Autoinflammatory disorders in patients with myelodysplastic syndrome: the role of distinctive karyotypes and somatic mutations

Introduction: A higher prevalence of autoimmune and autoinflammatory conditions, such as systemic vasculitis, inflammatory arthritis and neutrophilic skin disorders have been reported in patients with myelodysplastic syndrome (MDS). Our study aimed to shed light on the association between specific autoinflammatory manifestations and various MDS-associated cytogenetic karyotypes or somatic mutations.
Objective: to determine if there is a correlation between patients' demographic, clinical and molecular features of MDS with specific autoinflammatory complications and a long-term outcome.
Methods: This was a retrospective study of 140 MDS patients who were diagnosed by the Haematological Malignancy Diagnostic Service (HMDS) in Leeds, UK, between 2012-2018. All patients had detailed molecular studies including karyotypes assessment and targeted genetic sequencing performed as part of their diagnostic workup. Patients' medical records were examined to collect demographic, clinical information (40 categories) and to identify patients with autoinflammatory complications. Patients were classified as having 'non-specific autoinflammatory features' if C-Reactive Protein (CRP) was found to be elevated (>10.0 mg/L) on 5 or more separate occasions and this elevation could not be explained by infection, malignancy or autoimmunity. Treatment options and outcomes were assessed for MDS and the autoinflammatory conditions, where applicable.
Results: The average age was 77.08±11 years (median 79 years), with a (n=92, 65.7%) female preponderance. The 68 patients who had non-specific autoinflammatory features (48.6%) tended to be younger, and had more frequent arthritis (n=25, 34.7%, *versus* n=12, 17.6%, p=0.0225), arthralgia (n=32, 44.4%, *versus* n=18, 26.5%, p=0.0271), skin rash (n=22, 30.6%, *versus* n=10, 14.7%, p=0.0261), and pleuritis (16, 22.2%, *versus* n=3, 4.4%, p=0.0022). 29% of MDS patients had a well-defined diagnosis of autoinflammatory disorder, with neutrophilic dermatosis, and polymyalgia rheumatica as the most frequent conditions. Mutations affecting the transcription factor pathway (NPM1, RUNX1, BCOR, WTI, TP53, MYD88) (OR 3.15 [95%CI 1.04-9.56], p=0.0426) and deletion of chromosome 5 (OR 3.37 [95%CI 1.01-11.22], p=0.0479) were associated with autoinflammatory complications in general. Further stratification of the patients into well-defined and non-specific status, showed that deletion of chromosome 7 was associated with well-defined conditions, whilst deletion of chromosome 5 was linked with a non-specific autoinflammatory status. Furthermore, a higher rate of acute leukaemia transformation was reported in MDS patients with autoinflammatory status (n=25, 34.7%, *versus* n=8, 11.8%, p=0.0002).

Conclusions: Autoinflammatory conditions were found to be more prevalent than expected in patients with MDS and were also linked to a worse prognosis. Transcription factor pathway gene mutations and an abnormal karyotype were also associated with autoinflammation. Autoinflammatory features were associated with malignant transformation, hinting at the possibility that treatment of the autoinflammatory illness might play a role in preventing disease progression. Further studies are required to replicate our findings and study the effect of anti-inflammatory therapy on disease progression.

Key-words: myelodysplatic syndrome; autoinflammation; somatic mutations, karyotype