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The immune landscape of myelodysplastic syndromes

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ABSTRACT

Even though the pathogenesis of myelodysplastic syndromes (MDS) is dominated by specific molecular defects involving hematopoietic precursors, also immune mechanisms seem to play a fundamental functional role. In this review we will first describe the clinical and laboratory autoimmune manifestations often detectable in MDS patients. We will then focus on studies addressing the possible influence of different immune cell subpopulations on the disease onset and evolution. We will finally consider therapeutic approaches based on immunomodulation, ranging from immunosuppressants to vaccination and transplantation strategies.

1. Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematologic diseases, characterized by dysplastic haemopoiesis and by a variable degree of peripheral cytopenia. Although several studies have highlighted the pivotal role of specific genetic lesions involving the stem cell compartment

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Table 1
Immunological manifestations in MDS patients.

Clinical	Serological
acute systemic or skin vasculitis	direct Coombs' test positivity
arthritis	hypergammaglobulinaemia
autoimmune cytopenias	hypogammaglobulinaemia
colonic ulcerations	monoclonal paraproteinaemia
glomerulonephritis	positivity for auto-antibodies
peripheral polyneuropathy	
polychondritis	
pulmonary infiltrates	
Raynaud's phenomenon	
Sjogren's syndrome	
systemic lupus erythematosus	

(Papaemmanuil et al., 2013), clinical and laboratory findings suggest that different immune pathways could be deeply implicated in their pathogenesis (Fozza and Longinotti, 2013a, 2012). From the clinical point of view, a variety of autoimmune manifestations are reported in a large fraction of MDS patients (Okamoto et al., 1997; Giannouli et al., 2004a). Moreover some patients are known to respond to immunosuppressive treatments such as for instance antithymocyte globulin (ATG) (Molldrem et al., 1997). Noteworthy, aplastic anaemia, whose pathogenesis is driven by immune-mediated mechanisms, can evolve into a typical MDS with specific genetic lesions such as trisomy 8 or monosomy 7 (Maciejewski and Selleri, 2004). Moving to the laboratory setting, several cell subpopulations, more often within the T-cell compartment, display abnormal distributions in MDS patients. Finally, both in vitro and in vivo findings clearly suggest that patient T-cells can be responsible of the functional inhibition of hematopoietic precursors (Smith and Smith, 1991).

2. Clinical and laboratory immune manifestations

In 1996 Hamblin and colleagues described two cases of autoimmune haemolytic anaemia among 104 patients with MDS (Hamblin, 1996). Since then several studies reported an incidence of immune manifestations ranging around 10–15% in the overall MDS population. The different MDS associated immune phenomena are summarized in Table 1. Clinical manifestations are extremely polymorphic and include acute systemic or skin vasculitis, arthritis, autoimmune cytopenias, colonic ulcerations, glomerulonephritis, peripheral polyneuropathy, pulmonary infiltrates, Raynaud's phenomenon as well classic connective tissue disorders such as relapsing polychondritis, Sjogren's syndrome and systemic lupus erythematosus. Serological abnormalities include hyper- or hypogammaglobulinaemia, direct Coombs test positivity, monoclonal paraproteinaemia and positivity for different auto-antibodies (Okamoto et al., 1997; Mufti et al., 1986; Giannouli et al., 2004a). Very interestingly an increase in platelet-associated IgG was significantly associated with thrombocytopenia, which is usually ascribed to inefficient haemopoiesis in MDS patients (Gilli et al., 2012).

The onset of autoimmune disorders precedes the diagnosis of MDS in a minority of patients, while in most of them autoimmune manifestations develop during the course of MDS with no apparent influence on prognosis (Giannouli et al., 2004a). However a possible negative prognostic impact was suggested by a following study especially in patients with vasculitis and/or cryoglobulins (de Hollanda et al., 2011). On the other hand, a registry study focusing on the risk of developing myeloid malignancies in patients with different autoimmune diseases, reported an increased risk of developing MDS, particularly high in autoimmune haemolytic anaemia and polyarteritis nodosa (Anderson et al., 2009). By using a large population-based central registry, chronic immune stimulation was further shown to act as a possible trigger for the development of both acute myeloid leukaemia (AML) and MDS. In fact, a history of any infectious disease within 3 or more years before diagnosis as well as a previous history of any autoimmune disease was associated with an increased risk for both AML and MDS (Kristinsson et al., 2011). Interferon (IFN) regulatory factor-1 (IRF-1), a transcription factor involved in IFN signaling, was shown as a potential modulator of autoimmune phenomena in MDS patients (Giannouli et al., 2004b).

Noteworthy, after Azacytidine treatment a patient with concomitant MDS and systemic lupus erythematosus experienced not only a clear haematologic improvement but also the resolution of his autoimmune disorder. The potential ability of Azacytidine to modify the immunological milieu in these patients was further highlighted by a reduction in regulatory T-cells (Treg) (Al Ustwani et al., 2011). A complete resolution of intestinal Behçet's syndrome (Tanaka et al., 2013) and deep neutrophilic dermatosis (Raj et al., 2007) was demonstrated in two further patients treated with Azacitidine. These cases, although anecdotal, further highlight the interconnection between MDS clinical history and auotimmunity.

The understanding about the prognostic implications of autoimmune manifestations in MDS patients was very recently revolutionised by an extensive analysis performed on 1408 patients at King's College Hospital in London. Twenty-eight percent of the patients had autoimmune diseases, with hypothyroidism, idiopathic thrombocytopenic purpura, rheumatoid arthritis and psoriasis being the most common subtypes and accounting for 44%, 12%, 10% and 7% of patients, respectively. Autoimmune diseases were more common in female patients, in those with refractory anaemia (RA) or refractory cytopenia with multilineage dysplasia (RCMD) and in subjects less dependent on red blood cell transfusion. Quite strikingly median overall survival (OS) was 60 months for patients with autoimmune diseases versus 45 months for those without and by multivariate analysis autoimmune diseases were a statistically significant independent factor for OS. Moreover the rate of transformation into AML was 23% in MDS patients with autoimmune disease versus 30% in those without (Komrokji et al., 2016).

Much less studies are available for different neoplastic entities, in which the frequency of autoimmune disorders ranges between 8.6% in breast cancer (Sloand et al., 2005) to 13.5% in lung cancer (Lietzen et al., 2015). Some data also suggest an increased incidence of autoimmune and chronic inflammatory disorders in patients with lymphoma when compared with other neoplastic diseases (Khan et al., 2016). Interestingly an overview of the epidemiology of 29 different autoimmune diseases highlighted an estimated prevalence of 7.6–9.4% in the general population (Cooper et al., 2009). These data indirectly further confirm the increased occurrence of autoimmune manifestations in MDS patients, especially when taking into account the reduced frequency of such disorders observed in the elderly population (Vadasz et al., 2013).

In our opinion, even more when considering the potential favourable prognostic impact of autoimmune manifestations, no further examinations should be routinely performed in order to explore the immunologic profile of patients newly diagnosed with MDS or idiopathic cytopenia of undetermined significance (ICUS) (van de Schans et al., 2011). Rather more focused serological or radiological testing could be driven patient by patient by specific clinical clues.

3. The role of different immune cell subsets in the MDS pathogenesis

The potential influence on the MDS pathogenesis of a large number of immune cell subsets has been specifically investigated by