Case Study

Central Nervous System Myelomatosis in the Era of Precision Medicine

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Abstract: Multiple myeloma (MM) is a diverse clonal plasma cell malignancy with resultant organ damage including renal and bone marrow effects, as well as neurologic and immune dysfunction. MM is characterized as clinically and pathologically heterogeneous with significant variability in treatment response and survival. The genetically high-risk myeloma is often manifested as clinical relapsed and refractory disease. In this article, we summarize the most recent progress of molecular diagnosis and targeted treatment of multiple myeloma. We review the landscape of chromosomal abnormalities in myeloma and discuss the clinical impact on patient outcomes. We also present case report of a rare myeloma complication: central nervous system (CNS) myelomatosis. This study will help to understand the biology of CNS myeloma and its therapeutic implications in the era of precision medicine.

Keywords: myeloma, genetics, targeted therapy, molecular medicine

Introduction

In the continually evolving molecular era of medicine, the exponential rate of research and discovery yields way to a new understanding of the heterogeneity of many disease entities. Pathology is nestled at the critical interface of histopathologic diagnosis, clinical correlation, and molecular genetic analysis, ultimately vital in advancing precision medicine for treatment. Molecular diagnosis by conventional cytogenetics, fluorescence in situ hybridization (FISH) and next generation sequencing (NGS) provides the most powerful tool to developing precise evidence-based medical treatment strategies that can optimize overall patient outcomes. Genetic analysis can be utilized for individual patients to both predict response to therapy, but also to risk-stratify patients with minimal residual disease and aid in treatment choices for their respective genetic disease profiles. Plasma cell neoplasms are a diverse group of disorders which have rapidly evolved due to both a deeper understanding of disease molecular characteristics and ongoing treatment advancements.

Plasma cell neoplasms have a wide array of histopathologic and clinical presentations and we have to embrace the concept of biological heterogeneity of myeloma. This group of disorders encompasses monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma, plasma cell myeloma, plasmacytoma, and a wide spectrum of disease progression. MGUS is thought to be early within this spectrum of disease and is characterized by clonal plasma cells present within

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the bone marrow (<10% of the marrow cellularity) and presence of M-protein within the serum (<30g/L) without concomitant end-organ-damage. If the percentage of plasma cells increases beyond 10% or the M-protein levels within the serum rise above 30g/L, the diagnostic criteria of smoldering multiple myeloma are met. To diagnose plasma cell myelmoma, the preceding criteria for smoldering multiple myeloma are fulfilled, in addition to presence of end-organ-damage which can include hypercalcemia, renal insufficiency, anemia, and/or bone lesions. Plasmacytoma of bone is also composed of clonal plasma cells, but lacks systemic end-organ-damage. It presents as a bone lesion most-commonly affecting the vertebrae, ribs, or skull [1].

Plasma cell myeloma (commonly referred to as multiple myeloma) has a wide spectrum of clinical presentations, ranging from asymptomatic patients with incidental discovery of serum protein M-spike to more severe presentations of anemia, infection, lytic or osteopenic bone disease, and/or renal failure. The mean age at diagnosis is 69 years old with a slight male predominance [2]. Tests employed in initial diagnostic investigations include serum protein electrophoresis with immunofixation of serum and urine, complete blood count, complete metabolic panel, and bone marrow biopsy. These tests can help stratify patients as having MGUS, smoldering multiple myeloma, or plasma cell myeloma, with end-organ damage being the trigger for initiating treatment. The "CRAB criteria" is utilized to summarize the typical spectrum of end-organ-damage and includes hypercalcemia, renal failure, anemia, and bone lesions [2]. Challenges encountered in the treatment of plasma cell myeloma partially stem from the typical site of involvement: the bone marrow "niche" can make optimal drug delivery difficult [3]. In addition, other sites of involvement, such as the central nervous system, are also difficult to expose to optimal doses of standard myeloma treatments. Genetically, plasma cell myeloma is a complex disease with sub-clone populations showing significant genetic diversity. This notion is supported by occasional multiple clone disease and observed class-switching in cases of refractory or relapsed disease due to clonal selection or evolution [2]. Therefore, the response to treatment as a single entity is quite variable due to the biological heterogeneity of the myelomatous disease. Given the number of emerging treatment options of targeted therapy, it is an appealing strategy to utilize combinations of these novel agents in the high-risk and relapsed/refractory setting. These findings are strong evidence to support combination synergetic therapies which likely confer anti-myeloma effects through different and complementary mechanisms, presumably targeting coexisting disease sub-clones.

Current treatments available for plasma cell myeloma include immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies, and bone marrow transplant (autologous or allogenic). The initial recommended treatment for patients able to tolerate therapy includes induction with a novel agent followed by autologous stem cell transplant. In some cases of recurrence, a second autologous bone marrow transplantation can even be considered for select patients. Targeted therapy with anti-CD38 monoclonal antibody Daratumumab demonstrated promising response as a new treatment paradigm for patients with refractory multiple myeloma [4]. More novel therapies currently in clinical trials include alternative immunotherapeutic approaches targeting the same antigen, such as CD38-specific chimeric antigen receptor (CAR) T cells [5].

With the rapidly expanding anti-myeloma therapeutic armamentarium, it is becoming increasingly important to incorporate precision medicine in order to identify each individual patient who will benefit the most from each individual treatment.

Multiple myeloma (MM) is a diverse clonal plasma cell malignancy that results from complex interactions between malignant progenitor cells (mature B lymphocytes), bone marrow stromal cells, and the bone marrow microenvironment. Several factors are thought to play a role in the malignant transformation of plasma cells. In high-risk MM,

with continuing accrual of genetic abnormalities, the deregulated plasma cell acquires a clonal advantage, evolves, and expands, contributing to the increased risk of relapse or progression of disease [6]. Although neurologic manifestations often complicate the course of patients with MM, the direct central nervous system invasion presenting as CNS myelomatosis is rare. Cerebrospinal fluid examination in combination with targeted panel of flow cytometry remains the definitive test for diagnosing CNS myeloma.

According to the literature, CNS involvement by myeloma always had evidence of extensive systemic disease. Therefore, isolated CNS relapses with evidence of leptomeningeal seeding is a sign of aggressive MM rather than a sign of progression to more advanced disease. Despite that, we believe that treatment of leptomeningeal myelomatosis is indicated, given its potential for symptomatic relief and improvement in the quality of life. Physicians should be alert to the possibility of myeloma involvement of the CNS given its serious prognostic implications. Better understanding of the biology may allow prospective and earlier recognition and treatment of patients at risk for this complication [7].

Case Report

We report a case of a 51 year old Hispanic male who was initially diagnosed with IgA lambda monoclonal gammopathy. Four years after his initial presentation, he developed symptomatic lytic bone lesions and compression fractures. Bone marrow biopsy revealed plasma cell myeloma (70% of marrow cellularity) with multiple high-risk genetic abnormalities (1q rearrangement identified by cytogenetic G-banding analysis; monosomy 13, and t(4;14) identified by FISH).

After radiation and chemotherapy with Bortezomib/Lenalinomide/Dexamethasone, repeat bone marrow biopsy showed complete remission. Three years after his initial multiple myeloma diagnosis, he was referred to the oncology service due to concerns for recurrence and persistent neck pain. Magnetic resonance imaging performed to evaluate his neck pain revealed multiple enhancing intracranial intraaxial cortical and cerebellar lesions, with the largest measuring 19x16 mm (Figure 1).

Additionally, multiple enhancing lesions were identified within the spinal cord at C6-7, T11, and S1 levels. Cerebrospinal fluid cytology and flow cytometry confirmed myeloma involvement of the central nervous system, evidenced by numerous pleomorphic monoclonal plasma cells (Figure 2 and 3).

Thirteen months later, after receiving aggressive treatment with whole brain/craniospinal radiation and intrathecal Cytarabine, he passed away due to systemic involvement and multi-organ failure.

CNS Myelomatosis

Central nervous system involvement is a rare (1%) complication of myeloma with a poor clinical outcome [8]. A trial with involving thirty-eight centers across twenty countries identified 172 cases of patients with central nervous system involvement by multiple myeloma [9]. The median age at diagnosis of central nervous system involvement was 53 years with a median overall survival of 7 months. The subgroup of patients that received systemic therapy had an overall survival of 12 months, as compared to patients that did not receive systemic therapy who had an overall survival of 3 months. Overall, patients with CNS myeloma involvement had a 75% mortality within two years. Two risk factors identified in this study that portend a poor prognosis in this cohort were one or more prior treatments for multiple myeloma and >1 cytogenetic abnormality present. The overall survival of patients harboring these risk factors was 2 months [9]. A second trial of 35 patients noted a mean age at presentation of 72. The median interval from multiple myeloma diagnosis to central nervous system involvement was 15 months and median survival following central nervous system involvement was 4 months (range 1-13 months). Patients in this study most commonly presented

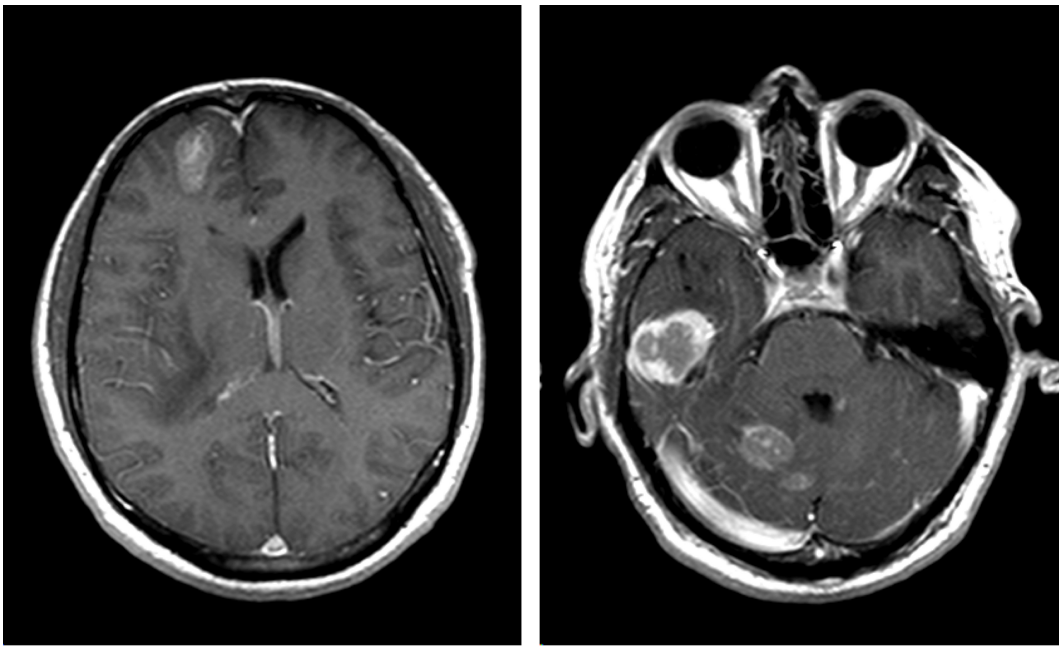

Figure 1: Magnetic resonance imaging T1 post-contrast illustrating numerous intracranial lesions.

with extremity weakness, confusion, and headache, with two patients being asymptomatic [10]. A third trial of 13 cases observed central nervous system involvement on average two years after initial diagnosis and neurologic complaints varied widely among patients. Overall survival in this cohort was 3 months, with the longest survival of 14 months in one patient. Cytogenetics in eight of thirteen patients revealed high risk cytogenetic alterations at the time of initial multiple myeloma diagnosis [11].

Overall the spectrum of presentation for CNS involvement includes localized intraparenchymal lesions, solitary cerebral plasmocytoma, or central nervous system myelomatosis. In addition, dural- or leptomeningeal-based lesions have been observed [11]. High-risk genetic abnormalities, lambda monotypical myeloma, multi-organ involvement, plasma cell leukemia, and prior therapy are associated with increased risk of central nervous system involvement and poor prognosis. Testing for confirmation of CNS involvement includes magnetic resonance imaging (MRI) which has been cited to have >90% sensitivity for identifying central nervous system involvement by multiple myeloma. Additionally, cerebrospinal fluid (CSF) analysis is diagnostic in 90% of cases, with deletion of 17p (TP53) identified in one study as the most common genetic aberration present in cases with CNS involvement [11]. Treatment options for multiple myeloma involving the central nervous system are challenging due to lack of blood-brain barrier penetration of most available treatments, making CNS penetration an important consideration in new drug development [10]. Thalidomide is one currently-available treatment option that has been shown to penetrate into the CNS [9]. Currently, no standard of care is established for these cases, with mixed results reported for the incorporation of intrathecal chemotherapy. Low dose radiotherapy has been shown to be effective in patients that have localized CNS disease [9]. Numerous genetic analytic approaches have been implemented in order to attempt to risk-stratify patients, as well as predict response to treatment, and these approaches will be discussed further below. Better understanding of

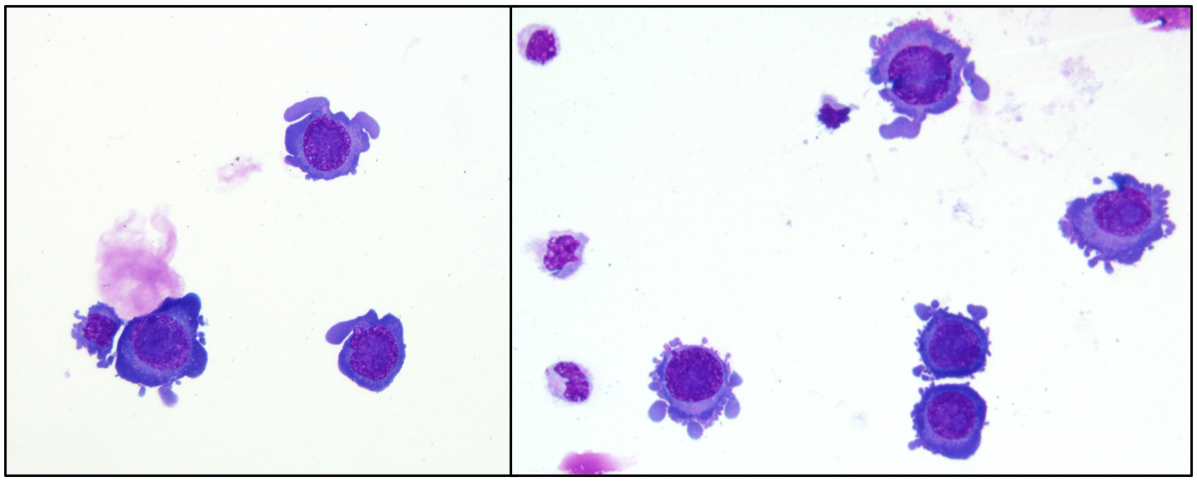

Figure 2: Cerebrospinal fluid cytology demonstrating abundant pleomorphic plasma cells.

the biology of CNS myeloma may allow prospective and earlier recognition and treatment of patients at risk for this complication.

Genetics - Analytic Approaches and Discussion

Identification of patients at high risk of relapse based on cytogenetics and comprehensive gene expression profiling is currently an active area of research. A significant portion of precision medicine efforts have been devoted to genetic analysis of various disease entities, in the hope of accurately risk-stratifying patients, guiding treatment decisions, and predicting response to therapy. Numerous analytic approaches are available that each harbor unique advantages and disadvantages. Traditional G-banding (Giemsa banding) is a technique used in cytogenetics to examine a chromosomal karyotype [12]. This technique can be challenging due to few plasma cells in marrow specimens with low proliferative activity. As discussed by Saxe and colleagues, treatment of cells with interleukin-4 can increase the detection of cytogenetic abnormalities with traditional G-banding up to 50% [13]. FISH analysis is another well-established analytic technique. To optimize this technique, plasma cells can be labeled with an antibody for immunoglobulin light chain and cells labeled with light chain antibodies are then only used for scoring. FISH methods can also include purification of plasma cells through selection for CD138 by magnetic assisted cell sorting [12, 13]. A more recent technique used to analyze the genetic makeup of these tumors is the single nucleotide polymorphisms microarray (SNP microarray). This technique offers higher resolution and a genome-wide view. In addition, this technique can also identify loss of heterozygosity (LOH) and chromothripsis/chromoanasynthesis, with chromothripsis correlating with more aggressive tumors and potentially therapy resistance [13]. In chromothripsis, microarray detects complex DNA rearrangements of oscillating copy number states with LOH. Chromoanasythesis is characterized by gained or amplified segments that retain heterozygosity [13]. Lastly, next generation sequencing has been recently implemented in multiple myeloma research [12]. Ruiz-Heredia and colleagues completed the first prospective study addressing the role of targeted squencing in a 79-patient cohort. Advantages they noted include increasing affordability and requirement of a small sample [14].

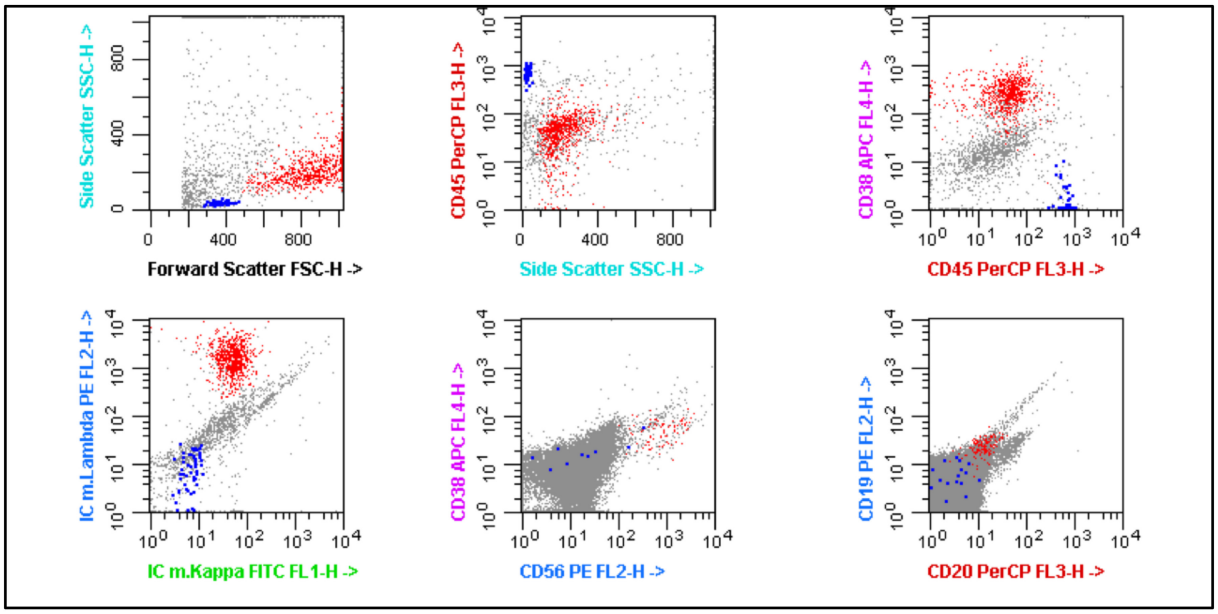

Figure 3: Cerebrospinal fluid cytology demonstrating abundant pleomorphic plasma cells.

Recent advances in molecular biology have given insights into the molecular basis of myeloma. Genetic alterations observed in multiple myeloma vary widely and include both large-scale genomic alterations and smaller gene mutations. Recognition of potential adverse cytogenetic and genomic abnormalities has led to identification of novel targets, translating to development of new treatments. Hyperdiploidy is seen in approximately 50% of cases and generally correlates with a favorable outcome. Hyperdiploidy rarely (in 5% of cases) occurs along with an IGH translocation. However, cases that harbor hyperdiploidy in addition to other cytogenetic abnormalities tend to have a worse prognosis. Hypodiploid, psudodiploid and near-tetraploid states have also been observed, with hypodiploidy having the worst outcome. A number of translocations have been observed in multiple myeloma. More than 90% of translocations involve the IGH focus on chromosome 14 and breakpoints can be variable. The translocations are typically associated with the nonhyperdiploid state. Translocation (4;14) is identified in approximately 15% of myeloma patients with a poor outcome of rapid relapse and resistance to alkylating agents [13, 15]. MYC translocations are also possible with various partners and are as-

Table 1: Common copy number aberrations with respective incidence and impact on prognosis

Aberration	Incidence	Impact on Prognosis
1q21 gain	35-40% of patients	Independent poor prognostic marker
1p deletion	30% of patients	Possible adverse impact
13q deletion *	45-50% of patients	Monosomy - adverse outcome Partial deletion - protective outcome
17p deletion	10% of newly diagnosed	Poor outcome

Note: *13q deletion rarely seen as isolated abnormality; more often seen in hypodiploid states [13, 17, 18].

sociated with a poor outcome [13]. In addition, the epigenetic modifiers such as DNA methylation and histone deacetylation are also involved in the progression and malignant phenotype of myeloma. Importantly, it should be noted that not all analytic methods are capable of detecting all of the abnormalities discussed above. For example, IGH rearrangements that are balanced cannot be detected by microarray [16]. However, LOH can be readily detected by microarray. The prognosis for regions with LOH appears similar to having loss of the region. Concurrent analysis of non-lesional/benign tissue should be done in cases of suspected loss of heterozygosity [13, 16]. Copy number aberrations are also frequently observed. Deletion or inactivation of the TP53 gene occurring at 17p13 is more frequent in advanced myeloma stages and has been identified as a clinical indicator of very poor prognosis because patients with del(17p) have more aggressive disease, higher prevalence of extramedullary disease, and overall shorter survival [17]. Additional common copy number aberrations are listed in Table 1.

As noted above, detection of genetic abnormalities in patients with multiple myeloma can help stratify patients based on their likely prognosis and can inform treatment decisions. In addition, knowing the genetic makeup of the tumor can aid in evaluating new treatment modalities currently under investigation. New treatment modalities currently undergoing evaluation include second-generation immunomodulatory drugs and second-generation protease inhibitors [19, 20]. Monoclonal antibodies, antibody-drug conjugates, tumor vaccines, immune checkpoint inhibitors, and CAR-T are undergoing clinical investigation [5]. As these treatments are being developed, new drug delivery methods to target specific microenvironments and decrease systemic toxicity are also being designed. For example, newly developed nanoparticle delivery methods can increase half-life of drugs, reduce systemic toxicity and deliver combination drugs that can have synergistic effects. Additionally, these new technologies can allow augmentation of release of the drugs with techniques such as ultrasound [3].

In order to improve the overall outcome of myeloma, we will take advantage of precision medicine and design specific combinations of treatments based on pathogenic molecular targets. The development of precise molecular tests is a prerequisite for risk stratification and subgrouping of patients for specific target entry strategies. The optimal approach will require a full understanding of the genetics of myeloma and the integration of this data with standard clinical prognostic information.

In conclusion, genetic analysis is invaluable to furthering precision medicine in many disease entities, including multiple myeloma. It is crucial not only for risk-stratification and prognosis, but also in the context of new drug development with the ultimate goal of impacting patient survival. The role of pathology in precision medicine involves complex integration of clinical and pathologic data, including not only histopathologic data, but advancements in genetics to optimize characterization of disease subtypes. This comprehensive approach can help elucidate the mechanisms behind patient response to treatment and aid in personalizing future treatment to optimize patient outcomes.

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