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Mast Cell Activation Syndrome as a Significant Comorbidity in Sickle Cell Disease

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Abstract: Some sickle cell anemia (SCA) patients suffer significantly worse phenotypes than others. Causes of such disparities are incompletely understood. Comorbid chronic inflammation likely is a factor. Recently, mast cell (MC) activation (creating an inflammatory state) was found to be a significant factor in sickle pathobiology and pain in a murine SCA model. Also, a new realm of relatively noncytoproliferative MC disease termed MC activation syndrome (MCAS) has been identified recently. MCAS has not previously been described in SCA. Some SCA patients experience pain patterns and other morbidities more congruent with MCAS than traditional SCA pathobiology (eg, vasoocclusion). Presented here are 32 poor-phenotype SCA patients who met MCAS diagnostic criteria; all improved with MCAS-targeted therapy. As hydroxyurea benefits some MCAS patients (particularly SCA-like pain), its benefit in SCA may be partly attributable to treatment of unrecognized MCAS. Further study will better characterize MCAS in SCA and identify optimal therapy.

Key Indexing Terms: sickle cell anemia; mast cell activation syndrome; KIT mutations; pain; hydroxyurea. **[Am J Med Sci 2014;348 (6):460–464.]**

The contrast between the mutational homogeneity (in beta globin) and clinical heterogeneity in sickle cell anemia (SCA) has long been recognized.[1,2] Putative factors associated with higher rates of painful vasoocclusive crises include higher hemoglobin concentration, lower hemoglobin F (HbF) concentration, higher hemolysis rate, higher blood viscosity and neutrophil activation, among others. Putative factors associated with higher mortality risk include vasoocclusive crises, acute chest syndrome, renal failure, seizures, lower hemoglobin concentration, lower HbF concentration and leukocytosis.[3] Nevertheless, there remains substantial variability in crisis rates among SCA patients sharing similar levels of these factors; some endure frequent crises, whereas others suffer few crises—and some suffer none at all. Primary and emergency care physicians and hematologists know well the "poor-phenotype" minority of their SCA population who disproportionately present with crises and other SCA complications. In 1 study, the 5.2% of SCA patients who averaged 3 or more pain crises per year accounted for 32.9% of the SCA pain crises treated by physicians at hospitals.[4]

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One group of factors proposed to account for the clinical heterogeneity of SCA is genetic polymorphisms affecting not only aspects of hemoglobin production other than hemoglobin S production (eg, upregulation of HbF production, alpha thalassemia) but also other systems impacted by erythrocyte sickling.[2,5–7] Another factor that may affect SCA clinical heterogeneity is inflammation, which might be consequential to the repeated vasoocclusive crises of SCA and/or other specific inflammatory ailments.[8]

Inflammation is a complex milieu of humoral and cellular factors. Although granulocytes and lymphocytes are often considered among these cellular factors, the role of the mast cell (MC) has been less commonly appreciated. Recently, MC activation was identified as a key factor in the pathobiology and pain of SCA in a murine model.[9] On the clinical front, there also has been recognition recently that the spectrum of primary MC disease extends beyond the various forms (eg, cutaneous, systemic) of the proliferative disease of mastocytosis to the relatively nonproliferative MC activation syndrome (MCAS).[10] The clonal origins of mastocytosis and other myeloproliferative neoplasms (MPNs) have been appreciated for some time; more recently, the heterogeneity of these mutations across patients, and the complexity of the mutation set in any given patient, are being increasingly recognized.[11–13] Similarly, there are preliminary data suggesting substantial intra-individual mutational complexity and interindividual mutational heterogeneity in MCAS.[14,15]

Reported here for the first time is the presence of MCAS in a cohort of poor-phenotype sickle cell disease (SCD) patients.

PATIENTS AND METHODS

In the course of their routine clinical care, after recognition that some of their symptoms were more easily attributable to MCAS, 38 patients followed by the author for poor-phenotype SCA (mostly genotype SS; leading to at least 3 emergency department presentations and/or hospitalizations for sickle cell crises per year for the previous 5 years, and/or engaged in a treatment program of chronic red cell transfusions or hydroxyurea [HU] to mitigate frequent crises) were diagnostically evaluated for MCAS as described in recent reviews.[10,16,17] In brief, testing included serum tryptase and chromogranin A (CgA) levels, plasma histamine and heparin and prostaglandin D_2 (PGD_2) levels, and spot and 24-hour urinary PGD_2 and *N*-methylhistamine (NMH) levels. Patients were cautioned to avoid nonsteroidal anti-inflammatory drugs (potentially reducing prostaglandin production) and proton pump inhibitors (potentially escalating CgA production) for at least 5 days before specimen acquisition, and all samples were chilled on ice immediately on acquisition (the 24-hour urine samples were kept continuously refrigerated throughout collection) and kept chilled throughout handling and transport.

RESULTS

Thirty-two of the 38 evaluated poor-phenotype SCA patients (84%) were found to meet the current proposed diagnostic criteria for MCAS.[10] This cohort of SCA/MCAS patients is summarily described in Table 1 and in more detail in **Supplemental Digital Content 1** (see **Table**,

http://links.lww.com/MAJ/A61). Three selected cases particularly well illustrating the scenario of frequent crises and other chronic complications initially attributed solely to SCA, with significant improvement then seen upon recognition and treatment of comorbid MCAS, are detailed in **Supplemental Digital Content 2** (see **Table**, http://links.lww.com/MAJ/A61).

Of note, the majority of the SCA/MCAS patients manifested normal serum tryptase levels, normal plasma histamine and urinary NMH levels, elevated PGD_2 levels and elevated heparin levels. PGD_2 and heparin levels were the most useful for defining the presence of MC activation; urinary NMH levels were the least helpful. Tryptase is expected to be normal to perhaps minimally elevated in MCAS, a point of distinction between MCAS and mastocytosis that highlights the relatively new understanding that tryptase levels correlate more with total body MC load than total body MC activation state.[16,18–22] Consistent with the known effects of chronic kidney disease (CKD) on serum levels of tryptase[19,23–25] and CgA,[26–31] mean tryptase and CgA levels were higher in SCA/MCAS patients with CKD than without CKD. However, although there was virtually no overlap in the ranges of CgA between SCA/MCAS cohorts with and without CKD, there was substantial overlap in the ranges of tryptase between these cohorts. Plasma heparin testing yields readings in terms of anti-Factor-Xa activity, and although such testing is more commonly pursued to determine the efficacy of low molecular weight heparin therapy, the same test as applied in individuals not on heparin therapy reveals endogenous levels of heparin, which seems to be a sensitive and specific indicator of MC activation because it is known to be produced in humans only by MCs[32] and indeed was the first MC mediator to be discovered nearly 80 years ago.[33]

Also, of note, all the SCA/MCAS patients evaluable for symptomatic improvement from MCAS-targeted therapy experienced at least partial improvement, and nearly 1 in 5 experienced complete improvement, perhaps providing a basis for encouragement for other poor-phenotype SCA patients (and their physicians). Oddly, although hospital and/or emergency department utilization declined dramatically for some (typically more compliant) patients following institution of effective MCAS therapy, mean annualized such usage across the evaluable cohort did not seem to decrease. However, loss of one third of the total cohort to follow-up may have skewed these results.

DISCUSSION

The sources of heterogeneity of clinical phenotype among SCA patients who all share the same point mutation in beta globin have long been investigated and debated. As noted above, a number of potential contributing factors have been identified, and yet it has generally been appreciated that a significant portion of the cause of poor-phenotype SCD (especially variants expected to be less morbid than SCA) remains poorly accounted. Inflammation has been proposed as a significant contributor to the morbidity and heterogeneity of such patients, but a common recurring cause of such inflammation has not yet been identified.

Recently, Vincent et al[9] found that in a murine model of SCA, MC activation underlies sickle pathophysiology leading to inflammation, vascular dysfunction, pain, and requirement for high doses of morphine, raising the questions of whether a similar process is present in sickle cell patients and whether therapies targeted at MC mediator production or action might help ameliorate some of the morbidities of SCD. The present series provides preliminary data that MC activation indeed is present in some poor-phenotype SCD patients, including not only those with SCA but also those with other sickle cell variants, and that therapy in such patients targeted at their MC activation can change the acuity of at least some of their clinical manifestations that traditionally have been attributed exclusively to their SCD.

Of hematopoietic origin, MCs are found in all human tissues, especially at the environmental interfaces and perivascular/perineural sites.[34] They serve largely as sentinels of environmental change and bodily insults and respond by releasing variable assortments and levels of molecular mediators that directly and indirectly influence behavior in other (local and distant) cells and tissues to respond to changes/insults so as to maintain, or restore, homeostasis. The transmembrane tyrosine kinase receptor KIT is the dominant MC regulatory element, shown to be critical for key MC functions including survival, differentiation, chemotaxis, and activation.[35]

Traditionally, MC disease has been thought to be principally a matter of neoplastic burdens of MCs (ie, mastocytosis), with symptoms resulting principally from an accompanying inappropriate release of mediators from these excessive MCs. Nearly a quarter century ago, though, the notion was first advanced that there might be forms of MC disease manifesting inappropriate mediator release with little to no accompanying MC cytoproliferation.[36] This theory appeared validated when the first recognized cases of what is now called MCAS were published in 2007.[14,37,38] MCAS typically causes chronic multisystem polymorbidity of a generally inflammatory theme.[10] Different patterns of aberrant expression of the large MC mediator repertoire in different MCAS patients make for markedly heterogeneous—and thus diagnostically challenging—presentations (see **Table**, **Supplemental Digital Content 3**, http://links.lww.com/MAJ/A61). The cause of such heterogeneity of mediator expression in MCAS is not yet clear. Provocatively, though, Molderings et al[14,15] have repeatedly found a broad array of (presumably mostly constitutively activating) mutations scattered across all domains of KIT in small cohorts of MCAS patients, with most of their studied patients bearing multiple mutations in no yet-apparent recurring patterns. (Interestingly, too, the MC KIT^{D816V} mutation—seemingly a driver of MC cytoproliferation, high serum tryptase levels, and other distinguishing features of mastocytosis[39]—seems rare in MCAS.) Although the findings by Molderings et al have not yet been independently confirmed, it is noteworthy that similar mutational complexity (in KIT and other cellular controllers) has been found, too, across the spectrum of chronic MPNs within which the MC disorders reside,[11] and in mastocytosis itself.[12,13]

Given these new biological and clinical insights, proposals have emerged to consider all MC diseases, including mastocytosis and MCAS, under the umbrella term of MC activation disease (MCAD).[40] It also has been proposed that the assorted systemic MCAD variants and clinical phenotypes represent not distinct disease entities but instead varying presentations of a common generic root process of MC dysfunction.[41] Despite its rarity, mastocytosis is fairly readily recognizable because of its distinctive clinicopathological presentation, whereas MCAS, although suspected to be far more prevalent in the whole[41,42] than mastocytosis, is more challenging to recognize in large part because of the heterogeneity of its variant presentations, some of which are already discretely recognized (eg, idiopathic anaphylaxis,[38] cryopyrin-associated periodic syndrome[43]), but most not.