To the editor:

**FLT3 internal tandem duplication mutations are rare in agnogenic myeloid metaplasia**

We were interested in the recent report by Kelly et al.1 that FLT3 internal tandem duplication (FLT3-ITD) mutations, while sufficient to induce a chronic myeloproliferative disease in a murine bone marrow transplant (BMT) assay, were not sufficient to induce an acute myeloid leukemia (AML) phenotype. These data suggest that FLT3-ITDs may require additional cooperating mutations to generate the AML phenotype. The authors suggested that it would be worthwhile to investigate chronic myeloproliferative syndromes, including myeloid metaplasia with fibrosis, for the presence of activating mutations in FLT3. We report here our findings from the study of FLT3-ITD mutations in 40 patients with agnogenic myeloid metaplasia (AMM).

Genomic DNA was prepared from peripheral blood samples, following informed consent, from 40 patients with well-characterized AMM using the Nucleon Biosciences BACC II kit (Tepnel Life Sciences, Manchester, United Kingdom). All cases of AMM fulfilled the following criteria: a leukoerythroblastic blood picture, teardrop poikilocytosis, absence of monocytosis, marked bone marrow fibrosis, and lack of the Philadelphia chromosome. Patients with the closely related disorders, postpolycythemic myelofibrosis, and myelodysplasia with myelofibrosis were excluded from the study. DNA was screened by polymerase chain reaction (PCR) and conformation-sensitive gel electrophoresis (CSGE) for the reported FLT3 internal tandem duplication mutations, in exon 13 and 14, as previously described.2,3 Positive control samples were included in the analyses (DNA from AML patients known to have FLT3-ITD mutations).

We did not find exon 13 or 14 FLT3-ITD mutations in the 40 cases of AMM studied, suggesting that such mutations do not play a significant pathogenetic role in the chronic phase of the disease. FLT3-ITD mutations, however, may emerge during transformation of MDS or at relapse of AML, suggesting that they promote leukemic progression.4,5 The lack of FLT3 mutations in AMM would support this conclusion, and it will be interesting to screen transformed patients to determine whether FLT3 mutations are involved in disease progression.

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References


To the editor:

**Platelet-dependent action of high-dose factor VIIa**

We read with interest the recent article by Butenas et al.1 who conclude that the prohemostatic effect of high-dose factor VIIa in hemophilic blood or a synthetic plasma system is strictly dependent on tissue factor (TF). The authors note that their proposed mechanism differs from our previously published conclusion that high-dose factor VIIa can, in the absence of TF, generate factor Xa on the surface of activated platelets and replaces the absent factor IXa/VIIIa complex to generate factor Xa, which then boosts platelet-surface thrombin generation.2 Our view is consistent with the observation that the tissue factor pathway is intact in hemophilic patients3 and, indeed, is responsible for platelet activation, accounting for the tendency of hemophiliacs to initially stop bleeding as a normal platelet plug forms4,5 but then suffer severe delayed rebleeding.

These disparate views of the mechanism of action of factor VIIa have important implications for dosing. The TF-dependent effect described by Butenas et al is saturated at levels below those now used therapeutically. By contrast, the binding of factor VIIa to the activated platelet surface is nowhere close to being saturated at therapeutically relevant concentrations. Thus, our mechanism

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