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Review

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Multiple Myeloma: A Review of the Literature and a Case Report Highlighting the Immunocompromised State of Myeloma Patients

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Abstract

Multiple myeloma (MM), a malignancy involving plasma cells, disproportionately affects older adults with an average age of diagnosis of about 70 years. Oftentimes, the therapies used in the treatment of MM are associated with a risk for immunotoxicity, lowering the ability of the immune system to fight off opportunistic infections. This is an important relationship for clinicians to realize as the incidence of opportunistic infections in myeloma patients is increasing. As an example, we present a case of a patient with MM who subsequently developed a cryptococcal infection. Our paper will highlight the key details of the case as well as shed light on the importance of understanding the immunodeficiencies in this patient population. We highlight important aspects of the current literature related to MM and relate them to the associated case.

Keywords: Multiple myeloma; Myeloma; Immunocompromised; Immunotherapy; Opportunistic infections; Cryptococcus

Introduction

Multiple myeloma (MM), a malignancy derived from B cells, is quite rare. Based on data extracted from the SEER database, the prevalence of MM in the United States (US) in the year 2020 was estimated at 170,405 people. In addition, when looking at age-adjusted data from the years 2016 - 2020, the rate of new cases of myeloma was 7.1 per 100,000 men and women per year. It is estimated that MM will have constituted approximately 1.8% of all new cancer diagnoses in 2023 [1]. In another study, noted for the year 2020, MM accounted for approximately 1.8% of all cancer diagnoses in the US [2]. The disease itself typically targets older individuals, with an average age of onset being 69 years old. With life expectancy increasing yearly, it is important to recognize that the prevalence of MM will only increase.

In regard to the disease itself, there are several stages of myeloma that present at different percentage levels of bone marrow (BM) plasma cells in association with the absence or presence of symptoms. In most cases, MM starts as an asymptomatic pre-malignant disease known as monoclonal gammopathy of undetermined significance (MGUS). In this stage, there is less than 10% of clonal BM plasma cells, and patients do not have symptoms related to MM. As the disease progresses, it reclassifies itself as smoldering MM (SMM), where the percentage of BM plasma cells falls between 10% and 60%. In SMM, patients remain asymptomatic [3]. On average, the time it takes for a person to progress from MGUS to SMM is approximately 5 years [4]. As for MM itself, it is defined as having a BM plasma cell level of greater than 10% along with symptoms of MM, which can include but are not limited to confusion, increased infections, fatigue, weakness, numbness, bone pain, weight loss, and blood clots. On average, MGUS will progress to MM at a rate of 1-2% of patients per year versus SMM which is approximately 10% per year [4].

The pathophysiologic hallmark of the disease is driven by a clonal proliferation of plasma cells which leads to elevated monoclonal immunoglobulin levels. The increased monoclonal immunoglobulin level precipitates a slew of different symptoms. Notably, MM is defined by the "CRAB" features: hypercalcemia, renal impairment, anemia, and bone pain [5]. The mechanisms leading to these specific symptoms will be defined in a later section of this paper, but in short, suppression in hematopoiesis leads to cytopenias, and increased osteoclast production leads to lytic bone lesions and subsequent hypercalcemia.

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There are myriad treatment regimens for MM, which will be discussed in more detail below. In general, common drug classes include alkylating agents, immunomodulatory drugs, proteasome inhibitors, and corticosteroids. In addition, there are several medications that target specific surface proteins. For example, daratumumab and isatuximab target CD38 and elotuzumab targets the SLAMF7 antigen. The treatment of choice for newly diagnosed patients is induction therapy which may then be followed by autologous stem cell transplantation (ASCT). However, specific criteria must be met in order to receive this therapy. Based on data collected and analyzed during the time period between 2012 and 2018, the 5-year survival rate of MM was 57% [6]. In comparison, the 5-year survival rate for all cancers combined, based on data collected and analyzed during the time period of 2009 - 2015, was 67% [7]. This disparity in the 5-year survival rate between MM and all cancers combined highlights the impact that MM has on individuals and their families.

Pathogenesis

As discussed in the introduction portion of this article, MM is a disease defined by an increased production of monoclonal immunoglobulins. Specifically, the disease state is determined by the percentage level of BM plasma cells and whether or not the patient is experiencing myeloma symptoms. MGUS, the initial phase of the disease, is defined by a BM plasma cell percentage of less than 10% and no evidence of symptoms. SMM occurs when the BM plasma cell percentage increases to above 10%; however, patients still remain symptom free. As for MM itself, the BM plasma cell percentage is greater than 10% and patients experience myeloma symptoms [3]. These symptoms are largely driven by the overproduction of monoclonal immunoglobulins and the subsequent effects thereafter. This section will briefly delve into the different pathognomonic features of MM.

Pancytopenia, defined by decreased production in all three cell lines, is often secondary to the replacement of normal hematopoietic cells with the proliferation of plasma cells. Other known causes include myeloma treatment-related side effects, the induction of apoptosis due to the engagement of Fas-by-Fas ligand, which is mediated by caspase activation, and cytokine-mediated BM failure through interleukin (IL)-6, IL-11, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Lastly, renal failure, a complication seen in some myeloma cases, has the potential to cause impaired erythropoietin production [8].

The effects of decreased red blood cells (RBCs), white blood cells, or platelets can be profound. When the cytopenias are combined, the effect is oftentimes magnified and further disabling. Anemia is often experienced as fatigue or tiredness, but patients can also experience shortness of breath or chest pain secondary to decreased RBC production. Decreased production of white blood cells leads to an increased risk for infection. At times, MM patients can be at risk for contracting opportunistic infections seen only in those with immunocompromised states, such as patients with human immunodeficiency virus (HIV). Thrombocytopenia increases the risk of bleeding.

There is research to suggest that myeloma cells are situated in close proximity to sites where active bone resorption happens. It is further theorized that the myeloma cells have a direct interaction with receptor activator of nuclear factor kappa-B ligand (RANKL) which in turn increases bone resorption through the activation of osteoclasts. The myeloma cells also secrete several osteoclast activating factors, including IL-1, IL-3, IL-6, and tumor necrosis factor-alpha (TNF-α). Myeloma cells also inhibit the formation of new bone through the inhibition of osteoblasts via interaction with Dickkopf-related protein 1 (DKK1), IL-3, hepatocyte growth factor (HGF), and transforming growth factor-beta (TGF-β). Bone-derived tumor growth factors, which are released from osseous structures, create a positive feedback loop with the myeloma cells [9]. The processes ultimately lead to hypercalcemia and induce states of increased risks for the development of osteoporosis. Hypercalcemia, in turn, can cause myriad symptoms, such as kidney stones, gastrointestinal issues, bone pain, and psychiatric ailments.

Renal dysfunction is a major comorbidity that many myeloma patients endure. One study estimates that upwards of 50% of patients with MM present with renal disease and approximately 5% of patients will go on to require some form of dialysis. Excess monoclonal free light chain (FLC) production is the major driving force in the development of renal impairment, with myeloma cast nephropathy (MCN) being the predominant renal pathology seen in myeloma patients presenting with renal disease. Other renal pathologies can be observed as well, such as amyloid light chain deposition and monoclonal immunoglobulin deposition [10].

Increased blood viscosity is precipitated by the increased production of circulating immunoglobulins. Immunoglobulins are glycoproteins, and as such they consist of many carbohydrate structures. These carbohydrates aid in aggregate formation, increasing osmotic pressure and ultimately reducing blood flow. There is also a degree of direct interaction between immunoglobulins and RBCs which creates a hindrance of the transport of RBC through vasculature [11]. Hyperviscosity syndrome, in combination with increased inflammation and the use of immunomodulatory agents, creates a physiologic state that poses an increased risk for thrombus formation. One study demonstrated that even when MM patients were treated with prophylactic antithrombotic medications, 5-8% of patients still went on to develop a blood clot [12].

Myeloma patients are at an increased risk for developing infections. This is through insult to both humoral and cellular immunity. With regard to the effects on cellular immunity, studies have shown that myeloma creates a state of impaired B-cell function, decreased synthesis of healthy immunoglobulins, hastened destruction of normal IgG, and hypogammaglobulinemia. As for the effects on cellular immunity, there is a diminished number of properly functioning T cells, dendritic cells and natural killer cells [13]. In addition, there is an increased number of immunosuppressive cells. On top of this, many of the medications used in the treatment of myeloma are immunosuppressive, further creating an immunocompromised state. This creates a potential for patients to develop infections that are rarely seen in immunocompetent individuals.

Phenotypic Variability

MM is a monoclonal plasma cell disorder on a spectrum from MGUS or SMM to MM. In 2014, the International Myeloma Working Group made changes to the diagnostic criteria for plasma cell disorders. MM diagnosis requires 10% or more clonal plasma cells on BM examination or a biopsy-proven plasmacytoma plus one or more myeloma-defining events [14]. Myeloma-defining events include: hypercalcemia, renal insufficiency, anemia, osteolytic bone lesion(s), clonal bone marrow plasma cells ≥ 60%, serum FLC ratio of 100 or higher, provided involved FLC level is 100 mg/L or higher, or more than one focal lesion on magnetic resonance imaging (MRI) [14]. Both MGUS and SMM are typically asymptomatic. These disease states are diagnosed when a monoclonal protein (M protein) is detected in the blood in a serum protein electrophoresis during workup of patients when MM is on the differential. For MGUS, serum monoclonal protein is found at a concentration < 3 g/dL or urinary monoclonal protein < 500 mg per 24 h, while it is ≥ 3 g/dL or urinary monoclonal protein ≥ 500 mg per 24 h for SMM [15]. Both have a risk of progression to lymphoplasmacytic malignancy including MM, Waldenstrom macroglobulinemia, and amyloid light-chain amyloidosis [15]. MGUS is a premalignant condition with multiple subtypes classified by the isotype of M protein found in the blood. The subtypes include IgM MGUS, non-IgM (IgG, IgA, or IgD) MGUS, and light-chain MGUS [15]. Each subtype of MGUS has different diagnostic criteria. MGUS has a risk of progression or malignant conversion of approximately 1% per year, but the risk varies slightly between subtypes [14]. SMM is a disease with characteristics between MGUS and MM with a 10% risk per year of progression or malignant transformation [14]. SMM is diagnosed if the patient meets the following criteria: serum monoclonal protein ≥ 3 g/dL, or urinary monoclonal protein ≥ 500 mg per 24 h and/or clonal BM plasma cells 10-60% in the absence of myeloma-defining events or amyloidosis [15]. In summary, monoclonal plasma cell disorders fall on a spectrum and can be broken down into several subtypes. Each involves proliferation of monoclonal plasma cells that lead to production of monoclonal proteins which can be detected in the blood. Each condition has unique diagnostic criteria and management.

Genetics

Genetic alterations play an essential role in the development and progression of MM and also play a role in stratifying the patient's disease into a risk category. Although there are no genetic alterations universal to all MM cases, many alterations can occur over the course of disease and are found in a significant proportion of the cases. Studies have shown that there are often two initiating events that lead to the initiation of disease. The first event described is often hyperdiploidy, which typically involves aneuploidy of certain odd-numbered chromosomes, and is found in approximately half of MM cases. The next alteration that commonly occurs involves chromosomal translocation of the portion of chromosome 14 containing the IgH gene locus and its enhancer, promoting upregulation of genes that lead to dysregulated cellular proliferation [16-18]. As MM progresses, secondary genetic alterations commonly occur, including MYC oncogene rearrangements and copy number alterations such as 1p deletion, 1q amplification, 13q deletion, and 17p deletion. Other genetic mutations that have been found in over 5% of MM cases include, but are not limited to, KRAS, NRAS, TP53, and DIS3 [16-18].

Certain genetic abnormalities, when present, can place a patient at higher risk of disease progression and can have implications in predicting response to treatment. The cytogenetic abnormalities associated with high-risk disease features include t(4;14), t(14;16), t(14;20), del(17pl), and del(1p) [19, 20]. However, genetic alterations are not the only factor used in stratifying the overall risk of disease and patient, and we must take into account other prognostic factors, including patient age, frailty, baseline health status such as renal function, and disease burden among others.

Epidemiology

As mentioned briefly in the introduction, MM is becoming more prevalent, with an estimated 143% increase in the number of patients diagnosed with the disease since 1975 [2]. The disease typically affects older individuals, with a median age of diagnosis of 69 years old, and over 60% of cases being diagnosed in patients who are older than 65 years old. Additionally, males are 1.5 times more likely to be diagnosed with the disease and African Americans are also at an increased risk compared to the remainder of the population. There also appears to be a genetic component to MM, with evidence showing that individuals with a first-degree family member diagnosed with the disease are approximately 3.7 times more likely to develop the disease than the general population. Furthermore, as mentioned previously, there are genetic variations unique to each patient's disease that may provide prognostic information for risk of progression and potential response to treatment. Although the incidence of MM has been increasing, there has also been a dramatic increase in survival from the disease with the evolution of management options for these patients. Currently, the mortality rate from MM is estimated to be 3.3 per 100,000, which is a significant decrease from the mortality rate of 4.0 per 100,000 only 29 years ago [2].

Treatment

The management of MM has come a long way since the introduction of melphalan and corticosteroids as the first effective treatment option in the mid-19th century. In the early 2000s, multiple drugs were found to be effective in management of the disease and were approved. Additionally, ASCTs were first introduced in the 1980s and have shown significant improvements in survival. Drug classes include alkylating agents, immunomodulators, proteasome inhibitors, corticosteroids and anti-CD38 monoclonal antibodies. There are also numerous novel therapeutic options, including antibody-drug conjugates (ADCs), bispecific

T-cell engagers (BiTEs), and chimeric antigen receptor T cells (CAR-T cells), that target MM-specific cellular antigens, including SLAMF7, BCMA, and CD138, among others, which are currently being utilized in clinical trials [21, 22].

The mechanisms by which these therapies work vary. Monoclonal antibodies work to target specific antigens expressed on MM cells, and once bound, can induce antibody-dependent cellular phagocytosis and complement activation, as well as triggering a direct effect on the targeted cells [23]. ADCs are composed of a monoclonal antibody, designed to target MM-specific antigens, attached to a therapeutic drug. Upon binding of the antibody to the MM-specific antigen, the complex is internalized by the MM cell and allows for direct delivery of the attached drug [24]. BiTEs are protein structures composed of two single chain variable fragments, one designed to target MM-specific antigens and the second designed to bind with specific T-cell antigens, usually CD3, connected by a flexible linker. BiTEs bind to the targeted cellular antigen and a T cell, connecting the MM cell and T cell. This results in T-cell activation, cytokine production, and specific tumor killing [25, 26]. CAR-T cells are genetically engineered T cells, composed of T-cell receptors with extracellular receptors specially designed to target tumor-specific antigens as well as transmembrane and intracellular domains that render co-stimulatory signaling and major histocompatibility complex (MHC) binding unnecessary to initiate an immune response. Binding of the CAR-T cell to its target cell results in cell death by various mechanisms, including release of cytotoxic granules, cytokine production to stimulate a local immune response, and activation of the Fas and Fas ligand axis [27, 28]. Although results of CAR-T cell therapy have been promising, this therapy is only currently FDA-approved for patients with MM refractory to multiple lines of therapy [21, 28].

Currently, the first step in deciding the treatment regimen for a patient with newly diagnosed MM is to determine whether or not they are a candidate for ASCT. Generally, patients who are ineligible for ASCT include those who are greater than 77 years old, have liver cirrhosis, have Eastern Cooperative Oncology Group (ECOG) performance status of 3-4, or have New York Heart Association (NYHA) functional status class 3-4. Regardless of transplant candidacy, patients are typically started on a triple regimen of bortezomib/lenalidomide/dexamethasone (Velcade/Revlimid/Dexamethasone, VRd), although other regimens are available depending on the patient's case and disease risk features. The SWOG trial, published in 2016, has shown that a triple regimen of VRd compared to Rd had statistically significant increases in progression-free and overall survival rates [29].

For patients deemed eligible for ASCT, they will start induction therapy, with a regimen such as the one listed above. After several cycles of induction treatment, the patient then begins the process of stem cell retrieval, collecting peripheral blood and isolating the desired stem cells. After collection and isolation of the stem cells, patients will receive a conditioning regimen, typically with high-dose melphalan, an alkylating agent, to ablate the BM in preparation for the reintroduction of the patient's autologous stem cells. Tandem ASCTs are a potential therapeutic option for patients who do not exhibit significant responses to the first ASCT [30, 31]. Once the ASCT has been completed, patients are typically started on a maintenance regimen, as relapse rates for MM are significant even if patients have good responses to the initial ASCT. Maintenance regimens may vary depending on the characteristics of the patient's disease and the patient's clinical status, but is usually a lenalidomide-based treatment, which will be continued on a long-term basis with routine follow-ups, lab work, BM analysis, and imaging studies to assess for bone involvement, looking for disease relapse and progression [25, 31].

Given that lenalidomide, and other thalidomide derivatives, is a cornerstone of MM maintenance therapy, it is important to review the mechanisms by which the drug targets and kills MM cells. Medications in this class are considered immunomodulatory drugs and work by stimulating T cells to release IL-2 and decrease proinflammatory cytokines [32]. These drugs also work by initiating ubiquitination and degradation of certain transcription factors, found within B cells, that trigger cellular death. It has been shown that the thalidomide-derived drugs target and bind to cereblon (CRBN), which is the substrate adaptor to $CRL4^{CRBN}$ E3 ubiquitin ligase, which in turn leads to the ubiquitination and proteasomal degradation of two B-cell transcription factors, IKZF1 and IKZF3, as well as casein kinase 1α (CK1α), leading to cellular death of the MM cells. Aside from MM, these medications are also implicated in the treatment of other malignancies, including myelodysplastic syndrome (MDS) with del(5q) and chronic lymphocytic leukemia (CLL) [32].

Once a patient is found to have disease relapse and progression, there are various medication options to consider, often depending on how long the patient has been in disease remission and how they responded to their previous induction and consolidation regimen. There are multiple different regiments that physicians can offer patients as well as clinical trials, which may be available for patients who meet eligibility criteria. Despite receiving multiple different drug regimens, some patients may continue to have relapsing and refractory disease, and once a patient has been treated with four different regimens, they may be eligible for CAR T-cell therapy [25].

Although treatment strategies have improved, they do not come without side effects. Some of the major adverse effects secondary to treatment regimens include increased risk of venous thromboembolism, immunosuppression, cytopenias, secondary malignancies, renal insufficiency, peripheral neuropathy, cardiac toxicity, gastrointestinal toxicity, and ocular toxicity [33, 34].

Case Report

A 69-year-old male with a medical history significant for lambda light chain MM, chronic leukopenia, chronic normocytic anemia secondary to combined iron deficiency and B12 deficiency, chronic kidney disease stage IIIb, hypertension and osteoporosis presented for the evaluation of multifocal pulmonary nodules. The patient had previously undergone chemotherapy with bortezomib, lenalidomide, and dexamethasone for a total of eight cycles in 2011. He has since been maintained on lenalidomide therapy, 10 mg orally, with a sched-

ule of 3 weeks on and 1 week off. Unfortunately, the patient was denied ASCT due to insurance issues. A bone survey performed in May of 2023 demonstrated multilevel stable compression fractures without any discrete lytic or blastic lesions, as well as an incidentally found right-sided lung lesion. Therefore, a follow-up computed tomography (CT) of the chest was completed which revealed multifocal pulmonary nodules, with the largest being in the right lower lobe. During this series of events, blood work was done which demonstrated normal cell lines, normal electrolytes and calcium, renal function which was at the patient's baseline and mildly elevated IgA with normal IgG and IgM.

A right lower lobe lung biopsy was performed in June of 2023 which returned positive for *Cryptococcus neoformans* and *Cryptococcus gattii* via a fungal PCR. Given his clinical history and recent imaging findings, the patient also underwent a positron emission tomography (PET) scan which demonstrated mild metabolic activity within the pulmonary nodules of question. Given his recent biopsy results, the PET scan findings were suggestive of chronic atypical pulmonary fungal infection.

The patient was referred to an infectious disease specialist. A serum cryptococcal antigen study returned positive. The patient was given the diagnosis of non-CNS focal pulmonary cryptococcus and was started on fluconazole 200 mg orally daily for a total planned treatment duration of 6 - 12 months. A repeat CT of the chest is planned after the patient has completed 9 months of treatment with fluconazole. The cryptococcal antigen level will be checked intermittently, via his serum, throughout the patient's treatment course, and will help guide medical therapy. There is potential that the patient may need to be maintained on life long antifungal therapy. The patient is tolerating treatment well without any medication side effects reported.

Discussion

MM is a malignancy involving the abnormal proliferation of plasma cells with incidence that has notably increased over the past decades. While the primary focus of the management lies in establishing optimal treatment strategies to achieve symptom control, the potential for immunocompromisation-related complications should not be overlooked. As illustrated with an example of this case report, patients who have been diagnosed with MM and treated for an extended period of time with immunotherapies, might face a risk of developing rare, potentially life-threatening infections, such as due to *Cryptococcus* species. The most likely mechanism behind the increased susceptibility of these patients involves the combination of pathophysiology of MM itself that is furthered by the immunosuppressive nature of therapies used. While the advances in therapies transformed a previously lethal disease into a chronic condition with relapses, they have also increased the risk for other comorbidities. As explained in Nucci et al (2009), type of infection risk depends on the specific therapy used. The most common infections affecting patients who have been started on the induction therapy with melphalan plus prednisone include pneumonia and bacteremia caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Escherichia coli* [35]. However, it should be noted that this treatment regimen has become a rare choice in clinical settings in the US recently. Use of high-dose dexamethasone regimens has been associated with mucosal candidiasis, herpes simplex virus (HSV) or varicella zoster virus (VZV) infections. Prophylactic use of either acyclovir or valacyclovir is recommended for prophylaxis against VZV reactivation to all patients receiving immunotherapy [36]. Thalidomide however was not associated with increased risk of infections. Bortezomib was found to be raising the risk for VZV infection, while lenalidomide was not conclusively linked to any particular infection [35]. Notably, autologous transplantation, which is another mode of treatment effective in managing MM, does increase infection risk through associated neutrophilia and mucositis pre-engraftment, as well as through depression of cell-mediated immunity post-engraftment. Associated infections include *Clostridium difficile*, VZV, cytomegalovirus (CMV) and *Pneumocystis jirovecii* [35].

While bacterial and viral infections tend to occur during the first year and again between years 4 and 9 after MM diagnosis, invasive fungal infections have been found to occur at much later stages in association with cumulative immunodeficiency [37]. Aspergillosis is the most common of this category of infection and most likely occurs due to neutropenia following administration of high-dose corticosteroids. Presentation with cryptococcosis is much more rare and related data are limited. A literature review performed by Chastain et al (2022) revealed that infections due to *Cryptococcus* species were mainly present in MM patients treated with corticosteroids, lenalidomide, pomalidomide, cyclophosphamide, and bortezomib [37]. The best form of primary management is dependent on the severity of the cryptococcal infection, and usually involves IV amphotericin B, flucytosine and oral fluconazole; however, other agents might be indicated.

Infection prevention prophylaxis in severely immunocompromised myeloma patients is of paramount importance to providing proper care for this population. In order to mitigate the risk, a multifaceted approach to infection prevention is crucial. An important first step is patient risk stratification based on tumor and host-related factors, through detailed past medical history, physical examination and organ function evaluation [35]. The mainstay of complication prevention is antimicrobial prophylaxis. Specific indications depend on particular disease indicators and risks. Agents used include but are not limited to trimethoprim-sulfamethoxazole in case of *P. jirovecii* prevention. CMV prophylaxis should be primarily based on the appropriate prophylactic combination of ganciclovir and valganciclovir [38]. Candidiasis infection is recommended to be pretreated with either topical or oral clotrimazole. In addition to antimicrobial prophylaxis, immune enhancement through vaccination is another facet of myeloma patient care. Vaccinations against influenza A and B, *S. pneumoniae*, *H. influenzae* and VZV remain as available options. Remaining measures revolve around lifestyle modifications including but not limited to smoking cessation, high personal hygiene standards, and broadly defined exposure avoidance, such as environmental, food preparation, travel, pets contact and recreational activities [35].

Future directions in the management of patients with MM with respect to immunocompromised state are imperative to prevent infectious complications such as those with *Cryptococcus* species. In addition to continuously enhancing supportive care measures, additional avenues can be explored. Personalized medicine with specific emphasis on immune profiling could enable more tailored treatment strategies, potentially minimizing immunosuppression-related complications. This approach still awaits validation but holds great promise [39]. Ongoing research is required to further determine the value of approaches such as CAR-T cell therapy, monoclonal antibodies, bispecific antibodies or ADCs [40]. The goal of refining future approaches is to enhance patients' immune responses while minimizing the risks associated with conventional treatments. These efforts collectively underscore the importance of a multifaceted management of immunocompromised patients with MM. Future research in these areas is anticipated to come to develop and expand our understanding of effective strategies for this complex patient population.

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Author Contributions

All authors contributed to literature review, academic writing and manuscript review and revisions.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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