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Multiple Myeloma: An In-depth Review of the Historical and Pathogenetic Processes

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Authors' contributions

This work was carried out in collaboration among all authors. Authors AJM, HCM and SO designed the study. Authors CN, HCM and SO conducted the literature search, authors AJM, CN, HCM and SO wrote the various sections of the manuscript. Authors HCM and SO did the final proof reading and correction. All authors read and approved the final manuscript.

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ABSTRACT

Myeloma is a plasma cell disorder which occurs with varying prevalence across different populations across the globe. Knowledge of the disease pathogenesis as well as its diagnosis and treatment has evolved over the years. The mutations that underlying the progression from benign gammopathy to overt clinical carcinomatosis has been studied extensively and has provided targets for immunotherapy. The causes of variations in incidence of multiple myeloma across different regional and socio-culturally diverse groups has been proposed to be multi-factorial, as denoted by the plethora of mutations driving disease progression in these groups. The sequence of mutation – primary and secondary events, in oncogenesis have been described though no apparent environmental or infective organism has been consistently link with myeloma. The impact of interleukin 6 and RANKL in the severity of myeloma bone disease has been observed to high and offers both contemporary and future therapeutic targets. This review is targeted at providing in-depth insight into the historical events as well as the molecular basis of this disease.

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1. INTRODUCTION

Plasma cell dyscrasias are a group of disorders of B lymphocytes ranging from pre-malignant conditions like monoclonal gammopathy to obvious malignancies like plasma cell leukaemia. Myelomatosis occurs as a result of clonal malignant proliferation of plasma cells in the bone marrow with attendant osteopaenia and excessive production of m-proteins by these cancer cells. There are variations in cancer prevalence across the different populations in various parts of the globe and myeloma is not an exception. These variations over a unique opportunity to study the factors (genetic or environmental) that may be responsible for carcinogenesis or that may play a protective role in these populations. This review was aimed at understudying the historical chronology, variations in prevalence and pathogenetic basis of multiple myeloma.

2. METHODOLOGY

The references, materials and relevant literature used in this review was sourced using online search engines and websites accessed were PubMed, Web of Science, Hinari, JSTOR and ARDI. The search was conducted using advanced search for the keywords myeloma, plasma cells, pathogenesis, m-protein and prevalence. This was done after each key word was processed with MeSH terms on PubMed. The initial search online search conducted using these MeSH terms yielded 163 published items which was further checked for relevance and date of publication**.** Final publications to be used were accessed and saved on Zetero referencing app. These included original research, review articles and case reports.

2.1 Myeloma Historical Perspective

Multiple myeloma (MM) is a plasma cell neoplasm characterized by abnormal serum and/or urine paraprotein or free immunoglobulin light chain as a result of clonal expansion of plasma cells, often accompanied by complications of enhanced bone loss associated with diffuse osteopenia or focal lytic lesions, hypercalcaemia, anaemia and renal failure [1]. It accounts for 1% of all cancers and is the second most common haematologic neoplasm after lymphoma [2].

One of the earliest best descriptions of MM was the patient Thomas Alexander McLean. He was a 45 years old well-known businessman, who had developed fatigue and had a problem with his urine. Henry Bence Jones was the Chemical Pathologist who first studied McLean's urine and observed the relationship between the urine and the patient's problem, later known as MM. However, Fleischer, in 1880, first named this abnormal protein as "Bence Jones protein" [3]. A 1928 report on 412 MM patients seen in various reports between 1848 and 1928 noted that anaemia, Bence Jones proteinuria, pathologic fractures and chronic renal disease were associated clinical findings [4]. In 1956, urinary Bence Jones proteins was found to be of two types: kappa and lambda [5]. A later landmark discovery showed the serum IgG myeloma light chain proteins were the same as the patient's urinary Bence Jones proteins [6,7].

The discovery that the gammopathies could be monoclonal or polyclonal was another critical step in the history of this disease [8]. The current terminology for such a condition is monoclonal gammopathy of undetermined significance (MGUS) [9]. Using the electrophoretic techniques, the serum globulins were later separated into α, β, and γ components [10].

The staging of MM started with the Durie-Salmon staging system in 1975 [11]. This system however had limitations, and the International Staging System (ISS) was developed [12] originally based on beta-2 microglobulin and albumin. With the discovery of several other prognostic factors, patients needed to be risk-stratified into standard or high risks based on the presence of factors such as; deletion 13 or hypodiploidy on conventional karyotyping, deletion 17p or immunoglobulin heavy chain translocations t(4;14) or t(14;16) on molecular genetic studies, and plasma cell labeling index of 3% or higher [13].

Lactate dehydrogenase (LDH) and cytogenetics were later added by the International Myeloma Working Group (IMWG) in 2015 to form the revised International Staging System (ISS) risk stratification system [14].

MGUS is a pre-malignant asymptomatic stage that almost always precedes multiple myeloma. The rate of progression of MGUS to myeloma is 0.5-1% per year. The precise risk of progression is however affected by the type and titre of monoclonal protein, bone marrow plasmacytosis, serum free light chain ratio, proportion of phenotypically clonal plasma cells and presence

of immunoparesis [15]. In-between MGUS and MM is Smouldering myeloma - an intermediate clinical stage with a higher risk of progression to malignant disease of about 10% per year within the first 5 years after diagnosis [16]. Considering the fact that, any delay in the definitive diagnosis of multiple myeloma and commencement of definitive therapy could have adverse effects on the patients, it became imperative that biomarkers which could very reliably predict the progression to multiple myeloma be identified early so that definitive therapy could be commenced as soon as possible [17]. The first identified predictive biomarker was a bone marrow monoclonal plasmacytosis (BMPC) of at least 60% from a study carried out at the Mayo Clinic [18]**.** It was identified that a BMPC of at least 60% had a 90% risk of progression to myeloma within 2 years. BMPC of at least 60% was therefore subsequently adopted as a diagnostic criteria for MM irrespective of the presence or absence of CRAB features. In a UK, London summit in 2011, the IMWG agreed that, if there was any reliable biomarker that had an 80% probability of predicting progression to myeloma within 2 years. Following this consensus and several validating studies, any one or more of the following biomarkers of malignancy became recognized as myeloma defining events: Clonal bone marrow plasma cell percentage ≥60%, involved : uninvolved serum free light chain ratio § ≥100 and >1 focal lesions on MRI studies [19] .

2.2 Variations in Prevalence Across Different Geographical Populations

Over time, marked variation in the prevalence of myeloma across the various geographical and ancestral populations have been observed. The disease ranges from being quite prevalent in some Black populations to being almost completely absent in some Caucasians. The prevalence ranges from 0.4 to 2.0% in some African countries [20,21] to 0.8 to 4.6% in parts of Australia, Europe and Asia [21]. This can be readily attributed to environment factors including presence of carcinogens in the environment - air, diet and foods peculiar to these groups. However, the fact that such high prevalence has continued to be noted in the progeny of black populations who had migrated to other parts of the globe over generations, makes it more likely to be a genetic rather than an environmental predisposition.

Within the Black Race and among people of African descent there still exist a marked disparity in prevalence of myeloma. This has been observed in previous studies by Madu et al. in a Nigerian cohort of patients. The prevalence of multiple myeloma had been noted to be 0.5% in South Africa, 0.9% in Cote D'Ivoire and 0.3% in Egypt [20,22,23]. This wide margin is also observed even across the different regions in Africa and may indicate a common ancestral descent of some populations. A remarkably low prevalence has been seen in some African Countries like South Africa, Mali and Tanzania and may indicate some genetic differences despite geographical proximity. It may also be due to the ameliorating effect of inter-racial marriages on disease predisposition. The genetic predispositions as well as the unique genotypic basis underlying the variation in disease prevalence is yet to be fully delineated. This pattern of variation with regards to cancer prevalence has also been noted in other malignancies and may provide some insight into the other epigenomic factors that may lead to myelomatosis.

Waxman et al. in a landmark, very large population-based study aimed at specifically examining the disparities in myeloma incidence and outcome by race, confirmed the 2 to 3 higher incidence in blacks than whites [24]. It has been observed that the increased incidence of MM among people of African descent is associated with the frequency of three cytogenetic subtypes: t(11;14), t(14;16), and t(14;20) [25]. The study revealed that the likelihood of having t(11;14), t(14;16), and t(14;20) cytogenetic subtypes increased with every 10% increase in the extent of African ancestry. Among the individuals of African ancestry with 1 of these three cytogenetic subtypes, t(11;14) was found to be the most common, making up 75% of the cases studied. Fortunately, the t(11;14) cytogenetic subtype is known to have a favorable prognosis in comparison to the other subtypes. Although the t(14;16) and t(14;20) cytogenetic subtypes are considered to have high risk, they are more rarely seen. The over-representation of the t(11;14) cytogenetic subtype among persons of the African race possibly explains why African Americans have shown better survival outcomes in comparison to their European American counterparts.

2.3 Cell of Origin and Pathogenesis of Multiple Myeloma

The ability to predict the origin of myeloma cells and the particular point at which malignant

transformation occurred has been a subject of intense research and controversial debate [26]. Adding to this controversy is the issue of myeloma stem cells which are believed to be cells within the malignant tissue that have self-renewal property and continuously proliferate to add to the growth of the malignant tissue [27]. The ability to properly understand the B-cell ontogeny goes a long way in helping solve the myeloma cell origin puzzle.

Development of B-cell is divided into the antigen-independent and the antigen-dependent stages which occur in the foetal liver/ bone marrow and the secondary lymphoid tissues respectively [28]. In the bone marrow, immunoglobulin gene rearrangement occurs with the recombination activating genes *RAG1* and *RAG2* recombining the variable (V), diversity (D) and the joining (J) of the immunoglobulin heavy chain gene [29]. The sequence is that of DJ segment rearrangement and thereafter V/DJ segment rearrangement. Subsequently, the V/J segment of the kappa light chain is rearranged but the lambda light chain is only rearranged if the kappa light chain rearrangement is unsuccessful. Following this, the B cell which is still immature expresses a surface immunoglobulin and thereafter transits to the secondary lymphoid tissues like the lymph node or spleen where they mature. Upon encountering antigen, the mature B cell enters the germinal center to undergo somatic hypermutation (SHM) and thereafter class switch recombination (CSR) [30,31]. These processes are initiated by activation induced cytidine deaminase (AID) and these serves to increase antigen binding capability of the B cell receptor. During these SHM and CSR, point mutations and double stranded breaks occurs which are repaired using the body's base pair repair and mismatch repair mechanism but it is important to note that this is highly error prone [32] and form points where molecular errors can lead to tumorigenesis. The aforementioned process generates high affinity antibody producing plasma cells and memory B cells which home to the bone marrow [33].

The myeloma cells are post germinal center B cells with oncogenic transformation most likely occurring in the secondary lymphoid organs [33]. The reasons for this assumption are that malignant plasma cells show high level of somatic mutation which can make one infer that oncogenic transformation happened following SHM. Secondly, the monoclonal immunoglobulins are essentially IgG and IgA but rarely IgM or IgD which gives credence to the fact that CSR would have occurred. Finally, analysis of major oncogenic events like recurrent translocations involving IgH gene showed that the switch regions are the areas in the IgH gene that are mostly involved suggests errors in CSR process [34,35].

CD138 also known as syndecan-1 is a specific marker for the normal terminally differentiated plasma cells [36] (12). It is a heparin sulphate proteoglycan and found to control survival, growth, adhesion of tumour cells and bone cell differentiation in myeloma [37]. It is the hallmark of plasma cells and myeloma cells with very high expression in newly diagnosed cases but decreased expression in relapsed/progressive disease [38]. Decreasing expression aside from signifying poor prognosis was also associated with immature phenotype and refractoriness to lenalidomide 39. Though myeloma cells just like normal plasma cells express CD138, in order to effectively differentiate neoplastic plasma cell from their normal counterpart, expression of CD19 , CD56, CD45, CD38, CD27 and to a lesser extent CD20, CD28, CD33, CD117, SmIg are used [39]. Malignant plasma cells almost constantly lack CD19 but show aberrant expression of CD56 (CD19-, CD56+) and/or CD28 [40–42] thus making these markers very important in measurement of minimal residual disease. It is also important to note that MGUS contains both immunophenotypic clones plasma cells thus implying that MGUS consists of phenotypically normal plasma cells and myeloma cells [43].

Knowledge gathered over the years has shown that myeloma is a progressive disease with spectrum ranging from MGUS to symptomatic MM. It starts as an asymptomatic monoclonal gammopathy of undetermined significance (MGUS) [44,45] to an intermediate known as smoldering myeloma, then to a symptomatic stage known as newly diagnosed multiple myeloma and finally relapsed/refractory multiple myeloma [15,46]. The progression of MGUS to symptomatic MM is about 1% per year but predicting which MGUS will progress to symptomatic MM has for long been a subject of research [41]. Presently, this high risk MGUS cases that will progress to symptomatic MM can be predicted using modern technique as such pointing to a novel targeted early therapy [47]. Long lived plasma cells are quiescent post germinal center B cells whose transformation to MGUS requires some genetic alterations that aid these plasma cells regain proliferation capacity [32]. These same genetic alterations which

confer proliferation capacity are found in MM and are thought to be primary genetic insults [32].

2.4 Molecular Pathogenesis of the Disease Process in Multiple Myeloma

The aetiopathogenesis of MM is multi-factorial with evidence of micro-environmental, genetic and molecular alteration.

3. INTERLEUKIN 6 (IL-6)

A network of cytokines has been implicated in the pathogenesis of MM. These cytokines are secreted by the myeloma cells as well as the stromal cells. They are released by the MM cells inducing osteoclast activity and causing bone resorption as well. With increasing bone resorption, more growth factors are released which in turn stimulate growth of myeloma cells, leading to a vicious cycle. [48,49], Notable among the cytokines is interleukin-6 (IL-6) which serves as both a growth factor and a survival factor for myeloma cells. Within the bone marrow (BM) milieu high levels of the complex IL-6 and its soluble receptor (IL-6/sIL-6R) constituting the main plasma cell growth factor during the initial steps of myeloma transformation. In addition, IL-6 acts as a survival factor. Later on, the malignant cell is transformed further and may become IL-6- and BM- independent. IL-6 is responsible for proliferation of myeloma cells, development of bone complications in MM and cancer metastasis [50] This property is made possible by its ability to inhibit apoptosis, down-regulate dephosphorylated retinoblastoma protein and its interaction with other factors including adhesion molecules, tumour suppressor genes and oncogenes [51–53]. IL-6 creates a perfect milieu for oncogenesis and metastasis. It modulates osteogenesis and the differentiation of osteoclasts 52, when over-expressed, it causes increased osteoclastic activity [54].

3.1 Receptor Activator of Nuclear Factor kappa-B and its Ligand

The molecules - receptor activator of nuclear factor kappa-B ligand (RNKM) and its ligand - receptor activator of nuclear factor kappa-B ligand (RNKM) belong to TNF superfamily. They are expressed on different tissues of the body including osteoblasts, activated lymphocytes, bone marrow stromal cells, liver, lung, thymus, kidney, etc. The production of RNKM is increased in the bone marrow stromal cells and osteoblasts through the interaction of myeloma cells with the bone marrow microenvironment and bone resorbing agents [51]. They primarily regulate bone remodeling (because of their strong expression on bone cells) and development of the immune system [54,55]. RNKM facilitates the fusion of myeloid progenitors into osteoclasts and promotes osteoclastogenesis [56]. It is continuously upregulated as the disease progresses [57] and its action is regulated by some protagonist including osteoprotegerin (OPG). The extent to which RNKM promotes osteoclastogenesis in MM is regulated by the equilibrium between RNKM and OPG, [49] the same equilibrium which has been found to correlate with expression of markers of angiogenesis. [58] Different studies have reported other uses of the RNKM/OPG ratio – it can be used to predict survival and prognosis where higher serum levels are associated with shorter survival [59–61]. While IL-6 promotes the expression of RNKM, it inhibits the secretion of OPG thereby promoting series of bone lesions including osteoporosis, rheumatoid arthritis and osteolysis [62,63].

3.1.1 Genetic mutations

Multiple myeloma is a heterogenous disease which is genetically complex and arises through a composite course in which malignancy results following accumulation of ‘insults’ in the form of genetic mutations on plasma cells [64]. These genetic ‘insults’ cause dysregulation of the intrinsic biology of plasma cells leading to the unique clinically appreciable spectrum of disorders ranging from the asymptomatic monoclonal gammopathy of undetermined significance and smoldering multiple myeloma through the multiple myeloma to plasma cell leukaemia. [15,60] The spectrum results from progressive assembling of genetic ‘insults’ that are randomly acquired. These genetic mutations play a crucial part in course and prognosis of MM.

Myeloma is characterized by two major genetic events: the primary event and the secondary event. The primary event determines if the disease is going to be hyperdiploidy or hypodiploidy. [34,65] The hypodiploidy MM involves translocation between the immunoglobulin heavy chain (IGH) alleles at chromosome 14q and any of the following chromosomes: 4, 6, 11, 16 and 20 juxtaposing the enhancer region on chromosome 14 to the oncogenes on the other chromosomes [60,63].

Up to half of MM cases are known to have chromosome 13/13q losses, a poor survival feature, and is associated with hypodiploidy, it has been linked to de-expression of a tumour suppressor gene [66].

Hyperdiploidy is thought to result from single major mitosis which brings about gain in chromosomes rather than serial accumulation over time [67]. It involves trisomies of the odd number chromosomes 3, 5, 7, 9, 11, 15, 19 and 21 with a few translocations in the IGH allele [68,69]. As a consequence, hyperdiploidy engenders dysfunctioning of Cyclin D genes and proteins in the MYC, NF-kB and MAPK signaling pathways [70]. Hyperdiploidy is generally associated with better survival. Among the high-risk chromosomal abnormalities, the most powerful ones are del(17p), t(4;14), and del(1p33) [71,72]. While some of these genetic mutations do not impact therapeutic response like del(17p), some impact on survival like del(12p) and t(14,16). [72] Hyperdiploidy occur more commonly in elderly patients with associated increase in the incidence of myeloma bone disease, occurring in about 50% of myeloma cases. It is interesting to know that it carries some sort of favourable prognostic value [60]. Primary events seem to ultimately lead to over expression of the cyclin D gene family. The secondary events include; secondary translocations, copy number variations acquired mutations, loss of heterozygosity and epigenetic modifications, and they determine how the disease will progress. [60] Secondary events occur later in the disease and do not always involve the IGH allele at chromosome 14q unlike the primary events [73].

Inherited genetic variations can predispose to the development of MGUS, a phase in the spectrum of myeloma which almost all cases of MM pass through [74,75]. Most of the genes affected are thought to regulate the proto-oncogenes [76]. Copy number variation can result from DNA gains or losses which can be affecting the whole or just part of the chromosome [65]. They are common occurrences in MM and could lead to gain of oncogenes or loss of tumor suppressor gene which contributes to disease pathogenesis and progression [65]. About 35-40% of patients with MM have gains of chromosome 1q which happens to be associated with poor prognosis [77]. Again, loss of chromosome 1p occurs in up to 30% of MM cases and is equally associated with a poor prognosis [78]. Loss of chromosome 17p which also affects a tumour suppressor gene is present in a tenth of MM cases at presentation. This frequency increases as the disease progressed [79]. It happens to be the most important molecular finding for prognostication as it is linked to an aggressive disease phenotype and a great degree of extramedullary disease and shortened survival [74]. Other genetic mutations occurring in lower frequency in MM also include 11q and 14q.

All these genetic mutations and many others bring about dysregulation of the myeloma cellular processes and pathways contributing to the aetiopathogenesis and progression of the disease.

3.2 Prevalence of Genetic Mutations in Different Populations

The prevalence of MM varies from one population to the other. MM is 2-3 times more prevalent in Blacks than in Whites and more in the older age group than in the younger age group [80,81]. There are also gender differences in the prevalence of MM. These variances are driven by genetic and environmental factors. Reports from investigations on the racial differences of genetic abnormalities in MM are evolving. Baker et al. reported that Africa-Americans have lower prevalence of translocation in the IGH when compared to the Whites [82]. Another study showed that Blacks were less likely to have t(11;14), t(4;14) and monosomies 13/del13q and 17/del17p [25]. Monosomies 13/del13q and 17/del17p as well as t(4;14) are associated with shorter survival whereas t(11;14) is associated with better survival [82,83].

3.3 Evolutions in the Treatment of Myeloma

Multiple myeloma is typically a disease of the elderly, although younger patients with the condition have been reported. At diagnosis, the median age of patients was about 66 - 70 years, although 37% of patients have been found to be younger than 65 years [84]. Myeloma is rarely seen in patients with age less than 30 years. It is slightly more commonly seen in men than women. Myeloma is twice as common in African-Americans than Caucasians [85]. Multiple myeloma evolves from an asymptomatic premalignant stage termed “monoclonal gammopathy of undetermined significance” (MGUS). Above the age of 50, MGUS is seen in more than 3% of the population. The rate of progression of MGUS to myeloma or similar

malignancy is 1% per year [9]. In-between MGUS and myeloma is an asymptomatic, more advanced, intermediate premalignant plasma cell dyscrasia, called smoldering multiple myeloma. One of the best historical discussions on multiple myeloma is the American Society of Haematology (ASH) 50th anniversary review by Kyle et al. [86]

3.4 Treatment of Newly Diagnosed Transplant Eligible Myeloma Patients

For a very long time, vincristine, doxorubicin, and dexamethasone (VAD) combination chemotherapy was the gold standard preparatory regimen used in newly diagnosed young myeloma patients who were fit for autologous haemopoietic stem cell transplant - HSCT. Newer drug combinations were later found to be significantly more superior to VAD. These combinations included triple drug regimens including thalidomide or Lenalidomide (such as Thalidomide, Doxorubicin, Dexamethasone or Thalidomide, Cyclophosphamide, Dexamethasone) or including Bortezomib (such as Bortezomib, Doxorubicin, Dexamethasone, or Bortezomib, Cyclophosphamide, Dexamethasone or Bortezomib, Thalidomide, Dexamethasone or Bortezomib, Lenalidomide, Dexamethasone). Thalidomide or Bortezomib based combinations were found not to affect stem cell mobilization and collection [87].

Following a successful induction of remission, autologous HSCT is offered to patients after a high dose chemotherapy based on melphalan. Maintenance treatment is offered after autologous HSCT. Maintenance was initially with interferon and/or corticosteroids. This has however been replaced with thalidomide or lenalidomide. Of the two, maintenance with Lenalidomide is superior to thalidomide. Currently, allogeneic HSCT remains the only curative therapeutic treatment modality in the management of myeloma patients. Unfortunately, high transplant related mortality (TRM of up to 20–40%) and morbidity (essentially because of chronic graft-versus-host disease) have remained the drawbacks of HSCT. Allogeneic HSCT should therefore be used with caution in carefully selected myeloma patients within the context of clinical trials [87].

3.5 Treatment of Newly Diagnosed TransplantIneligible Myeloma Patients

Before newer agents became available, Melphalan and Prednisone (MP) combination chemotherapy was the available gold standard for over 40 years. Modifications of this regimen were later made with the aim of achieving better results. Such modifications included combining Melphalan and Prednisone with Thalidomide (MPT), or combining Melphalan and Prednisone with Bortezomib or Lenalidomide. Several possible combinations of drugs including Bortezomib, lenalidomide and Thalidomide have also been tried. In a recent network meta-analysis of these various combinations, the authors observed that continuous Bortezomib, Lenalidomide and Dexamethasone showed the highest overall survival benefits [88]. Furthermore, in order to reduce toxicity in elderly newly diagnosed untreated myeloma patients using Bortezomib, Melphalan, Prednisolone, it is now recommended to offer bortezomib as a once weekly dose instead of administering it as a twice-weekly dose. It has been shown that the once weekly efficacy is similar to that of the twice weekly dosing with significant increased tolerability [87].

3.6 Newer Drugs in the Management of Multiple Myeloma

Developments in research efforts have led to the discovery of new drugs including new Proteasome inhibitors (Carfilzomib), novel IMIDs (Pomalidomide), Histone Deacetylase (HiDAC) inhibitors (Pabinostat, Vorinostat), anti-CD38 monoclonal antibodies (Daratuzumab, Isatuximab), anti-Signaling Lymphocytic Activation Molecule F7 (SLAM7; Elotuzumab) and Selinexor (an oral selective inhibitor of nuclear export which targets Exportin1). In development is the Chimeric Antigen Receptor (CAR) T cell therapy targeting the B Cell Maturation Antigen (BCMA- this antigen is expressed primarily on plasma cells and some B cells but not on haematopoietic stem cells) is used. An issue affecting the management of multiple myeloma is the marked variability in genetic mutations in these patients (intra- and inter-patient genetic variability). The frequent occurrence of somatic mutations in adhesion molecules in myeloma plays critical roles in the biology of the interaction between the malignant plasma cells and their bone marrow microenvironment [89]. Designing drugs to target these mutations will revolutionize targeted therapy in the management of myeloma patients.

3.6.1 Myeloma bone disease

Myeloma bone disease (MBD) is a group of bone lesions - focal or diffuse, occurring in 80 -90% of patients with MM [65]. It includes a range of

disorders presenting as pain, fracture, cord compression and hypercalcaemia [65]. MBD is quite disabling and constitutes major a cause of morbidity and financial stress in MM patients [90]. Many pathogenetic pathways involving several genes have been identified as causal in MBD. In health, bone remodeling is neatly driven by osteoblasts and osteoclasts controlled by certain cytokines and hormones [91,92]. The normal balance is lost in MM in favour of osteoclastogenesis [93]. Factors involved are closely related where one stimulates the activity or expression of the other eventually upregulating osteoclastogenesis or/and downregulating osteoblastogenesis [94,95].

Interaction between the myeloma cells, T-lymphocytes, bone marrow stromal cells and microenvironment all play a role in osteoclastogenesis [93]. Of all these factors, the RANKL/OPG plays a major causative role in MBD. RANKL/RANK receptors on the osteoclasts stimulate their differentiation and reduce their apoptosis thereby increasing osteoclast activity [96] Imbalance in RANKL and OPG leads to osteolysis and responsible for MBD [97]. Other factors include macrophage inflammatory peptide 1alpha (MIP-1alpha), IL-3, IL-6, IL-7, stromal derived growth factor-1alpha (SDF-1alpha) and vascular endothelial growth factor. MIP-1alpha is produced by bone marrow stromal cells and normally functions as a cell adhesion and migration molecule [98]. It directly activates osteoclasts and indirectly increases bone resorption through the stimulation of RANKL expression. There is direct correlation of MBD severity and MIP-1 alpha levels. Decoy receptor is a protein that stimulates osteoclast differentiation and activation. In MM, it is overexpressed by myeloma cells and T-lymphocytes [99]. IL-6 increases survival of myeloma cells ,enhances osteoclastogenesis and upregulates IL-7 [100]. IL-7 in itself increases the expression of RANKL and bone resorption [101]. IL-3 in conjunction with IL-6 promotes myeloma cell growth and also work in synergy with RANKL and MIP-1alpha to enhance osteoclastic activity [102]. Myeloma cell stimulate cytokine secretion, bone marrow stromal cells and osteoblasts to activate RANKL/OPG. Furthermore, myeloma cells and bone marrow stromal cells upregulate RANKL and IL-6. T-lymphocytes and other immune cells regulate osteoclast and osteoblast function and survival [103].

Osteoblastic activity plays a pivotal role in MBD. Initially, it keeps pace with osteoclast and patients with MM do not develop MBD until its unable to measure up due to downregulation of osteoclasts.[104] A number of factors have been identified to stimulate its downregulation - noteworthy among them are those found in the Wngless (Wnt) pathway whose activation stimulates osteoblasts. In MM, Dickkopf (Dkk-1) overexpressed by osteoblasts and bone marrow stromal cells inhibit the pathway [95]. Secreted frizzled related protein 2 (sFRZ-2) is also involved in regulation of bone metabolism by inhibiting the Wnt pathway [105]. Other chemokines such as IL-3 and IL-7 play a dual role in MBD by upregulating osteoclasts and downregulating osteoblasts [106,107]. MBD is seen more in patients with hyperdiploid and these patients generally have shorter overall survival [108].

4. CONCLUSION

The historical perspective of myelomatosis is replete with intercalated clinical and laboratory advances and increasing diagnostic precision. The molecular landscape of the various stages of the disease offers a unique opportunity for the study of the chronicle of mutations leading to a clinically discernable disease entity. Future research should be targeted at studying the use of antibodies and enzymatic pathways that may be useful in inhibiting disease progression and bone disease.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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