Scholastic Medical Sciences

Case Study

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Overview of Laboratory Diagnosis and Findings of Multiple Myeloma

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1.0 Pathogenesis and epidemiology of multiple myeloma

Multiple myeloma (MM) is defined as a hematologic disorder discovered first time in 1984 known as a monoclonal plasma cell malignancy that proliferate in bone marrow (1). This proliferation caused produce of monoclonal para-protein, skeletal destruction, anemia, and displacement of the hematopoietic cells ending by organ damage (1). **Figure 1** below shows plasma cells and bone marrow.

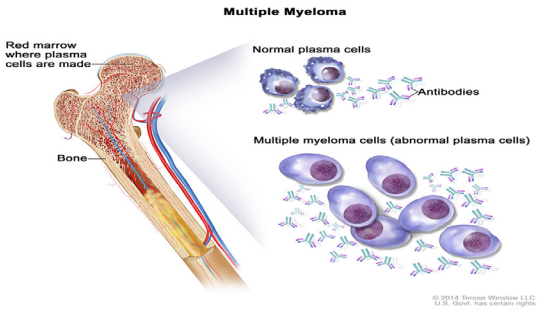

Figure 1: plasma cell in multiple myeloma disease. *source, https://www.cdc.gov/cancer/myeloma/index.htm*

Recent studies demonstrate that multiple myeloma is reported higher in developed countries than others (2). Multiple myeloma mostly diagnosed in patients over 60 years and the median age is 70 years old (2). In the last decade, the rate of new cases of multiple myeloma rising 0.7% per year. Multiple myeloma accounts about 1% of cancers and around 10% of hematologic malignancies (2).

2.0 Current WHO criteria of diagnosis and classification of multiple myeloma and related plasma cell disorders

Multiple myeloma can be diagnosed by the finding of 10% or more of monoclonal plasma cells in bone marrow aspiration in addition of presence of one or more myeloma events such as biomarker malignancy (3). **Figure 2** below shows the presence of plasma cells in bone marrow aspiration of multiple myeloma patient.

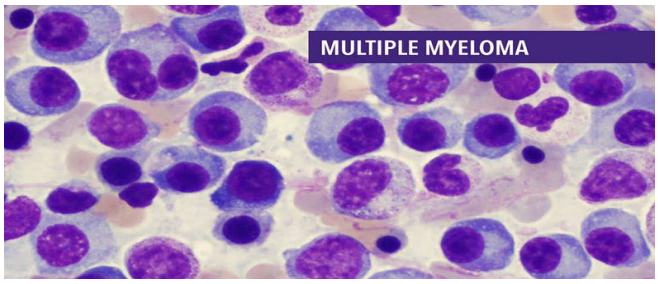

Figure 2: Shows the presence of plasma cells in bone marrow aspiration of multiple myeloma patient. *source, https://news.cancerconnect.com/multiple-myeloma/overview-of-multiple-myeloma-QqL1TvWacka3wFYyelSQbA*

Other biochemistry blood tests show abnormality in cases of multiple myeloma including, high total protein concentration, presence of mono-clonal protein, increase the uric acid concentration, high level of calcium (hypercalcemia), high level of creatinine, elevated C reactive protein (CRP), beta 2 microglobulin and lactate dehydrogenase. In the other hand, the abnormality of routine hematology tests such as, high erythrocyte sedimentation rate (ESR), leukopenia, thrombocytopenia, anemia (normocytic) and rouleaux formation erythrocytes (3). **Table 1** below, shows the difference hematologic parameters for patients with multiple myeloma disease.

M protein which is antibody monoclonal immunoglobulin secreted from Myeloma cells. **Blood and urine tests are used to** determine the extent of multiple myeloma disease and to monitor the effectiveness of treatment in multiple myeloma patients. Serum protein electrophoresis is used to measure the amount of M protein in the blood or urine (4).

Hematological Parameters

Parameters	Patients Mean ±SD	Controls Mean ±SD	p-value
Hemoglobin (g/dl)	8.7±1.8	13.8±1.2	p <0.01; significant
RBC count ($x10^{12}$/L)	3.21±0.75	4.62±0.44	p <0.01; significant
MCV (fl)	87.1±9.5	89.4±4.4	p =0.240; not significant
MCH (pg)	27.4±2.9	29.9±2.1	p <0.01; significant
TLC ($x10^{9}$/L)	8.9±2.6	8.0±1.4	p =0.105; not significant
Platelet count ($x10^{9}$/L)	211±127	246±75	p =0.207; not significant
ESR(mm 1st hr)	78±37	11±5	p<0.01; significant

SD, Standard Deviation; RBC, Red Blodd Cell; MCV, Mean Corpuscular Volume; MCH, Mean Corpuscular Hemoglobin; TLC, Total Leucocyte count; ESR, Erythrocytic Sedimentation

Table 1: Shows the hematologic parameters in multiple myeloma disease. *Source, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5844606/*

Immunoglobulin levels help to check the amount of antibody levels in the blood including, immunoglobulin M (IgM), immunoglobulin G (IgG) and immunoglobulin A (IgA) (4).

Multiple myeloma classified based on the International Myeloma Working Group (IMWG) diagnostic criteria (5). **Table 2,** below explains the classification criteria for multiple myeloma disease.

Stage	Frequency (% of Patients)	5-Year Survival Rate (%)
Stage I	28	82
ISS stage I (serum albumin > 3.5, serum beta-2-microglobulin < 3.5) and		
No high-risk cytogenetics		
Normal LDH		
Stage II	62	62
Neither stage I or III		
Stage III	10	40
ISS stage III (serum beta-2-microglobulin > 5.5) and		
High-risk cytogenetics [t(4;14), t(14;16), or del(17p)] or elevated LDH		

Abbreviations: LDH, lactate dehydrogenase; ISS, International Staging System.
Derived from Palumbo et al.[33]

Table 2: Muliple myeloma classification criteria. *source, https://ascopubs.org/doi/10.1200/EDBK_159009*

3.0 The microenvironment and molecular biology of multiple myeloma and its link to the clinical symptoms of the disease

Bone marrow microenvironment has a major role and involvement in tumor growth, bone diseases, angiogenesis and drug resistance (6). There are several interactions between bone marrow microenvironment different components and the multiple myeloma cells. These interactions are necessary and plays a major role in migration regulation, differentiations, proliferations and survival of plasma cells (6).

4.0 Signs and symptoms of multiple myeloma (clinical picture of the disease)

Patients with multiple myeloma may have one or more symptoms. These symptoms can be vary and early on the disease (7).

4.1 Fatigue, due to the over accumulating of monoclonal plasma cells in bone marrow resulting in replacement of normal and necessary bone marrow cells.

4.2 Bone problems, this occurs because of weak making new and fresh bone cells. Causing bone pain, weak and broken bones.

4.3 Kidney disease, as a result of production of harmful proteins that damage kidney.

4.4 Leukocytopenia and anemia, because the over excess of myeloma cells in bone marrow.

4.5 Bruising, due to thrombocytopenia (low platelet count).

4.6 Other common sign and symptoms including, frequent infections, weight loss, nausea, loss of appetite, dizziness and confusing (7).

5.0 The role of cytogenetics lab in multiple myeloma and the cytogenetic abnormalities in multiple myeloma disease

Cytogenetic testing is the study of chromosomes in the cell nucleus during cell division. There are to cytogenetic tests used in cytogenetic lab for diagnosis of multiple myeloma disease (8).

5.1 Karyotyping, which study the number of chromosomes in the cell nucleus by using bone marrow sample of diagnosed myeloma patient. Cytogenetic test is targeting the loss of chromosome 13 in the division of myeloma cells (8).

5.2 Fluorescence In-Situ Hybridisation (FISH)

FISH test used to find the genetic map including genes and genes portions in myeloma cell. FISH test demonstrates the translocation and or mutation of genetic materials such as translocation of chromosome number 4 to 14 (4;14) and chromosome number 14 to 16 (14;16) also the loss of top part (short arm) of chromosome number 17 (deletion 17p) (8).

6.0 The role of flowcytometry lab in multiple myeloma and the immunophenotype of plasma cells and multiple myeloma

Flowcytometry immunophenotyping becomes useful tool to identify neoplasm plasma cell population in multiple myeloma patients using their bone marrow aspiration. This technique is using several antigens to distinguish distinct plasma cells population, including CD38, CD56, CD138, CD117, CD19, CD52 and CD45 (9).

7.0 The hemostatic abnormalities in multiple myeloma patients and the effect of multiple myeloma disease on platelet and coagulation system

Many hemostatic abnormalities have been reported in multiple myeloma patients which predispose to venous thrombosis and bleeding. It is known that multiple myeloma dyscrasias leads to hemorrhagic and thrombotic events (10).

Multiple myeloma as a malignancy disease can cause low platelet count (thrombocytopenia) leads to bleeding and easy bruising. Platelet dysfunctional can be happen due to a high level of immunoglobulins in plasma and marked hyperproteinemia (10).

Increased factor VIII and von Wille brand factor activity, acquired resistance to activated protein C and decreased protein S activity are associated with increase the risk of venous thromboembolism in myeloma patients. Also, coagulation factors deficiency that caused by amyloid adsorption are the main reason of bleeding diathesis (10).

Abnormal results of coagulation profile test, including, thrombin time (TT), prothrombin time (PT) and activated partial thromboplastin time (APTT) are commonly prolonged in patients with plasma cell neoplasms and are not associated with significant bleeding. **Table 3,** below shows the hemostatic changes and coagulation profile for multiple myeloma patients (10).

Screening Tests of Hemostasis

Parameter	Patients	Controls	Abnormality in patients	
	Mean±SD	Mean±SD	No.	%
PT (secs)	14.1±3.3*	12.4±0.9*	14	48.3
APTT (secs)	39.6±10.1*	29.6±1.3*	20	68.9
TT (secs)	11.3±2.7*	9.8±0.5*	10	34.5

*p<0.01, significant; SD, Standard Deviation; PT, Prothrombin Time; APTT, Activated Partial Thromboplatin Time; TT, Thrombin Time.

Table 3: Shows the hemostatic changes and coagulation profile for multiple myeloma patients. *Source, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5844606/*

8.0 Cytogenetic abnormalities and clinical course and prognosis in multiple myeloma

Multiple myeloma characterized by the presence of several cytogenetic abnormalities which can happen during a various time within the disease course (11). Cytogenetic abnormalities start initially at the time of transforming of a normal plasma cells into the limited clonal-proliferative state of MGUS. While other abnormalities occur later in the course of the disease as the malignancy progresses to relapsed refractory state. **Figure 3,** shows cytogenetic abnormalities in multiple myeloma disease. Shows normal plasma cell, MGUS/SMM and myeloma (11).

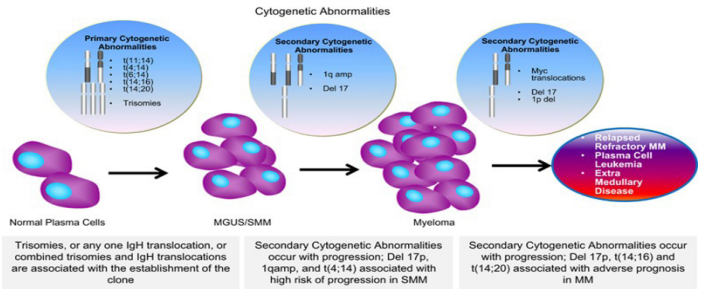

Figure 3: Cytogenetic abnormalities in multiple myeloma disease. Shows normal plasma cell, MGUS/SMM and myeloma. *Source https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4635200/*

The international staging system helps to predict the survival of multiple myeloma patients, with a median survival around 5 years for stage-1 multiple myeloma disease, 3.7 years for stage-2 multiple myeloma disease, and approximately 2.4 years for stage-3 multiple myeloma disease (11).

Chromosomal abnormalities usually is presented in multiple myeloma disease, such as trisomy of multiple odd numbered chromosomes, t(11;14), and del(13q), are not associated with a bad prognosis. However, about 25% of newly diagnosed multiple myeloma disease patients have many abnormalities associated with a worse prognosis, like t(4;14), t(14;16), and del(17p). The other less common cytogenetic abnormalities associated with a worse prognosis include t(14;20) and ≥4 copies of 1q (11).

9.0 Treatment options and indications for treatment in multiple myeloma disease

Over the past 50 years, treatment of multiple myeloma disease has been changed beyond recognition (12). In 1983, high dose of intravenous melphalan was used and was followed by autologous stem cell transplantation (12). Then the use of autologous stem cell transplantation became the standard care for patient younger than 65 years old. The potentially successful management for multiple myeloma remains high dose of therapy followed by autologous stem cell transplant using donor stem cells (allogeneic stem cell transplant) (12).

Multiple myeloma treatment depends on whether the patients are experiencing symptoms and the overall health of the patients.

The types of systemic therapies used for multiple myeloma treatment include, chemotherapy, targeted therapy, immunomodulatory drugs, steroids and bone-modifying drugs (12).

There are three phases for treatment of multiple myeloma including, three or four drugs induction chemotherapy, autologous stem cell transplant (ACST) with high dose chemotherapy, and maintenance therapy to control the myeloma and prevent resistant to therapy (12).

10.0 The role of autologous stem cell transplantation in multiple myeloma and patient eligibility for this treatment

In the last 30 years, autologous stem cell transplantation becomes an essential way to treat patients with multiple myeloma disease (12). Although, a lot of trials have confirmed that survival was improved of autologous stem cell transplantation compared with these who have not undergoing this treatment (12). Autologous stem cell transplantation treatment is considered as the standard of care for multiple myeloma young patients who have adequate organ function (12).

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