Systemic vasculitis in myelodysplastic syndromes

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ABSTRACT

The development of immunological abnormalities in various neoplasms is a rather common phenomenon. The prevalence of life-threatening systemic vasculitis in malignancy, however, is much lower. Nonetheless we found an unexpected frequency of several autoimmune manifestations, including systemic vasculitis, in certain myelodysplastic syndromes. We illustrate this finding with the case of a 43-year-old man with signs of polyarteritis nodosa-like systemic vasculitis during progression of chronic myelomonocytic leukaemia. Subsequently, we review the literature on the combination of myelodysplastic syndromes and systemic vasculitis and discuss the prognostic consequences, considerations for treatment and possible pathophysiological mechanisms.

KEYWORDS

Chronic myelomonocytic leukaemia, myelodysplastic syndromes, polyarteritis nodosa, vasculitis

INTRODUCTION

The myelodysplastic syndromes (MDS) comprise a heterogeneous group of haematological diseases, characterised by cytopenia and the presence of dysplastic blood cells. According to the World Health Organisation (WHO) classification of the myeloid neoplasms, chronic myelomonocytic leukaemia (CMML) is classified as an overlap syndrome of myelodysplastic syndromes and myeloproliferative neoplasms (MDS/MPN), since it can present with both myelodysplastic symptoms such as cytopenia and proliferative features such as remarkable leucocytosis and splenomegaly.15 CMML is a relatively rare disease with an annual incidence rate of 0.3 to 0.5 per 100,000 persons in all ages, and around 3 per 100,000 in persons of 60 years and older. Median survival is poor with 18 to 40 months, which justifies the use of aggressive therapy such as stem cell transplantation in selected patients.3–5

The combination of MDS with autoimmune manifestations has been described before in a number of case reports. In 1997 Pirayesh et al. published a review of the literature on the combination of MDS and vasculitis, of which the majority had leucocytoclastic cutaneous vasculitis.6 Other reports also state that the autoimmune manifestations seen in MDS largely concern cases of mild rheumatological symptoms or cutaneous vasculitis.7,8 In this article, we present a case of a 43-year-old man who developed severe symptoms consistent with systemic vasculitis in the same period he was diagnosed with progressive CMML. In addition we review the literature on the combination of systemic vasculitis with MDS or MDS/MPN, describing previously reported cases with their treatment and outcomes, and discuss possible pathophysiological mechanisms.

CASE REPORT

A 43-year-old male with progressive CMML presented with pain in the left upper abdomen and fever. Abdominal CT scanning showed splenomegaly with areas of both infarction and haemorrhage, which caused rupture of the splenic capsule. After emergency splenectomy he developed respiratory failure due to pleural and pericardial fluids, containing 42% monocytic cells, and high-resolution CT scanning showed multiple intrapulmonary abnormalities (figure 1). Furthermore,
he developed hypovolaemic shock, which turned out to be caused by massive bleeding from multiple microaneurysms in both kidneys (figure 2).

A medium-sized vessel vasculitis was suspected because of these characteristic abnormalities at imaging. Also, no alternative explanation for this combination of symptoms was found. He qualified for a diagnosis of polyarteritis nodosa (PAN) as he fulfilled five out of ten American College of Rheumatology (ACR) 1990 criteria for PAN.

High-dose corticosteroids were started, but the recurring severe haemoptysis remained. It was then decided to treat the underlying malignancy more vigorously and induction chemotherapy (idarubicin and cytarabine) was started, leading to a complete remission. Remarkably, all symptoms of vasculitis then quickly diminished and the pulmonary CT scan normalised completely within three months.

**DISCUSSION**

In our case a clinical diagnosis of PAN was made using the 1990 criteria of the ACR. We attain the same diagnosis when applying the clinical algorithm for differentiation between types of vasculitis of Kallenberg et al.

A histological diagnosis could not be obtained because renal biopsy was considered to be too dangerous in the presence of aneurysms in the kidneys, prolonged coagulation and low platelet count. Unfortunately, histological examination of the spleen could not confirm the presence of vasculitis because of extensive localisation of CMML and haemorrhage.

Like other haematological malignancies, MDS is associated with extrahaematological manifestations, mainly immunological features. However, these appear to occur more often in MDS and especially CMML than in other haematological neoplasms, with a reported prevalence of autoimmune manifestations of 10 to 18% in CMML.

A wide spectrum of autoimmune abnormalities has been reported in patients with MDS (table 1). In the literature several types of vasculitis have been associated with MDS: most frequently cutaneous leucocytoclastic vasculitis, but also various types of systemic vasculitis.

In this review we will focus on systemic vasculitis, since...
Remarkably, in four of the described cases spontaneous
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includes 26 cases of MDS in combination with PAN, of
autoimmune disorders have shown conflicting results.

Prognosis and treatment considerations
Previous reports about the prognosis of patients with
haematological malignancies in combination with
autoimmune disorders have shown conflicting results.

this autoimmune phenomenon will probably most affect
prognosis and treatment choices.

MDS and systemic vasculitis
We reviewed all English, Spanish, French, German and
Dutch literature on the combination of MDS with systemic
vasculitis. We found 23 publications with 55 cases in
total (table 2). The prevalence of PAN in the normal
population is around 3 per 100,000, hence the chance of
one individual accidentally having both CMML and PAN
would normally be very small. Nonetheless, our review
includes 26 cases of MDS in combination with PAN, of
which 17 cases of CMML with PAN.

Remarkably, in four of the described cases spontaneous
bilateral perirenal haemorrhage from microaneurysms
occurred, as was seen in our patient. The kidney is the
most affected organ in PAN with or without
associated myelodysplasia, with involvement in 70 to
80% of patients, but this most frequently leads to renal
insufficiency, hypertension, proteinuria and sometimes
modest haematuria. Spontaneous renal haemorrhages
from microaneurysms in isolated PAN are rare and when
it occurs it is usually unilateral. Spontaneous bilateral
perirenal haemorrhage thus seems to develop more
often in patients with underlying MDS. In addition to
perirenal haemorrhages, also haemorrhage from other
organs such as the gastrointestinal tract or the lungs is
reported in the described patients. Probably this is caused
by the simultaneous presence of thrombocytopenia and
other coagulation disorders in combination with (micro)
aneurysms and other vessel abnormalities.

Prognosis and treatment considerations
Previous reports about the prognosis of patients with
haematological malignancies in combination with
autoimmune disorders have shown conflicting results.

In some retrospective reports a worse outcome in MDS
patients with immunological manifestations or with
systemic vasculitis was demonstrated when compared with
other MDS patients. However, in a prospective study
by Giannouli et al. in 13 patients no influence on median
survival was reported, when corrected for the International
Prognostic Scoring System (IPSS) score. Moreover, they
did not find any association between IPSS score and risk
of development of autoimmune abnormalities. But in
this study patients with various types of autoimmune
manifestations of variable severity were included; only two
of the studied patients had a systemic vasculitis.29

In contrast, when we analyse the outcome in our reviewed
cases of systemic vasculitis in MDS, we find that nine of 55
patients died from possible vasculitis-related causes such
as haemorrhage and embolism. Another nine patients died
from infection during treatment with immunosuppressive
agents and one died due to an unspecified cause shortly
after the diagnosis of vasculitis. Five patients developed
steroid dependence, in six patients the MDS transformed
into acute leukaemia and only three patients had long-term
stable MDS without signs of active vasculitis and no need
for treatment. From the other 22 patients the outcome
could not be deduced. Taken together, this suggests that
the development of a systemic vasculitis is associated
with worse outcome in MDS patients. Treatment of the
vasculitis itself with immunosuppressive medication can
indeed improve symptoms, but also seems to be associated
with an increased risk of fatal infections in the long term.
Of course, publication bias in these reviewed cases cannot
be excluded.

Our case illustrates that successful treatment of the
underlying MDS can cure secondary vasculitis. This
underscores the importance of a rapid diagnosis of
MDS-related vasculitis and immediate treatment of
MDS in the case of severe accompanying immunological
manifestations.

Pathogenesis
The pathogenesis of vasculitis in MDS is still largely
unknown. In patients with CMML, high numbers of
circulating monocytes and related cytokines are found
which may lead to vascular inflammation. At the
same time phagocytic clearance is impaired, leading
to prolonged circulation of immune complexes with
subsequent activation of inflammatory mediators. This
is assumed to be the result of gammapathies, abnormally
functioning B and T lymphocytes, reduced CD4 count,
immature natural killer cells and impaired function of
monocytes and dendritic cells with abnormal antigen
presentation. These features may result from abnormal
stimulation by dysplastic bone marrow stem cells.

Furthermore the presence of interferon regulatory
factor-1 (IRF-1) has been associated with the development

<table>
<thead>
<tr>
<th>Table 1. Autoimmune manifestations in MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of autoimmune manifestation in MDS</td>
</tr>
<tr>
<td>Systemic vasculitis</td>
</tr>
<tr>
<td>Isolated autoimmune disorders</td>
</tr>
<tr>
<td>Classical connective tissue disorders</td>
</tr>
<tr>
<td>Autoimmune haematological disorders</td>
</tr>
<tr>
<td>Asymptomatic immunological serological abnormalities</td>
</tr>
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</table>
### Table 2. Overview of reported cases of MDS in combination with systemic vasculitis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex</th>
<th>Age</th>
<th>MDS type</th>
<th>Vasculitis type</th>
<th>Diagnosis vasculitis</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saif⁷</td>
<td>Female</td>
<td>59</td>
<td>CMML</td>
<td>Systemic, ns</td>
<td>Histology (fung, skin, bowel)</td>
<td>CS</td>
<td>Death from gastrointestinal haemorrhage</td>
</tr>
<tr>
<td>Lopez⁸</td>
<td>Female</td>
<td>52</td>
<td>RAEB-t</td>
<td>Aortitis</td>
<td>CT-scan / MRI scan</td>
<td>CS, ASCT</td>
<td>Death from infection</td>
</tr>
<tr>
<td>Espinosa⁹</td>
<td>Female</td>
<td>73</td>
<td>RAEB</td>
<td>Giant-cell arteritis</td>
<td>Histology (art. temp)</td>
<td>CS</td>
<td>Death from infection</td>
</tr>
<tr>
<td>Hamidou⁴</td>
<td>Male</td>
<td>58</td>
<td>CMML</td>
<td>Giant-cell arteritis</td>
<td>Clinical criteria</td>
<td>CS</td>
<td>Steroid dependence</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>57</td>
<td>CMML</td>
<td>PAN</td>
<td>Histology (fung)</td>
<td>CS, CP</td>
<td>Death from infection</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>67</td>
<td>CMML</td>
<td>PAN, perirenal haematoma</td>
<td>Angiography</td>
<td>CS, CP</td>
<td>Stable MDS without active vasculitis</td>
</tr>
<tr>
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<td>Male</td>
<td>58</td>
<td>CMML</td>
<td>PAN</td>
<td>Histology (stomach)</td>
<td>CS</td>
<td>Death from gastrointestinal haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>72</td>
<td>CMML</td>
<td>PAN</td>
<td>Histology (skin)</td>
<td>CS</td>
<td>Death from myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>73</td>
<td>CMML</td>
<td>PAN</td>
<td>Histology (art. temp)</td>
<td>CS, MTX</td>
<td>Death from possible CNS vasculitis</td>
</tr>
<tr>
<td>Fain⁷</td>
<td>Male</td>
<td>66</td>
<td>CMML</td>
<td>PAN</td>
<td>Angiography</td>
<td>CS, CP</td>
<td>Death from infection</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>66</td>
<td>CMML</td>
<td>PAN</td>
<td>Clinical criteria</td>
<td>CS, MTX</td>
<td>Death from infection</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>67</td>
<td>CMML</td>
<td>PAN</td>
<td>Clinical criteria</td>
<td>CS, MTX</td>
<td>Death from infection</td>
</tr>
<tr>
<td></td>
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<td>58</td>
<td>CMML</td>
<td>PAN</td>
<td>Clinical criteria</td>
<td>CS, MTX</td>
<td>Death from possible CNS vasculitis</td>
</tr>
<tr>
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<td>Male</td>
<td>72</td>
<td>CMML</td>
<td>PAN</td>
<td>Clinical criteria</td>
<td>CS, MTX</td>
<td>Death from possible CNS vasculitis</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>73</td>
<td>CMML</td>
<td>PAN</td>
<td>Clinical criteria</td>
<td>CS, MTX</td>
<td>Death from possible CNS vasculitis</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>76</td>
<td>CMML</td>
<td>PAN</td>
<td>Clinical criteria</td>
<td>CS, MTX</td>
<td>Death from possible CNS vasculitis</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>66</td>
<td>CMML</td>
<td>PAN</td>
<td>Clinical criteria</td>
<td>CS, MTX</td>
<td>Death from possible CNS vasculitis</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>67</td>
<td>CMML</td>
<td>PAN</td>
<td>Clinical criteria</td>
<td>CS, MTX</td>
<td>Death from possible CNS vasculitis</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>59</td>
<td>RAEB-t</td>
<td>PAN</td>
<td>Clinical criteria</td>
<td>CS, MTX</td>
<td>Death from possible CNS vasculitis</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>78</td>
<td>RCMD</td>
<td>Systemic, small-vessel</td>
<td>Histology (autopsy)</td>
<td>CS, AZ</td>
<td>Death from pulmonary embolism</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>71</td>
<td>RAEB</td>
<td>Systemic, ns</td>
<td>Clinical criteria</td>
<td>CS</td>
<td>Steroid dependence</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>67</td>
<td>RAEB</td>
<td>Systemic, large-vessel</td>
<td>CT scan</td>
<td>CS</td>
<td>Steroid dependence</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>60</td>
<td>RAEB</td>
<td>Aortitis</td>
<td>CT scan</td>
<td>CS</td>
<td>Steroid dependence</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>72</td>
<td>RAEB</td>
<td>Systemic, small-vessel</td>
<td>Histology (skin)</td>
<td>ns</td>
<td>ns</td>
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<td>CMML</td>
<td>PAN</td>
<td>Histology (kidney)</td>
<td>CS, CP</td>
<td>Death from infection</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>66</td>
<td>RAEB</td>
<td>MPA</td>
<td>Histology (skin)</td>
<td>CS</td>
<td>Transformation to leukaemia</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>68</td>
<td>RAEB</td>
<td>PAN</td>
<td>Histology (skin, testis)</td>
<td>CS</td>
<td>Steroid-dependence</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>27</td>
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<td>Systemic, small-vessel</td>
<td>Histology (fung)</td>
<td>CS</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>68</td>
<td>CMML</td>
<td>Wegener</td>
<td>Histology (sinus)</td>
<td>CS, CP</td>
<td>Transformation to leukaemia</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>75</td>
<td>RA</td>
<td>Wegener</td>
<td>Histology (sinus)</td>
<td>CS</td>
<td>ns</td>
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<tr>
<td></td>
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<td>75</td>
<td>RA</td>
<td>PAN</td>
<td>Histology (nerve)</td>
<td>CS</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>77</td>
<td>RA</td>
<td>PAN</td>
<td>Histology (skin)</td>
<td>CS</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>57</td>
<td>RA</td>
<td>PAN</td>
<td>Histology (skin, nerve)</td>
<td>CS, CP</td>
<td>Steroid-dependence</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>58</td>
<td>RARS</td>
<td>Systemic, ns</td>
<td>Histology (skin)</td>
<td>CS</td>
<td>Death from infection</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>73</td>
<td>RA</td>
<td>PAN</td>
<td>ns</td>
<td>CS, CP, MTX</td>
<td>Death from unspecified cause</td>
</tr>
<tr>
<td></td>
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<td>79</td>
<td>RARS</td>
<td>Systemic, ns</td>
<td>ns</td>
<td>CS, CP, MTX</td>
<td>Death from infection</td>
</tr>
<tr>
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<td>Male</td>
<td>59</td>
<td>RA</td>
<td>Systemic, ns</td>
<td>ns</td>
<td>CS, AZ</td>
<td>Death from infection</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>58</td>
<td>RAEB/ RARS/ RA</td>
<td>Giant-cell arteritis/ PAN</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td></td>
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<td>54</td>
<td>CMML</td>
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<td>CS, CP</td>
<td>Transformation to leukaemia</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>62</td>
<td>RCMD</td>
<td>Takayasu</td>
<td>ns</td>
<td>CS, MTX</td>
<td>Transformation to leukaemia</td>
</tr>
</tbody>
</table>

Art. temp = temporal artery; ASCT = allogeneic stem cell transplantation; AZ = azathioprine; CMML = chronic myelomonocytic leukaemia; CP = cyclophosphamide; CS = corticosteroids; CY = cyclosporine; ET = etoposide; MTX = methotrexate; MPA = microscopic polyangiitis; ns = not specified; PAN = polyarteritis nodosa; RA = refractory anaemia; RAEB = refractory anaemia with excess blasts; RAEB-t = refractory anaemia with excess blasts in transformation; RARS = Refractory anaemia with ringed sideroblasts; RCMD= refractory cytopenia with multilineage dysplasia.
of autoimmune deregulation in MDS. The IRFs are transcriptional factors, known to be involved in both cell growth control and tumour suppression. In myeloproliferative diseases a decrease in IRF can lead to weakened tumour suppression and this is associated with progressive disease and drug resistance. IRF-1 also plays a role in the induction of immune responses. IRF-1 is usually low in MDS patients when compared with healthy individuals. This decrease probably plays a role in the pathogenesis of MDS and in the transformation to acute leukaemia. However, in an observational study of 14 patients with MDS, increased levels of IRF-1 were seen in the seven MDS patients with accompanying autoimmune manifestations when compared with the other seven MDS patients without autoimmune manifestations. In this small group it could not be demonstrated that this increased level of IRF-1 was associated with a lower rate of transformation to leukaemia. In our patient with both CMML and PAN, we evaluated the IRF-1 immunoexpression level in bone marrow and indeed found an increased level (figure 3). Other previously stated hypotheses for the development of autoimmunity in MDS are the existence of one common trigger predisposing for both myeloid and lymphoid disorders or the presence of an immune deregulation preceding and possibly causing the development of MDS. These hypotheses could, however, not be confirmed by experimental studies.

In conclusion, systemic vasculitis is more prevalent in patients with MDS and in particular CMML, in comparison with the general population, with a particular risk of bilateral renal haemorrhage. The pathogenesis is incompletely understood and seems multifactorial, but IRF-1 appears to be one factor that plays a role in the development of immunological manifestations in MDS.

According to our review the prognosis of MDS patients with systemic vasculitis is worse than similar patients without vasculitis, because of the risk of both vasculitis-related and treatment-related complications. Therefore we recommend to treat the underlying haematological disease as soon and effectively as possible, when an associated vasculitis is diagnosed.

REFERENCES


