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Application Value of Different Detection Methods in Diagnosis and Prognosis of Multiple Myeloma

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Abstract. Multiple myeloma (MM), being a hematological tumor with a high incidence, has seriously threatened people's health and drawn the attention of numerous research. In recent years, along with the continuous advancement of research, an increasing number of technologies have been utilized in the diagnosis and prognosis evaluation of MM, and the approaches for the diagnosis and prognosis assessment of MM have become increasingly diversified. Cytogenetic detection, molecular biology detection, hematological detection and imaging detection are widely used in the diagnosis and prognosis evaluation of MM. In addition, researchers are also using immunological detection, detection of circulating tumor cells and DNA, machine learning and other methods to actively search for new biological targets, and try the combined application of multiple diagnostic pathways to continuously optimize the diagnosis and prognosis evaluation of MM. This paper reviewed several methods for the diagnosis and prognostic evaluation of MM, analyzed some advantages and disadvantages of each method in the diagnosis and prognostic evaluation, and put forward some thoughts for future research directions.

Keywords: Multiple myeloma; diagnosis; prognosis.

1. Introduction

MM is a malignant tumor with abnormal proliferation of clonal plasma cells, which mainly occurs in middle-aged and elderly people, and the incidence of male is higher than that of female [1]. Its incidence accounts for about 1/10 of the total incidence of hematological tumors, and its incidence ranks the second in some countries [2]. It is considered that more than half a million people are diagnosed with the disease globally each year [3]. The main clinical manifestations are anemia, bone disease, renal insufficiency and hypercalcemia. Due to the low survival rate, high incidence of related complications, and easy misdiagnosis or delayed diagnosis, timely and accurate diagnosis of MM is important, which can significantly upgrade the quality of patients ' lives and reduce complications.At present, multiple myeloma is mainly diagnosed by laboratory examination, imaging examination and other methods, combined with clinical symptoms.Now for evaluating method on the diagnosis and prognosis of MM, there is no system of inductive and interpretation, this paper aims to evaluate the diagnosis and prognosis of previous methods.

2. Cytogenetic testing

Primary and secondary chromosomal events such as hyperdiploidy, IGH ectopic, 1q21 amplification, del (17p), and MYC translocation are common genetic factors in MM.For the time being, cytogenetic testing is predominantly carried out through interphase fluorescence in situ hybridization (FISH). Primary chromosomal abnormalities occur in 90% of patients approximately, mainly involving chromosome number changes and chromosome heterotopia [4]. Trisomy of chromosomes 3, 5, 7, 9, 11, 15, 17 is already present in precancerous lesions and can be used as an indicator for early diagnosis [5, 6]. In addition, there are other cases of primary chromosome numerical abnormalities such as hypodiploidy, pseudodiploidy, and nearly tetraploid.In active myeloma, hyperdiploidy is generally considered to be the standard risk, with a median overall survival of around 9 years, whereas the 5-year survival rate for hyperhaploid is extremely low, only 23.1%.Changes in the number of specific chromosomes also have an effect on the median survival, such as a shorter median survival for

trisomy 21 [4, 7]. IGH translocations (14q32) occur in 50% of MM patients involving chromosomal translocations. The most frequently seen IGH translocations in descending order are t (11; 14) (20%), t (4; 14) (15%), t (14; 16) (less than 5%), t(6; 14) and t (14; 20) (both 1%), where t (11; 14), t (14; 16), t (6; 14), t (14; 20) is generally regarded as the standard risk of smoldering myeloma progressing to active myeloma [4-6]. Notably, t (11; 14) is accompanied by obvious changes in plasma cell morphology and increased BCL-2 level under normal conditions, which has unique diagnostic significance for rare lesions such as light chain myeloma and non-secretory myeloma [4, 8]. In addition, in primary plasma cell leukemia, t (11; 14) often implies a relatively good prognosis [9]. In the presence of other standard and high-risk ISS biomarkers, t (4; 14) translocation is regarded as high risk [6]. Some studies have shown that in the AMM stage, t (14; 16) is generally regarded as a high-risk cytogenetic defect, and t (6; 14) can be considered as a standard risk at all stages of myeloma progression [4, 6].

In multiple myeloma, secondary chromosomal abnormalities mainly include 1q amplification, 1p deletion, 17p deletion, MYC translocation, etc. [4].The amplification of 1q usually occur in the 1q21 region, which occurs early in the course of the disease and can be used as an indicator of early diagnosis [4, 10]. Most of the 1p deletions are interstitial deletions, mainly occurred in 1p12 and 1p32.3, and a few were complete deletions of 1p chromosome arm [11, 12]. 1p32.3 deletion includes monoallelic deletion and biallelic deletion, and biallelic deletion is defined as an ultra-high risk factor with a significantly poor prognosis in particular with some other high-risk chromosomal abnormalities [13]. 17p deletion is a high-stake cytogenetic abnormality, mainly present in newly diagnosed, relapsed or refractory multiple myeloma, and has a higher adverse effect on the progression of MM than 1p32 [6]. Biallelic deletion of TP53 has the worst prognosis in patients with 17p deletion [14]. MYC translocation is usually found in the late stage of the progression of MM, and widely exists in the process of smoky MM progressing to AMM. It is usually a non-reciprocal translocation, involving the third chromosome, and the chromosomal changes are mainly replication, amplification and inversion [4]. However, its prognostic role remains unclear.Notably, in IGH translocation, especially 2/3 of t (4; 14), which is also accompanied by an increase in 1q [15]. In SMM, increased 1q is potentially relevant to a high risk of progression to AMM [6]. In addition, the presence of 1q21+ at relapse is accompanied by a significantly reduced survival, indicating a poor prognosis [10].

The high accuracy of cytogenetic testing plays a crucial part in the diagnosis, prognosis evaluation and treatment decision-making of multiple myeloma. Cytogenetic testing can identify high-risk factors in the occurrence and progression of multiple myeloma. Early detection of these indicators and active intervention can effectively improve the quality of life of patients. Cytogenetic testing can monitor the progression of the disease during treatment. The changes of cytogenetic abnormalities in patients may indicate disease recurrence or progression, and the treatment plan needs to be adjusted in time.

However, cytogenetic testing has high requirements for detection technology and sample quality. False negative results may occur if the operation is improper or there are few tumor cells at the puncture site.At the same time, for some minor or atypical gene mutations, cytogenetic testing is also difficult to play a role.

3. Blood Tests

3.1. Blood Routine Tests

Blood tests are important for the diagnosis of MM.Routine blood test indicators such as albumin (Alb), globulin (Glo), albumin/globulin (A/G), crinine (Cr), calcium (Ca), hemoglobin (Hb), lactate dehydrogenase (LDH), platelet count (Plt) and platelet distribution width (PDW) are associated with MM diagnosis, subtype, and international staging System (ISS) staging and prognosis [16]. Studies have shown that, except Ca, the differences of other blood indicators are statistically significant,

among which Hb, Alb and PDW can predict the occurrence of MM (OR<1), and the diagnostic model established based on this has an AUC of 0.960, a sensitivity of 0.860, and a specificity of 0.957, which has good clinical value.Blood tests are also important for the staging of multiple myeloma.ISS stage is positively correlated with Cr and negatively correlated with Hb. The levels of A/G and Hb in SSII stage are significantly lower than those in ISSI stage. The levels of Cr and LDH in ISS stage III are significantly higher than those in ISSI stage, Cr and Ca are significantly higher than those in ISSII stage, and Hb is lower than that in stage II.Among them, Cr had the greatest predictive significance, with an AUC of 0.828, which was slightly higher than the multivariate prediction model of Cr, Ca and Hb [16]. Systemic inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) or monocyte-to-lymphocyte ratio (MLR) are also used as diagnostic and prognostic markers in multiple myeloma. NLR is associated with ISS, progression-free survival, isotype, and response to therapy. High NLR before treatment often predicts short overall survival and poor prognosis.In ISSIII, NLR was significantly increased [17]. Higher LMR is significantly correlated with better progression-free survival and longer overall survival. Compare with ISS III, the levels of LMR in ISS I and ISS II are higher, indicating a good prognosis [18]. In addition, the combined application of NAR(NLR/ALB) and NHR(NLR/HDL-C) is also considered as a diagnostic and prognostic factor. Patients with MM often have higher NAR and NHR, and higher NAR levels are usually related to decreased albumin, β2-MG, higher creatinine, and higher ISS stage. Higher NHR levels are usually associated with β2-MG and higher ISS stages [19]. The median OS and DFS of patients with higher NAR are reduced by 24 months and 29 months, respectively, compared with those of patients with normal NAR; for patients with high NHR, these values were 15 months and 16 months, respectively [19]. Studies have shown that the critical values of NLR, PLR, and LMR that can lead to poor prognosis of newly diagnosed patients are 4, 100, and 3, respectively [20].

3.2. Tests for Certain Blood Proteins

In addition to the detection and analysis of some routine indicators in blood, the definite diagnosis of MM depends more on the detection of some characteristic proteins, and these proteins are also of great significance for the judgment of stage and prognosis.Such as serum light chain (sLC), β2 -microglobulin (β2--MG), M protein, etc. One study showed that the median sLC ratio of MM patients was 11.5333, the minimum value was 0.86, and the maximum value was 326.19, which were significantly higher than the corresponding indexes of non-MM group (1.9293, 0.59, 17.16, $p<0.001$) [21].The abnormal sLC ratio indicates the monoclonal abnormal proliferation of plasma cells, and the abnormal proliferation of plasma cells is an important indicator for the diagnosis of MM.It may be that clonal plasma cells secrete a single immunoglobulin, which makes the light chains excessive and the ratio unbalanced.The results indicated that sLC had a high value in the diagnosis of MM under the premise of statistical significance.The detection of serum free light chain (SFLC) is the main diagnostic method for the diagnosis of MM with high sensitivity and is suitable for asymptomatic MM patients. Almost all MM patients are accompanied by abnormal FLC ratio, and FLC can predict the progression of MM [21]. β2-MG is a key indicator for the diagnosis of MM, and also an important indicator for the judgment of staging.One study found that as the stage increased and the level of β2-MG has also risen ($p<0.05$) [22]. As a plasma cell disease, it can be clinically diagnosed by detecting monoclonal immunoglobulin produced by multiple myeloma. The detection of M protein mainly includes immunofixation electrophoresis (IFE), clonopeptide method and intact Ig light chain method.As a traditional method, immunofixation electrophoresis can effectively diagnose and detect multiple myeloma, but it cannot effectively evaluate minimal residual disease (MRD). The latter two techniques based on mass spectrometry (MS) can effectively detect MRD. In the cloning peptide method, the cut-off value of M protein was 0.001 g/L.However, this method also has certain limitations, and its clinical value still needs to be further elucidated. The intact Ig light chain method has higher clinical sensitivity than IFE in detecting M protein in patients with abnormal FLC ratio [23].

Early diagnosis and assessment of disease progression can be achieved by the detection of some biological indicators in the blood. Detection of some proteins in the blood can provide effective evidence for the diagnosis of multiple myeloma. However, hematological tests can only reflect the overall situation of the body and cannot specifically determine the location of the disease. At the same time, most hematological tests are not sensitive enough for the detection of minimal residual disease.

4. Imageologocal Examination

Bone radiography used to be the main imaging method for assessing bone lesions in MM, but it has been gradually replaced by other imaging techniques due to its low sensitivity.In X-ray images, osteolytic lesions caused by MMare manifested as well-demarcated punctiform defects or poorly demarcated radioluent areas. The limitation is that 30% or more bone loss is required to show up in the images [24]. PET-CT uses 18F-fluorodeoxyglucose (FDG) as a tracer, which can detect the metabolic activity of tumor cells and has important value in the diagnosis and staging of MM [25]. The number of lesions with high FDG uptake detected by PET-CT is related to the disease progression and prognosis of patients, and the presence of 4 or more lesions with high uptake is associated with poor prognosis and lower survival rate [26]. The higher the standardized uptake value (SUV) of patients, the higher the FDG uptake, the stronger the metabolic activity, the more serious the disease progression, and the worse the prognosis [27]. For SMM patients, positive PET-CT indicates a higher risk of disease progression (75% vs 30%) [28]. Relevant studies have shown that PET-CT and MRD double negativity are important indicators for predicting the prognosis of patients who achieve at least complete remission [29]. PET-CT can assess tumor burden and determine whether it is active metabolism, but it is prone to false negative results when blood glucose is elevated, steroids are used extensively and osteolytic lesions are sub-centimeter [30]. MRI is the gold standard for detecting bone marrow infiltration and enables a comprehensive assessment of disease burden, including the detection of diffuse bone marrow infiltration and focal lesions [31]. Because of the low fat content, focal lesions of myeloma are usually hy-intense on T1-weighted images and hyperintense on fat-suppressed T2-weighted and STIR images [30]. In addition to conventional MRI, which has poor specificity, there are weighted imaging (DWI) and dynamic contrast-enhanced MRI(DCE-MRI). The detection sensitivity of DWI for bone marrow lesions other than the skull, especially for patients with low percentage of plasma cells, is higher than that of PET-CT. For extramedullary lesions, the sensitivity of both is equivalent [32]. MM usually shows high signal intensity in DWI images. It is worth noting that for patients with a low percentage of plasma cells (less than 30%), DWI can show higher sensitivity than other methods [32].Different parameters based on DCE-MRI: peak enhancement intensity (PEI), time to PEI (TPEI) and the ratio of maximum intensity to time (MITR: PEI/TPEI) of DCE-MRI can significantly distinguish the stage of MM.PEI values increase and TPEI values decrease from MGUS to active myeloma [33].The PEI value between MGUS and SMM ($p = 0.1$) and the TPEI value between SMM and AMM ($p = 0.056$) were statistically significant, and TPEI and PEI were complementary. However, MITR can increase the significance level between MGUS and SMM, and between SMM and AMM [33]. Of note, among the biomarkers, the medullary monoclonal plasma cell percentage values showed a strong correlation with PE I($p<10-6$) [33].

In imaging diagnosis, X-ray is simple to use and can detect osteolytic lesions caused by multiple myeloma, but it has been gradually replaced by other techniques due to its low sensitivity. PET-CT plays a crucial part in the diagnosis and staging of MM, but whose specificity is not high and it is prone to false negative results. MRI, especially DWI and DCE-MRI, has a high sensitivity in the detection of bone marrow lesions, which plays a vital role in the diagnosis and treatment evaluation of MM.

5. Other Methods

In addition to the above methods, with the progress of technology, more explorations have been made for the diagnosis and prognosis evaluation of MM, and new diagnostic indicators have also emerged.

However, the clinical value and feasibility of a considerable number of new methods still need to be further elucidated.The next generation sequencing technology can overcome the shortcomings of traditional cytogenetic testing, and can sequence multiple genes in massive parallel, which can detect some gene mutations and minimal residual disease that are difficult to find.Multiparameter flow cytometry mainly detects the immunophenotypic characteristics of abnormal plasma cells such as CD38 and CD58, which can find abnormal plasma cells earlier and has certain value for early diagnosis. In addition, there are detection of circulating tumor cells and detection of circulating tumor DNA. METTL23 has also been used as a diagnostic marker for MMin some studies. Moreover, some researchers have combined a variety of indicators to try to screen out some of the most relevant indicators for MM through machine learning methods. These methods provide new ideas for the diagnosis of MM.

6. Conclusion

In this paper, a variety of diagnostic methods are reviewed and summarized, and some common diagnostic methods and their advantages and disadvantages are described in detail, aiming to provide a more comprehensive diagnostic idea for the diagnosis of MM, and lay the foundation for the research of combined diagnosis of MM.

Cytogenetic testing plays a crucial part in the diagnosis and prognosis evaluation of MM. Through cytogenetic testing, we can clarify the changes of MMat the gene level, and find some new and efficient biomarkers, which will make the diagnosis and prognosis evaluation of MM more accurate, and also provide ideas for the search of therapeutic targets. Although cytogenetic mutations have been regarded as reliable evidence for multiple myeloma, more precise risk stratification has not been achieved due to the small sample size, low mutation proportion and uncommon mutations in relevant studies. New detection techniques and molecular biology techniques such as targeted sequencing have been gradually applied in clinical practice, and the era of personalized diagnosis based on molecular features has come.

Hematological tests provide a basis for the diagnosis and prognosis evaluation of MMfrom a quantitative point of view by detecting some biochemical indicators and specific proteins. However, hematological tests can not accurately locate the lesion site, nor can they reflect the metastasis of the disease. Because many hematological indicators are not specific, differential diagnosis with other diseases is required.

Imageologocal examination is playing an increasingly vital role in the diagnosis and prognosis evaluation of multiple myeloma. Different imaging techniques can diagnose MMfrom different perspectives, especially the application of PET-CT and various MRI provides more reliable evidence for the diagnosis and prognosis evaluation of MM from a quantitative perspective. The combined application of multiple imaging techniques can improve the sensitivity and specificity of diagnosis.Imaging techniques, in particular with MRI, can accurately evaluate the prognosis and risk stratification of multiple myeloma, which can be regarded as a great advantage of imaging testing over other detection methods.

In addition, the specific mechanism of some indicators in MM is still unclear, and the priority order of different indicators is still unclear. At the same time, the research on the combination of multiple methods has not been carried out on a large scale, and its theoretical basis still needs to be further explored.In the future, machine learning methods such as vector machine model and random forest model can be used to screen out high correlation indicators and establish a diagnostic model for to improve the accuracy and sensitivity of diagnosis.With the progress of technology, new diagnostic and prognostic evaluation methods are constantly proposed, and follow-up studies should be conducted around these new methods to clarify their clinical application value.

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