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REVIEW ARTICLE

Multiple myeloma - Modern and Ayurvedic perspective- a critical review

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Abstract

Multiple myeloma (MM) represents a malignant proliferation of plasma cells derived from a single clone. It's the most important of the class of diseases included under plasma cell dyscrasias. Multiple myeloma is the second most common haematological malignancy. Recent studies state that in India there is reporting of 2 cases for every 100,000 individuals which translates that there would be 50,000 new cases a year and that might be just the tip of the iceberg considering the large number of people. The etiopathogenesis and diagnosis of Multiple Myeloma have intrigued modern oncology researchers for decades, and it is still a rapidly growing area in medicine. MM is not a single disease, but rather a collection of related diseases which is diagnosed based on aberrant cellular changes. Since this is established by modern medical science, it becomes important to understand it from the perspective of *Ayurveda*. Even though there are a few endeavours in this area, in the past decades, unprecedented progress was made in research with a focus on understanding Myeloma biology, its pathogenesis, and the development of novel drugs. Even though lots of advancements have been made in the understanding of this disease, it has still not made its way into the category of curable diseases. This special issue reflects the understanding of multiple myeloma from an *Ayurvedic* point of view to be able to work towards turning Myeloma into a manageable one.

Introduction

Multiple myeloma (MM) is a clonal plasma cell proliferative disorder characterized by the abnormal increase of monoclonal immunoglobulins. It is a heterogeneous disease, with survival duration ranging from a few months to more than 10 years. Unchecked, the excess production of these plasma cells can ultimately lead to specific end-organ damage. Most commonly, this is seen when at least one of the following clinical manifestations are present i.e., hypercalcemia, renal dysfunction, anaemia, or bone pain accompanied by lytic lesions, but it is imperative to bear in mind that improved outcomes are available if timely interventions are made. The exact aetiology of multiple myeloma is unknown. [1]

Several lines of evidence point to a genetic predisposition to MM and other plasma cell dyscrasias. Until recent years, only case-control studies and reports of occasional high-risk families supported this view. More recently, the

identification of hyperphosphorylated Paratarg proteins and the identification of putative susceptibility loci by GWASs (Genome-Wide Association Studies) have provided more firm evidence indicating an inherited predisposition to MM and related disorders. However, frequent alterations and translocations in the promoter genes, especially chromosome 14, are commonly found in multiple myeloma and likely play a role in disease development. In addition, certain oncogenes may participate in plasma cell proliferation. Other factors contributing to disease occurrence include obesity, alcohol consumption, environmental causes such as insecticides, organic solvents, agent orange, and radiation exposure.[2]

AIMS AND OBJECTIVES

To systematically understand Multiple myeloma in the Ayurveda framework and propose its probable *Samprapti* (pathogenic process) based on classical literature and interpretations.

MATERIALS AND METHODS

A manual and electronic search was done on available literature about multiple myeloma and *Ayurveda* understanding of various *arbudas*

Opinions and suggestions from faculties of the Department of *Kaya Chikitsa* were sought.

PATHOPHYSIOLOGY

MM is essentially a stage in the spectrum of monoclonal gammopathy. It is thought to arise from a pre-malignant, asymptomatic phase of clonal plasma cell growth called monoclonal gammopathy of undetermined significance (MGUS). MGUS is defined as detecting monoclonal immunoglobulins in the blood or urine without evidence of end-organ damage. This is quite common and is known to be detectable in over 3% of persons above age 50. It appears that the cell of origin is a post-germinal centre plasma cell. This is typically a benign condition, although as noted above, it has a risk of progression to MM of about 1% per year.[3] The exact causes of MGUS development and progression to MM remain unknown. However, as noted above, genetic alterations may cause an increased expression of promoter genes or resistance to apoptosis, resulting in higher plasma cell proliferation and population. Under the "second hit" hypothesis, progression could also be a consequence of additional cytogenetic lesions gained by the original plasma cell clone, caused either by genetic instability or chromosomal abnormalities in the hematopoietic microenvironment.[4]

Regardless of the molecular driver, once there are excess monoclonal immunoglobulins, hyperviscosity, platelet dysfunction, and renal tubular damage can occur, leading to neurologic derangements, bleeding, and renal failure respectively. Bone marrow occupation by the expanding plasma cell clone usually manifests as anaemia, thrombocytopenia, and leukopenia. In addition, the interaction between myeloma cells and the bone microenvironment ultimately leads to the activation of osteoclasts and suppression of osteoblasts, resulting in bone loss. Several intracellular and intercellular signalling cascades, numerous chemokines, and interleukins are implicated in this complex process.[5]

HISTOPATHOLOGY

A bone marrow aspirate and biopsy are usually performed to estimate the percentage of abnormal plasma cells. This percentage is required in the diagnostic criteria for myeloma. The plasma cells seen in multiple myeloma have several possible morphologies. Firstly, they could take the form of a mature, normal plasma cell (a large cell, two or three times the size of a lymphocyte, with a single eccentric nucleus displaced by an abundant, basophilic cytoplasm). The Golgi apparatus typically produces a light-coloured area next to the nucleus, called a perinuclear halo. Secondly, they can have features of immaturity, such as low nuclear-cytoplasmic ratio, larger size, and loose chromatin (i.e.,a plasma blast). Other possible morphologies are bizarre, multinucleated cells, "flame cells" with fiery red cytoplasm, or Mott cells that show multiple clustered cytoplasmic droplets. The bone marrow is usually hypercellular and diffusely infiltrated by plasma cells. Rarely, plasma cells can be seen in peripheral blood (plasma cell leukaemia). Immunohistochemistry can detect plasma cells that express immunoglobulin in the cytoplasm and occasionally on the cell surface; myeloma cells are typically CD56, CD38, CD 138, CD319-positive, CD19, and CD45-negative. Clonality is confirmed by kappa or lambda light chain restriction.[6]

CLINICAL PRESENTATION

The presentation of MM is quite variable. It is typically more subacute and insidious in onset but certainly can present with severe symptoms. With that said, it is often seen in an older adult with some variation of constitutional symptoms or CRAB (hypercalcemia, renal dysfunction, anaemia, and/or bone pain with lytic lesions). In newly diagnosed MM, the following symptoms were most commonly anaemia (73%), bone pain (58%), elevated creatinine (48%), fatigue (32%), hypercalcemia (28%), and weight loss (24%).[6] More specifically, hypercalcemia caused by bone demineralization can result in increased thirst and urination, bone pain, abdominal pain, nausea or vomiting, and/or altered mental status. Renal failure resulting from light chain case nephropathy and/or hypercalcemia can lead to oedema, acidosis, and electrolyte disturbances. Anaemia develops likely secondary to bone marrow replacement, or decreased

erythropoietin levels can result in fatigue, pallor, palpitation, and worsening previous heart failure or angina. Bone pain resulting from the osteolytic lesions often results in pathologic fractures and vertebral collapse, reducing height, spinal cord compression, radicular pain, or kyphosis. Although rare, peripheral neuropathy and carpal tunnel syndrome may be present. If identified, further workup should be undertaken as this is typically more related to an underlying component of amyloidosis. Also uncommon, hyperviscosity symptoms may be present, including bleeding, confusion, neurologic symptoms, vision changes, or heart failure. Despite being rare, it is crucial to identify these findings as it is a medical emergency. Finally, MM patients seem to be more prone to infections, mostly pneumonia, and pyelonephritis, so assessing for recurrent illness is important.[6]

STAGES OF MULTIPLE MYELOMA

Monoclonal Gammopathy of Undetermined Significance (MGUS)-People who have MGUS harbour a small number of myeloma cells in the bone marrow, but these cells are not forming a tumour, and symptoms of the myeloma are not present. This condition is usually discovered during a routine blood exam that shows unusual levels of protein in the blood. MGUS is a pre-cancerous condition. Therefore, check-ups should occur every six months to monitor the condition and make sure that it does not develop into multiple myeloma, even though this only happens in a small number of patients.

Asymptomatic (smouldering/indolent) myeloma-Asymptomatic myeloma falls somewhere between MGUS and overt, symptomatic multiple myeloma. In this condition, a person has a greater number of myeloma cells than a person with MGUS.

However, the disease does not cause any damage to the body and the typical myeloma symptoms are not present, though patients may exhibit anaemia due to causes other than the myeloma. Asymptomatic myeloma can be stable for many months or years, but it ultimately tends to progress.

Symptomatic (active) myeloma-This type of myeloma represents overt cancer. A person with symptomatic myeloma has more myeloma cells than a person with asymptomatic myeloma or MGUS. At this point, the disease is causing damage to the body, like bone damage, anaemia, kidney problems, or hypercalcemia (high levels of calcium in the blood).[7]

Diagnostic Criteria for Multiple Myeloma[8]

Major criteria:

- Bone marrow plasmacytosis >30 per cent
- Plasmacytoma on biopsy
- Presence of a monoclonal protein (M-component) in serum or urine
- Serum IgG >3.5 g/dL, or
- Serum IgA >2 g/dL, or
- Urine Bence-Jones protein >1g/24 hours

Minor criteria

- Bone marrow plasmacytosis of 10 to 30 per cent
- A monoclonal protein is present but less than the above concentrations
- Presence of lytic bone lesions
- Reduced normal immunoglobulins to <50 per cent of normal
- IgG <600 mg/dL, or
- IgA <100 mg/dL, or
- IgM <50 mg/Dl

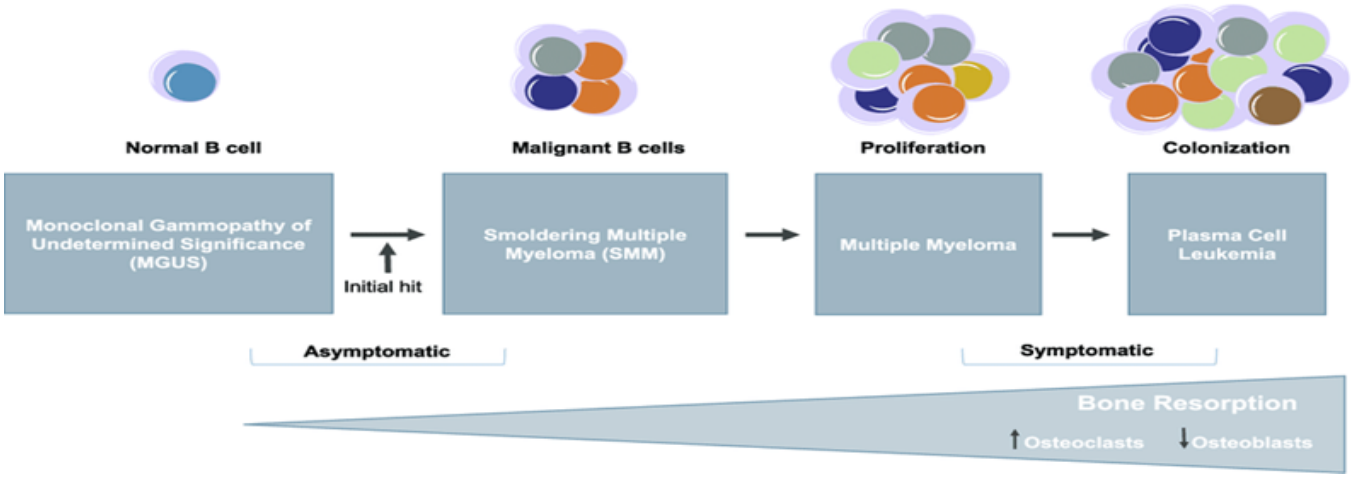


Fig. 1. Stages of Multiple myeloma (MM) progression. The malignant transformation of B cells occurs through a stepwise process involving multiple genetic aberrations and interaction of the B cells with the BM microenvironment. MM evolves from being asymptomatic to symptomatic through the acquisition of a fundamental genetic instability followed by further genetic and epigenetic changes to develop a diverse plasma cell clone with the oncogenic potential that enhances the bone resorption process throughout the disease progression stages. MM progresses from MGUS (Monoclonal gammopathy of undetermined significance) to SMM (smouldering multiple myeloma) followed by medullary and extra medullary MM to plasma cell leukaemia. fig.1[21]

Diagnostic requirements

The diagnosis of multiple myeloma requires a minimum of one major criterion and one minor criterion, or three minor criteria which must include bone marrow plasmacytosis of 10-30 per cent and the presence of a monoclonal protein. These criteria must be manifest in a symptomatic patient with progressive disease.

Besides the diagnostic criteria, the two authors have also devised a multiple myeloma classification system- DURIE AND SALMON STAGING SYSTEM[9]

Table 1[9]: Durie Salom Staging System

MM staging	Description
Stage I (all present)	Hemoglobin value >100 g/L (>10 g/dL) Serum calcium value normal or 3.0 mmol/L or less (12 mg/dL or less) Bone x-ray: normal bone structure or solitary bone plasmacytoma only Low M-component production rate (IgG value <50 g/L [<5 g/dL]; IgA value <30,000 mg/L [<3 g/dL]; Bence Jones protein <4 g/24 hours).
Stage II	(neither stage I nor stage III)
Stage III (one or more present) Stage IIIA – normal renal function Stage IIIB – abnormal renal function	Hemoglobin value <85 g/L (<8.5 g/dL) Serum calcium value >3.0 mmol/L (>12 mg/dL) Advanced lytic bone lesions (>3) High M-component production rate (IgG value >70 g/L [>7 g/dL]); IgA value >50,000 mg/L [>5 g/dL]; Bence Jones protein >12 g/24 hours).

AYURVEDIC VIEW

The aetiology of Multiple Myeloma is poorly understood. The risk factors that play a major role in malignant diseases, such as tobacco consumption and diet, have not been found strongly involved in multiple myeloma aetiology. Nevertheless, some consistency seems to be in the findings about a risk elevation with age and obesity.

Despite some contradicting results, indications of the role of ionizing radiation persist. Also, infections with HIV and Hepatitis C virus appear related to an elevated multiple myeloma risk. Currently, large efforts are being undertaken to unravel the aetiology of malignant lymphoma including those of multiple myeloma. [10]

A risk factor is anything that increases a person's chance of developing a disease. For instance, in Multiple myeloma, although risk factors often influence the development of cancer, most do not directly cause cancer. Some people with several risk factors never develop cancer, while others with no known risk factors do. Although the mutations that cause myeloma are acquired and not inherited, family history is a known risk factor for multiple myeloma. First-degree relatives of people with multiple myeloma have a 2 to 3 times higher risk of developing the disease. The factors which can raise a person's risk of developing myeloma are age, race, radiation exposure, and exposure to toxins and chemicals.

This above explanation about the dilemmatic aetiology and risk factor of multiple myeloma finds a difficult roadmap to be traced to arrive at a clear *samprapti* of this disease in Ayurveda, however, few conclusions were derived from the available correlations, literature reviews, and commentaries of the major *samhitas* of Ayurveda. As per Ayurveda, Arbuda (cancer) is one of the most asadhya vyadhi in the 20th century and spreading further with continuance and increasing incidence in the 21st century. The word Cancer is derived from the Greek meaning 'CRAB'.

Cancer is not a new term in Ayurveda. It had already been described by the great trio of our acharya such as charaka samhita, sushruta samhita, and ashtanga hridya. The father of Indian surgery Acharya Sushruta mentioned granthi and arbuda, as having a resemblance with cancer. Cancer as inflammatory or non-inflammatory swelling has been mentioned as either Granthi (minor neoplasm) or Arbuda (major neoplasm).

A matter of fact that not all advanced aged population develop multiple myeloma, not all those exposed to radiation, toxins, and chemicals develop multiple myeloma, and not all the family members of an afflicted individual develop a susceptibility to Multiple myeloma, the concept of *Vikara Vighata Bhava Abhava* by Chakrapanidutta in his commentary provides a justifiable correlation

CONCEPT OF VIKARA VIGHATA BHAVA ABHAVA PRATIVISHESHAS:

According to *Ayurveda* presence of *nidana* (causative factor), *dosha* (three humours of the body), and *dooshyas* (*dhatus/upadhatus/malas*) is essential for the manifestation of a disease. But the presence of these three is not an absolute assurance for the manifestation of a disease. The presence or absence of a fourth factor called *Vikara Vighata* Bhava will decide the occurrence and non-occurrence of a

disease in an individual. Acharya Charaka explains like "manifestation and the non-manifestation of a disease depends upon the *prativisheshas* of *Nidana, Dosha, Dooshya* and *Visheshas* towards *Vikara Vighata Bhava* and *Vikara Vighata Bhava Abhava*. A factor that inhibits/hinders the manifestation of a disease in an individual is known as *Vikara Vighata Bhava.* In the absence of *Vikara Vighata Bhava* manifestation of a disease is possible easily. [11]

Nidana vitiates *dosha* only when it gets *anubandha* with *dosha. Anubandha* between *nidana* and *dosha* is possible only when *nidana* and *dosha* are homogenous in terms of *Dravya, Guna, Karma,* and *Prabhava*. Similarly, *dhatushaithilyam* and *khavaigunya* is the prerequisite for the *dooshyas* to get associated with vitiated *doshas*. In the presence of *Vikara Vighata Bhava* association between *Trayonidanadi Visheshas (nidana, dosha,* and *dooshyas*) is not permitted. This leads to the non-manifestation of a disease.

Sometimes *anubandha* of *nidanadi visheshas* happens after a long gap (*Kalaprakarshyad Anubadnanti*) when the person repeats the consumption of the same *nidana*. This is due to the existence of similarity between *kala* and *dosha* or *hetu* and *dosha* as time passes. This leads to the delayed manifestation of a disease. Whenever *nidanadi visheshas* encounter *Vikara Vighata Abhava, anubandha* between these three factors happens very fast and leads to the early manifestation of a disease. The absence of *Vikara Vighata Bhav*a causes pre-existing *dhatushaithilya* and there causes severe vitiation *in dooshyas*. This leads to the manifestation of severe disease *(Asadhya/Kastha Sadhya Vyadhi*) and may lead to complications. [12]This interplay of *trayo nidanadi visheshas* and *vikara vighata bhava abhava* could be the probable reason for the manifestation of Multiple myeloma in only some individuals with risk factors.

DISEASE-SPECIFIC SAMPRAPTI

The cardinal feature of Multiple myeloma is anaemia, bone pain and lytic bone lesions. From an *Ayurveda* point of view, these conditions have proximity to *Pandu roga* and *asthi kshaya*. Those individuals with *vishesha nidana seven* of *pandu roga* and *mithya ahara vihara* specific to *pandu roga* will have the *pitta pradhana tri dosha* in their bodies. The vitiated *pachaka pitta* along with *kledaka kapha* leads to *agni mandhya*, leading to *amarasa utpatti*, causing *rasa dhatu dushti*. Ill-formed rasa dhatu would be incapable of forming healthy *rakta dhatu* thereby decreasing the production *of rakt*a and *rakta kshaya* sets in. Also, there will be vitiation of *sadhaka pitta* located in the heart and abnormal functioning of heart activity would lead to aggravation of *vyana vayu*. This aggravated *vata* will cause the *Vimarga gamana* of *pitta* and lodge it on *twak mamsantara*.*Rakta kshaya* would lead to vitiation of *Uttarottara dhatus* by virtue of *anulomana kshaya*.

Prolonged *sthilitha* of *dhatus* due to lodged *pitta* in between them results in *kshaya* of *bala*, *varna, sneha* and *ojas*. There will be *alpa rakta, and medas* inside the *asthi dhatu*s and this hampers the erythropoiesis, further reducing the production of *rakta* from *asthi majja*. As the disease progresses, it will affect *majja dhatu* and manifest as *asthikshaya* and *asthi soushirya* which is manifested as osteoclastic activity and punched-out lesions within the bone. This increases the porosity of bones which leads to multiple fractures- *bhagna*.

To have a proper interpretation of the *Samprapti* of *asthi kshaya*, apart from the normal *vata prakopa nidana*, the main factors for the materialization of the disease, *srotopradusaka nidanas* of *medovaha*, *asthivaha, majjavaha* and *purisavaha srotas* should not be neglected, as they also play a definite role, either directly or indirectly in the pathogenesis of *asthi kshaya*. The proper functioning of *jataragni, bhutagni, dhatwagni* is essential for the *samyak dhatu posana prakriya*.

Functional deformity in any of these *agnis* especially the *dhatwagni* leads to the *vikruti* in the transformation *of posaka dhatu* into *posya* or *sthayi dhatu*, resulting in *dhatuvikruti*. Hence, an adaptation of the principles of *dhatu posana krama* has a key role in the manifestation of disease.

Ayurveda classical textbooks described *asthi-kshaya* mentioned under *dhatu kshaya*. Acharya Charaka described eighteen types of *kshaya* in *adhyaya - kiyanta shirashiya – sutrasthana*. The disease and its pathology can be understood by *ashraya-ashrayi bhava*- the relationship between *asthi* and *vayu* is called "*Asrayasrayi Sambandha*". [13] When *asthi kshaya* occurs there will be aggravation of *vata* which will be responsible for the excessive multiplication of plasma b cells, dislodgment of the formed blastomas and producing complications. Why *vata* only provokes the excessive multiplication of plasma b cells is answered by justifying that the earlier *pandu roga* that had set in leads to depletion of *rakta* and *medas* within the *mahat asthi* and thereby producing more of *kitta bhaga* of *rasa* and *rakta* i.e *mala roopa kapha* and *pitta* which can be co-related to monoclonal immunoglobulins.

Acharya Dalhana opines that the causative factors responsible for the vitiation of *purishavaha srotas* are also responsible for *asthikshaya indirectly through vata vitiation*. Thus all those factors responsible for *agni vaishamyam* will cause *purishadhara kala* deformation and affect the *asthi dhatu* where *sthana samshraya* of Multiple myeloma takes place. Acharya Dalhana has considered purishadhara kala same as Asthidhara kala(*Dalhan tika susrutha samhitha*

commentator Dr Ambikadatta Sastri) Vegadharana (suppression of natural urges) is often overlooked as a primary cause of many acute and chronic ailments[14]. It can be habitual or oblivious. It separately or simultaneously impacts the chemical, cellular, tissue, organ, and organ system, of the structural organization of the human body. Suppression of urges creates defective and improper signalling in the autonomic nervous system and hence makes way for causing diseases. Exposure to air pollution, second-hand smoke, radon, ultraviolet radiation, asbestos, certain chemicals and other pollutants cause over 10% of all cancers.[15]

Cumulative evidence from across the globe shows that exposure to environmental pollution, and radiradiationld escalate the susceptibility to the impaired functions of cancer regulatory genes within humans and bodies which would pave the way to developing malignant conditions including Multiple myeloma.

In the absence of *nidanas* contributing to *vishama agn*i at *jathara* and *dhatu* level, the role of *beeja bhaga avayava dushti* has to be thought of since whenever *sthana samsraya* occurs there is a legacy of *beeja dushti* behind the pathology.

UNDERSTANDING THE GENETIC INHERITANCE OF MM FROM AN AYURVEDA POINT OF VIEW

Ayurveda, the ancient Indian medical system has given due emphasis on therapeutic intervention to prevent and manage congenital malformation. The conglomeration of *Shadgarbhkarabhavas* such as *matrija*, *pitrija*, *aatmaja*, *rasaja*, *satmyaja* and *sattvaja*, these procreative factors are a must for healthy progeny.[16] Each procreative factor is assigned with a certain organogenesis/functional/psychological phenomenon, during its intrauterine life. Negligence towards any of these factors becomes a cause for unhealthy and defective childbirth. Data reveals that 30–50% of post-neonatal deaths are due to congenital malformations and 15% per cent of all cancers have an inherited susceptibility.[16] Sometimes mutations in DNA can cause changes in the way a cell behaves. Mutations can be inherited; this means that if a parent has a mutation in his or her DNA, then the mutation is passed on to his or her children. This type of mutation is called a germline mutation. Other than these mutations, epigenetics is also responsible for congenital and genetic abnormalities. Epigenetic mechanisms are influenced by several factors and processes including development in utero and childhood, environmental chemicals, drugs and pharmaceuticals, ageing and diet. [17]

In the process of DNA expression, the two strands of DNA separate, and the knowledge present in the strand is replicated and comes out as messenger ribonucleic acid (mRNA). The knowledge carried in mRNA is then utilized by transfer RNA (tRNA), which lines up the designated amino acids to form the specified protein. It is proposed that mRNA, tRNA, and rRNA proteins have features and properties that represent *Vata, Pitta, and Kapha* at the cellular level. Hence it could be postulated that Messenger RNA corresponds with *Vata* (transmission of information), tRNA corresponds with *Pitta* (transformation), and protein corresponds with *Kapha* (structure). [18]

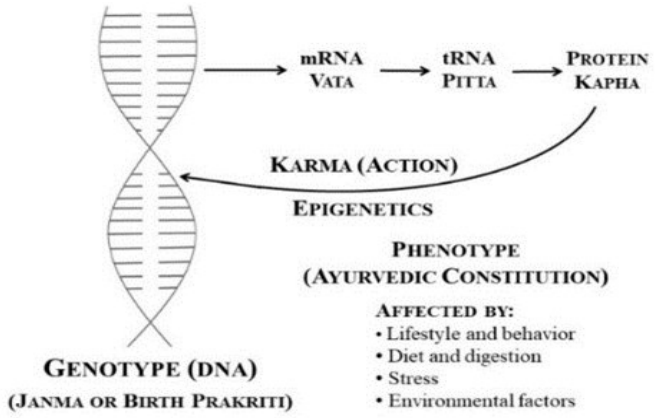


Figure 2: DNA and cellular function and correlation with Ayurveda. mRNA, messenger ribonucleic acid; tRNA, transfer ribonucleic acid; DNA, deoxyribonucleic acid. Modified and reprinted from [1], with permission from Select Books, 2018[18]

The instability of mRNA is the driving force for the defective action of tRNA as well as proteins. It must be noted that although proteins are only structurally attributed to *kapha*, the *karmas* of those proteins are a result of the messenger RNA which imbibes each of their functions. Any deviation in the normal physiology of the interplay among these at the level of *rasa dhatu*, *ojas,* and *agni* both *jatharagni* and *dhatwagni* would be aiming toward generating a pathology that is common for any genetically inherited diseases or congenital malformations.

LAYING THE STEPPING STONE

Normally growing cells in an organ are related to the neighbouring cells-they grow under growth controls, perform assigned functions and there is a balance between the rate of proliferation and rate of cell death including cell suicide (i.e. apoptosis). These normal functions are carried out by 4 regulatory genes such as proto-oncogenes, anti-onco genes, apoptosis regulatory genes and DNA repair genes. Thus, normal cells are socially desirable. However, in cancer, the transformed cells damage the normal cell controlling using activation of growth-promoting oncogenes, inactivation of cancer suppressor genes, abnormal apoptosis regulatory genes and failure of DNA repair genes. Thus, it can be well said that cancer cells exhibit anti-social behaviour.[19] This is exactly what occurs in that one single clone of plasma cells in bone marrow leading to MM.

Multiple myeloma (MM) is a plasma cell malignancy in which monoclonal plasma cells proliferate in bone marrow, resulting in an overabundance of monoclonal paraprotein (M protein), destruction of bone, and displacement of other hematopoietic cell lines. Myeloma begins with one abnormal plasma cell in the bone marrow that fills the bones. The abnormal cell then multiplies rapidly, instead they accumulate. This primary pathology can be correlated to the *atipravrutti* of that one cell inside the bone marrow. The culprit behind this action can be attributed to the failure of mRNA to be able to cease the proliferation from one to numerous ones or rather mRNA stimulating overproduction. As mentioned above the DNA strands getting separated, the knowledge present in the strand is replicated and comes out as messenger ribonucleic acid (mRNA). *Atipravrutti* of that one cell mRNA can also be understood as the *smriti bhramsa* of that cell to act normally. The provoking factor can be either an environmental change, exposure to toxins and chemicals, or genetic inheritance since the aetiology of multiple myeloma is unknown.

Pravartana is the function of *vata dosa* hence *atipravartti* is the *prakupita swarupa* of *vata* rather than mere *vruddha avastha*. Prakupita vata creates havoc in the dhatu i.e., *"kopastu unmarga gamita*". This results in impairment in the functions of other *doshas* causing defects in other *dhatus* as well. Why *asthi majja* is targeted here is because here the *sthana samshraya* is attributed to beeja dushti and beeja bhaga avayava dushti of asthi majja primarily. Later in bheda avastha other dhatus are affected and get deteriorated. This is the basic *samprapti – "yatha dushtena doshena"* of multiple myeloma. What happens because of this monoclonal plasma cell proliferation in bone marrow i.e.- "yatha cha anuvisarpatha" determines the secondary manifestations affecting multiple organs posing MM as one of the grave diseases.

RISK FACTORS AND THEIR CONTRIBUTION TO DISEASE MANIFESTATION

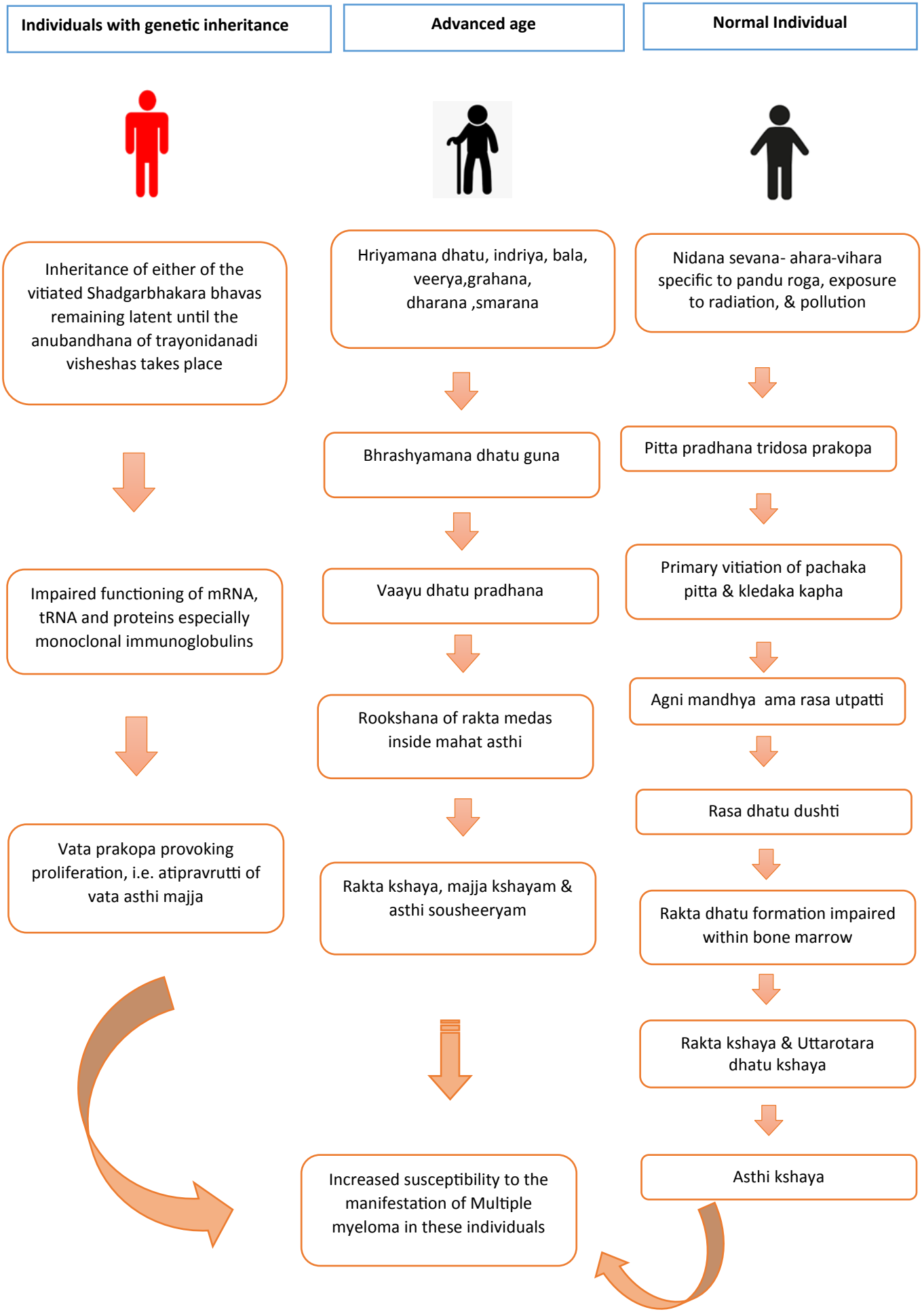
The risk factors of multiple myeloma as per modern literature include advancing age above 50, obesity, environmental changes, radiation exposure etc so considering the first risk factor i.e age- from Charaka Samhita *sareera sthana*, Acharya Charaka states that when *vardhakya* sets in i.e. 60 years and above there is depletion in *bala* of *dhatu*,*indriyas*, ojas i.e vitality and virility, there is a progressive deterioration of the structural entities inside the body and hence *vata dosha* occupy the prime position in this age criteria. This must be borne in mind while considering any diseases related to age above 60 years as per ayurveda classics and multiple myeloma is no exception. The second important risk factor that can be considered is obesity which, in Ayurveda is considered as "*Sthaulya*" a condition wherein there is an abnormal increase in *vaikruta medodhatu*. In *Sthaulya* there is obstructive pathology where the excessive increase of *meda* cause obstruction of *strotas* and nutrition of further dhatus is hampered. *Dusti* of *agni, rasavaha srotas,* and *rasadhatu* initiates the formation of ama which affects *dhatvagni* by causing *srotoavrodha. Sanga* due to *avarana* either caused by *medo vrudhi* or accumulation of ama would deprive the *rasa dhatu* to nourish the *rakta dhatu* and so on resulting in less nourishment to the *asthi-majja dhatu* and going in hand with the MGUS stage of multiple myeloma. Exposure to radiation and toxins can be understood by pitta pradhana tridosha dushti as explained earlier in correlation with pandu roga.

UNDERSTANDING SECONDARY MANIFESTATIONS IN MULTIPLE MYELOMA

Atipravriti in *rasavaha srotasas* by v*ata prakopa* due to age advancement might be leading to over production of plasma cells as in the smouldering stage of MM thereby producing *lakshanas* depending upon the dosha *utkleshana avastha. vaikruta dhatu poshana which propels the production of vaikruta rakta dhatu from rasa causing anaemia as explained earlier. Atipravrutti* activity of *srotas* can be considered as the intercellular and intracellular signalling cascades altering the microenvironment of the *koshta*. In Multiple myeloma predominant symptom is bone pain due to the osteoclastic activity by neoplastic plasma cells i.e correlatable to *Vata kopa* in its place – *Asthi*, causing *rookshna* of *rakta* and *meda* inside *mahat asthi* causing *rakta kshayam*- anaemia, *bhrama*, *timira darshanam - majja kshayam,asthi sousheeryam*- bone pain, pathological fractures, hypercalcemia. The *vata prakopa lakshana sramsa*- hampered activity,*vyadha*- destroying nature,*varta*-producing round shaped substances in the viscera or lumen,*parushya*- drying up of *sneha dravya* in the body or *koshta,soushirya*-developing cavities or porosity leading to *dhatu kshaya* is important to be considered.

Ayurveda vyadhis like *arbuda, rakta arbudam,asthi granthi, asadhya vidradhi, pandu* and vatarakta can be found to be having to share the *nidana samprapti* with multiple myeloma in one or the other way. Multiple myeloma can be related to *Pandu roga* since it manifests as *rakta kshaya* in the MGUS stage- the early stage itself, so also the main pathology takes place in *majja* where erythropoiesis takes place. It can also be related to *vata rakta samprathi* which also can be closely related to an acquired mutation happening in cells leading to *gambheera vaikruta avastha of dhatu*.

Flowchart of Samprapti- Multiple Myeloma



Many of the *Vaidyas* opine about a weakening of the *dhatu agni* (weakened metabolic strength of the tissue in which cancer originates) as important in the development of cancer. The *samprapti* (pathogenesis) occurs due to various causes, such as repeated exposure to environmental toxins, which are *pitta*-provoking factors at the deeper cellular level. The increased *pitta* at the cellular level can cause micro-inflammatory changes, which disturb the cellular components of *agni* called *pilu agni* and *pithar agni*. *Nyaya Vaisheshikas* state that all changes at the macroscopic and microscopic, organic and inorganic level are due to pakas i.e. chemical actions brought under the influence of *Agni*. Thus impaired *pilu agni* and *pithara agni* produces poorly formed *dhatus*. This implies that deranged *jatharagni* and *dhatwagni* lead to the accumulation of *dhatu mala* within the *srotas* rather than being excreted from the body.[20]

The *dhatu mala* accumulation is related to not only the accumulation of Bence Jones proteins but also to hyperviscosity, platelet dysfunctions and tubular damage, hypercalcemia and the inability of kidneys to excrete them. Cancer is closely related to *granthi* and *arbuda*. The *nidana sevanas* like *virudha dushta gara upasrushtra annam, achesta* causes *tridosha dushti* invading the *shasti dhara kala- rohini* causing *granthi, apachi, arbuda* etc diseases. Acharya Sushruta while narrating the aetiology of *rakta arabudam* stated that aggravated dosha causes *sampeedana,sankocha* of *siras* aiding the *aashuvrudhi* of *rakta kshaya* and developing *upadravas.*[22] *Asthi granthi* is favourable to consider as there are recurrences of multiple fractures and injuries to the bone in Multiple Myeloma. Since there are hypercellular and diffusely infiltered plasma cells in bone marrow it is similar to the presence of *salya* inside *asthi majja* causing life-threatening distress to the MM-afflicted patients which are rightly mentioned in Sushruta nidana in the context of *asadhya vidradhi*.

In *Ayurvedic* pathogenesis, *vaikruta vata* is the active *dosha* and it is involved in the progression of metastasis. *Vaikruta kapha* being heavy and gross is responsible for the abnormal growth of the cells creating the malignant tumour, and the *tejas* component of *vaikruta pitta* enhances the metabolic activity of the cancerous cells. According to *Ayurveda*, cancer is a *tridoshic* disorder which can spread due to the interplay of abnormal *vata*, *pitta*, and *kapha*. Although it is a *kapha*-predominant disease there is always an association of *vata*, because the multiplication of cells cannot go in excess without the imbalance of *vata* in it and the *dhatu agni* (metabolic rate of the tissues) is diminished.

SHATKRIYAKALA FRAMEWORK OF MULTIPLE MYELOMA

SANCHAYA: Early stages of neoplastic changes i.e., when the growth is only localized.

Sanchaya, the first stage of *kriyakala,* describes the collection or accumulation of *doshas* due to various causative factors. In this stage, *doshas* are accumulated but do not leave their place i.e. *vata* builds up in the bones, *pitta* in the blood and *kapha* in the lymph and muscles. The symptoms in *the sanchaya* stage are due to increased *doshas*, but not due to any disease. The aetiology of *sanchaya* can be of either *kala swabhava* (natural) or *trividha hetu* (three causative factors). [23]

The three causative factors are *prajnaparadha* (misleading), *astamendriyartha samyoga* (improper use of sensory organs) and *vyapanna hetu* (inherent cause), which include seasonal changes, day-night changes, and changes

TABLE 2: COMPARING THE PATHOLOGY OF MULTIPLE MYELOMA AT THE DHATU LEVEL

DHATU	**DERANGEMENTS IN PATHOLOGICAL STATE ON MULTIPLE MYELOMA**	AYURVEDA VIEW
RASA	-Overproduction of plasma cells, crowding out in bone marrow, -formation of excess proteins like interleukin 6, M protein, cytokines and antibodies, hyperviscosity	-*Agni sadanam*, production of *vikruta rasa* leads to production of *mala* -*Gaurava, alasya* at the cellular level can be correlated to hyperviscosity
RAKTA	-Angiogenesis is a constant hallmark of multiple myeloma (MM) progression -involves direct production of angiogenic cytokines by plasma cells -their induction within the bone marrow microenvironment.	-diminished *dhatwagni* -hampered *parinama* of *rasa* to *rakta dhatu* -causes *sira shaithilyam* and *rookshata*
MAMSA	-impairment in glycan binding proteins -Pain, weakness, and numbness or tingling	-*anga glani, sandhi vedana*
MEDAS	**-** MM cells induce lipolysis in BM adipocytes. -The released FFAs are taken up by myeloma cells through fatty acid transporter proteins, leading to growth or lipotoxicity.	-*krushangata* probably due to lipolysis
ASTHI	-osteopenia, osteolytic bone lesions and fractures	-*asthi toda, shatanam*
MAJJA	-bone marrow is usually hypercellular and diffusely infiltrated by plasma cells	-*sousheeryam*

in food and regimen. This stage can be diagnosed easily based on specific symptoms like accumulation of *vata, pitta and kapha.*[24]

PRAKOPA:Transformation of primary growths into metastatic tumours i.e., invasion.

In the *prakopa* (vitiation) stage, the accumulation stage has persisted for a long time and the responsible factors have been continuously present. This stage occurs while the *dosha* is ready to move from their place to another. Based on this observation, it is assumed that the *prakopa* stage is developed due to continuous intake of improper *Ahara* (food), *Vihara* (regimen) and *Aushadha* (medicine). The *dosha vriddhi* (increase in biological humours) occurs in a liquid state at its place, which is of two types, i.e., *Chaya purvaka* and *achaya purvaka prakopa. Chayapurvaka* describes reaching *Prakopa* after passing through *Sanchaya*, whereas *Achayapurvaka Prakopa* is characterized by reaching *Prakopa* without prior accumulation. In *Achayapurvaka Prakopa*, although *doshas* become abnormal, the damage caused by these abnormal *Doshas* can be curable.[25]

The *prakopa* stage can be diagnosed based on continuous *chaya lakshanas* (features of aggravated biological factors), desire for opposite *gunas* (fundamental attributes) and aversion to similar *gunas*, as well as based on common symptoms like a subluxation, breakdown of function, fatigue and pain at a particular cancer site.[23]

PRASARA: Metastasis (in the development of cancer stage of invasion is followed by metastasis)

Prasara is a stage of spreading, in which the causative factors continue and *the prakopa* stage has affected the Doshas. In the *prakopa* stage, the *doshas*, which have remained in place so far, become ready to move. The *doshas* overflow and spread or move to other areas or organs of the body. The pathogenesis of *the prasara* stage has been described in most of the Samhitas (ancient texts) due to its significance in the manifestation of a disease.[26]

In this stage, doshas spread all over the body starting from the head to toe. *Pitta* and *kapha doshas*, as well as *dhatus and malas*, are inert substances and can be increased in quantity but cannot move from one place to another. *Vata Dosha*, on the other hand, helps to move *Pitta*, *kapha, dhatus and malas* to other places. Thus, it appears that the *vata* is a key factor that mediates the *prasara* stage in the cancer manifestation process and pitta is the substantiating factor for its speedy progressive nature. In this stage, the vitiated *doshas* continuously spread outside of their normal sites unless the causative agent is treated. However, failing to treat causative factors at this stage can lead to irreversible pathogenesis. In the p*rasara* stage, a diagnosis can be made with the help of clinical involvement.[26]

STHANA SAMSRAYA: The stage when metastasis is complete, and secondaries developed at another place outside the place of origin of the tumour.

Sthanasamsraya (localization) or the settlement of *doshas* at a particular place occurs when vitiated *doshas* are circulating and settle in areas of *srotovaigunya*. Certain causative factors which have enough potential to cause damage are responsible to settle *doshas* at a particular site. There are only a few sites, called *khavaigunya* (weak or defective sites), which are prone to the settlement of *doshas.* These weak or defective sites may have tissue depletion or certain disturbances in their normal surface.[27]

Furthermore, a specific causative factor may have an affinity towards channels or tissues, which leads to a defective site and the manifestation of a disease. It is assumed that an exogenous factor itself by triggering doshas causes tissue depletion which can be called the foundation of a disease. Besides, if *khavaigunya* already exists at the time of *dosha Prakopa* (perhaps due to *dhatu kshaya* or depletion of body tissues), in such conditions, the Doshas may cause any kind of disease. In such conditions, the union of *doshas/dushyas* at a particular site is called *sthanasamsraya.* Since this is a seeding stage of cancer, a complete picture of cancer does not appear in this stage. However, based on *purvarupas* (prodromal symptoms) of a particular disease at a particular channel, the disease (including cancer) can be diagnosed.[27]

VYAKTI: The stage where clinical signs and symptoms of neoplasm are expressed (usually many tumours remain asymptomatic and obscure till late stages).

If the causative factors present in *Sthanasamshraya* are not treated and continue to cause the disease, *dosha* enters into the *Vyakti* (manifestation) stage, in which all the symptoms of cancer appear. In other words, during the manifestation stage, all symptoms appear on the surface of a cancer site. Hence, *Vyakti* is the stage where disease manifests itself completely. A particular disease depends upon the vitiation of a particular *dosha* and the interaction of a particular *dhatu*, as well as the extent of their mixture. The symptoms that appear at this stage are used by medical professionals to examine and diagnose cancer, which helps in developing a treatment plan.[28],[29]

BHEDA: The stage where differentiation of growths is made into specific groups based on histopathology.

Bhedha is the final stage where the progression of the disease reaches an end. Complications may bring about other diseases and finally may lead to death. In this stage,

multiple myeloma is usually diagnosed by its complications; However, in *Bhedha,* the survival rate is generally decreased.[29]

DISCUSSION

Plasma cell disorders represent a constellation of hematologic diseases characterized by clonal hematopoiesis of B-cells and the over-production of monoclonal proteins. Multiple Myeloma accounts for approximately 17% of all hematologic malignancies and often presents with end-organ dysfunction such as hypercalcemia, renal dysfunction, anaemia, bone pain, and significantly impaired quality of life. The precursor states of MGUS and SMM may be asymptomatic; however, symptoms of neuropathy, fatigue, and reduced quality of life may be present. Patients newly diagnosed with MM are often treated with proteosome inhibitors, Immunomodulatory agents, steroids, CD 38 directed monoclonal antibodies, and autologous stem cell transplant, if eligible. Therapy-related side effects including fatigue, peripheral sensory neuropathy, diarrhoea, nausea, and psychosocial disruption are prevalent during induction therapy. The expanding armamentarium of MM therapeutics has improved patient survival substantially however, the chronicity of treatment with multiple therapeutic targets often leads to debilitating symptoms and reduced quality of life. While supportive care medications are helpful, the addition of other medications creates the potential for additional adverse events and may have poor efficacy. As such, MM patients often experience decades of unrelieved symptoms, leaving a large unmet need for symptom control in the patient population.

Integrative oncology is the combination of complementary medicine in conjunction with conventional cancer treatment and is developing as a supportive care modality in cancer treatment. It is a patient-centred, evidence-informed field that uses mind and body practices, natural products, and lifestyle modifications from multiple traditions alongside traditional cancer treatment to optimize health, quality of life, and clinical outcomes.[30] With modern medicine hopping to the integrative approach making use of immune-modulating agents and neutraceuticals for disease prevention and ceasing the progression, Ayurveda principles have plenty of answers to provide. But this is possible only if the disease understanding is made thorough. Hence it is the need of the hour for the Ayurveda population to express their reviews and understanding from all possible vents of discussions and to bring a treatment modality for the careful management of Multiple Myeloma Ayurveda.

LIMITATIONS

Treatment of multiple myeloma has galloped over the period as the one with myeloma a decade back was nothing short of a dead end. But in the current scenario with the advancement of science and technology and advents of modern medicine, there have been chemotherapies, blood transplantation and monoclonal antibodies being administered to suffering patients with a possibility of finding remission. Very recently modern medicine also started administering immune-modulating agents to combat the disease progression and to improve the quality of life. This provides a ray of hope as Ayurveda has got its speciality of enhancing the so-called *vyadhi kshamatva* i.e. immunity inherited and acquired, for the elimination of causation of disease and breaching of disease pathology. But not all treatment modalities could be easily and comfortably administered to the sufferers as this disease would announce itself in the *vruddha avastha* i.e 50-60 years by the time of which the *samprapti* anchors itself deep enough, spreading to the *saptadhatus* leading to profound *dhatu kshaya* and *ojas kshaya*. It is therefore difficult to administer the panchakarma therapies to the patients owing to their weakened *dhatu* and *kshaya avastha*. Administering the bahya kriya karmas would make the patient prone to multiple fractures- *asthi bhagna*, worsening the condition. It is therefore the biggest challenge for the Ayurveda fraternity to find a cure for Multiple Myeloma. This paper provides a thorough understanding of the disease, to be able to select appropriate measures and interventions either in the form of internal or mild external therapy. Considering the dosa pradhanatva and dhatu pradoshaktvam mentioned elaborately in this review, would help find drugs and formulations of choice in this disease.

Conclusion

The role of *jatharagni, dhatwagni* and *khavaigunya* due to multiple factors including *sahaja nidanas* emphasises the correction of various *agni* and *srotas* at the subtle level. By this, the process of *dhatu parinama* from *rasa* to *rakta* can be modified and corrected. The importance of periodic *shodhana* and *vidhivat prayoga* of *rasayanas* can reduce the disease progression, thereby improving the Quality of Life of patients with multiple myeloma. Interventions according to *kriyakalas* – stages of disease progression is also a treatment concept exclusive to *Ayurveda.* Clinical knowledge however excellent always demands a proper understanding of the disease hence this article summarises a comprehensive *samprapti* of Multiple myeloma. Initially, *Vata i*s the most influential factor *(vimargagamana and atipruvrutti*) that initiates a pathway to cancer; *Pitta*

however is responsible for the rapid progression (multiplication) of cancer. Finally, *Kapha (sanga)*stands in the way of derangement in the normal structural units.

Cancer has become a major challenge and concern for biologists and physicians not only due to problems in treatment but more so due to its increased prevalence worldwide. The growing knowledge about the nature of the disease with the help of modern science and technology has not been translated to great benefits in control or treatment. Nevertheless, tremendous progress has been made in understanding the complex pathological process and thus the diagnosis of cancer seldom remains speculative.

To understand cancer and leukaemia, in its proper perspective, and then in the context of Ayurveda, there have not been serious attempts due to innate difficulties. In addition, despite advances in oncology, *Ayurveda* physicians remain isolated in their understanding of cancer. Modern medical pathology has taken a quantum leap in the precise diagnosis of leukaemia, especially with developments in human genetics.

The scientific research in the field of medicine and other allied systems has not been very rewarding to *Ayurveda*. The difficulties mainly relate to the problem of arriving at a diagnosis due to the absence of definitive methods and facilities for such studies, and the lack of understanding of the pathology, pathogenesis, and histopathology from an Ayurveda point of view. Clinical knowledge however excellent always demands a proper understanding of the disease hence this article summarises a comprehensive *samprapti* of Multiple myeloma.

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