Introduction

Autoimmune diseases (ADs) are pathologic conditions resulting from an immune system malfunction and affecting 3–10% of the general population [1]. They are characterized by the production of high-affinity autoantibodies which target the “self” molecules of any part of the body [2, 3]. Among others, the hematopoietic system can be affected, leading to peripheral cytopenias. Myelodysplastic syndrome (MDS) is a disorder affecting the bone marrow stem cells [4, 5]. It is characterized by dysmyelopoiesis, affecting erythroid, myeloid and megakaryocytic lineages to variable degrees [6]. Therefore, anemia, neutropenia and/or thrombocytopenia are its main clinical manifestations [7].

The association between ADs and MDS has been widely recognized [8]. However, little is known about the exact mechanism of this association and the causal link has yet to be determined. In addition, the non-rare frequency of cytopenias seen with ADs makes the diagnosis of an associated MDS challenging in some situations.

The aim of this review is to study the clinical association between MDS and ADs and analyze its pathogenic, therapeutic, and prognostic aspects, so as not to miss the diagnosis of an underlying MDS when dealing with ADs.

Epidemiological data and diagnostic delay

Autoimmune diseases affect 5–10% of the world’s population and can sometimes result in morbidity and mortality rates as high as those seen in cardiovascular diseases or cancers [9]. To date, there have been identified over 80 types of ADs, half of which are considered rare [9]. A clear female predominance is noted [1] and the median age of onset depends on the disease.

In contrast, MDS is considered to be a disease of the elderly, most often males with a median age of diagnosis around 70 years [4].

Autoimmune diseases and MDS can be associated. They may be diagnosed either simultaneously or with a time leg. Several studies evaluating the risk of myeloid hematologic malignancies in ADs have proved a significant excess of MDS cases among several ADs, such as systemic lupus erythematosus, rheumatoid arthritis and inflammatory bowel diseases, of which Crohn’s...
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The fortuitous or coincidental relationship of this association could be raised but seems to be less plausible given the non-negligible frequency of coexistence of these two. However, not much is known about whether one disease is partly responsible for the development of the other. Indeed, despite the identification of several possible factors contributing to this association, no hypothesis in particular was supported. It might be more...
Table I. Autoimmune diseases associated with myelodysplastic syndrome

<table>
<thead>
<tr>
<th>Subsets of systemic MDS-related ADs</th>
<th>Frequency</th>
<th>Manifestations</th>
<th>Particularities</th>
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<tr>
<td></td>
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<td>Giant cell arteritis (23%) [11]</td>
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<td>ANCA-negative leukocytoclastic vasculitis (10–30%) [22, 23]</td>
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<td>Behçet’s like syndrome, usually with incomplete forms and predominant digestive involvement (15–20%) [24–26]</td>
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<td>ANCA-associated vasculitis, Takayasu’s arteritis and IgA vasculitis: exceptionally reported [11]</td>
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<td>Connective tissue disorders</td>
<td>25–30% [15]</td>
<td>Relapsing polychondritis (60%) [15]</td>
<td>Skin lesions in relapsing polychondritis are more frequent, particularly neutrophilic dermatosis [28, 29]</td>
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<td>Systemic lupus erythematosus (30%) [15]</td>
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<td>Sjögren’s syndrome (SS) or myositis: exceptionally reported [16, 23]</td>
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<td>Systemic sclerosis: never reported [16, 23]</td>
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<tr>
<td>Inflammatory arthritis</td>
<td>23%</td>
<td>Undifferentiated arthritis: the most frequent entity and typically present as polyarticular and symmetrical arthritis, usually without structural progression [15]</td>
<td>Patients tend to be older with male dominance and more involved joints [32]</td>
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<td></td>
<td></td>
<td>Polymyalgia rheumatica (10%) (sometimes associated with giant cell arteritis [16, 30, 31]</td>
<td>Undifferentiated arthritis typically present as symmetrical polyarticular arthritis, usually without structural progression [15]</td>
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<tr>
<td>Neutrophilic dermatosis</td>
<td>10% [15]</td>
<td>Sweet syndrome (10–15%) [33]</td>
<td>Sweet syndrome can be induced by G-CSF use or chemotherapy [34]. It is associated with a worse prognosis of MDS [33]</td>
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<td>Other organ-specific diseases</td>
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<td>Pulmonary alveolar proteinosis</td>
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<td></td>
<td></td>
<td>Inflammatory bowel diseases, particularly Crohn’s disease [11]</td>
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reasonable to study the pathophysiological basis of this association by considering the chronology of installation of the two entities. In cases where AD characterizes the initial clinical presentation, susceptibility to MDS is the result of impaired immune surveillance [10]. Indeed, a chronic immunologic dysregulation with a permanent immune stimulation resulting in bone marrow lesions or infiltration is suggested [8, 10]. However, in this context, drug etiology is the most adopted and MDS is thought to be a therapy-related myeloid neoplasm arising as a delayed effect of treatment of AD [10]. In effect, immunosuppressive therapy used in ADs includes several drug classes, notably antimetabolites (such as azathioprine, methotrexate and 6-mercaptopurine) and alkylator agents (such as cyclophosphamide and DNA-topoisomerase II inhibitors/mitoxantrone) [10]. These treatments are responsible for many molecular mechanisms that underpin leukemogenesis but without a proved correlation between the risk of myeloid neoplasms and the duration of drug exposure [37]. Of note, the carcinogenic potential was best documented with azathioprine, followed by cyclophosphamide and to a lesser extent with mitoxantrone [37–39].

In cases where MDS precedes immunological manifestations, ADs are thought to result from MDS-related immune dysregulation disorders [40]. Thus, a deficient tolerance including both cellular and humoral immunity [7] may be associated with reduced anti-tumor responses and could lead to the emergence of autoreactive cells and hence to impaired immune regulation [11]. Increased cytokine production, mainly of interleukins-1 and -6 (IL-1 and IL-6) and tumor necrosis factor α (TNF-α), by malignant monocytes principally in chronic myelomonocytic leukemia or from the lymphocytes being part of the abnormal dysplastic clone, has also been reported [41]. However, further studies are needed to better
understand the exact mechanisms that induce ADs in MDS patients.

In the context of concurrent AD and MDS, shared trigger factors and/or genetic susceptibilities between the two disorders is then evoked [10, 19]. Hochman et al. even raised the question whether MDS and ADs and systemic inflammatory disorders are actually "two sides of the same coin" based on the idea of a likely shared underlying disease state that may manifest as an autoimmune disorder, a myeloid neoplasm, or both [40]. As for environmental factors, exposure to some chemical products such as tobacco has been identified as a risk factor of occurrence of both MDS and ADs [42, 43].

Therapeutic options

Treatment of MDS-associated ADs is not codified. The main challenge here is to achieve remission of the autoimmune manifestations without aggravating MDS-related cytopenias. Glucocorticosteroids (GCs) alone, as a first-line treatment, have been reported to be effective against autoimmune manifestations in up to 80% of cases in some series [15]. However, this response is not always complete or durable, and high rates of steroid-dependent or refractory cases have been reported [44]. Moreover, MDS' responses to GCs used to treat autoimmune conditions are variable. Cases of improved, refractory or even worsened cytopenias have been registered [15–17].

Immunosuppressive treatments can be used as second-line therapies. However, in most cases, no hematological response has been reported but rather a worsening of the MDS-related cytopenias with all the ensuing complications, especially infectious ones [15, 16, 45].

Biologic targeted treatments are also a possible therapeutic option for MDS-associated ADs but with lower response rates compared to GCs and compared to non MDS-related ADs [25]. Moreover, they have no effect on cytopenias of the underlying MDS [25, 46]. Rituximab proved to be the most efficient among biologics, with an overall response of 58%, mainly in vasculitis. However, a high rate of adverse effects was reported with these therapies [25]. In contrast, MDS treatment, in particular azacitidine, has been found to have a good effect on associated ADs with regard to the dose of GCs and the number of steroid-dependent patients [15]. As for hypomethylating agents, their efficacy in terms of outcome in MDS-associated ADs has to be confirmed. Interestingly, hematopoietic stem cell transplantation (H SCT), which is the only satisfactory option reported for MDS management, is currently also considered as an effective option in treating severe, refractory AD through reconstituting the hematopoietic system and restoring immune functions as well [47, 48].

Prognostic specific aspects

The heterogeneity of ADs associated with MDS makes the prognostic significance of this association controversial. However, in general, whereas the AD develops before the MDS or during its course, no differences in overall survival or in the rates of acute myeloid leukemia and death have been reported in patients with ADs and MDS compared to with patients with MDS [8, 11, 20]. Nonetheless, systemic vasculitis has been reported as a poor prognostic factor in patients with MDS, mainly due to the presence of high-risk MDS features, and Sweet syndrome has been associated with progression of MDS [11]. Cryoglobulinemic vasculitis was also associated with lower median overall survival [17] due to a higher infectious rate [20]. However, in the presence of an associated AD, the underlying cytogenetic features of MDS do not seem to be influenced [11].

Conclusions

Myelodysplastic syndrome and ADs may coexist or complicate each other with a delay of months to years. Myelodysplastic syndrome-associated ADs have some epidemiological and clinical specific aspects but no major effects on survival. Although this association has been established by several studies, it is sometimes difficult to diagnose, and MDS should always be considered in the diagnostic algorithm of patients having ADs when cytopenia(s) cannot be explained by the immunological disorders.

The authors declare no conflict of interest.

References


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