Chronic mast cell leukaemia with exon 9 *KIT* mutation A502_Y503dup: a rare imatinib responsive variant

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DESCRIPTION

Mast cell leukaemia (MCL) is a very rare aggressive form of systemic mastocytosis (SM), representing <1% of cases of adult SM in the USA. The diagnosis of MCL requires the presence of SM criteria accompanied by mast cells accounting for at least 20% of nucleated cells in bone marrow (BM) aspirate or 10% of peripheral blood white cells; cutaneous lesions are often absent.¹ In patients with MCL, the absence of organ damage, the so-called 'C findings', serves as a diagnostic criterion of the chronic subvariant of MCL.² Herein, we present a case of an aleukaemic chronic MCL with a rare *KIT* exon 9 mutation A502_Y503dup. A 60-year-old man developed recurrent episodes of flushing, headaches, dizziness and fluctuating blood pressure. Complete blood count showed a white blood cell count $13 \times 10^9/L$, haemoglobin 123 g/L, haematocrit 35.7%, mean corpuscular volume 98 fL and platelets $213 \times 10^9/L$. A tryptase level was 71.9 µg/L. Initial BM evaluation was consistent with SM with aberrant expression of CD2 and CD25. Allele-specific PCR for the *KIT* D816V mutation was negative. Repeat BM biopsy was obtained for *KIT* gene sequencing and showed an extensive mast cell infiltrate that was positive for CD2 (moderate, 27%) and CD25 (weak, 29%) and represented 60%–70% of marrow cellularity (figures 1–4). Next-generation sequencing revealed a *KIT* exon 9 mutation A502_Y503dup with an allele frequency of 3.4%, as well as an *ASXL1* variant (p.R402Q). Systemic imaging did not show any evidence of hepatosplenomegaly or lymphadenopathy. The absence of C findings, relatively low tryptase, low Ki-67 (<5%) and the preponderance of immature mast cells without blastic morphology were

Figure 2 H&E stained bone marrow trephine biopsy showing large mononuclear or spindle mast cells on 20x view.

compatible with the non-WHO described chronic MCL variant of MCL. Cladribine or interferon-alpha are no longer considered first-line treatments for cytoreduction due to modest overall response rates. Midostaurin is a multikinase/*KIT* inhibitor that is FDA-approved for the treatment of advanced SM, including MCL.³ Imatinib is effective in a minority of SM patients only, as the most common

Figure 1 Wright-Giemsa stained bone marrow aspirate showing mast cells on 100x view.

Figure 3 Immunohistochemistry of bone marrow core biopsy showing positive staining of tryptase containing mast cells on 40x view.

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Figure 4 Immunohistochemistry of bone marrow core biopsy showing the CD117 positivity of mast cells on 20× view.

KIT mutation (D816V) is resistant to imatinib.⁴ In this case, given the presence of the rare variant exon 9 *KIT* mutation, imatinib was recommended as initial therapy. The patient had persistent anaphylaxis that was refractory to standard supportive care, and omalizumab was recommended. The patient was recently started on imatinib 800mg daily. The anaphylactic episodes have resolved. MCL is a rare form of advanced SM, and in the absence of the typical *KIT* D816V mutation, a search for other mutations by sequencing the entire *KIT* gene should be considered, as this can influence the choice of treatment. The *KIT* exon 9 mutation A502_Y503dup was previously reported in patients with gastrointestinal stromal tumours. There has been no case of chronic MCL with this variant *KIT* mutation reported in the literature. Only one case of acute MCL with this variant *KIT* mutation has been reported previously in the literature, with a favourable response to imatinib.⁵

Learning points

- Mast cell leukaemia (MCL) is a rare and aggressive form of systemic mastocytosis (SM) characterised by leukaemic expansion of mostly immature mast cells, organ damage, drug-resistance and confers a poor prognosis.
- The diagnosis of MCL requires the presence of SM criteria accompanied by mast cells accounting for at least 20% of nucleated cells in bone marrow aspirate or 10% of peripheral blood white cells. The absence of organ damage, the so-called 'C findings', serves as a diagnostic criterion of the chronic subvariant of MCL.
- Neoplastic mast cells display *KIT* D816V in only 50%–70% of the cases. In the remaining MCL cases, other *KIT* mutations or no *KIT* mutations are found. A search for other mutations by sequencing the entire *KIT* gene should be considered, as this can influence the choice of treatment.
- Chronic MCL is an extremely rare but morphologically recognisable pathological variant of MCL.

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