

# Case Report

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## TRISOMY 8, 19, 21 ASSOCIATED MYELOPROLIFERATIVE/ MYELOYDYSPLASTIC SYNDROME

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### ABSTRACT

**Objectives:** To present a case of Myeloproliferative disorder with features of Myelodysplastic Syndrome associated with Trisomy 8, 19 and 21.

**Study Design:** Case Report

**Setting:** University of Perpetual Help Dalta Medical Center – a tertiary hospital.

**Case Summary:** This is a case of a 75 year old male admitted due to gum bleeding. Pertinent findings include hepatosplenomegaly, pallor and jaundice. Bone marrow studies showed hypercellular marrow with myeloid cell series proliferation consistent of Myeloproliferative disorder. On the other hand, some dysplastic features such as binucleated erythroids, giant bands and hypolobulated megakaryocytes were suggestive of Myelodysplasia. Patient was classified as Myelodysplasia. Patient was classified as Myelodysplasia/Myeloproliferative Disease (MDS/MPD) unclassified however the possibility of an accelerated/transitional phase of MPS is also considered. Cytogenetic studies revealed all cells carrying three copies of chromosome 8, 19 and 21. The significance of these studies are still limited and under further study. With risks and benefits in mind, patient was started on Hydroxyurea and supportive treatment such as blood transfusion and empiric antibiotics.

**Keywords:** Myeloproliferative Disorder, Myelodysplastic Syndrome.

### INTRODUCTION

Chronic Myeloproliferative Diseases (CMPDs) are clonal hematopoietic stem cell disorders characterized by proliferation in the bone marrow of one or more of the myeloid (i.e. granulocytic, erythroid and megakaryocytic) lineages.<sup>2</sup>

In contrast with CMPDs, Myelodysplastic Syndrome is a group of clonal hematopoietic stem cell diseases characterized by dysplasia and ineffective

hematopoiesis in one or more of the major myeloid cell lines.

Myelodysplastic/Myeloproliferative disease (MDS/MDP) are characterized by hypercellularity of the bone marrow due to proliferation of one or more of the myeloid lineages.<sup>1</sup> The proliferation in one or more lineages is effective and results in increased number of circulating cells; however they may be morphologically and functionally dysplastic. The incidence of MDS/MDP is still unknown worldwide.

This report describes a case of myeloproliferative/myelodysplastic syndrome associated with Trisomy 8, 19 and 21 detected through cytogenetic studies.

### Case Report

A 75 year old male, previously well, was admitted in our institution due to persistent gum bleeding since he had a tooth extraction 3 weeks prior to admission. He had no other bleeding focus, likewise he denied febrile episodes, weight loss and malaise.

On physical examination, he appeared well nourished but clinically pale but with stable vital signs. He had anicteric sclera with no cervical lymphadenopathy. Heart and lung findings were unremarkable. Liver and spleen were not palpable.

Initial work-up revealed haemoglobin of 100, white blood cells of 94.6, with predominance of segmenters with a blast count of 8%. Nucleated RBC was also noted, platelet count was 100. Reticulocyte count was elevated and coagulation factors were normal. He had trace proteinuria. Review of Peripheral blood smears showed normocytic, slightly hypochromic red blood cells with mild anisopoikilocytosis. Platelets appear decreased in quantity while white blood cells are markedly increased in numbers with predominance of mature and immature cells belonging to granulocytic series. Bone marrow biopsy showed hypercellular marrow (95% cellularity). There is myeloid cell series proliferation with evident maturation. Megakaryocytes are adequate. The above findings were compatible with a myeloproliferative disorder. Some dysplastic features such as binucleated erythroids, giant bands and hypolobated megakaryocytes were noted which were suggestive of Myelodysplasia.

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Immunophenotyping revealed phenotypically heterogeneous population of cells with 2.4% CD 34 positivity. The differentiating granulocytes and monocytes are moderately increased at 71.3% of the white cells. The lymphocyte cells subsets are present at 2.7% of the gated cells. A leukemic blast cell population is not detected. The cell distribution pattern, together with the finding of peripheral leukocytosis and monocytosis is suspicious for an underlying myeloproliferative/myelodysplastic process. Cytogenetic studies revealed all cells carrying three copies of chromosome 8, 19 and 21. Reverse transcriptase-polymerase chain reaction detection for BCR-ABL fusion gene was negative.

Patient returned with considerable pallor and generalized malaise. He also developed intermittent low to moderate grade fever, loss of appetite and gum bleeding. Repeat blood count showed haemoglobin of 87, white blood cell count of 3.05 with blast count of 10%. Patient was treated for Community Acquired Pneumonia and Gingivitis gaining improvement with Coamoxiclav 1 gm 1 tablet BID, Ciprofloxacin 500mg 1 tab BID and packed red cell transfusion.

The presence of jaundice and gum bleeding prompted the patient's return. These were accompanied by right upper quadrant pain and early satiety. Physical examination showed stable vital signs and hepatosplenomegaly. Complete blood count showed haemoglobin of 104, white blood cell of 122.3, with predominance of segmenters of 0.48 and platelet count of 60. Elevated liver enzymes and abnormal coagulation factors were noted. Patient managed with Carnitine and Multivitamin (Godex) 1 tablet TID and transfusion of 6 units of platelet concentrate.

Definitive treatment strategies were contemplated at the time. If emphasis will be given on Chronic Myeloproliferative Disease, patient may be started on Imatinib mesylate or Interferon. Imatinib mesylate causes inhibition of BCR-ABL tyrosine kinase activity, which is essential in signal transduction and cell proliferation of specific cell lineages. However, patient is BCR-ABL negative, so response to treatment may be variable. Interferon, on the other hand, can be less expensive alternative however, due to common side effects of debilitating flu-like symptoms and toxicities such as neuropsychologic symptoms, liver function test abnormality and autoimmune changes, it may not be a suited choice for the patient. Hydroxyurea is useful for initial cytoreduction in patients of advancing age and in whom imatinib and IFN cannot be tolerated and is ineffective. If emphasis, however, is given to Myelodysplastic Syndrome, Azacitidine

and Thalidomide is of value. Although highly effective, they cause myelosuppression, cell cycle arrest and apoptosis.

Pending decision making in this 75 year old male, weighing the risks, benefits and cost of treatment. Patient was managed with Hydroxyurea, transfusion of needed blood components and supportive care.

On close follow-up, WBC count decreased with no blast cells and a platelet count above 100. Patient noted to have decreasing size of liver and spleen. There was also marked improvement in appetite and over-all well being but still needed packed RBC transfusion.

## DISCUSSION

Chronic Myeloproliferative Diseases (CMPDs) are clonal hematopoietic stem cell disorders characterized by proliferation in the bone marrow of one or more of the myeloid (i.e. granulocytic, erythroid and megakaryocytic) lineages. The proliferation is associated with relatively normal maturation that is effective, resulting in increased numbers of granulocytes, red blood cells and/or platelets in the peripheral blood. Splenomegaly and hepatomegaly is commonly found. Bleeding occurs in approximately one-third of patients with myeloproliferative disorders. Bleeding usually involves the skin and mucous membranes but may occur after an invasive procedure and trauma consistent in our patient. Chronic Myelogenous Leukemia (CML) is a myeloproliferative disease that originates in an abnormal pluripotent bone marrow stem cell and is consistently associated with the Philadelphia Chromosome (Ph) and/or BCR-ABL fusion gene. Negativity of BCR-ABL and absence of the Ph chromosome makes CML an unlikely diagnosis in this case. Likewise, Polycythemia vera and Essential Thrombocythemia can be ruled out because our patient presented with anemia and thrombocytopenia. Chronic Idiopathic Myelofibrosis is least considered due to the presence of hypercellularity on bone marrow biopsy in our patient instead of marked fibrosis.

In contrast with CMPDs, Myelodysplastic Syndrome is a group of clonal hematopoietic stem cell diseases characterized by dysplasia and ineffective hematopoiesis in one or more of the major myeloid cell lines. Hallmark for the diagnosis includes cytopenia (anemia and thrombocytopenia) despite hypercellularity of the bone marrow. Patients may be asymptomatic or if anemia is severe, can have pallor,

weakness, loss of a sense of well-being and exertional dyspnea. Hepatomegaly or splenomegaly occurs in approximately 5-10% of patients respectively.

<sup>1</sup>Myelodysplastic/Myeloproliferative diseases (MDS/MDP) are characterized by hypercellularity of the bone marrow due to proliferation of one or more of the myeloid lineages. Frequently the proliferation in one or more lineages is effective and results in increased number of circulating cells; however they may be morphologically and functionally dysplastic. Simultaneously, one or more of the other lineages may exhibit ineffective proliferation, so that cytopenia may be present as well.

<sup>1</sup>Our patient can be classified as Myelodysplastic/Myeloproliferative Disease, Unclassifiable. The incidence of MDS/MDP unclassifiable is unknown. These disorders are characterized by proliferation of one or more of the myeloid lineages that is ineffective, dysplastic or both, and simultaneously, effective proliferation, with or without dysplasia, in one or more of the other myeloid lineages. WHO diagnostic criteria of MDS/MPD, unclassifiable includes:

- ✓ The case has clinical, laboratory and morphologic features of one of the categories of MDS with less than 20% blasts in the blood and bone marrow

AND

- ✓ Has prominent myeloproliferative features e.g. platelet count equal to or greater than  $600 \times 10^9$  /L associated with megakaryocytic proliferation, or WBC equal to or greater than  $13.0 \times 10^9$  with or without prominent splenomegaly.

AND

- ✓ Has no preceding history of an underlying CMPD or of MDS, no history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic or myeloproliferative features and no Philadelphia chromosome or BCR-ABL fusion gene, del (5q), t(3;3)(q21;q26) or inv(3)(q21q26)

OR

- ✓ The patient has mixed myeloproliferative and myelodysplastic features and cannot be assigned to any other category of MDS, CMPD or MDS/MPD.

The identification of such cases can be of clinical importance because both the myelodysplastic and

the myeloproliferative features may have to be considered in choice of therapy. There is a dilemma in trying to suppress a lineage when the other lineages are already diminished.

<sup>1</sup>A close differential diagnosis is Chronic Myelomonocytic Leukemia (CMML) which is a clonal disorder of a bone marrow stem cell, in which monocytosis is the major defining factor. WHO diagnostic criteria consist of (1) persistent peripheral blood monocytosis  $> 1 \times 10^9$ /L, (2) absence of a Philadelphia chromosome and BCR/ABL fusion gene, (3) fewer than 20% blasts in the blood or bone marrow and (4) dysplasia involving one or more myeloid lineages. The clinical, hematologic and morphologic features of CMML are heterogenous, and vary along a spectrum from predominantly myelodysplastic to mainly myeloproliferative in nature. In approximately 50% of cases, the white blood cell count (WBC) is normal or lightly decreased. In the remaining patients, the WBC count is increased at the time of diagnosis, and the disease has features that are more myeloproliferative in nature. Peripheral blood monocytosis is the hallmark of CMML. Mild anemia, often normocytic but sometimes macrocytic, is common. Platelet counts vary but moderate thrombocytopenia is often present. The bone marrow is hypercellular in over 75% of cases. The number of blasts, usually account for fewer than 5% of the peripheral blood WBC and less than 10% of the nucleated marrow cells at the time of diagnosis.

<sup>1</sup>Another possibility is the likelihood of an accelerated or transformation phase of some myeloproliferative disorders resulting in poor response to therapy that formerly controlled the chronic phase. Progression is reflected in a more disordered growth and maturation pattern of progenitor cells ultimately mimicking the growth failure of acute leukaemia and in increased morphologic and functional abnormalities of blood cells, eventuating in a block in maturation and replacement of blood and marrow by blast cells. The features that signal the conversion of chronic to the accelerated phase include unexplained fever, bone pain, weakness, night sweats, weight loss, loss of sense of well-being, arthralgias and left upper quadrant pain related to splenic infarcts or enlargements. Laboratory findings include anemia with increasing poikilocytosis, anisocytosis and anisochromia. The total leukocyte count may fall without treatment. A decrease in the platelet count to less than 100,000/ul develops. The bone marrow findings are widely variable. Marked dysmorphic changes in one, two, or three of the major cell lineages is seen.

Immunophenotypic data have become an integral part of the diagnosis and classification of many marrow based malignancies. Once an abnormal population is identified for analysis, its phenotypic profile can be characterized by simultaneous analysis of various cell surface markers, to determine cell lineage (lymphoid, B cell, T cell, myeloid, monocytic). 4CD 34 is an early progenitor marker of the stem cell. An increased percentage of CD 34+ cells may be associated with early transformation to acute leukaemia.

Cytogenetic analysis provides pathologists and clinicians with a powerful tool for the diagnosis and classification of hematologic malignant diseases. The appearance of new abnormalities in the karyotype of a patient under observation often signals clonal evolution and more aggressive behaviors. The disappearance of a chromosomal abnormality present at diagnosis is an important indicator of complete remission following treatment, and its reappearance invariably heralds relapse of the disease.

<sup>3</sup>There are limited studies regarding the presence of Trisomy 8, 19 and 21 in patients suspected of a myelodysplastic/myeloproliferative disease. Cytogenetic abnormalities are found in 40% to 70% of primary and 80% to 90% of secondary MDS. Typically, trisomy 8 and monosomy 5 or 7 will be present, CD34 cells from patients with trisomy 7 myelodysplastic syndrome (MDS) are distinguished from other MDS cells and from normal hematopoietic cells by their pronounced expression of apoptotic markers. Paradoxically, trisomy 8 clones can persist in patients with bone marrow failure and expand following immunosuppression. Findings of these abnormalities in patients with frank AML indicate probable evolution (which may be subclinical) from an antecedent MDS – which confers a worse prognosis. Trisomy 8 is also a common chromosomal abnormality in CMML

occurring in 35% of patients. Trisomy 8 and 19 are also described in the accelerated phase of CMPD. Trisomy 21 is described mostly in Acute Myelogenous Leukemia and Transient Myeloproliferative Disease (TMD) in infancy.

<sup>2</sup>Supportive care consists of improving quality of life with specific treatment of cytopenias or their complications and providing psychosocial support, while monitoring at intervals the patient's clinical status. Red cell transfusions should be administered for symptomatic anemia. Platelet transfusion can be utilized for thrombocytopenic bleeding and antibiotics are used to treat infections.

In conclusion, very little information can be gathered in the management of CMPD/MDS and can provide a clinical dilemma. A full diagnostic work up of blood and bone marrow including cytogeneticse and immunophenotyping, in addition to a good history and physical examination, can provide important clinical data to better classify the disease and in turn provide an appropriate treatment strategy.

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