Dual diagnosis of De novo Myelodysplastic Syndrome and Multiple Myeloma: Youngest Case to be Reported and Literature Review

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Abstract

Simultaneous presentation of dual lineage hematological malignancy is an uncommon entity. Particularly de-novo Myelodysplastic Syndrome (MDS) and Multiple Myeloma (MM) is very rare co-occurrence. Co-existent presentation of de novo MM and MDS in young patient has not been reported in English literature. Here we present a unique case of 30 year old patient with dual diagnosis of primary MDS and MM. Both of these hematological malignancies affect mainly elderly patients with and both of these conditions are currently incurable. The prognosis of such patients remains usually poor. No curative treatment is currently available for MDS and MM; Allogeneic Hematopoietic Stem Cell Transplantation (Allo-HSCT) is the only potential curative option.

Keywords: Multiple Myeloma; Myelodysplastic Syndrome; simultaneous; De Novo; Allo-HSCT

Introduction

Simultaneous presentation of dual lineage hematological malignancy is an uncommon entity. Particularly de-novo Myelodysplastic Syndrome (MDS) and MULTIPLE MYELOMA (MM) is very rare co-occurrence. Co-existent presentation of de novo MM and MDS in young patient has not been reported in English literature. Here we present a unique case-the youngest patient ever reported in literature with co-existent non-iatrogenic MDS and MM.

Case Presentation

Thirty years old female was referred to hematology for mild pancytopenia since December 2017. She is generally in good health but in December 2017 she was experiencing unexplained tiredness and a subsequently blood test showed her to have Hemoglobin 110 g/L, Mean Corpuscular Volume (MCV) 85 femtoliter, neutrophil count 0.8 × 10^9/L and platelet count of 137 × 10^9/L. Her pancytopenia continues to get worse and blood test on June 2018 showed Hemoglobin 90 g/L, neutrophils count 0.9 × 10^9/L and platelets count 125 × 10^9/L. She had normal ferritin level, normal serum vitamin B12 level and normal serum folate level. Her autoantibody profile as well as viral screen negative and she had normal renal and liver profile. Coagulation profile normal.

Her IgG level was elevated at 20.85 g/L with normal IgM and IgA levels. Serum protein electrophoresis showed IgG kappa para protein of 8.2 g/L and serum kappa light chain level 268.08 mg/L, serum lambda light chain level 11.78 mg/L and kappa and lambda 22.68. Her serum LDH 201 U/L, rheumatoid factor <9 IU/L, Double Stranded DNA (dsDNA) anti body level was 11 U/L, Anti-Tissue Trans Glutaminase Antibody (anti-TTG) level 0.1 U/ml, Direct Anti-Globulin Test (DAT) negative, PNH screen negative. She did not have any physical signs to suggest an underlying constitutional cause for pancytopenia. She has no relevant family history. Her peripheral blood film examination did not reveal significant finding.

Bone marrow aspirate showed increased erythropoiesis with dysplastic changes (>10%), nuclear cytoplasmic asynchrony, bi-nucleate erythroid precursors, inter-nuclear bridging, as well as cytoplasmic bridges. Markedly reduced granulopoiesis but no excess blast seen, some dysgranulopoiesis noted. There was over 10% plasma cell. Megakaryocytes are reduced, some hypo-lobated form seen. Features are consistent with MDS with Multi-Lineage Dysplasia (MDS- MLD). Bone marrow trephine biopsy showed erythroid hyperplasia, immune-histochemistry did not show excess CD34 and CD117 staining blast. Some hypo-lobated megakaryocytes seen and immune-histochemical staining with CD61 confirmed micro-megakaryocyte. There was increase in plasma...
cell which were KLC restricted and MUM-1 positive, CD20 negative, amounting >10 to 15%. Features were consistent with co-existent diagnosis of MM and MDS.

Her Erythropoietin level is 378 i.u/ml. Single Nucleotide Polymorphism and mutation analysis (SNP-A) result showed (Xq 26.2 to 26.3) deletion. Fluorescence in Situ Hybridization (FISH) showed 1q gain. Diffusion Weighted whole body Magnetic Resonance Imaging (MRI) did not show any abnormal feature to suggest myeloma deposit. Her ECOG Performance Status 0 and apart from feeling tired on exertion she remain otherwise well and so far has not been given any active treatment but she is currently undergoing screening and investigations to receive Allogeneic-Hematopoietic Stem Cell Transplant (Allo-HSCT).

**Discussion**

Coexistence of primary MDS and MM is extremely rare and only limited number of cases are reported in literature and those entire cases involved older group of patients as expected as these two malignancies usually affect older patients [3,4]. A recent large study showed that a pre-malignant plasma cell disorder-Monoclonal Gammopathy of Undetermined Significance (MGUS) patients had a significantly higher risk of developing MDS compared with controls, hazard ratio 2.4 (95% CI 1.08, 5.32), P=0.031. However, all of the study showed that a pre-malignant plasma cell disorder-Monoclonal Gammopathy of Undetermined Significance (MGUS) patients had a significantly higher risk of developing MDS compared with controls, hazard ratio 2.4 (95% CI 1.08, 5.32), P=0.031. However, all of the small proportion of myeloma patient will eventually develop AML with a resultant decrease in immune surveillance. Incipient leukemic clones might escape immune elimination and the resulting AML may bring the pre-existing myeloma to clinical attention [22].

In a recent study of a transgenic mouse model expressing MAF-B in hematopoietic progenitor cells, Vicente-Duenas et al. [23] demonstrated that these mice develop plasma cell neoplasm suggesting a novel mechanism involved in tumorogenesis where progenitor cells that are different from phenotypic cell of origin may be epigenetically reprogrammed to become terminally differentiated tumor cells. This study may imply possible novel cell of origin for MM at progenitor cell level which could explain the simultaneous or metachronous development of MDS.

The treatment decision regarding the dual BM disorders may be complex and should be individualized. No curative treatment is currently available for MDS and MM, allo-HSCT is the only potential option for cure of these conditions [9]. Some patients can just be monitored without any active drug treatment. Sometimes only one entity of the dual diagnosis may need treatment and treatment should be decided upon the indication for treatment, patient’s co-morbidities, overall performance status and patient’s wishes and views about any particular treatment. The indications of treatment slowly disease evolved from precancersous (MGUS) [16], this may lead to chromosomal instability and immunosuppression with failure to eliminate clones of malignant cells.MM may also initiate the growth of additional leukemias/lymphomas via the numerous potential gene expression profiles and molecular pathways. Studies have revealed the ability of MM cells to result in pleiotropic proliferative and anti-apoptotic properties [17,18].

A shared pathogenesis, if any, of concurrent MM and MDS is not known. There is current evidence for the existence of a common progenitor for myeloid and lymphoid cell lines [19,20]. Nevertheless; it is unlikely that the two malignancies represent a single neoplastic event occurring in a common stem cell. Chronic lymphocytic leukemia occurs more frequently than expected in MM but when examined can almost invariably be shown to be expressing a different type of immunoglobulin from that secreted by the MM [21]. A few hypotheses describe these as disorders of multipotent stem cells [8,14] that occur due to continuous exposure to some environmental risk factors and infection or other antigenic stimuli [8]. Another explanation relies on the fact that multiple myeloma is a slowly evolving disease with a resultant decrease in immune surveillance. Incipient leukemic clones might escape immune elimination and the resulting AML may bring the pre-existing myeloma to clinical attention [22].
for myeloma according to international myeloma working group [24] is presented in (Table 1) and suggested treatment for newly diagnosed myeloma according to recent publications [25-36] are presented in (Figure 1 and 2).

Because the median age at diagnosis of MDS is 70 years, patients frequently have co-morbid conditions that may influence outcomes and treatment approaches [37,38]. Risk stratification of MDS patients using most commonly used Revised International Prognostic Scoring System (IPSS-R) is important to allocate appropriate treatment for individual patient.

Some patients with MDS have mild cytopenias and are asymptomatic at the time of diagnosis. Early treatment of MDS is not known to be beneficial in terms of preventing clonal evolution or death. Therefore, observation is appropriate for asymptomatic lower risk patients until their cytopenias worsen or they become more symptomatic. Support of patients with severe symptomatic anemia with red cell transfusions and severe thrombocytopenia with platelet transfusions is a mainstay of therapy for MDS. Fevers in patients with MDS must be taken seriously, and antimicrobial protocols for febrile neutropenia followed carefully, as infection is the leading cause of death in MDS [2,39]. The benefit of prophylactic antimicrobials is controversial.

For patients with lower risk disease and anemia associated with MDS, two parameters are important in treatment choice. First, the serum Erythropoietin (sEPO) level reflects endogenous renal response to anemia and is a strong predictor of the likelihood of clinical response to Erythropoietin Stimulating Agent (ESA) [40]. Patients with lower risk MDS who have a sEPO <100 U/L have a greater than 70% chance of responding to ESA, while for those patients with sEPO >500 U/L, a trial of ESA is usually not warranted because the response rate is <10%. Second, the presence of a clonally restricted deletion of the long arm of chromosome 5 (del5q) is associated with a high erythroid response rate to lenalidomide (65% to 70% transfusion independence, and 30% to 40% cytogenetic remission) [41,42].

For patients with lower risk MDS who have other severe cytopenias beyond anemia, the most appropriate treatment approach is less clear [43]. Neutropenia in patients with MDS often does respond to use of myeloid growth factors, but these have never been shown to improve survival in MDS and have minimal effect on reducing infection risk [44]. The Thrombopoietin Receptor Agonist (TPO) eltrombopag or romiplostim can reduce platelet transfusion needs and clinically significant bleeding events in some patients with severe thrombocytopenia [45-48]. Although a randomized trial of romiplostim in lower risk MDS was discontinued early by a data safety monitoring committee because of excess leukemia [49], hence it may be reasonable to wait till further evidence becomes available.

Immunosuppressive Therapy (IST) - Anti Thrombocyte Globulin (ATG), corticosteroids, and cyclosporine or tacrolimus or Hypomethylating Agents (HMA) are frequently considered for these patients, especially if ESA or lenalidomide failure. Selection of appropriate patients for IST is challenging. However, excess blasts, therapy-related disease, and a complex or monosomal karyotype predict lower likelihood of response to IST [50]. A recent multi-center analysis of more than 300 MDS patients treated with IST other than corticosteroid monotherapy demonstrated that marrow cellularity less than 20% and blast proportion less than 5% were associated with a higher likelihood of transfusion independence and improved survival after immunosuppressive therapy [51].

For patients with higher risk MDS, the first question that must be answered is whether the patient is a candidate for Allogeneic Hematopoietic Stem Cell Transplantation (ASCT). Two mathematical modeling analyses based on Center for International Blood and Marrow Transplant Research (CIBMTR) data-one analysis focused on conventional myeloablative transplant, the other inclusive of patients aged 60 to 70 years treated with a Reduced-Intensity Conditioning (RIC) approaches—show that life expectancy is improved by early transplant in this subgroup, if feasible [52,53]. Increased availability of alternate donors, including haploidentical donors and cord blood, mean that larger proportion of patients has

### Table 1: Indication of treatment for Myeloma.

|Any one or more of the following myeloma defining events:| Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder. Hypercalcemia: >2.75 mmol/L (>11 mg/dL), Renal insufficiency: or serum creatinine >177 mol/L (>2 mg/dL), Anemia: hemoglobin value of >2 g/dL below the lower limit of normal, or a hemoglobin value <10 g/dL, Bone lesions: one or more osteolytic lesions on skeletal radiography, Computed Tomography (CT), or Positron Emission Tomography-CT (PET-CT). | Clonal bone marrow plasma cell 60% or more. |

Involved: uninvolved serum Free Light Chain (FLC) ratio 100 or more (involved free light chain level must be 100 mg/L or more). 

>1 focal lesions on Magnetic Resonance Imaging (MRI) studies (at least 5 mm in size).
the opportunity to undergo SCT. Patients up to age 75 routinely undergo transplant now, and in the future age may not be a limitation to ASCIT if performance status remains excellent.

Pre-transplant cytoreductive therapy can also be considered in those for whom there will be a delay in transplant due to lack of donor availability or insurance approval. In the past, intensive AML-type induction chemotherapy was commonly used for pre-transplant cytoreduction in MDS, but today HMA therapy is used far more frequently and outcomes are at least as good with HMA as with intensive chemotherapy [54]. For those patients who are not transplant candidates, HMA therapy is most appropriate. In a randomized trial of 358 higher risk MDS patients, azacitidine treatment was associated with a median survival of 24 months compared to 15 months in patients treated with intensive chemotherapy, low-dose cytarabine, or best supportive care [55]. Figure 3 illustrated the suggested treatment algorithm for MDS.

In conclusion, further studies need to be completed in order to conclude the exact causes of the rare occurrence of MM and MDS. After close examination of the current literature, it is likely that the coexistence of hematopoietic neoplasm is multi-factorial. It is doubtful for this occurrence to be entirely dependent upon one factor since the literature clearly shows variable factors that have likely resulted in secondary malignancies. We also need to consider the diagnosis of these malignant entities to the possibility of pure chance. The precise mechanism of our extremely unique case remains unknown; hence further investigation and monitoring of potential associated factors are needed. Treatment of these conditions needs to be tailored according to patient’s comorbidities, patient wishes and according to risk stratification of the diseases.

References


