Spontaneous morphological and cytogenetic remission of MDS: A case report and review of the literature

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ABSTRACT

Introduction: Myelodysplastic syndromes (MDS) are a group of haemopoietic stem cell disorders characterised by cytopenias and dysplasia in one or more myeloid cell lines with a risk of developing acute leukaemia. MDS can occur as a primary event or following exposure to chemotherapy or radiotherapy. Spontaneous remission can occur but is rare. Case Report: In this case report, a 39-year-old female developed MDS with a cytogenetic abnormality t (1;7) during treatment with cyclophosphamide for Wegener’s granulomatosis. A spontaneous morphological and cytogenetic remission occurred six years after initial diagnosis. Conclusion: Case reports of spontaneous remission in patients with primary MDS occasionally appear in the literature however there are very few reports concerning remission of therapy related MDS. This case is unusual as the patient achieved complete haematological and cytogenetic remission of treatment related MDS on a reduction of cyclophosphamide.

Keywords: Myelodysplastic syndromes, Haemopoietic stem, Acute leukaemia, MDS

INTRODUCTION

Myelodysplastic syndromes (MDS) are a group of haemopoietic stem cell disorders characterised by cytopenias and dysplasia in one or more myeloid cell lines with a risk of developing acute leukaemia. MDS can occur as a primary event or following exposure to chemotherapy or radiotherapy. Spontaneous remission can occur but is rare.

CASE REPORT

A 39-year-old female presented in June 1999 with bilateral visual disturbances, eye pain and right sided face and ear pain. Clinical examination showed reduced visual acuity bilaterally with normal fundoscopic and otoscopic examination. On laboratory examination full blood count (FBC), liver enzymes and coagulation was normal with a mildly deranged renal function. MRI showed demyelination of the optic nerves but no oligoclonal bands were detected in the CSF. Visual evoked potential showed demyelination in the optic nerve only. A diagnosis of retrobulbar neuritis was made and the patient commenced on high dose steroids, initially with 500 mg intravenous methylprednisolone followed by 60 mg prednisolone. She was maintained on 2 mg dexamethasone twice a day. Although her visual
abnormalities improved, she developed psychiatric symptoms whilst taking steroids. She was referred to a neurologist in a London based hospital in August 2000 who diagnosed her with Wegener’s Granulomatosis based on the clinical and laboratory findings with positive cytoplasmic antineutrophil cytoplasmic antibodies. She was commenced on cyclophosphamide 100 mg once a day and her visual evoked potentials normalised by 2003.

In October 2003 in was noted that the patient was mildly anaemic with haemoglobin 11.2 gm/dl and borderline macrocytosis. Iron and vit B12 levels were normal. A peripheral blood film showed macrocytosis with normal myeloid lineage and normal platelets. A bone marrow aspirate was normocellular with hypo granular neutrophils normal megakaryocytes and normal cytogenetics. In February 2004, 50 mg of azathioprine twice daily was added to her treatment with a view to stopping the cyclophosphamide because of the risk of myelodysplastic syndrome (MDS).

In June 2004 the patient was admitted to hospital with a Hb 4.9 gm/dl, white cell count 1.2x10^9/L, neutrophils - 0.8x10^9/L, platelets 18x10^9/L, mean corpuscular volume (MCV) - 116 fl. B12, folate and iron levels were within the normal range.

A peripheral blood film showed anisocytosis, poikilocytosis, hypersegmented neutrophils and normal appearance of platelets. Bone marrow examination was hypocellular with marked dysplasia in the erythroid and granulocytic lineages. Cytogenetics demonstrated t (1;7) in 3/10 metaphases. A diagnosis of MDS was made based on these findings, possibly related to cyclophosphamide use. The patient required 24 units of red cells in the 12 months of 2004-2005. The cyclophosphamide dose was reduced to 50 mg once a day in September 2004.

Repeat bone marrow in October 2007 showed persistence of the clonal abnormality. The patient was referred to the local bone marrow transplant unit and a search for an unrelated donor was commenced. The dose of cyclophosphamide was further reduced to 50 mg on alternate days and the azathioprine was continued at 100 mg once a day. During this period the patient began to drink heavily and it was decided that she would not be an appropriate candidate for transplantation whilst she was still drinking excessively. The Wegener’s granulomatosis remained controlled throughout this period despite the reduction in cyclophosphamide.

By January 2007, the patient was transfusion independent and her complete blood count (CBC) was normalising. Her vit B12 and folate. Levels were both found to be low and replacement started. She had a persistent macrocytosis caused by a combination of alcoholism, myelodysplasia and low vitamin B12 and folate levels.

By September 2009 she had ceased drinking and her CBC was as follows; Hb - 14.3 gm/dl, white cell count 6.5x10^9/L, neutrophils - 3.4x10^9/L, platelets 196x10^9/L and MCV - 98x10^9/L. A peripheral blood film showed normal platelets and erythroid and myeloid cells.

Repeat bone marrow aspirate in September 2009 showed normal tri-lineage haemopoiesis and complete disappearance of t (1;7).

**DISCUSSION**

Therapy related MDS and AML are late complications of cytotoxic therapy which accounts for 10-20% of all cases of MDS/AML. Drugs commonly implicated include alkylating agents (cyclophosphamide, melphalan, chlorambucil, and busulphan), topoisomerase - 2 inhibitors (etoposide), antimetabolites and antitubulin agents. Interestingly, a t (1;7) is commonly associated with cyclophosphamide related MDS as in our case. Often MDS follows treatment for solid malignancy, however, MDS is recognized in those receiving treatment for non-malignant disease. Indeed, the case presented here occurred during treatment for Wegener’s granulomatosis. In a report by McCarthy et al, eight patients with rheumatic disease developed MDS following treatment with cyclophosphamide (seven patients) and chlorambucil (one patient) [1].

Cytotoxic therapy induces mutational events in haemopoietic stem cells. Unbalanced translocations occur in approximately 70% of cases with therapy related MDS/AML (t MDS/AML). These involve full or partial loss of chromosome 5 and/or 7, often with additional chromosomal abnormalities resulting in a complex karyotype. The other 20-30% have balanced translocations. Deletions or loss of chromosomes 5 or 7 are strongly associated with alkylating agents [2].

The prognosis of t MDS/AML is poor with an overall 5-year survival of <10%. Smith et al. published a series of 306 patients. The median time from diagnosis to death was eight months [3]. Cases with abnormalities of chromosome 5 or 7 have a particularly poor outcome [4].

Case reports of spontaneous remission in patients with primary MDS occasionally appear in literature [5, 6, 7]. Marisavijec et al. reported five adult patients who had a spontaneous remission without treatment. Only three out of the five patients had a cytogenetic abnormality. The median time to complete remission was 51 months [8]. Mantadakis et al. reported a series of five paediatric cases with MDS associated with monosomy 7 who had spontaneous haematological remission. Two of the children had chemotherapy related MDS. One child relapsed years later and died, however the other four children had a durable remission [9].

There are very few reports in the literature concerning remission of therapy related MDS. Rennebood et al described a case of MDS with monosomy 7 following immunosuppression with azathioprine post renal transplant [10]. Four months following cessation of treatment, there was complete haematological improvement with a normal karyotype. Chu et al reported a case of MDS with del 5 which occurred after the patient received chemotherapy for
The patient demonstrated spontaneous haematological and cytogenetic resolution of the MDS [11]. The unbalanced translocation t (1;7) is considered a variant of del 7q sub group and is assigned a poor risk karyotype score in the MDS IPSS and a short overall survival [12]. Recently Slovak et al have questioned whether MDS with t (1;7) could constitute a distinct risk group with an intermediate rather than a poor risk score. They compared the features of 12 patients with der (1;7) to 51 patients with Del (7q). There was no significant difference in the risk of transformation to AML or 5 year survival rates between the two groups.

CONCLUSION

This case report is unusual as the patient achieved a complete haematological and cytogenetic remission of a poor risk treatment related MDS on a reduction but not complete cessation of cyclophosphamide. This could be explained by better immunosurveillance following the reduction in dose. In addition; there could be role for endogenous cytokines in stimulating control of the abnormal cytogenetic clone. Understanding the mechanism of remission in these rare cases may improve our knowledge of leukaemogenesis. In addition, this case illustrates the importance of a period of observation before proceeding to transplant, even in MDS with an apparent poor prognosis.

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Author’s Contribution
Mohamed Ifraz Hamid – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Rebecca Maddams – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
The authors declare no conflict of interest.

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