaemia (aCML) and unclassifiable myelodysplastic/myeloproliferative diseases.¹⁰ Among these, CMML and JMML were easily ruled out as this patient had no monocytosis in peripheral blood and was in the fourth decade of life, respectively.¹¹

In the 2008 WHO classification, aCML is defined by persistent leucocytosis ($\geq 13 \times 10^9/\text{L}$) with immature circulating myeloid precursors ($\geq 10\%$ of leucocytes) and marked dysgranulopoiesis, with absent/minimal monocytosis ($< 1 \times 10^9/\text{L}$ and $< 10\%$ of leucocytes) or basophilia (often $< 2\%$). The presence of BCR-ABL1 or rearrangements of PDGFRA, PDGFRB, or FGFR1, precludes a diagnosis of aCML as well as any MDS/MPN subtype.¹² SETBP1 mutations are detected in 25–32% of aCML and 10% of MDS/MPN-U cases.³

In contrast to the chronic phase of CML, aCML usually has typical dysplastic changes that may involve all cell lines. These features fit well to our patient's profile, suggesting aCML as the most probable diagnosis. Atypical chronic myeloid leukaemia (aCML) is a rare subtype of myelodysplastic/MPN's (MDS/MPN) largely defined morphologically. Wang *et al*³ stated that it was unclear, however, whether aCML-associated features are distinctive enough to allow its separation from unclassifiable MDS/MPN (MDS/MPN-U).

Figure 3 Section of BM trephine biopsy showing packed marrow with a marked increase in granulocytic cells. BM, bone marrow.

Learning points

- This case report underlines the importance of giving due attention to all—including non-specific and minor—symptoms, so that the underlying major diseases will not be missed.
- Atypical chronic myeloid leukaemia (CML) has a more aggressive course than CML.
- There is no uniform guideline on the management of patients with atypical CML. We hope that, with more detection of such cases due to increased awareness among physicians, a generalised consensus regarding the management of these patients will be formed.

Massive splenic infarct due to chronic myeloid leukaemia is extremely rare. In chronic myeloid leukaemia, increased splenic oxygen requirements secondary to an increased splenic mass, coupled with a decreased oxygen-carrying capacity secondary to the anaemia of hypersplenism, lead to infarction.¹³ Atypical CML presenting with left upper quadrant abdominal pain due to splenic infarction as a sole presenting complaint has not been documented in the literature.

Contributors DB and TDB treated the patient and prepared the manuscript. SM and AH helped in management and information gathering.

Competing interests None declared.

Patient consent Obtained.

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REFERENCES

- Oscier DG. Atypical chronic myeloid leukaemia, a distinct clinical entity related to the myelodysplastic syndrome. *Br J Haematol* 1996;92:582–6.
- Bennett JM, Catovsky D, Daniel MT, *et al.* The chronic myeloid leukemias: guidelines for distinguishing chronic granulocytic, atypical chronic myeloid, and chronic myelomonocytic leukemia: proposals by the French-American-British Cooperative Leukaemia Group. *Br J Haematol* 1994;87:746–54.
- Wang SA, Hasserjian RP, Fox PS, *et al.* Atypical chronic myeloid leukemia is clinically distinct from unclassifiable myelodysplastic/myeloproliferative neoplasms. *Blood* 2014;123:2645–51.
- Tefferi A, Vardiman JW. Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organization criteria and point-of-care diagnostic algorithms. *Leukemia* 2008;22:14–22.
- Pane F, Frigeri F, Sindona M, *et al.* Neutrophilic chronic myeloid leukemia: a distinct disease with a specific molecular marker (BCR/ABL with C3/A2 junction). *Blood* 1996;88:2410–14.
- Levine RL, Pardanani A, Tefferi A, *et al.* Role of JAK2 in the pathogenesis and therapy of myeloproliferative disorders. *Nat Rev Cancer* 2007;7:673–83.
- Barosi G. Myelofibrosis with myeloid metaplasia. *Hematol Oncol Clin North Am* 2003;17:1211–26.
- Baxter EJ, Scott LM, Campbell PJ, *et al.* Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. *Lancet* 2005;365:1054–61.
- Eliott MA, Dewald GW, Tefferi A, *et al.* Chronic neutrophilic leukemia (CNL): a clinical and pathological entity. *Leukemia* 2001;15:35.
- Kouides PA, Bennett JM. Morphology and classification of the myelodysplastic syndromes and their pathologic variants. *Semin Hematol* 1996;33:95–110.
- Arico M, Biondi A, Pui CH. Juvenile myelomonocytic leukemia. *Blood* 1997;90:479–88.
- Vardiman JW, Bain BJ, Brunning RD, Thiele J. Atypical chronic myeloid leukaemia, BCR-ABL1 negative. In: Swerdlow SHCE, Lee Harris N, *et al.* eds. *WHO classification of tumors of haematopoietic and lymphoid tissues*. Lyon, France: IARC Press, 2008:80–1.
- Parikh M, Geibel J. *Splenic infarct*. Emedicine, 2014.

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