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Scientific Letter

Routine Inflammatory Markers Are Elevated in Myelodysplastic Syndromes at Presentation

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To the editor.

The pathogenesis of myelodysplastic syndromes (MDS)[1] is complex, and major players include the immune system and inflammatory processes.[2,3]

Despite the recognition of the involvement of inflammatory processes in MDS pathogenesis, using inflammatory markers in daily practice as a part of the diagnostic, prognostic or therapeutic course, is limited. We report here our observation of C-reactive-protein (CRP) and/or erythrocyte sedimentation rate (ESR) in patients with MDS at presentation.

Patients and Methods. Records of MDS patients from our center who had BM examination (BME) and either CRP or ESR labs at presentation, were reviewed. Patients were excluded if the MDS diagnosis was questionable, or if they had comorbidities known to be associated with high inflammatory markers.

Normal level of CRP in our lab is 0-5 mg/L. Thus, values >5mg/L were considered high (abnormal). Abnormally high ESR was defined as >25mm in the first hour.[4]

As controls we used the data of 100 consecutive outpatient subjects (non MDS), undergoing workup including BME, who were at least 50yr old and had either CRP or ESR tested at the time of workup.

The study was approved by the local IRB Helsinki committee.

Results. The mean age was 74.6 ± 11.2 and 70.5 ± 9.6 yr for the MDS and control groups, respectively (p=0.001); 43% and 37% of them, respectively, were females (p=0.47). As expected, the mean hemoglobin (Hb; 10.5 and 11.6 g/dL, respectively, p=0.001), white blood cell count (WBC; 5.1 and 7.5 x10^9/L, respectively, p<0.001), absolute neutrophil count (ANC; 2.9 and 7.5 x10^9/L, respectively, p<0.001) were significantly lower in the MDS patients compared with controls, while the mean corpuscular volume (MCV) was significantly higher (96 and 92 Fl, respectively, p=0.005). Platelets were only slightly and non-significantly lower in the MDS group (164 and 179 x10^9/L, respectively).

The mean CRP level was 11.9 [95% CI: 7.1, 16.7] mg/L in the MDS group compared with 4.1 mg/L [95% CI: 3.1, 5.1] in the controls (**Table 1**, p=0.028). The mean ESR was 33.2 [95% CI: 23.1, 43.4] mm and 27.8 [95% CI: 19.0, 36.6] mm in the MDS and controls, respectively (p=0.277).

In the MDS group 31 of 80 patients (38.8%) demonstrated high CRP, compared with only 23/95 (24.2%) controls (**Table 2**, p=0.049). Elevated ESR was observed in 17/33 (51.5%) in the MDS group and in 13/30 (43.3%) in the control group (**Table 2**, p=0.616).

The 31 MDS patients and 23 controls with elevated

Table 1. CRP and ESR mean values.

Parameter Mean [95% CI]	**Controls**		**MDS**		**P**
	N	**Value**	**N**	**Value**	
CRP* (mg/L)	95	**4.1** [3.1, 5.1]	80	**11.9 [7.1, 16.7]**	**0.028**
ESR** (mm/1h)	30	**27.8** [19.0, 36.6]	33	**33.2** [23.1, 43.4]	**0.277**

Our normal ranges: *CRP: 0-5 mg/L. **ESR: ≤ 25 mm in 1 hour.

Table 2. Elevated CRP and ESR.

Test	Controls			MDS			P
	N Total	N elevated	% elevated	N Total	N elevated	% elevated	
CRP	95	23	**24.2%**	80	31	**38.8%**	**0.049**
ESR	30	13	**43.3%**	33	17	**51.5%**	**0.616**

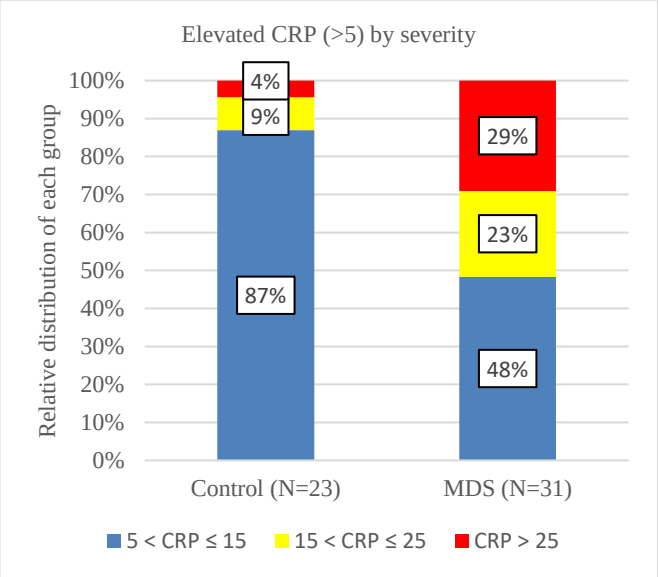

Figure 1. Bar graphs depicting the relative distribution of patients with elevated CRP. Among the 23 control patients with elevated CRP (left bar), the vast majority (87%) of them were in the the mildest group (5<CRP≤15, blue), while 9% and 4% of them were in the moderate (15<CRP≤25, yellow), and highest (CRP>25, red) groups respectively. Among the MDS patients with CRP elevation (right bar), however, only 48% were in the mildest group. The majority were either in the moderate group (23%), or in the highest group (29%). P=0.0038 for trend.

CRP were stratified according to the severity of the abnormal CRP (**Figure 1**). 1) Mildest CRP elevation (5<CRP≤15 mg/L, blue): 48.4% (MDS) vs 87.0% (controls); 2) Moderate elevation (15<CRP≤25 mg/L, yellow): 22.6% vs 8.7%, respectively; 3) Highest elevation (CRP>25 mg/L, red): 29.0% vs 4.3%, respectively. P=0.0038 for the trend. This demonstrates that in the control group the vast majority have milder elevation (left bar, blue), while in the MDS group, most are either in the moderate or highest elevation group (right bar, yellow and red).

Discussion. The involvement of the immune system and inflammatory processes in MDS pathogenesis has gained attention over the last decades. Cytokine abnormalities have been reported,[2] including high levels of interleukin (IL)-6, tumor necrosis factor (NTF)-α, and IL-10, as well as low levels of transforming growth factor (TGF)-β1, and S100A4. Sallman and List focused on the role of inflammation in the pathogenesis of MDS.[3] Aberrant innate immune activation and pro-inflammatory signaling within the malignant clone and the bone marrow (BM) microenvironment were identified as key pathogenic drivers of MDS. In particular, S100A9-mediated NOD-like receptor protein 3 (NLRP3) inflammasome activation directs an inflammatory, lytic form of cell death termed pyroptosis that underlies many of the hallmark features of the disease.

Aging has been found to be a major player. Over the last decade the biological phenomenon age-related clonal hematopoiesis (ARCH) has been well-described.[5,6] Emerging data suggest that the association between clonal hematopoiesis and nonmalignant comorbidity may be bidirectional. Macrophage and inflammasome activation in clonal hematopoiesis contribute to the etiology of inflammaging conditions, such as atherosclerosis, and the systemic inflammation caused by age-related inflammatory comorbidity, may also drive clonal expansion and selection in the pathogenesis of myeloid neoplasia.[7] Thus, "inflammaging", the inflammatory process facilitated by aging, becomes important in MDS pathogenesis.[7-9]

Despite the recognition that inflammatory processes and markers play a role in the pathogenesis of MDS, little has been done so far to use it as an assisting tool in daily practice. Inflammatory markers can help in establishing diagnosis, staging and prognostication, and might also serve as potential therapeutic targets.

In our study, we provide another piece of evidence for the involvement of inflammation in MDS at presentation. The work suggests the importance of using these simple, readily available markers in clinical practice. The mean CRP level was higher in MDS patients at presentation compared with controls (**Table 1**). Moreover, a higher percentage of MDS patients than controls had abnormal CRP and ESR. Separation of the elevated CRP values into 3 levels of severity demonstrated that despite the small numbers in each subgroup, most of the MDS patients had a CRP with highest levels of elevation, while the vast majority of controls had CRP values in the mildest group. Since we excluded patients with active infections or immune diseases (often with exceedingly high CRP levels), the

results might be more significant.

Our study suffers from several limitations. The retrospective nature of the study and the relatively small number of tested individuals are the most significant. The small numbers do not allow separation of the patients into risk categories. Also, the possibility that some patients (and controls) could have had another unrecognized reason for the high CRP or ESR, could shift the results and the conclusions.

Nevertheless, this preliminary study points to the involvement of the inflammatory-immune system in MDS pathogenesis, Records of MDS patients from our center who had these markers in practice. Future studies will examine the use of these inflammatory markers in patient prognosis and will hopefully lead to another group of potential therapeutic targets as well.

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Competing interests: The authors declare no conflict of Interest.

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