To the editor:

Why make a diagnosis?

I read with interest Dr Evan Sadler’s commentary regarding the papers by Goodeve and colleagues and James and colleagues in a recent issue of Blood.1 Since 2 large studies failed to associate a mutation with people followed in bleeding disorder clinics who have mild type 1 von Willebrand disease, why give them a diagnosis? Fair-skin people are more at risk of sunburn and melanoma than dark-skinned people. Do they have “premelanoma syndrome”? We just advise (prescribe) sun block. Similarly, if a person has a mild bleeding history, bruises easily, is blood type O, and their ristocetin cofactor is slightly low, why all these machinations about “making a diagnosis”? Just write a note in their medical record about your rationale for prescribing DDAVP before their dental extraction.

In certain clinical situations, we should consider other therapeutic paradigms than making a diagnosis before treating.

Richard Lipton

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References

Response:

Diagnosing VWD type 1: when is it useful and when illogical?

Dr Lipton raises an important question about the best strategy for managing patients with moderately decreased levels of von Willebrand factor (VWF). One need not medicalize every small predisposition to a future adverse event by giving it an eponymous diagnosis. I like the comparison to fair skin as a risk factor for skin cancer, and I’ve used it myself in discussing von Willebrand disease (VWD) type 1. We also take a similar approach to high blood pressure, managing it empirically as a modest risk factor for cardiovascular events. With respect to low VWF levels, the community is still figuring out the best approach. The problem was discussed in some detail in the revised guidelines for diagnosing VWD that were published recently on behalf of the International Society on Thrombosis and Haemostasis.3 This paper prompted a similar exchange of letters about how to define VWD type 1 and which patients should be considered simply to have “low VWF” instead.2 On one hand, VWF levels lower than 20 IU/dL usually are associated with VWF mutations, significant bleeding symptoms, and a high likelihood of transmitting the condition to progeny. A diagnosis of VWD type 1 seems appropriate in such cases. On the other hand, VWF levels closer to 50 IU/dL have none of these properties, and a label of “disease” is illogical. For the troublesome intermediate levels, we need more information, especially about the risk of bleeding and the benefits of treatment. Is there a threshold, a natural boundary that separates patients into useful categories? If so, then we could treat those below as VWD type 1 and those above as possessors of low VWF, a risk factor for mild bleeding. The ongoing studies of VWD in Europe and in Canada are starting to provide this information and should help to define a more satisfactory approach to diagnosing, treating, and advising our patients with modest, quantitative decreases in VWF.

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References

To the editor:

Myelofibrosis evolving during imatinib treatment of a chronic myeloproliferative disease with coexisting BCR-ABL translocation and JAK2V617F mutation

Among the more than 100 published cases of Philadelphia chromosome–positive chronic myelogenous leukemia (Ph+ CML) investigated for the 1849G > T mutation of the Janus kinase 2 (JAK2V617F),1 no mutated cases have been found so far.2,3 Selected patients with Ph+ CML with marked thrombocytosis also proved to be negative for the JAK2V617F mutation.3 We report for the first time a case of coexisting JAK2V617F mutation in Ph+ CML evolving to myelofibrosis during imatinib treatment.

The 55-year-old white man presented with splenomegaly, leukocytosis (white blood cell [WBC] count of 163 × 10⁹/L), a low hemoglobin (Hb) level (115 g/L), and an elevated lactate dehydrogenase (LDH) level (1337 U/L). A total of 14% blast cells in peripheral blood indicated acceleration. Peripheral blood smears revealed typical features of a CML, and molecular analysis showed a rare variant of bcr-abl fusion gene (e19a2). Imatinib therapy induced normalization of the patient’s blood parameters within 11
months (WBC count, $5 \times 10^9$/L; Hb, 138 g/L; LDH, 232 U/L; and 0% blast cells), including cytogenetic and molecular remission, with no detectable BCR-ABL fusion transcripts in the bone marrow. Furthermore, splenomegaly was no longer present. Follow-up biopsies of the bone marrow 11, 14, and 23 months after initial diagnosis and onset of treatment revealed an increasing accumulation of megakaryocytes and focal deposition of argyrophilic fibers (Figure 1). Whereas histomorphology suggested persistence or relapse of the Ph$^+$ CML clone, no BCR-ABL fusion transcripts could be detected in the bone marrow. Consequently, a JAK2V617F mutation was analyzed with a highly sensitive pyrosequencer assay, and in the initial biopsy, 5% mutated alleles were found, which increased to 15% and 23% after 14 and 23 months, respectively (Figure 1). During the first 23 months of follow-up red blood cell counts, Hb, platelets, and WBC counts remained stable and within normal range. When the initial pretherapeutic trephine was re-evaluated, minor focal fibrosis was obvious, but besides a BCR-ABL fusion, there was evidence for a small JAK2V617F-mutated clone encompassing 5% of alleles. In rare cases, JAK2V617F can occur simultaneously with the recently discovered thrombopoietin receptor point mutation in the oncogene of myeloproliferative leukemia (MPL 1544G $>$ T/W515L), but pyrosequencing and direct sequencing revealed a MPL wild-type status in all biopsies.

This case demonstrates for the first time that BCR-ABL translocation and JAK2 mutation may be concomitantly detectable in hematopoietic cells of a single patient. The suppression of the Ph$^+$ CML clone beyond the level of detection by imatinib therapy while the JAK2V617F-mutated alleles steadily increased argues in favor of 2 independently growing aberrant stem cell clones in this patient. The clinical and histopathologic diversity of Ph$^+$ chronic myeloproliferative disease (CMPD), encompassing polycythemia vera, essential thrombocythemia, and chronic idiopathic myelofibrosis, all of which share the JAK2V617F mutation, is still unexplained. Recently, it has been hypothesized by Kralovics et al$^2$ that a varying combination of different molecular defects in 1 pathologic stem cell might be responsible for the phenotypic heterogeneity, but this case indicates that at least in a subfraction of patients, heterogeneity might also be caused by independently coexisting abnormal hematopoietic stem cell clones. Furthermore, persistent anemia or evolving myelofibrosis during imatinib treatment of Ph$^+$ CML despite molecular suppression might be caused by a coexisting Ph$^+$ CMPD clone.

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