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REVIEW

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.[1,2] 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]

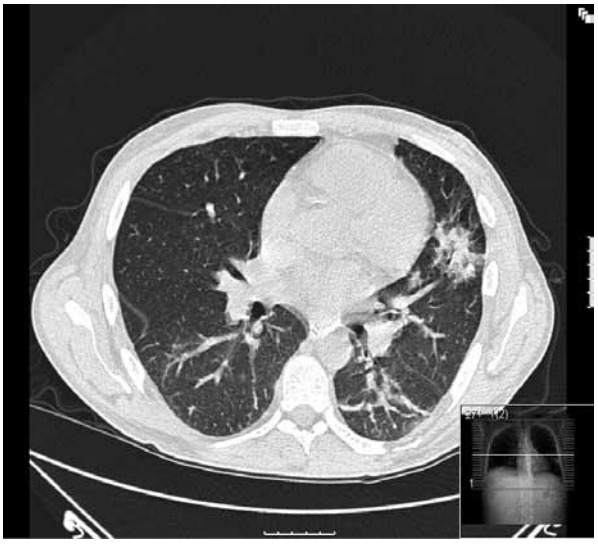
The combination of MDS with autoimmune manifestations has been described before in a number of case reports. In 1997 Pirayesh *et al.* published a review of the literature on the combination of MDS and vasculitis, of which the majority had leucocytoclastic cutaneous vasculitis.[6] Other reports also 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.[9]
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.

Figure 1. *Infiltrative and nodular abnormalities with ground glass aspect on the pulmonary CT scan, suggestive of polyarteritis nodosa*



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.*[10] 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.[8,11] A wide spectrum of autoimmune abnormalities has been reported in patients with MDS (*table 1*).[7] In the literature several types of vasculitis have been associated with MDS: most frequently cutaneous leucocytoclastic vasculitis, but also various types of systemic vasculitis.[12-14] In this review we will focus on systemic vasculitis, since

Figure 2. *Typical microaneurysms in medium-sized arteries of the kidney (left), bleeding from these microaneurysms led to enormous bilateral haematomas (right) and haemorrhagic shock*

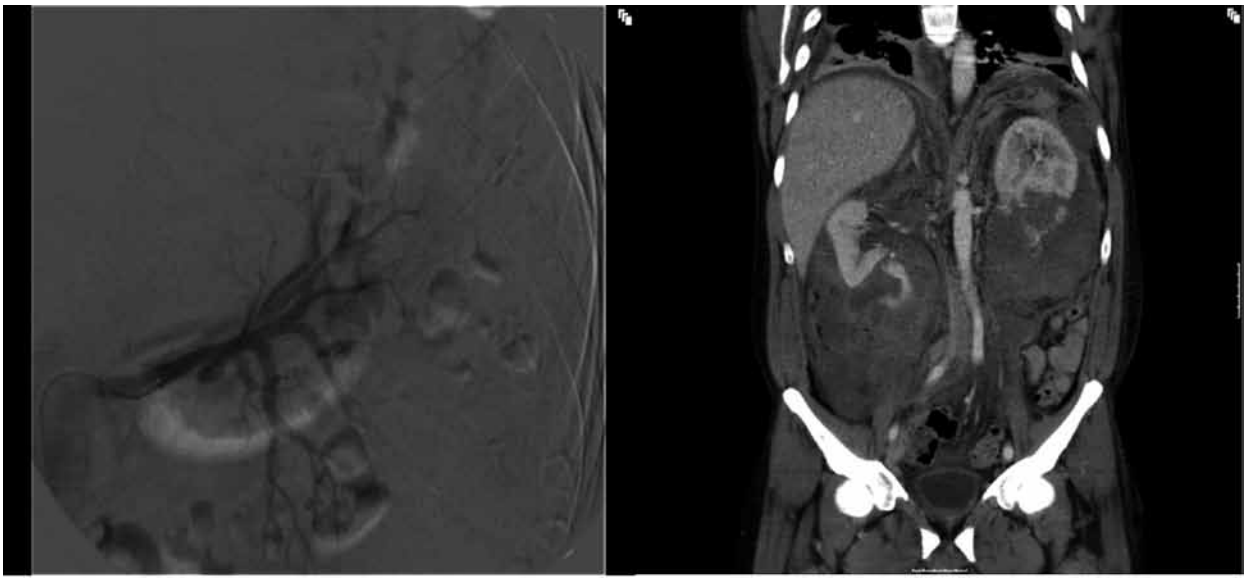


Table 1. *Autoimmune manifestations in MDS*

Type of autoimmune manifestation in MDS	Examples
Systemic vasculitis	Giant-cell arteritis Aortitis Medium- and small-sized vessel vasculitis
Isolated autoimmune disorders	Cutaneous vasculitis Polyarthritis Polyneuropathy
Classical connective tissue disorders	Systemic lupus erythematosus Raynaud's disease Polymyalgia rheumatica
Autoimmune haematological disorders	Autoimmune haemolytic anaemia Immune thrombocytopenia
Asymptomatic immunological serological abnormalities	Positive antineutrophil antibody Positive rheumatoid factor

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.[15-18] 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.[14,19,20] 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.[19,21] 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.[8,22] 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.[23]

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 gammopathies, 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.[12,19,24,25] Furthermore the presence of interferon regulatory factor-1 (IRF-1) has been associated with the development

Table 2. *Overview of reported cases of MDS in combination with systemic vasculitis*

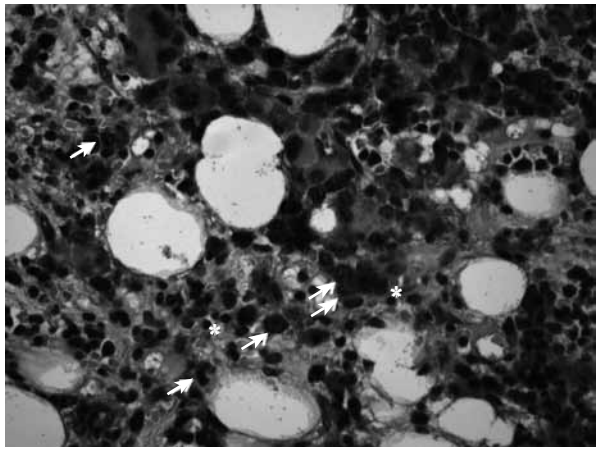
Reference	Sex	Age	MDS type	Vasculitis type	Diagnosis vasculitis	Treatment	Outcome
Saif[7]	Female	59	CMML	Systemic, ns	Histology (lung, skin, bowel)	CS	Death from gastrointestinal haemorrhage
Lopez[12]	Female	52	RAEB-t	Aortitis	CT-scan / MRI scan	CS, ASCT	Death from infection
Espinosa[13]	Female	75	RAEB	Giant-cell arteriitis	Histology (art. temp)	CS	Death from infection
	Male	79	CMML	Giant-cell arteriitis	Clinical criteria	CS	Steroid dependence
Hamidou[14]	Male	58	CMML	PAN	Histology (lung)	CS, CP	Death from infection
	Female	57	CMML	PAN	Angiography	CS, CP, ET	Death from myocarditis and encephalitis
	Female	67	CMML	PAN	Histology (stomach)	CS	Death from gastrointestinal haemorrhage
	Male	58	CMML	PAN, perirenal haematoma	Angiography	CS, CP	Stable MDS without active vasculitis
	Male	72	CMML	PAN	Histology (skin)	CS	Death from myocardial infarction
	Male	73	CMML	PAN	Histology (art. temp)	CS, MTX	Death from possible CNS vasculitis
	Male	76	CMML	PAN	Angiography	CS, CP	Death from infection
	Male	66	CMML	PAN	Clinical criteria	CS, MTX	Death from infection
Fain[17]	6 patients, ns		CMML	PAN	Histology	ns	ns
	3 patients, ns		ns	PAN	Histology	ns	ns
	1 patient, ns		ns	Wegener	Histology	ns	ns
	3 patients, ns		ns	MPA	Histology	ns	ns
Aslangul[19]	Male	61	CMML	PAN, perirenal haematoma	Histology (gall bladder)	CS	Death from bowel perforation
	Female	73	CMML	PAN, perirenal haematoma	Angiography	CS, CP	Death from gastrointestinal haemorrhage
Brickner[20]	Female	63	RAEB-t	PAN, perirenal haematoma	Angiography	CS	Stable MDS without active vasculitis
Giannouli[23, 29]	Male	67	RAEB	Systemic, small-vessel	Histology (lung)	CS	Stable MDS without active vasculitis
	Male	59	RAEB-t	MPA	Histology (skin, nerve)	CS, CY	Death from pulmonary haemorrhage
Incalzi[30]	Female	78	RCMD	Systemic, small-vessel	Histology (autopsy)	CS, AZ	Death from pulmonary embolism
Belizna[31]	Male	71	RAEB	Systemic, ns	Clinical criteria	CS	Steroid dependence
Steurer[32]	Male	67	RAEB	Systemic, large-vessel	CT scan	CS	Steroid dependence
	Male	60	RAEB	Aortitis	CT scan	CS	Transformation to leukaemia
Warren[33]	Male	72	RAEB	Systemic, small-vessel	Histology (skin)	ns	ns
Leung[34]	Male	67	CMML	PAN	Histology (kidney)	CS, CP	Death from infection
van Rijn[35]	Male	66	RAEB	MPA	Histology (skin)	CS	Transformation to leukaemia
Philippe[36]	Male	68	RAEB	PAN	Histology (skin, testis)	CS	Steroid-dependence
	Male	27	RA	Systemic, small-vessel	Histology (lung)	CS	ns
Smail[37]	Female	68	CMML	Wegener	Histology (sinus)	CS, CP	Transformation to leukaemia
Taillan[38]	Male	75	RA	Wegener	Histology (sinus)	CS	Transformation to leukaemia
Constans[39]	Male	75	RA	PAN	Histology (nerve)	CS	ns
	Male	77	RA	PAN	Histology (skin)	CS	ns
Fernandez[40]	Male	57	RA	PAN	Histology (skin, nerve)	CS, CP	Steroid-dependence
	Female	58	RARS	Systemic, ns	Histology (skin)	CS	Death from infection
Roy-Peaud[41]	Male	75	RA	PAN	ns	CS, CP	Death from unspecified cause
	Male	79	RARS	Systemic, ns	ns	CS, CP, MTX	Death from infection
	Male	59	RA	Systemic, ns	ns	CS, AZ	Death from infection
Berthier[42]	5 patients, ns		RAEB/ RARS/ RA	Giant-cell arteritis/ PAN	ns	ns	ns
Park[43]	Female	54	CMML	Systemic, large-vessel	CT scan	CS, CP	Transformation to leukaemia
Cohen[44]	Male	62	RCMD	Takayasu	ns	CS, MTX	Transformation to leukaemia

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 anemia 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.[26] 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.[27,28] 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.[29] 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.[7,30]

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.

Figure 3. *High IRF-1 expression in mature (arrows) and precursor (arrow heads) myeloid cells in bone marrow from the described patient; erythroid cells are low in IRF-1 (asterisks)*



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