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CASE REPORT

Complete remission of MDS RAEB following immunosuppressive treatment in a patient with Sweet's syndrome

J. ten Oever[1*], P.H.M. Kuijper[2], A.L.A. Kuijpers[3], M.W. Dercksen[1], G. Vreugdenhil[1]

Departments of [1]Internal Medicine and [3]Dermatology, [2]Laboratory of Clinical Chemistry, Máxima Medical Centre Veldhoven, Veldhoven, the Netherlands, *corresponding author: tel.: +31 (0)40-888 80 00, fax: +31 (0)40-888 82 46, e-mail: j.tenoever@mmc.nl

ABSTRACT

We report on a patient with myelodysplastic syndrome (MDS), classified as refractory anaemia with excess of blasts-2, and histiocytoid Sweet's syndrome. The skin lesions disappeared after initiation of corticosteroids and doxycycline. Remarkably, two months later a complete remission of the MDS occurred. Fourteen months later both the skin lesions and the MDS relapsed. Antileukaemic activity following reversion of the impaired cellular immunity due to an increased number of natural killer cells in his bone marrow may be responsible for this rare event. Inhibition of T-cell mediated myelosuppression by corticosteroids or a proapoptotic effect of doxycycline may have attributed as well.

KEYWORDS

Complete remission, corticosteroids; doxycycline, histiocytoid Sweet's syndrome, myelodysplastic syndrome, natural killer cells

INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of haematological disorders characterised by dysplasia in one or more of the major myeloid cell lines, ineffective haematopoiesis resulting in peripheral cytopenias and increased risk of acute myeloid leukaemia (AML). High age and poor performance status of most patients with MDS hamper allogeneic stem cell transplantation and intensive chemotherapy, which are the most effective treatment options.[1] Spontaneous remissions in MDS and AML are rare, usually not long lasting and generally occur after blood transfusions or severe infections.[2] Several different immune responses are held responsible for this phenomenon[2-5] and have been the target in clinical trials.[6]

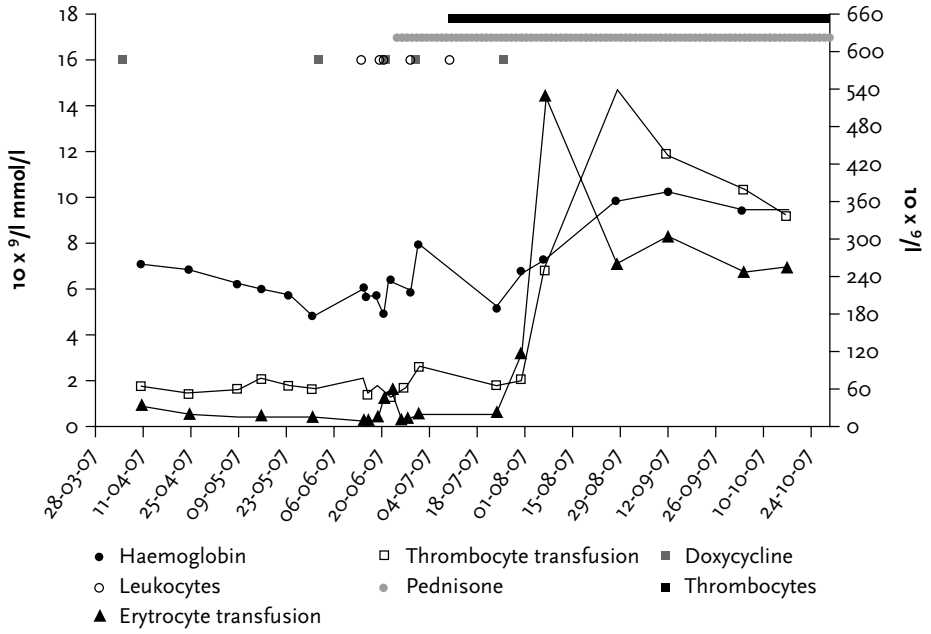
We present a patient with a complete remission of MDS in transformation to AML after treatment for extensive histiocytoid Sweet's syndrome and discuss the contributing factors.

CASE REPORT

A 73-year-old male presented with a five-day history of fever. Besides progressive non-itching lesions on his trunk and to a lesser extent on his extremities no symptoms were present. His medical history comprised endoscopic resection of bladder carcinoma two years before, for which he intermittently received BCG instillations, and in the last year a pancytopenia due to an MDS (RAEB-2 according to the WHO classification) for which he was treated with vitamin B6, folic acid, and with increasing frequency, ultimately every three weeks, supported by erythrocyte and thrombocyte transfusions. Treatment with erythropoietin did not result in any significant effect.

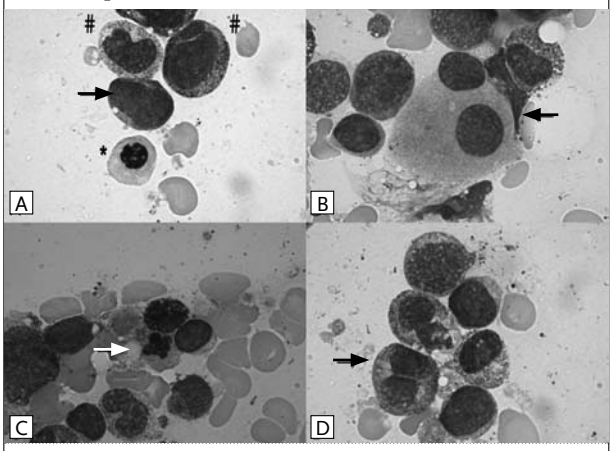
Examination of his skin showed multiple red tender plaques on his trunk and upper extremities varying in size from 0.5 to 5 cm. The blood count showed a deterioration of the pancytopenia. The haemoglobin level was 5.7 mmol/l, the white blood cell count was 1.4 x 10^9/l with 0.9 x 10^9/l neutrophils in the differentiation and the platelet count was 13 x 10^9/l (*figure 1*). The C-reactive protein was 66 mg/l. Despite four days of treatment with ceftriaxone the fever persisted and the skin lesions expanded. Blood and urine cultures were negative and there were no signs of infection

Figure 1. *The course of haemoglobin, leukocytes and thrombocytes in relation to erythrocyte and thrombocyte transfusions and the treatment with prednisone and doxycycline around the time of the complete remission*



on a chest X-ray. Skin cultures were negative for fungi and bacteria. The auramine stain was negative. A skin biopsy showed papillar oedema with a dermal infiltrate consisting of small lymphocytes in the subepithelial zone and larger mononuclear cells containing atypical nuclei with karyorrhexis and nucleoli in the deeper layers. These cells were positive for CD68/KP1, myeloperoxidase and muramidase and negative for CD34 and CD117 and subsequently proved to be (immature) myeloid cells. These cells exhibited a high proliferative activity in the MIB-1 stain. Immunofluorescence was negative for IgG, IgA, IgM, fibrinogen, albumin, C3 and C1q. This morphological and immunophenotypic picture is compatible with both histiocytoid Sweet's syndrome and differentiated myeloid sarcoma and the real nature of these lesions is debatable. Prednisone 70 mg/day as treatment for Sweet's syndrome was started and followed by immediate defervescence and disappearance of the lesions. Because of the association of Sweet's syndrome with (recurrence or progression of) solid and haematological malignancies and the possibility of myeloid sarcoma further investigations were carried out. No metastases or tumour were found on a chest and abdominal CT scan. Urine cytology was negative for malignant cells. Bone marrow aspirate (on the first day of prednisone therapy) showed myelodysplastic features with an excess of blasts (18%) (*figure 2*). Immunophenotyping of bone marrow by flow cytometry revealed 14% blasts (CD34+) and 10% natural killer cells (NK cells) (CD56/16+/CD3-). Bone marrow biopsy was hypercellular and with signs of myelodysplasia, hence MDS with excess of blasts

Figure 2. *Bone marrow aspirate showing multiple dysplastic features at the time of diagnosis of histiocytoid Sweet's syndrome*



A) An erythroblast (*), a myeloid blast (?) and two myeloid precursors (#). B) A small megakaryocyte with two nuclei and mature cytoplasm (?). C) An erythroblast in the centre with karyorrhexis (?). D dysplays a dysplastic myeloid precursor with nuclear anomaly (?)

(RAEB-2) was diagnosed. Tapering to 40 mg/day resulted in a recurrence of the skin lesions after which the dosage was increased and doxycycline was added, resulting in a remission. Six weeks after the start of the prednisone the haemoglobin level, the leucocyte and the thrombocyte counts were rising and were within normal range after eight weeks (*figure 1*). As before, he received blood transfusions in the intermediary period. Bone marrow

examination showed normocellular morphologically normal bone marrow with 2% of blasts and less than 1% of NK cells. The bone marrow cells had a normal karyotype on examination. The complete remission lasted 14 months. Corticosteroids were successfully tapered slowly to 2.5 mg every other day over six months and were stopped ten months after presentation. Treatment with doxycycline was stopped after 13 months. Unfortunately, two weeks after cessation of doxycycline similar skin lesions recurred together with low-grade fever. A skin biopsy showed a dermal infiltrate predominantly in the surroundings of hair follicles consisting of large atypical cells with large nuclei, some with nucleoli, and many mitotic figures. These cells were partly positive for CD68/KP1 and myeloperoxidase and possibly positive for CD34 and negative for CD15 and CD61. Apoptosis was abundant. No mature granulocytes were seen; some scattered lymphocytes were present. These skin changes were characterised as myeloid sarcoma. Histiocytoid Sweet's syndrome could not be excluded, but appeared less likely because of the absence of mature granulocytes and the possible presence of blasts. These lesions were accompanied by a pancytopenia: haemoglobin 8.4 mmol/l, leucocytes 1.9 x 10^9/l with 0.7 x 10^9/l neutrophils and 5% blasts in the differentiation and platelets 46 x 10^9/l. Prednisone 20 mg per day, increased to 70 mg in three weeks, and doxycycline 100 mg twice daily resulted in disappearance of the lesions in several weeks without alteration of peripheral blood cells. Two months later the same skin lesions with extended purpura recurred. The pancytopenia deteriorated and 1 to 8% of blasts were present in peripheral blood. The bone marrow aspirate was hypocellular which hampered assessment of the specimen. Six percent of myeloid blasts and a normal proportion of NK cells were present. Bone marrow biopsy contained 70% adipose tissue, but was morphologically the same as before the remission. Cytogenetic analysis revealed a deletion of chromosome 7q22q33 in combination with trisomy of chromosome 21 in the majority of the bone marrow cells. Despite a seven-day course of methylprednisolone 1 gram/day, started one day before bone marrow aspiration and biopsy, his condition deteriorated and he died of a bilateral pneumonia.

DISCUSSION

Complete remission is rare in MDS, predominantly due to the inability of the often older patients to receive intensive but potentially curative treatment. Many therapies have been tried but intensive chemotherapy and allogeneic stem cell transplantation are the only ones with a significant impact on survival.[1] As with treatment-induced complete remissions, spontaneous remissions in patients with MDS and AML are rare.[2,3] Spontaneous remissions are often, but not necessarily, triggered by severe infections and blood transfusions. Many mechanisms have been proposed: antibodies directed against the malignant clone (for example acquired through transfusion or infection), increased numbers of NK cells with subsequent cytotoxic effect for malignant cells and graft versus leukaemia effect of transfused allogeneic lymphocytes.[3-5] MDS is a clonal haematopoietic stem cell disease of which the pathophysiology is not completely elucidated. However, it is clear that altered cytokine and apoptosis rates and immune dysregulation contribute to the initiation and progression of MDS.[7-9] This role of the immune system in the pathogenesis of MDS and the contribution of immunological responses to spontaneous remissions offer explanations for the observed remission in our patient.

One of the immunological abnormalities in MDS is a defective immune surveillance caused by a decreased cytolytic function of NK cells.[10] The subsequent diminished antileukaemic immune response of NK cells seems to play a role in the progression of MDS.[9] In clinical studies aimed at induction of haematological improvement by IL-2 and other NK cell-stimulating drugs the results were disappointing.[6,11] However, some patients seem to benefit from stimulation of NK cells in MDS.[11,12]

It can be hypothesised that the increased number of natural killer cells in our case was responsible for reversing impaired cellular immunity as well as inducing antileukaemic activity, resulting in the observed remission. Alternatively, as is reported in some cases, the NK cells may be part of the MDS clone and did not contribute to the reversal of MDS.[10] After complete remission had occurred the NK cells were no longer detectable as one would perhaps expect if the NK cells played a major role in eliminating the malignant MDS clone. However, in a case report of a spontaneous remission of AML the high serum concentration of tumour necrosis factor alpha (TNFα) and IL-2 (as stimulus for activation of NK cells) declined to normal values within one month.[5] Consequently, only a temporary rise in NK cells may be sufficient to induce normalisation of haematopoiesis and is not a requisite for maintaining it.

Neoantigens on MDS cells are probably responsible for evoking a T-cell mediated suppression of haematopoiesis.[8] Increased production of TNFα and other proapoptotic cytokines and expression of transmembrane ligands result in increased apoptosis and myelosuppression in early MDS. On the contrary, in advanced disease and in case of progression to AML antiapoptotic mechanisms prevail.[7,8]

The involvement of immune system is the rationale for immunosuppressive treatment in MDS. Antithymocyte globulin, cyclosporine, thalidomide and corticosteroids have been used with variable success.[8,13] Patients with hypoplastic MDS share an overlap of characteristics with

patients with aplastic anaemia and the observed T-cell mediated myelosuppression makes them theoretically more susceptible for immunosuppressive therapy.[14] In our patient corticosteroids could have resulted in inhibiting the expansion of cytotoxic lymphocytes and in suppression of T-cell derived inhibitors of haematopoiesis like TNFα.[15]
Besides antibiotic effects, doxycycline can induce a proliferation arrest in leukaemic cells, probably by inhibition of mitochondrial protein synthesis. No *in vivo* studies concerning doxycycline as treatment for MDS or AML are available. However, human and animal *in vitro* studies show increased apoptosis in leukaemia cells, with increased caspase-3 activity after doxycycline incubation in one study.[16,17] Enhanced activity of antiapoptotic mechanisms is characteristic of high-risk MDS. Consequently, it can be hypothesised that by inducing apoptosis doxycycline may have had an (additional) effect in the occurrence of the complete remission. The occurrence of the remission after the introduction of doxycycline and the rapid recurrence of MDS after cessation of doxycycline supports this hypothesis.
After the recurrence of the MDS the same treatment was started as 16 months before. Despite increasing the dose of steroids and a higher probability of responding to immunosuppression (because of the bone marrow hypocellularity) no improvement of the pancytopenia occurred. There was no excess of NK cells this time. The cytogenetic abnormalities which were not present at the time of the remission may be responsible for treatment failure. Chromosome 7 abnormalities are associated with poor prognosis[7] and the genetic instability could have made the clonal cells unsusceptible for the treatment.

CONCLUSION

Complete remissions of high-risk MDS, both spontaneous and therapy-related, are rare. Several immunological mechanisms play a role in the pathophysiology of MDS and can be a target for treatment. These mechanisms are complex and theoretically can have counteracting effects. Increased tumour lysis by NK cells, inhibitory T-cell suppression by corticosteroids, an unidentified immune mechanism triggered by blood transfusion or a proapoptotic effect of doxycycline can be responsible for the observed complete remission lasting 14 months in this case.

REFERENCES

1. Atallah E, Garcia-Manero G. Treatment strategies in myelodysplastic syndromes. Cancer Invest. 2008;26:208-16.
2. Marisavljevic D, Rolovic Z, Ludoski-Pantic M, Djordjevic V, Novak A. Spontaneous remission in adults with primary myelodysplastic syndromes: incidence and characteristics of patients. Med Oncol. 2005;22:407-10.
3. Maywald O, Buchheidt D, Bergmann J, et al. Spontaneous remission in adult myeloid leukemia in association with systemic bacterial infection – case report and review of the literature. Ann Hematol. 2004;83:189-94.
4. Mitterbauer M, Fritzer-Szekeres M, Mitterbauer G, et al. Spontaneous remission of acute myeloid leukemia after infection and blood transfusion associated with hypergammaglobulinaemia. Ann Hematol. 1996;73:189-93.
5. Musto P, D'Arena G, Melillo L, et al. Spontaneous remission in acute myeloid leukaemia: a role for endogenous production of tumour necrosis factor and interleukin-2? Br J Haematol. 1994;87:879-80.
6. Nand S, Stock W, Stiff P, Sosman J, Martone B, Radvany R. A phase II trial of interleukin-2 in myelodysplastic syndromes. Br J Haematol. 1998;101:205-7.
7. Warlick ED, Smith BD. Myelodysplastic syndromes: review of pathophysiology and current novel treatment approaches. Curr Cancer Drug Targets. 2007;7:541-58.
8. Sloand EM, Rezvani K. The role of the immune system in myelodysplasia: implications for therapy. Semin Hematol. 2008;45:39-48.
9. Kiladjian JJ, Fenaux P, Caignard A. Defects of immune surveillance offer new insights into the pathophysiology and therapy of myelodysplastic syndromes. Leukemia. 2007;21:2237-9.
10. Kiladjian JJ, Bourgeois E, Lobke I et al. Cytolytic function of natural killer cells are severely altered in myelodysplastic syndromes. Leukemia. 2006;20:463-70.
11. Rosenfeld CS, Zeigler ZR, Shadduck RK, Nilsson B. Phase II study of roquinimex in myelodysplastic syndrome. Am J Clin Oncol. 1997;20:189-92.
12. Toze CL, Barnett MJ, Klingemann HG. Response of therapy-related myelodysplasia to low-dose interleukin-2. Leukemia. 1993;7:463-5.
13. Yamada T, Tsurumi H, Kasahara S, Hara T, Sawada M, Moriwaki H. Immunosuppressive therapy for myelodysplastic syndrome: efficacy of methylprednisolone pulse therapy with or without cyclosporin A. J Cancer Res Clin Oncol. 2003;129:485-91.
14. Barrett J, Sauntharajah Y, Molldrem J. Myelodysplastic syndrome and aplastic anemia: distinct entities or diseases linked by a common pathophysiology? Semin Hematol. 2000;37:15-29.
15. Reza S, Shetty V, Dar S, Qawi H, Raza A. Tumor necrosis factor-alpha levels decrease with anticytokine therapy in patients with myelodysplastic syndromes. J Interferon Cytokine Res. 1998;18:871-7.
16. Iwasaki H, Inoue H, Mitsuke Y, Badran A, Ikegaya S, Ueda T. Doxycycline induces apoptosis by way of caspase-3 activation with inhibition of matrix metalloproteinase in human T-lymphoblastic leukemia CCRF-CEM cells. J Lab Clin Med. 2002;140:382-6.
17. Van den Bogert C, Dontje BH, Kroon AM. Doxycycline in combination chemotherapy of a rat leukemia. Cancer Res. 1988;48:6686-90.