Correspondence

To the editor:

The t(4;14)(p16.3;q32) is strongly associated with chromosome 13 abnormalities in both multiple myeloma and monoclonal gammopathy of undetermined significance

We read with great interest the paper by Chesi et al regarding FGFR3 that further supports the role of FGFR3 in the pathogenesis of multiple myeloma (MM).1 Monoclonal gammopathy of undetermined significance (MGUS) also has genetic abnormalities seen in MM, including the t(4;14)(p16.3;q32)2-3 with presumptive up-regulation of the FGFR3 oncogene. Here we provide additional data attesting that the pathogenetic pathways in MM are highly specific. Specifically, we find that in MGUS and MM the t(4;14)(p16.3;q32) is strongly associated with 13.

We tested 155 patients with MM and 52 patients with MGUS/SMM (50 with MGUS and 2 with SMM) for evidence of the t(4;14)(p16.3;q32) using cIg-FISH with a fusion strategy for detection of the abnormality. For IgH locus we used the previously published probes by Gabrea et al4 (VH and CH probes), and both probes were directly labeled with SpectrumGreen (Downers Grove, IL). For the 4p16.3 locus, we used the PAC probe previously used by Chesi et al (FGFR3 PAC184d6/385). We also used a BAC clone containing sequences of the centromeric most cosmid (96a2) in the contig described by Chesi et al6 retrieved with the PCR primers 5’-ACAAGACGCTACTGTTTTCC-3’ and 5’-TCTAGATCTCTGCATCGACG-3’ and purchased from Incyte Genomics (human BAC Release II; Palo Alto, CA). Both 4p16.3 probes were directly labeled with SpectrumRed (Vysis). A patient was considered to have the t(4;14)(p16.3;q32) if the percent of abnormal plasma cells exceeded 10% of signals with an abnormal pattern (fusions) indicative of a t(4;14)(p16.3;q32). All of these patients were also tested for 13 by the previously published strategy and methods using the probes LSI13-Rb and D13S319.8

Of 155 MM patients, 16 (10.3%) had an abnormal pattern consistent with the t(4;14)(p16.3;q32). The median percentage of abnormal plasma cells (MPAPC) was 88% (range, 40%-100%). Fifteen of 16 MM patients (94%) with the t(4;14)(p16.3;q32) had 13 (MPAPC 99%; range, 96%-100%). Likewise, we found the t(4;14)(p16.3;q32) in a similar proportion, 5 (9.6%) of 52 patients with MGUS/SMM (3 MGUS, 1 SMM) (MPAPC 86%; range, 49%-100%). In 3 of 4 (75%) patients with MGUS/SMM and the t(4;14)(p16.3;q32), we found concurrent 13 (MPAPC 91%; 91%, 91%, and 98%). The incidence of 13 in MGUS, SMM, and MM is strikingly different from what we and others have previously reported in MM3 (about 50%) and MGUS (about 30%).7

We believe this study provides important information regarding the progression pathways from MGUS to MM. First, as previously mentioned,7 we have shown in MM a striking association of the t(4;14)(p16.3;q32) with 13 in both MM and MGUS. This would suggest that 13 is an important factor in the pathogenesis of MGUS/MM with the t(4;14)(p16.3;q32) rather than being a factor promoting progression from MGUS to MM. The near-obligate presence of 13 in MM with the t(4;14)(p16.3;q32), but not the opposite, suggests that 13 occurs prior to the translocation event. Because of the low prevalence of ras mutations, the association with FGFR3 mutations, and the striking associations with 13, we postulate that MM with the t(4;14)(p16.3;q32) represents a unique subtype of MM. We thus propose a refinement in the model, as shown in Figure 1, that incorporates the t(4;14)(p16.3;q32), 13, ras, and FGFR3 mutations. The results of this study also highlight the high likelihood that subgroups of MGUS patients, classified according to the underlying genetic abnormalities, may be at different risk of progression to MM. This is in need of a prospective study.

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References


To the editor:

Misleading information about ALIP and VEGF in myelodysplasia

The study by Bellamy et al.1 has numerous critical limitations. First, the authors incorrectly assume that abnormal localization of immature precursors (ALIPs) can be identified in the bone marrow clot section, which has no bony trabeculae. It should be pointed out that ALIPs are collections of immature myeloid precursors in the central, intertrabecular region of the bone marrow trephine biopsy section.2,3 Moreover, this is a feature of microarchitecture disorganization in the bone marrow biopsy sections in myelodysplastic syndromes (MDSs), which also show disorganized erythroid and megakaryocytic precursors in the trabecular region.3,4 In a normal human bone marrow biopsy, myeloid precursors are near the trabecular region, and erythroid and megakaryocytic precursors are in the intertrabecular region.5 This physiologic cell distribution may be reversed in the bone marrow biopsy of cases with MDS.4 The data presented by Bellamy et al.1 show only myeloid and monocytoid blasts in a clot section without bony trabeculae, which is typical of blasts seen in a bone marrow aspirate. Moreover, it is reported that most myeloid blasts and myeloid leukemia cell lines express vascular endothelial growth factors (VEGFs) and their receptors.6,7 This simply indicates that, like acute myeloid leukemia blasts, immature myeloid cells in MDS do express VEGF and this is not specific to displaced/ectopic blasts or ALIP.

Second, the authors show absence of VEGF in a healthy human bone marrow clot section, but their data highlight only the absence of VEGF in mature myeloid cells (neutrophils). Like normal bone marrow, Figure 4 in Bellamy et al clearly demonstrates absence of VEGF in all mature myeloid cells in cases with MDS. Therefore, we do not know whether healthy human bone marrow blasts differ from “dislocated myeloid precursors” (Bellamy et al.), and they do not have autocrine or paracrine promotion by VEGF.

Third, their data show that cases with refractory anemia (RA, or low-risk MDS) were 100% (8 of 8) positive for VEGF, and only 72% (16 of 22) of cases with refractory anemia with excess of blasts (RAEB) and RAEB in transformation (RAEBt) show positivity for VEGF. According to our experience1,4 and that of others,2 only 30% of cases with RA show presence of ALIP and more than 95% of cases with RAEB/RAEBt (high-risk MDS) do have ALIP in their bone marrow biopsies. Bellamy et al.1 do not clarify how many RA and RAEB/RAEBt cases were with ALIP and without ALIP, why RAEB/RAEBt cases with ALIP do not demonstrate positivity for VEGF, and what is the explanation for VEGF positivity in RA cases without ALIP.

Fourth, the authors do not mention anything about the international prognostic scoring system (IPSS) in MDS.5 This scoring system is used by most physicians to make a therapeutic decision in cases with MDS. It will be interesting to know about any correlation between VEGF expression and IPSS risk categories.

Finally, most investigators will agree that lymph-node fine-needle aspirates do not give enough information about lymph node architecture. Likewise, bone marrow clot sections are not suitable to start assuming about architectural disorganization in MDS. To get the full picture about ALIP in MDS and the autocrine or paracrine promotion by VEGF or other growth factors, authors should justify their conclusions on the basis of bone marrow biopsy examinations.

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