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Editorial

Oddball and Gyre-Plasma Cell Myeloma

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Editorial

Plasma cell myeloma is a multifocal plasma cell neoplasm preponderantly incriminating the bone marrow demonstrating monoclonal immunoglobulin (M protein) within serum or urine and accompanying end organ damage. Additionally designated as multiple myeloma, myeloma, medullary plasmacytoma, myelomatosis, Kahler disease, smoldering or asymptomatic plasma cell myeloma, non-secretory myeloma or plasma cell leukemia, plasma cell myeloma is appropriately discerned an amalgamation of clinical, biochemical, hematological, radiological and histological features. Evaluation of serum or urinary M protein, monoclonal plasma cells confined to bone marrow and occurrence of end organ damage contingent to the myeloma is confirmatory. Appearance of urinary Bence Jones proteins was previously denominated as a preliminary tumour marker. Plasma cell myeloma configures ~20% of hematopoietic neoplasms or mortality due to hematopoietic malignancies. A slight male preponderance is observed with male to female proportion of 1.2:1. Median age of disease emergence is ~70 years whereas pediatric population or adults <30 years are exceptionally incriminated. A genetic predisposition is observed with proportionate possible development of myeloma ~ 2 within first degree relatives.

Bone marrow is a preponderant site of disease emergence as concordance between bone marrow stroma and neoplastic plasma cells can directly engender the disorder with contribution from interleukin 6 (IL6) which sustains survival and expansion of myeloma cells. Interleukin 6 (IL6) and accompanying cytokines promote osteoclastic activity and lytic bone lesions. Monoclonal myeloma cells restrict differentiation and proliferation of osteoblasts in addition to inducing osteoclastic differentiation and hyper-function. Multiple myeloma is posited to emerge from diverse contributory factors as chronic antigenic stimulation and exposure to radiation or toxins. Nevertheless, the majority of instances may be devoid of the aforesaid associated factors. Plasma cell myeloma preponderantly occurs in subjects with precursor lesion of monoclonal gammopathy of undetermined significance (MGUS). Monoclonal myeloma cells depict clonal rearrangement of immunoglobulin heavy and light chain genes. An intense somatic hyper-mutation of IGHV gene ensues. Light chain only disease may display abnormalities within IGH genetic rearrangement. Conventional cytogenetics demonstrates chromosomal anomalies within ~33% instances as discerned with fluorescent (FISH), such as trisomy, chromosomal deletions and translocations. Plasma cell fraction can be enriched with magnetic cell sorting (MACS) and fluorescence activated cell sorting (FACS) which amplifies detection of cytogenetic anomalies within interphase cells [1]. Monoclonal myeloma cells depict IGH genetic translocation situated upon chromosome 14q32 in ~ 40% neoplasms.

Besides, Reoccurring Oncogenes as

a) ~t(4;14) FGFR3 / MMSET (NSD2) situated upon chromosome 4p16.3.

b) ~t(6;14) cyclin D3 situated upon chromosome 6p21.

c) ~t(11;14) cyclin D1 situated upon chromosome 11q13.

d) ~t(14;16) MAF situated upon chromosome 16q23.

e) ~t(14;20) MAFB situated upon chromosome 20q11.

f) ~MAFA situated upon chromosome 8q24.

g) ~Cyclin D2 situated upon chromosome 12p13 can be observed.

Myelomas devoid of one of frequent IGH genetic rearrangement appear as hyper-diploid with gains of odd numbered chromosomes 3, 5, 7, 9, 11, 15, 19 and 21. Monosomy or partial deletion of chromosome 13 (13q14) may occur within 50% myelomas as discerned with fluorescent in situ hybridization(FISH). MYC

genetic rearrangements and activating mutations within of KRAS, NRAS or BRAF may be observed. Additionally, anomalies such as TP53 deletion or mutation, gain of 1q, loss of 1p, NF kappa B pathway activation, inactivation of CDKN2C, RB1, FAM46C, DIS3 and altered DNA methylation may be exemplified. Clinically, bone disease appears as a frequent, disease defining symptom with accompanying lytic bone lesions commonly confined to thoracic vertebrae, ribs, skull, shoulders, pelvis and long bones. Besides, spinal cord compression or peripheral neuropathy are uncommonly discerned, initial clinical symptoms. Renal failure ensues with elevated serum creatinine. Hyperuricemia with monoclonal light chain proteinuria engenders renal tubular damage. Hypercalcemia and hypoalbuminemia may occur. Repetitive bacterial infections due to impaired humoral immunity are common as immunoglobulin production is frequently < 50% of normal levels. Anemia is frequently observed due to bone marrow infiltration within areas of active hematopoiesis along with decimated erythropoietin induced due to renal failure. Extramedullary involvement is associated with advanced disease.

Clinical Symptoms Pertaining to Multiple Myeloma (CRAB) are Designated as

a) Elevated serum calcium or hypercalcemia > 0.25 millimoles/Liter above upper limit of normal (ULN) or values > 2.75 millimoles/Liter.

b) Renal symptoms associated with elevated serum creatinine> 173 millimoles/Liter.

c) Anemia with haemoglobin < lower limit of normal by 2 grams/deciliter or haemoglobin < 10 grams/deciliter.

d) Bone pain or lytic lesions, osteoporosis or compression fracture of spine.

Additionally, features such as symptomatic hyper-viscosity, amyloidosis or recurrent, severe bacterial infections with > 2 episodes within 12 months may be encountered. Individuals with ≥ 1 CRAB clinical features mandate active therapy for myeloma. Precise treatment of multiple myeloma may be adopted in the absence of CRAB for symptoms such as ~> 60% plasma cells infiltrating the bone marrow ~involved(monoclonal) to uninvolved(polyclonal) serum free light chain(kappa or lambda) ratio is > 100 with absolute values > 100 milligram/Liter or >10 milligram/deciliter ~bone lesions are discernible upon magnetic resonance imaging (MRI) or positron emission tomography (PET/CT) scan. Individuals may lack symptoms of myeloma although demonstrate abnormal plasma cells which configure M protein. Therapy may be initiated with end organ damage or symptomatic myeloma.

Plasma Cell Myeloma Exemplifies Distinct Variants as

a) Smoldering or asymptomatic disease which commonly progresses to symptomatic myeloma, in contrast to monoclonal gammopathy of uncertain significance (MGUS). Aforesaid conditions depict gammopathy in the absence of concrete myeloma defining events as hypercalcemia, anemia, bone lesions and renal insufficiency. Proportionate disease progression is ~10% per year for an initial 5 years whereas proportionate disease progression decimates following 5 years of initial disease discernment. In contrast to monoclonal gammopathy of undetermined significance (MGUS), smoldering or asymptomatic myeloma demonstrates elevated levels of M protein and excessive plasma cells confined to bone marrow wherein 10% to 60% of bone marrow cells are plasma cells. However, clinical symptoms of overt myeloma as significant bone disease or anemia may be absent. Bisphosphonates may be employed for treating symptoms of osteoporosis or osteopenia. Close monitoring is recommended as disease progression may be associated with symptomatic emergence within 18 months to 2 years.

b) Monoclonal gammopathy of undetermined significance (MGUS) is associated with minimal M protein levels indicative of miniscule quantities of abnormal plasma cells in the absence of additional evidence of myeloma as bone damage, excessive plasma cells within bone marrow or minimal marrow vascular constituents as red blood cells, white blood cells or platelets. The condition is associated with cumulative 1% per year possible emergence of myeloma or exceptional disorders as chronic lymphocytic leukemia (CLL), lymphoma, Waldenström macroglobulinemia or amyloidosis. Regular monitoring is recommended.

c) Non-secretory myeloma (~1%) can be adequately discerned as non-reactive for serum or urinary M protein upon serum protein electrophoresis (SPE) or immuno-fixation electrophoresis (IFE). Majority (85%) of instances demonstrate impaired secretion along with cytoplasmic immunoglobulin (Ig) discernible with cogent immunohistochemistry. Around ~15% subjects are 'non producers' with absent serum or urinary M protein although serum free light chains may be detected. Minimal occurrence of renal insufficiency, hypercalcemia and decimation of normal immunoglobulin G (IgG) levels is encountered. The condition requires segregation from the exceptional (immunoglobulin D (IgD) and immunoglobulin E (IgE) myelomas.

d) Plasma cell leukemia is typically associated with an aggressive clinical course and disease associated survival < 1 year. The condition denominates circulating neoplastic, monoclonal plasma cells > 2 x 109/Liter or 20% of leukocyte count upon differential leukocyte count. Primary plasma cell leukemia configures ~0.6% of myeloma or may arise as delayed transformation as secondary plasma cell leukemia. Majority (~80%) of lesions lack immune reactivity to CD56 and delineate frequent, high risk genetic anomalies. Besides, bone pain and osteolytic lesions are uncommon. Typically, the disorder is associated with extramedullary lesions such as effusion of body cavities, regional lymph node enlargement and organomegaly.

e) Recurrent myeloma or relapsed myeloma is categorized as myeloma which reappears following a duration of disease control with cogent therapy. Reoccurring myeloma necessitates re-staging.

Newly diagnosed myeloma is classified as

a) asymptomatic wherein subject is devoid of signs and symptoms indicative of disease and may be managed with simple observation or active surveillance for smoldering myeloma.

b) symptomatic wherein subject depicts cogent signs and clinical symptoms of disease and requires pertinent therapy [2]. Upon cytological examination, variably quantifiable plasma cells are discerned. Mature plasma cells are comprised of elliptical cells imbued with abundant, basophilic cytoplasm, spherical, eccentric nuclei with a perinuclear hof, 'clock face' nuclear chromatin and indiscernible nucleoli. Immature plasma cells exhibit elevated nucleo-cytoplasmic ratio, abundant cytoplasm, perinuclear hof, dispersed nuclear chromatin and prominent nucleoli.

Plasmolysis cells are imbued with minimal cytoplasm, enlarged nuclei >10 μ, decimated or absent perinuclear hof, fine, reticular nuclear chromatin or enlarged nucleolus > 2 μ. Pleomorphic plasma cells appear as poly-lobed, multinucleated cells. Exceptionally, the myeloma depicts miniature, lymphoid-like plasma cells or plasma cells with significantly lobed nuclei. Reactive plasma cell proliferation infrequently depicts immature or pleomorphic cellular features. Osseous or extra-osseous plasmacytomas may be subjected to frozen section of tissue samples obtained from sites such as mucosa of upper respiratory tract, lymph nodes, thyroid, testes, breast, salivary gland or central nervous system. Discernible morphology varies from monotonous plasma cells to irregular, multinucleated or pleomorphic plasma cells delineated within advanced multiple myeloma. Upon gross examination, bone defects are permeated with soft, gelatinous. 'Fish flesh', haemorrhagic tissue. Upon microscopy, core needle biopsy demonstrates interstitial clusters, nodules or sheets of neoplastic plasma cell. Bone marrow may demonstrate foci of preserved hematopoiesis, diffuse infiltration of neoplastic plasma cells or significantly suppressed hematopoiesis. Osteoclastic activity can be prominent. Clonal plasma cell infiltrate can be subjected to immunohistochemistry with CD138 and staining for immunoglobulin (Ig) kappa and lambda. Cytological examination appropriately demonstrates plasma cell morphology as mature or immature plasma cells or plasmolysis cells.

Additional Morphologic Features are Designated as

a) Mott cells or morula cells demonstrating multiple, grape-like cytoplasmic inclusions constituted of crystalized immunoglobulin.

b) Russell bodies are comprised of hyaline, intracytoplasmic inclusions.

c) Flame cells exhibit vermillion staining pattern on account of glycogen- rich immunoglobulin A (IgA) confined to diverse cytoplasmic projections ~Pseudo-Gaucher cells or thesauruses appear overstuffed with packaged fibrils.

d) Cytoplasmic crystals are occasionally discerned in multiple myeloma.

e) Dutcher bodies appear as pale staining, cytoplasmic invaginations into the nucleus or as a singular, enlarged, intra-nuclear inclusion wherein cytoplasm is permeated with immunoglobulins. Dutcher bodies are commonly encountered within IgA myeloma.

Peripheral Blood Smear Demonstrates

a) Rouleaux formation is a non-specific feature wherein erythrocytes simulate 'stacked coins'. The configuration is contingent to quantity and subtype of M protein and is engendered due to altered plasma proteins.

b) Leucoerythroblastic reaction may ensue with extensive incrimination of bone marrow.

c) Circulating plasma cells appear in ~15% instances whereas plasma cell leukemia requires occurrence of > 2 x 109/Liter or 20% of leukocyte count as circulating neoplastic plasma cells. Ultrastructural examination of monoclonal plasma cells demonstrates a prominent rough endoplasmic reticulum with frequently discerned, budding Russell bodies (Figures 1 & 2). Contingent to levels of serum albumin, serum lactate dehydrogenase(LDH), serum beta-2 micro-globulin (β2M) and high-risk chromosomes discerned by fluorescent in situ hybridization, the *Revised International Staging System (R-ISS*) is commonly adopted to classify multiple myeloma, assess disease survival and prognostic outcomes.

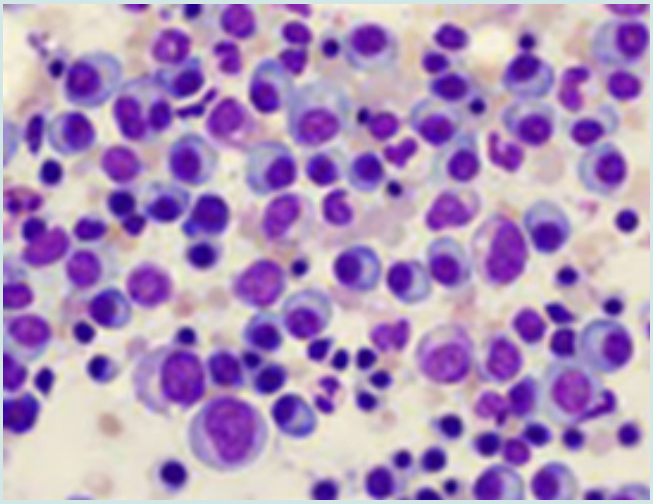

Figure 1: Multiple myeloma demonstrating an infiltrate of mature and immature plasma cells with eccentric nuclei, cartwheel or vesicular chromatin and prominent nucleoli [5].

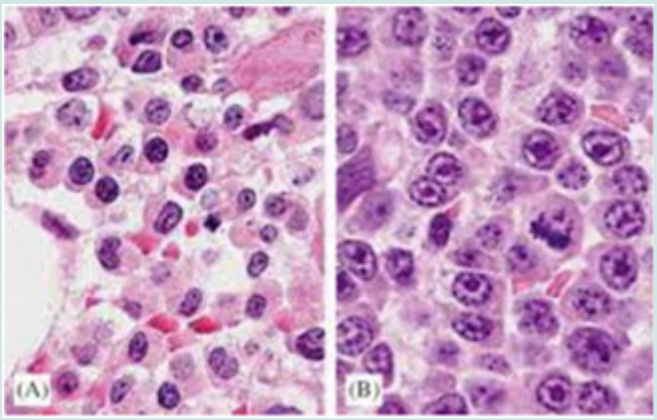

Figure 2: Multiple myeloma delineating an infiltrate of mature and immature plasma cells with eccentric, vesicular nuclei, open ended chromatin and conspicuous nucleoli abutting bone marrow trabeculae [6].

Besides, Gene Expression within Myeloma Cells May be Adopted for Disease Classification

Stage I is comprised of

a) Serum beta-2 micro-globulin (β2M) < 3.5 milligram/Litre

b) Serum albumin ≥3.5 grams/decilitre

c) Normal serum LDH

d) Absence of high-risk chromosomal alterations within myeloma cells as discerned by FISH or absence of chromosomal anomalies as del(17p), t(4:14) or t(14,16).

Stage II: It is defined by disease parameters inadequate for classifying stage I or stage III.

Stage III is constituted of

Serum β2M > 5.5 milligram/Liter along with one of following parameters myeloma cells delineating high risk chromosomes as detected by FISH or chromosomal anomalies as del(17p), t(4:14) or t(14,16) serum LDH > upper limit of normal which is indicative of inferior prognosis [3]. Plasma cell myeloma is immune reactive to CD38, CD138, VS38c, MUM1, EMA, CD79a, CD56,CD200, CD28, CD117/c-KIT, CD20, CD52, CD10, monoclonal light chain, cyclin D1, B cell markers situated upon clonal plasma cells as CD19, CD20, CD79a and an elevated expression of MYC. Plasma cell myeloma is immune non-reactive to CD19, CD45, CD27 or CD81. Besides, the majority (~80%) of plasma cell leukemia are immune non-reactive to CD56. Upon flow cytometry, monotypic cytoplasmic immunoglobulin G (Ig) is observed along with lack of surface light chain. Monoclonal myeloma cells may enunciate CD38, CD138, CD56+ or CD117+. Partial reactivity to CD45 is observed. Myeloma cells are immune non-reactive to CD10, CD19 and CD20. Exceptionally, multiple myeloma demonstrating chromosomal translocation t(11:14) is comprised of monoclonal plasma cells reactive to B cell markers as CD19 and CD20. Multiple myeloma requires segregation from neoplasms such as mature B cell lymphoma with extensive plasmocytic differentiation as marginal zone or lymphoplasmacytic lymphoma, monoclonal gammopathy of undetermined significance (MGUS), plasmolysis lymphoma, primary effusion lymphoma, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome, reactive plasmacytosis, solitary plasmacytoma of bone, systemic AL amyloidosis, telangiectasia, elevated erythropoietin and erythrocytosis, monoclonal gammopathy, perinephric fluid collection and intrapulmonary shunting (TEMPI) syndrome.

Categorization of Multiple Myeloma is Mandatory for Appropriate Therapy and Myeloma is Categorized as

Multiple (symptomatic) myeloma demonstrates monoclonal plasma cells accumulated within bone marrow ≥ 10% or bony or extramedullary plasmacytoma as detected with surgical sampling along with ≥ 1 of myeloma defining events denominated as serum calcium > 1 milligram/deciliter above upper limit of normal or > 11 milligram/deciliter. renal insufficiency with serum creatinine > 2 milligram/deciliter or creatinine clearance < 40 milliliter/minute. haemoglobin < 10 grams/deciliter or > 2 grams/deciliter below lower limit of normal ≥1 osteolytic bone lesions as discerned upon skeletal radiography, computerized tomography (CT) or fluor-deoxy glucose positron emission tomography (FDG PET / CT) monoclonal plasma cells contributing to ≥ 60% of bone marrow cellularity. involved(monoclonal)/ uninvolved(polyclonal) serum free light chain (FLC) ratio ≥ 100 and involved free light chain concentration ≥10 milligram/deciliter. >singular focal lesion ≥ 5 millimeters magnitude discernible upon magnetic resonance imaging (MRI) ~traditional clinical symptoms (CRAB) associated with myeloma as end organ damage with hypercalcemia, renal failure, anemia and osteolytic bone lesions. Besides, specific biomarkers denominating possible progression (~80%) into end organ damage as ≥ 60% monoclonal plasma cells confined to bone marrow, serum free light chain (FLC) ≥ 100 with FLC level ≥ 10 milligram/deciliter or > singular focal lesion as detected by MRI may be expounded. Suspected or proven light chain cast nephropathy is contemplated to be a multiple myeloma defining event. Surgical tissue samples from renal parenchyma may be evaluated if FLC appears < 500 milligram/liter.

Smoldering (asymptomatic) Myeloma Denominates

Serum M protein (IgG or IgA) at ≥ 3 gram/deciliter. or Bence Jones protein ≥ 500 milligrams/24 hour urine

~or 10% to 59% monoclonal plasma cells confined to bone marrow. ~absence of concurrent tissue damage or myeloma defining event or amyloidosis. Absence of bone lesions mandate an extensive bone survey with whole body magnetic resonance imaging (MRI), fluor-deoxy glucose positron emission tomography (FDG PET / CT) or low dose computerized tomography (CT). The majority (~97%) instances depict serum or urinary M protein whereas ~3% myelomas are non-secretory. Generally, immunoglobulin G (IgG ~50%), immunoglobulin A (IgA ~20%), light chains (20%) or immunoglobulin D (IgD), immunoglobulin E

(IgE), immunoglobulin M (IgM) and bi-clonal lesions (<10%) are exemplified(3,4). Upon protein electrophoresis, myeloma proteins appear as a spike confined to gamma globulin region. Urine protein electrophoresis demonstrates urinary monoclonal light chains as Bence Jones proteins. Immuno-fixation (IFE) can be adopted to classify M spike as it reacts with specific immunoglobulin heavy chains IgG, IgA, IgM, IgD, IgE and light chains kappa or lambda. Serum free light chain assay (SFLCA) is a sensitive technique for monitoring light chain disease and non-secretory myeloma Mass spectrometry may demonstrate outcomes equivalent to immuno-fixation with superior differentiation of M protein, in contrast to therapeutic antibodies. Chromosomal abnormalities or genetic mutations as determined with fluorescent in situ hybridization of neoplastic cells are delineated with aggressive multiple myeloma.

Plasma cell labelling index can be appropriately assayed upon bone marrow samples for evaluating neoplastic cellular turnover. Upon radiographic examination, evidence of ≥ 1 site of osteolytic bone destruction minimally measuring 5 millimeters in magnitude is observed. Osteolytic bone lesions can be detected by low dose whole body computerized tomography(CT), magnetic resonance imaging (MRI), positron emission tomography (PET/CT) and 18F fluorodeoxyglucose positron emission tomography (FDG PET). A preliminary radiographic bone survey is recommended for aptly discerning smoldering multiple myeloma or solitary plasmacytoma. Enhanced radiotracer uptake discernible upon singular positron emission tomography (PET/CT) appears unsatisfactory for diagnosis in the absence of evident, underlying osteolytic bone destruction and may require confirmation with surgical sampling of bone.

Following adoption of updated diagnostic criteria recommended by International Myeloma Working Group for initiating cogent therapy with appropriate imaging is beneficial in subjects demonstrating CRAB clinical symptoms preceding end organ damage. As per National Comprehensive Cancer Network (NCCN) guidelines, cogent therapeutic strategies are comprised of ~an amalgamation of proteasome inhibitors, immunomodulatory drugs, steroids, antibody-based therapy as elotuzumab (anti-SLAM7), daratumumab and isatuximab (CD38), contemporary B cell maturation antigen (BCMA) targeting agents, traditional chemotherapeutic agents or radiation therapy. ~autologous bone marrow transplant is particularly beneficial in young subjects with newly diagnosed plasma cell myeloma. Evaluation of minimal residual disease (MRD) is an appropriate assessment of response to therapy and may be adopted to guide pertinent therapeutic strategies. Techniques such as flow cytometry, molecular methodologies monitoring immunoglobulin rearrangement with next generation sequencing (NGS), assessing clonotypic peptides with mass spectrometry along with liquid chromatography with tandem mass spectrometry (LC-MS / MS) can be advantageously adopted. Absence of minimal residual disease (MRD) is associated with superior progression free survival. Plasma cell myeloma is incurable and exhibits a median survival of ~5.5 years and 5 year proportionate survival of ~54%. Ameliorated therapeutic strategies demonstrate superior survival [4]. Prognostic outcomes are contingent to ~elevated levels of serum beta-2 micro-globulin(β2M) indicates significant proportion of myeloma cells with accompanying renal damage. Advancing myeloma is associated with elevated β2 micro-globulin.

~decimated serum albumin or elevated serum LDH is associated with inferior prognosis. Elevated proportion of disease emergence is encountered with. ~enhanced serum β2 micro-globulin, lactate dehydrogenase, C reactive protein, serum soluble receptor for interleukin 6(IL6) along with prominent plasma cell proliferation or infiltration of bone marrow ~decimated values of polyclonal (uninvolved) serum immunoglobulins ~plasmablastic cellular morphology ~chromosomal anomalies discerned with conventional cytogenetics Inferior prognostic outcomes are observed with ~chromosomal anomalies such as t(4;14), MAF translocations, t(14;16) and t(14;20), del(17p), del 13, aneuploidy or hypo-diploidy. Superior prognostic outcomes are associated with ~hyperdiploidy, t(11;14), t(6;14) and immune reactive cyclin D1 or cyclin D3. Analysis of prognostic value of frequently discerned chromosomal alterations within newly diagnosed, symptomatic myeloma appears advantageous. Elevated possibility of progression of smoldering myeloma is assessed with independent risk factors denominated as ~serum monoclonal protein > 2 gram/deciliter ~involved(monoclonal) to uninvolved (polyclonal) serum free light chain ratio > 20 ~bone marrow plasma cells > 20%. Contingent to appropriate evaluation, plasma cell myeloma is categorized as ~low risk (0 factor) ~ intermediate risk (1 factor) ~high risk (2 or 3 factors) wherein aforesaid categories demonstrate enhanced 2-year proportionate progression into overt multiple myeloma.

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6. Image 2 Courtesy: Science direct.com.

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