A Tale of Two Immunodeficiencies: A Case of Multiple Myeloma Associated with Profound Immune Defect Mimicking Common Variable Immunodeficiency Syndrome

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ABSTRACT

Introduction: Multiple myeloma (MM) is a clonal plasma cell disorder commonly associated with secondary immune deficiency. By contrast, common variable immunodeficiency (CVID) is a primary immunodeficiency characterized by low serum levels of immunoglobulins (IgG, IgA, and/or IgM) and inability to produce specific protective antibodies in response to infections and immunizations. Besides a defective immune system and susceptibility to infections, CVID is associated with autoimmune disorders, gastrointestinal tract inflammation, granulomatous disease, and malignancies. Although MM and CVID both manifest an abnormal immune system homeostasis, the pathogenesis of the immune defect is distinctly different: Quantitative deficiency of the normal plasma cells in the former and qualitative defect in plasma cell maturation in the latter.

Case Presentation: An unusual case of MM associated with profound immunodeficiency mimicking CVID occurred in a 51-year-old man with a history of numerous bacterial infections and low γ-globulin levels.

Discussion: A hypothetical connection between MM and CVID is discussed. Patients with MM who have an unusually high burden of infections and profound immune deficit persisting even after successful myeloma therapy merit recognition as a distinct cohort that warrants heightened attention from clinicians and scientists.

INTRODUCTION

Multiple myeloma (MM) is a plasma cell malignancy that is recognized for immune system disturbances primarily affecting normal immune globulin (antibody) production with resultant frequent morbidity and mortality. The extent of the immune deficiency varies broadly in patients with myeloma, ranging from severe to nonexistent. The cause of such variation remains largely unknown.

Common variable immunodeficiency (CVID) is a syndrome characterized by defective antibody production and recurrent bacterial infections, with an estimated worldwide prevalence of 1 in 25,000 to 1 in 117,000.[1] Pathogenesis involves impaired B-cell differentiation with diminished secretion of immunoglobulins and a suboptimal antibody response to vaccinations.[2] Today, CVID is recognized as a heterogeneous disorder with different clinical phenotypes exhibiting variable susceptibility to infections, autoimmune disorders, and malignancies. The cause of CVID remains unknown, but mutations in at least 10 genes have been associated with CVID, most commonly the *TNFRSF13B* (*TACI*, transmembrane activator and calcium-modulating cyclophilin ligand interactor) gene found in 10% to 15% of individuals with CVID.[3]

We present a case of MM that demonstrated immune deficiency clinically mimicking CVID.

CASE PRESENTATION

Presenting Concerns

A 51-year-old man was referred to the Immunology Department because of numerous infections escalating in severity in the previous 10 years. Eleven months earlier, he was hospitalized for treatment of bacterial meningitis and pneumonia. Three months before presentation, he experienced recurrent pneumonia and sepsis. The patient denied any history of gastrointestinal symptoms, skin disorders, or autoimmune diseases. His family history included kidney and liver cancers, leukemia, and lupus. The patient's white blood cell count was 5300/μL (5.3 × 10^9/L); hemoglobin level, 10.2 g/dL; and platelet count, 429 × 10^3/μL (429 × 10^9/L). Despite his receiving the pneumococcal polysaccharide vaccine 10 months earlier, his antibody titers were undetectable. The patient received another pneumococcal vaccination with a conjugate vaccine (Prevnar13). Six weeks later pneumococcal antibody titers remained undetectable for all tested serotypes.

Herpes simplex virus type 2 immunoglobulin G (IgG) antibodies were negative. Antibodies to HIV-1 and 2 were nonreactive. *Clostridium tetani* antibody and cytomegalovirus antibodies (immunoglobulin M [IgM] and IgG) were not detectable. T-cell subsets (CD3, CD4, CD8) results were normal; CD19+, 214/μL (normal = 99-566/μL); CD16+CD56+, 63/μL (normal = 79-730/μL). The TACI-associated CVID sequencing showed no mutation in the *TNFRSF13B* gene (ARUP Laboratories, Salt Lake City, UT). A review of old medical records revealed a low level (< 5%) of monoclonal protein and a γ-globulin level of 0.7 g/dL (normal = 0.7-1.7 g/dL) 9 years before presentation. Because of the patient's history of numerous bacterial infections and low γ-globulin levels, a diagnosis of CVID was considered highly probable. Simultaneously, the serum protein immunofixation studies revealed the following levels: IgG, 3080 mg/dL (normal = 600-1600 mg/dL); IgA, 12 mg/dL (normal = 40-135 mg/dL); IgM, 16 mg/dL (normal = 30-190 mg/dL); and a monoclonal spike of 2.8 g/dL in the γ region.

The patient was referred to the oncologist. At the time, he reported a

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recent onset of rib and back pain. The total serum protein level was 8.9 g/dL (normal = 6.0-7.7 g/dL) with a spike in the γ region. Serum immunoelectrophoresis results showed a monoclonal IgG, and repeated quantitative immunoglobulins demonstrated these levels: IgG, 2850 mg/dL; IgA, 10 mg/dL; and IgM, 13 mg/dL. A skeletal survey exhibited multiple lucencies throughout the axial skeleton. A bone marrow biopsy specimen demonstrated kappa light chain-restricted plasma cells comprising 30% cellularity. A stain for human herpesvirus 8 was negative. Results of cytogenetic studies and interphase fluorescent in situ hybridization were normal. The diagnosis of MM was established.

Therapeutic Intervention and Treatment

Treatment was initiated with lenalidomide, bortezomib, dexamethasone (VRD), and monthly pamidronate infusions. After 1 month of treatment, the IgG level normalized, but after 2 months it plummeted to 204 mg/dL (Figure 1). The IgA and IgM levels remained extremely low at 7 mg/dL. After an additional 6 months of treatment, serum protein electrophoresis results showed the γ fraction of 0.23 g/dL. Accordingly, all immunoglobulin types remained severely depleted (Figure 1). The total IgG level was 271 mg/dL; IgG subclass 1 was 202 mg/dL (normal = 382-929 mg/dL), subclass 2 was 44 mg/dL (normal = 241-700 mg/dL), subclass 3 was 6 mg/dL (normal = 22-178 mg/dL), and subclass 4 was 4.4 mg/dL (normal = 4-86 mg/dL). Because of profoundly low immunoglobulin levels, the usual diagnostic tests to confirm CVID—checking protective antitetanus and antidiphtheria antibody levels before and after booster immunization—were omitted.

Follow-up and Outcomes

Despite the excellent response of the myeloma to therapy, the patient's deficient immunity failed to recover; therefore, treatment with monthly intravenous immunoglobulin infusions was commenced. Notably, continuous intravenous immunoglobulin infusions were necessary to maintain satisfactory immunoglobulin levels during the following 5 years of treatment, although the patient's infections were slow to diminish. Table 1 shows a timeline of the case.

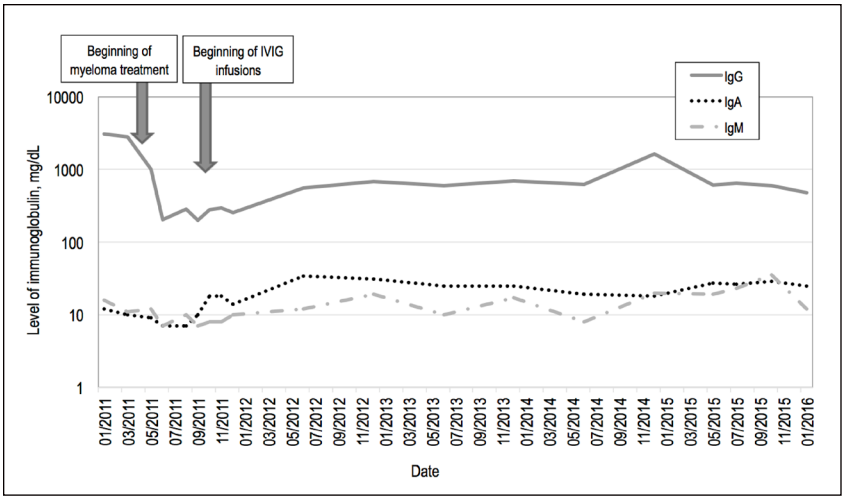

Figure 1. Patient's immunoglobulin (IgG, IgA, and IgM) levels during treatment of multiple myeloma (semi-log graph).[a]

[a] Dates are month/year.

IVIG = intravenous immunoglobulin.

DISCUSSION

We describe a patient with MM whose distinct clinical presentation and conspicuous laboratory findings were highly suggestive of a concomitant CVID. The presentation of MM prompting an immunologist consultation because of recurrent, unusually severe bacterial infections for 10 years preceding the diagnosis was unique for ordinary myeloma. Although infectious complications are common in MM, most follow the diagnosis of MM and have not been reported during such an extended premyeloma period, to our knowledge.[4] Moreover, the number of infections and their burden necessitating frequent hospitalizations were overwhelming by myeloma standards. Of note, the patient lacked any common risk factors for infectious complications such as renal failure, immunosuppressive therapy, complement deficiency, T-cell abnormalities, or neutropenia. Additionally, despite receiving a pneumococcal vaccine 10 months before his myeloma diagnosis, antibody titers were undetectable. Furthermore, the patient's pretreatment immune deficiency failed to improve after the otherwise excellent response to the treatment, resulting in undetectable M protein concentrations. On the contrary, the treatment exposed a striking depletion of the polyclonal IgG, which is uncharacteristic of ordinary myeloma but was commensurate with the patient's history of major infections. Because the patient continued to experience unrelenting, life-threatening infections, supportive treatment with intravenous immunoglobulin infusions was believed necessary.

The immune deficiency in patients with MM is commonly attributed, in addition to the disease, to adverse effects of myeloma treatment. It is important to point out that no detrimental effects of lenalidomide or bortezomib on humoral immunity have been reported to date.[5,6] In fact, the VRD combination that was used in the patient has been associated with a median increase of 81% in uninvolved immunoglobulins after 4 cycles.[7]

The patient exhibited borderline hypogammaglobulinemia and monoclonal gammopathy of undetermined significance (MGUS) 10 years before the myeloma diagnosis. Although such a "mixed" dysproteinemia is not uncommon,[8,9] the cause of low immunoglobulin levels in such cases is not clearly established. It is hypothesized that MGUS may be associated with an underlying immunodeficiency.[9,10] Supporting this hypothesis are the observations of increased risk of infections,

including pneumonia and sepsis, in patients with MGUS.[9,10] Two cases of monoclonal protein associated with CVID have been reported,[8,11] so a coexisting primary immunodeficiency ought to be considered in such cases. Furthermore, the reduction in 1 or 2 polyclonal immunoglobulins has been shown to be associated with a several-fold increase in the relative risk of MM developing from MGUS.[12,13] Even in the general population, exposure to infectious antigens and immune disturbance present several years before a diagnosis of MM has been implicated.[14]

The patient described in this report tested negative for the *TACI* gene mutation. Because the *TACI* gene mutation is found in only 10% to 15% of individuals with CVID and may also be found in healthy controls and nonimmunodeficient relatives, it is not considered diagnostic of CVID or predictive of the development of immunodeficiency.

The association between CVID and cancer is well established. The most commonly reported malignancies are non-Hodgkin lymphomas and gastric cancer, followed by colon cancer, lung cancer, and breast cancer.[2,15] A review of the literature revealed 1 case that was identified as myeloma among 117 patients with CVID.[15] Although that patient was reported as having myeloma, the disease description with monoclonal IgM; the treatments consisting of plasmapheresis; combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone and with methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone; and the patient's death caused by undifferentiated lymphoma were incompatible with the diagnosis. The lack of unambiguous reports of MM in patients with CVID may result from the tremendous diagnostic challenge of identifying both conditions simultaneously, or perhaps the 2 conditions are simply pathogenetically incompatible. The difficulty of concomitantly identifying the 2 conditions in practice is evident. In fact, because CVID lacks firmly established diagnostic criteria and represents a diagnosis of exclusion,[16,17] the coexistence of both conditions is formally disallowed. This prerequisite, although acceptable from a practical standpoint, may not be unconditionally true. CVID demonstrates variable gravity of immune defects and predilection to malignancies. Likewise, MM manifests considerable variability in the normal immunoglobulin production, with some patients exhibiting profound immunodeficiency and others (15%-30%) maintaining normal or near-normal immunoglobulin concentrations.[18] Such a heterogeneity in the presentation of both diseases prompts speculation as to whether their co-occurrence is possible conceptually. None of the major registry criteria[16,19] attempt to address the complex association of hypogammaglobulinemia/CVID with malignancy because it can be very difficult to determine whether hypogammaglobulinemia/CVID is the cause or the effect of malignancy. Some evidence, however, may call into question the notion that individuals with CVID are naturally protected from the development of MM. For example, an immunodeficiency state is a well-established favorable milieu for tumor growth in clonotypic myeloma cell

Table 1. Timeline of the case

A 51-year-old man was referred to the Immunology Department because of numerous infections escalating in severity in the previous 10 years. He had a history significant for nephrolithiasis, schwannoma, and cholesteatoma. His family history was significant for kidney and liver cancers, leukemia, and lupus.

Date	Clinical summary	Diagnostic testing	Interventions
2001-2010	Patient had recurrent sinusitis, otitis, pharyngitis, and bronchitis	Immunizations	Antimicrobial therapy
April-May 2010	Patient had bacterial meningitis and pneumonia; immune deficiency was suspected	None	Aggressive antimicrobial treatment, pneumococcal vaccination
December 2010	Patient had pneumonia and sepsis	Chest x-ray, blood cultures	Aggressive antimicrobial treatment
January 2011	On presentation to our clinic, CVID was suspected on clinical grounds	Immunizations and immunoglobulin testing	Immunology consultation: Immune deficiency and multiple antibodies undetectable; CVID suspected
March 2011	Serum M-protein was detected	Diagnostic bone marrow biopsy, proteinogram, and immunofixation	Oncology referral: Diagnosis of multiple myeloma confirmed
April 2011	The patient developed symptomatic myeloma (bone pain)	Skeletal survey	Myeloma treatment initiated (see Figure 1) with symptomatic improvement
January 2012	The patient had recurrent pneumonia and profound immune deficiency despite an excellent myeloma response to treatment	Chest x-rays, blood cultures, immunofixation	Infections treated and IVIG initiated for immune deficiency with symptomatic improvement
May 2012	Patient had recurrent pneumonia and profound immune deficiency despite an excellent myeloma response to treatment	Chest x-rays, blood cultures, immunofixation	Infections treated and IVIG continued for immune deficiency: Patient had symptomatic improvement
January 2013	Patient had recurrent pneumonia and profound immune deficiency despite an excellent myeloma response to treatment	Chest x-rays, blood cultures, immunofixation	Infections treated and IVIG continued for immune deficiency: Patient had symptomatic improvement
2016-2019	Patient was lost for follow-up	Not available	Not applicable

CVID = common variable immunodeficiency; IVIG = intravenous immunoglobulin.

animal models.[20] Furthermore, although impaired B-cell differentiation is a hallmark of CVID, the immune defects vary greatly, with some individuals demonstrating near-normal populations of myeloma cell progenitors (postgerminal center CD27+ memory B cells)[21] or CD138 (syndecan 1) positive plasma cells in lymph nodes[22] and the gastrointestinal tract.[23] Additionally, CVID B cells demonstrate functional competence by differentiating into IgG-, IgA-, and IgM-producing plasma cells not only in culture[21] but also in vivo, as evidenced by small but quantifiable immunoglobulin production in patients with CVID.

CONCLUSION

A diagnosis of primary immunodeficiency in a patient with MM could represent an enormous challenge because of the lack of firm diagnostic criteria for CVID and overshadowing secondary immunodeficiency. However, because of these diagnostic challenges, both conditions might hypothetically coexist more frequently than we currently know. Our patient with MM exhibited profound immune deficiency mimicking CVID. As such, the case elicits an intriguing "cause and effect" question of the possible supportive milieu of underlying CVID, and resultant infections, for the development of MGUS and MM. This is important because if primary immunodeficiency is implicated in some MM cases, the protective antibody transfusions may not only reduce the risk of life-threatening infections but also hypothetically affect a natural course of MM by slowing its progression and/or reducing the relapse rate.

Our case demonstrates 2 important practical points. First, it serves as a reminder that patients with severe, escalating infections ought to be evaluated earlier for immunodeficiency and, if a diagnosis of immunodeficiency is established, should be monitored for malignancy. Second, patients with MM who have an unusually high burden of infections and profound immune deficit persisting even after successful myeloma therapy merit recognition as a distinct cohort that warrants heightened attention from clinicians and scientists. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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