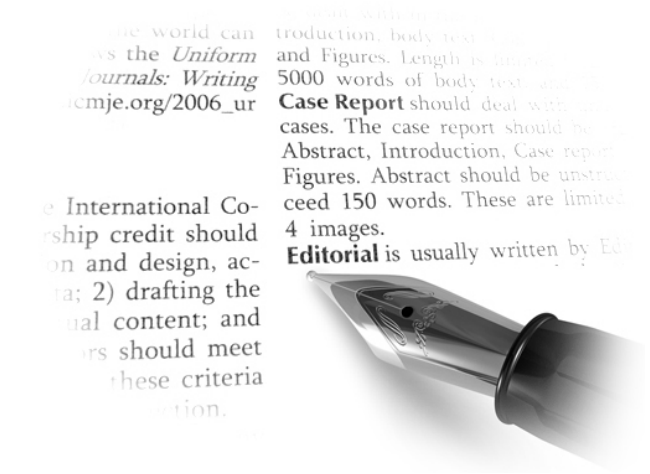

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# Editorial

## Application of next generation sequencing in the diagnosis and management of mast cell leukemia

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Mast cell diseases are difficult to diagnose due to its protean symptoms and presence of coexisting conditions [1]. Symptoms are associated with clonal proliferation of mast cells and include from mild flushing to cardiac arrest following anaphylactic reaction [2]. In some cases, the patients are finally diagnosed with mast cell disease after several emergency room visits for cardiopulmonary resuscitations. Mast cell leukemia (MCL) is an extremely rare but aggressive subtype of systemic mastocytosis and the prognosis is just as abysmal with median survival of less than 6 months. Probably, some patients die even before a diagnosis is made if the physician was not aware of that there is link between the recurrent idiopathic anaphylaxis with mast cell leukemia and further evaluation for mast cell leukemia was not carried out.

The evaluation algorism proposed for possible mastocytosis emphasizes testing for basal tryptase level greater or equal to 20.0 ng/mL or 20% above baseline after symptomatic event [1]. However, a recent study showed that a diagnosis of systemic mastocytosis cannot be ruled out by a normal serum tryptase level alone [3]. MCL is often characterized by somatically acquired activating mutations in the *KIT* receptor gene which causes uncontrolled ligand-independent signaling by KIT and increased proliferation of mast cells [4]. Studies have shown that the *KIT* D816V is the most frequently found mutation that also causes resistance to imatinib therapy in MCL. The presence of *KIT* D816V mutation has been included in the major diagnostic criteria of systemic mastocytosis by World Health Organization, and European Competence Network on Mastocytosis has recommended that *KIT* mutation should be evaluated using peripheral blood or bone marrow samples using more sensitive routine method that can detect low number of mast cells [5]. However, other mutations in *SRSF2*, *ASXL1* and/or *RUNX1* have also been found in the patients with *KIT* D816V positive systemic mastocytosis, indicating that mutations in more than one gene may be necessary for leukemogenesis [5, 6]. In this issue of the **Blood Research**, Youk *et al.* [7] used next generation sequencing (NGS) to find mutations possibly causing the disease in a patient diagnosed with MCL. The whole exome sequencing revealed *KIT* S476I and whole transcriptome sequencing demonstrated possibly *RARα-B2M* fusion gene, and the authors used the results in personalized treatment. In addition, the RNA expression analysis revealed the upregulation of PI3K/AKT pathway downstream of mammalian target of rapamycin (mTOR). The all-trans retinoic acid (ATRA), dasatinib, and everolimus targeting mTOR pathway were used in sequence following the NGS data. Although the patient did not survive even after the tailored therapy, she survived longer than the median survival of MCL. The PI3K inhibitor could have been tried to prolong survival but was not available in Korea. This was the second exome sequencing study in MCL after a report by Spector *et al.*, in which *KIT* V654A and *MS4A2* L188F variants were found [8]. In both studies, *KIT* D816V was not detected, which is

consistent with previous study showing that *KIT* D816V is not as frequent in MCL compared to other form of mast cell disorders [9]. Thus, more comprehensive method should be used to sequence *KIT* as well as finding other gene mutations possibly responsible for mast cell leukemogenesis to be measured for mutant allele burden in the follow up studies. Due to rarity of the disease and therefore lack of data, comprehensive molecular testing by NGS on more cases of MCL would be valuable to find new biomarkers and better treatment modalities including combination of drugs to cure such a devastating disease. Routine implementation of NGS testing still has some obstacles, such as limited ability to interpret techniques and high cost, but could be beneficial in molecular profiling of tumors for targeted therapies and promising approach in identifying novel genetic alteration of rare disease.

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