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EARLY DIAGNOSTICS OF ONCOLOGICAL DISEASES IN THE EXAMPLE OF MULTIPLE MYELOMA: MODERN TECHNOLOGIES

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Abstract

In modern times, where oncological diseases are prevalent in this fast-paced society and thus forming a great challenge to healthcare settings, a very common form of such malignancy is Multiple myeloma affecting millions of individuals. It is a type of plasma cell clonal proliferative disorder that predominately affects the bone. Other systemic complications such as anemia, renal dysfunction, lytic lesions in bone, and immunosuppression. Misdiagnosis or diagnosis at an advanced-stage is very common scenario due to the insidious onset as a result of the nonspecific nature of its symptoms. The emphasis of this study is on early diagnosis by combining clinical assessment, laboratory markers such as serum protein electrophoresis, immunofixation, and free light chain assay, advanced imaging modalities including MRI, PET-CT, and low-dose whole-body CT. Thus, better prognosis due to early diagnosis by new biomarkers and genetic profiling is attributed to timely initiation of targeted therapies, lesser complications, and improved overall survival rates and quality of life.

Keywords

Multiple myeloma, early diagnosis, oncological disease, hematologic malignancy, plasma cell disorder, biomarkers, MGUS, PET-CT, serum protein electrophoresis, bone marrow biopsy.

Introduction

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Multiple myeloma is most common type of primary bone neoplasm and chief plasma cell dyscrasia (paraproteinemia). It is responsible for 45% of all bone tumors [1], 1.8% of all malignancy, and 1% cancer deaths in western world. Higher incidence in older male adults (69 years as median age of diagnosis) and in African decent have been noted. Bony lesions are one of the commonest features of this disease. Degradation of bone tissue is a contributor to advancement of illness and disease. If untreated, patients with multiple myeloma rarely survive for more than 6 to 12 months. It is extremely important to diagnose it at early stage as that may increase patients' survival rate and life span. Also, early diagnosis of other forms of myeloma holds high importance. The other types of plasmacytoma presents with nonspecific symptom, weight loss, lymphadenopathy, fatigue, making it hard to diagnose. Approximately 75% Patients of smoldering myeloma may progress to multiple myeloma over a 15 years period [5]. Similarly, 10 to 20 years or longer time period it may take for Solitary osseous plasmacytoma to progress to multiple myeloma. Approximately 1% patients of Monoclonal gammopathy of undetermined significance develop multiple myeloma per year. Progression of these variants to multiple myeloma is unpredictable, early diagnosis and monitoring becomes a necessary for a better prognosis and deciding Treatment methods.

Etiology

Genetic predisposition, ionizing radiation exposure such as nuclear warheads in WW2, chemicals like benzene are some risk factors. Neoplastic plasma cells secrete monoclonal Ig or ig fragments which serve as tumor marker. It is a malignant proliferation of single clone of plasma cell (M protein). Trisomy of 3,5,7,9,11,15 and translocation in 14q32 including t(11;14) (q13;32) are common genetic abnormalities. Apart from these, deletion of 13q14, 17p containing TP53 tumor suppressor locus, rearrangements of cycling D1, D3, severe cases myc rearrangements are some genetic mechanisms behind development of multiple myeloma. Primary cytogenetic abnormalities of being lymphocyte can produce mgus and random second Heat maybe r a s mutation or c-myc abnormalities or increased level of interleukin 6 may ultimately lead to multiple myeloma [1,6].

Clinical features

Multiple punched out lytic lesions are some prominent bony manifestations of this disease. Osteoclast activating factors produced by myeloma cell leads to skeletal deformation specially at lumbosacral region and eventually pathological fractures become a common scenario. Bead like nodules of myeloma cell infiltration at chest clavicle may develop in some cases. Bone resolutions lead to hypercalcemia and chronic pain and the former is responsible for the neurological manifestations,

lethargy. In advanced cases, spinal cord compression, hyperviscosity, irreversible renal failure development [5]. Hyperviscosity (normal relative serum viscosity is 1.8) may attribute to headache, visual disturbance, ataxia, vertigo retinopathy even coma. Infiltration of amyloid in peripheral never may cause neuropathic, carpal tunnel syndrome. Malfunction of antibody coated platelets may produce severe clotting defect, deep vein thrombosis. Hypogammaglobinumia can be a risk factor for pneumonia and urinary tract infection. Light chain cast neuropathy which is actually manifested as interstitial nephritis caused by Lambda or kappa chain is one of the major causes of acute kidney injury in multiple myeloma [1,5].

Diagnosis

Clinicopathologic diagnosis relies on identification of clonal plasma cells in bone marrow and CRAB criteria (Hypercalcemia, Renal function impairment, Anaemia and Bone lesion) [1]. Conventional tools for diagnosis include monitoring serum calcium level, creatinine clearance, haemoglobin level, bone lesions detection in radiography like CT scan. Bone marrow biopsy, serum protein electrophoresis are useful to detect monoclonal protein and are considered gold standard. Serum protein electrophoresis and measurement of serum immunoglobulin, light chains can characterize M spikes. If supplemented by immunoelectrophoresis, it can yield better results by detecting low concentration of M protein. But conventional methods have some limitations too. A few percentages of patients have no identifiable M protein and due to renal metabolism renal light chains are also undetectable. And in some cases light chain disease may be associated with IgD myeloma which may have different disease behaviour [9,10].

Modern Technologies in Diagnosis:

Revolution in Radiological techniques:

Whole body low dose combined tomography (WBLDCT) can identify lytic bone lesions more effectively with high sensitivity, that's why new recommendations suggest replacement of traditional X-ray with WBLDCT. Tumor invasion inside medulla cavity can be analysed by Dual Energy CT. It is more sensitive than conventional CT and has better efficacy similar MRI. Invasive procedures can be avoided by using diffusion weighted Imaging. the mechanism of action of this method uses Brownian motion detect ions inside the bone marrow. ADC mapping obtained from diffusion weighted Imaging technique helps to differentiate relapse and Active cases. Monitoring of efficacy of a particular treatment can be done using accessing ADC values after 20 weeks of commencement of chemotherapy. MRI proves to be one of the best radiological methods to detect multiple myeloma. More than 1 focal lesions of size more than 5

mm on MRI is a diagnostic criteria advised. Radiation free nature, soft tissue resolution multi sequence Imaging and greater efficacy make MRI one of the high standard techniques to detect multiple myeloma [2,3,4]. Whole body magnetic resonance imaging can evaluate clinical results better. Dixon technique for magnetic resonance imaging water fat separation can diagnose MM and help in determining prognosis. The principal mechanism behind this method is the disparity between the molecules of lipid and water. Combined image of water and fat is produced by disparity in resonance frequency of both. Precise separation of water and fat component images are done later by refining them with equal Symmetry and least Square estimation quantification sequence known as ideal IQ. The whole method warrants reduction in total time required [2]. T2 Dixson fat only images has greater efficacy among other variants. Positron Emission Tomography Computed Tomography (PET CT) holds a superior position in diagnosis of MM than conventional radiological methods like x-ray. 18F-Fluorodeoxyglucose (18F-FDG) is commonly used in PET-CT, it is a glucose analogue and its distribution pattern in body can indicate the rate of proliferation and differentiation of neoplastic cells. Once it has entered the cell with help of glucose transport proteins, hexokinase enzyme acts upon it and produce a compound. Then, on acted upon by glucose phosphatase, it is converted into 1F-FDG-6-PO4, which acts as glucose analogue of 18F-FDG. Increased glucose breakdown is linked to increased neoplastic cell proliferation. cases and hexokinase is upregulated and glucose phosphorylase expression is down regulated this changes at molecular level apple pet city scan the distribution of one is fdg identification of focus of malignant cell is possible affected and metastatic zones are also identifiable the location and shape dimension tissue invention of metastasis is detectable. New tracers that bind to different molecular signatures, and hence biologic properties of myeloma, will supply better knowledge of disease progression and enable personalized management of patients [2,3]. Neoplastic Myeloma cells have a highly unique characteristics that is it is capable of metabolizing exogenous acetate for de novo membrane biosynthesis via fatty acid synthase and entry into tricarboxylic acid cycle. Fatty acid synthase is over expressed in MM cells and has been found to maintain the biogenesis of lipids from extracellular acetate. 11C-acetate is a potential PET imaging agent that is sensitive to bone metastases, mainly prostate cancer, and also explored in malignancy of low avidity to 18F-FDG. Radiolabelled choline (11C or 18F) and their analogues are precursors to cellular membrane phospholipid synthesis and can be utilized as a PET marker of cellular metabolism and turnover of membranes. The method has future potential but require intense studies before using it in pillar of radiologic diagnostic method. Special targeted

transporters of amino acid is a potential imaging drugs class as there is high transport rate of amino acid in cancer cell. Tumor accumulation of tracers of amino acid is mainly a reflection of transport rate and transport mechanism more than of other destinations of metabolism such as protein synthesis. 11C-methionine is a potential PET imaging agent of MM, LAT-1 mediates cellular transport of amino acid independent of sodium for protein synthesis and other metabolism, and high expression of LAT-1 is related to proliferating cancer [4].

Newer Biomarkers for Diagnosis and Prognostication of Multiple myeloma

Following ever-growing cases of MM, despite markers utilized for prognosis and diagnostics, several new-generation markers have recently been discovered, possibly for disease prognosis and disease management improvement. In below sections, new markers discovered with molecular mechanism have been discussed.

We present below their avenues for improvement and potential for developing these markers for future early diagnostics and proper evaluation of disease [7].

Markers for Angiogenesis

To maintain increased proliferation and growth of cells, malignancies cause new blood vessel development, a mechanism of angiogenesis, in an attempt to deliver effectively oxygen and nutrition, and for disposal of wastes . In malignancies, it may involve over-expression of activators (pro-angiogenic factors) and loss of inhibition (anti-angiogenic factors). Hence, angiogenic markers have been considered significant markers for malignancies. After some recent researches during past two decades , Hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and angiopoietins are considered significant pro-angiogenic . Like that, the VEGF over-expression in a range of malignancies has been observed and it has been well studied for its role in acting a therapeutic target. In MM, VEGF, together with HGF, angiopoietins and JunB, over-regulation, and in them, a marker for prognosis and diagnostics was seen. Experimental down-regulation of VEGF with chemotherapy drugs and herbal compounds showed a significant loss in proliferation of cells and increased myeloma cells undergoing apoptosis [1,6,8]. Additionally, expression of angiopoietin-1, angiopoietin-2 and HGF, being pro-angiogenic factors, were down-regulated through such therapeutic interventions, and, thus, have a role in prognosis. The molecular mechanism regulating angiogenesis in MM is epidermal growth factor receptor (EGFR) and its ligand, HB-EGF (heparin-binding EGF-like growth factor). HB-EGF-EGFR cascade was found to stimulate proliferation in in vivo and in in vitro angiogenesis in BM in endothelial cells. Besides, high expression of HB-EGF and EGFR in MM cells, in contrast to cells in subjects with MGUS, showed a high proportion of MM PCs. Besides, inhibition of

HB-EGF–EGFR activity suppressed angiogenetic activity in BM endothelial cells. Other angiogenetic processes include BM thrombopoietin (TPO), noticed to preserve and stimulate angiogenesis in MM. Remarkably, level of TPO appreciably varies at disparate stages of MM. For instance, TPO in serum and in BM increased appreciatively with progression towards MM in MGUS/SMM, and its use in a potential marker in prognosis and in diagnosing MM is discussed. TPO receptors in BM endothelial cells become stimulated and induce intracellular angiogenetic processes, including increased migration and chemotaxis in in vitro and increased expression of MMP-9 and MMP-2, disturbing angiogenetic/anti-angiogenetic factors' balance in the BM. Mesenchymal stromal cells are multi-potent, non-haematopoietic cells with an important role in development and progression of MM through coordination between angiogenesis stimulation and cellular migration. Stromal cells, when co-cultured with MM cell lines (U266/Lp-1) under hypoxia, exhibited an association with increased level of α-smooth muscle actin, hypoxia-inducible factor (HIF)-2α and integrin-linked kinase proteins, implicating a role for them to function as angiogenic markers. Notably, HIF-2α inhibition inhibited both α-smooth muscle actin and integrin-linked kinase, and inhibited angiogenesis in in vitro studies. Mechanistically, HIF-2α produced by stromal cells triggers angiogenesis through increased adhesion and angiogenetic factors' excretion of Q-dot labelled cells. Besides angiogenic markers' role in prognosis/diagnosis of MM, these have a therapeutic target potential. Role of angiogenic markers' use in clinic have been increasingly important. In a recently performed clinic study, Hofmann et al. analysed serum level of pro-angiogenic markers in subjects with confirmed diagnosis of MM and non-progressing MGUS. In present study, three angiogenesis markers, namely, EGF, HGF and angiopoietins-2, have been determined to have positive relation with future development of progression of MGUS to MM and have been included in composite angiogenic biomarkers, a potential for a stratified risk for progression of MGUS to MM, to include in current protocols for improvement of current risk stratification model for MGUS patients. Besides, high level of FGF-2 and VEGF in plasma have been a poor prognosis marker and correlated with poor OS in therapy in MM patients. Clinical studies with larger population and additional angiogenes-related markers are warranted in future to make them sensitive and specific [7,8].

MicroRNAs

MicroRNAs (miRNAs) 18–25 nucleotides long non-coding RNAs regulating gene expression through target-ing involved in many processes such as proliferation, migration and apoptosis in cells. miRNAs have years long

characterized for malignancies development and progression. miRNAs can act both a tumor oncogene and a tumor suppressor gene for developing and inhibiting a tumor growth, respectively. Previously, in detail, discussed about miRNAs' role in diagnosing and prognosis in MM. miRNAs can possibly act molecular markers for MM, because variable miRNAs can detect at variable disease stage, and therefore information can use for diagnosing/prognosing MM patients .Besides, miRNAs can detect in variety of bodily fluids, such as, plasma, serum and urine, and even for several hours' duration, even at room temperature, miRNAs' stability, therefore taking an advantage and feasibility in using non-invasive methodologies for miRNAs' characterization .In a following table, several miRNAs have been included, utilizing for diagnosing/prognosing MM .The distinguishing miRNAs regarding MM-free controls and both MM and MGUS cases include upregulated miR-34a and downregulated let-7e. Additionally, there were advanced potential biomarkers as high expressions of miR-125b-5p, miR-29a and miR-4449 and low expressions of miR-30d and miR-203 were noted .Of note is the presence of some specific miRNAs like miR-125b-5p which were noted solely in the his advanced extramedullary phase of MM.Beyond the scope of diagnosis, miRNAas also showed their prognostic capabilities in MM. For example, low expression of miR-15a resulted in clinically statistically lower values of PFS and OS. On the other hand, in MM patients with high miR-194 there was noted a significantly higher values of OS. The inverse correlation was observed with overexpression of miR-17 and miR-886-5p which was undetected in OS. Similarly, MM cases exhibiting low abundance of miR-410 and miR-19a suffered from clinically lower PFS and OS values . On the other hand downregulation of miR-153, miR490, miR500, miR642 correlated with improved event-free survival. In addition to serum or plasma miRNAs, circulatory exosomal miRNAs such as let-7b and miR-18a have a prognostic indication for MM progression [1,5,10].

Exercise of Telomerase

Telomeres are a form of nucleoprotein stones that lie on the terminal ends of chromosomes, and are essential in guarding the chromosomes from destruction. For the purpose of keeping chromosomal stability and integrity, telomeres are stops at the ends of chromosomes, preventing the arms of chromosomes from being subject to undesirable DNA repair reactions and also ceasing the erosion of essential genes next to the chromosome's ends. Telomerase is a ribonucleoprotein complex responsible for providing a template for adding telomeric repeats onto the end of the chromosomes. Each telomere is lost every cycle of cell division, cells will enter senescence and apoptosis once a certain length reduction of the telomeres is reached, thus capping the division and differentiation of various cells types.

However, in malignant cells, senescence is not triggered by shortened telomeres. Instead, so-called "selfish" telomeres obtained through some processes such as TERT mutations, rearrangements, TERT promoter methylation, and changes of architecture and physic properties of telomeres were implicated to enhance uncontrolled proliferation and immortality of malignant cells. All of these events point out the critical importance of telomere maintenance in unlimited cell division and malignancy tumorigenesis. Compare to the control, MM patients display longer
telomeres [8,9,10].

Conclusion

Early diagnosis of multiple myeloma significantly improves clinical outcomes since therapeutic intervention may be instituted much earlier before the occurrence of irreversible organ damage. In the modern era, integration of laboratory markers, imaging techniques, and genetic profiling is allowing increased diagnostic precision that, therefore, allows risk stratification and personalized treatment approaches. The other significant preventive strategy is the screening in high-risk populations-those that prevent disease progression in populations at risk, such as people suffering from MGUS and smoldering myeloma. With these developments in diagnostic methodologies, it promises that in the future, detection will be much earlier with improved newer pet ct, liquid biopsy and next-generation sequencing. Clinical awareness and uniform diagnostic protocols are the ways to early detection, better treatment, and longer survival of patients with MM.

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