

The Relationship Between Hypogammaglobulinemia, Monoclonal Gammopathy of Undetermined Significance and Humoral Immunodeficiency: a Case Series

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Abstract Hypogammaglobulinemia of the non-monoclonal immunoglobulin heavy chain classes has been reported in monoclonal gammopathy of undetermined significance (MGUS) patients. Whether low polyclonal immunoglobulin levels are associated with impaired specific antibody production and whether they represent a risk factor for the development of recurrent bacterial infections have not been established in this population. We determined the frequency of MGUS in patients referred to a tertiary care clinical immunology ambulatory care practice for evaluation of hypogammaglobulinemia, who were assessed for deficits in specific antibody production and the presence of recurrent infections. Of the 133 patients evaluated for hypogammaglobulinemia, 68 were screened for monoclonal gammopathy and 5 were found to have MGUS. Three had MGUS associated hypogammaglobulinemia in the absence of a defining primary immunodeficiency, one possibly had common variable immunodeficiency, and one had an uncertain diagnosis. Thus, MGUS may be uncovered in patients presenting with hypogammaglobulinemia even in those who lack an elevated serum level of IgG, IgM, or IgA.

Keywords Hypogammaglobulinemia · MGUS · antibody production · CVID

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is characterized by a monoclonal proliferation of plasma cells and defined by the presence of a monoclonal protein measuring less than 3,000 mg/dl in the serum with clonal plasma cells in the bone marrow consisting of less than 10% of total cells and the absence of end-organ damage that can be attributed to the plasma cell proliferative disorder such as hypercalcemia, renal insufficiency, anemia, and bone lesions [1–5]. The prevalence of MGUS has been reported as 3.2% among patients 50 years of age or older and 5.3% among persons 70 years of age or older in a population based study with 21,463 subjects in Minnesota [2]. Elsewhere, the prevalence has ranged from 0.5% to 3.6% in varying ages and populations [2, 6–14].

Like multiple myeloma, MGUS has been associated with polyclonal hypogammaglobulinemia although at a much lower frequency. Hypogammaglobulinemia of the non-monoclonal immunoglobulin heavy chain classes has been reported in 20–33% of MGUS patients [15–19] and has been shown to be a risk factor for malignant transformation [15, 20]. However, whether such low polyclonal immunoglobulin levels are associated with impaired specific antibody production, and whether they represent a risk factor for the development of recurrent bacterial infections, have not been determined.

Unlike myeloma patients, MGUS patients often have a serum level of monoclonal protein that falls within or below the normal range of the corresponding immunoglobulin heavy chain class. This fact, along with the absence of defining organ pathology in MGUS, raises the possibility that its diagnosis in patients presenting with hypogammaglobulinemia could be missed unless a serum protein electrophoresis or, for that matter, a serum immunofixation

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is performed. This is not the standard practice of most clinical immunologists.

To address this possibility, we reviewed all patients referred to our tertiary clinical immunology practice with the diagnosis of hypogammaglobulinemia with or without recurrent bacterial infections. We discovered five patients with MGUS. In reporting these patients, we sought to determine whether they had recurrent bacterial infections and impaired antibody response to bacterial vaccines. When MGUS was associated with recurrent bacterial infections and impaired antibody function, we attempted to determine if these patients otherwise satisfied the diagnosis of CVID. It could be argued that patients diagnosed with MGUS should not also be diagnosed with CVID, since by definition, CVID is a diagnosis of exclusion. However, CVID patients previously have not been systematically analyzed for the presence of MGUS even though MGUS has previously been shown to occur in other chronic inflammatory disorders associated with CVID such as autoimmune disorders and recurrent infections [21].

Methods

A retrospective chart review was performed at the Allergy and Immunology practice at the Hospital of the University of Pennsylvania to identify patients with MGUS and possible humoral immunodeficiency. Patients were obtained by querying our computerized database for ICD-9 codes 273.1 (monoclonal paraproteinemia), 279.00 (hypogammaglobulinemia, unspecified), and 279.06 (common variable immunodeficiency) captured during charge entry of patients seen at the practice over a 2-year period between September 2006 and September 2008. Laboratory data of all extracted patients were reviewed for the presence of serum protein electrophoresis (SPEP) testing and the presence of a monoclonal gammopathy. Patients with a prior diagnosis of multiple myeloma, Waldenstrom's macroglobulinemia, or lymphoma and patients without a complete medical record available were excluded from further analysis. The patients' charts were then examined for infection history; IgG, IgM, and IgA levels; and humoral immune response to vaccination.

SPEP was done on a split gel electrophoresis. For serum immunofixation, antisera specific for heavy chains (IgG, IgM, IgA) and kappa and lambda light chains were applied with a template on the same gel. The gels were analyzed by a SPIFE 3000 instrument (Helena Laboratories, Inc, Beaumont, TX). For the purpose of the study, the diagnoses of hypogammaglobulinemia, MGUS, and CVID were

based on the appropriate ICD-9 codes. The definition of MGUS was then confirmed by the presence of a monoclonal protein measuring less than 3,000 mg/dl in the serum with clonal plasma cells in the bone marrow consisting of less than 10% of total cells (if measured) and the absence of associated end-organ damage. Appropriate humoral response to vaccination was defined as achieving protective IgG antibody titers against (1) tetanus toxoid (>0.15 IU/ml), (2) *Haemophilus influenzae B* (>1 mcg/ml) and (3) 70% of *Streptococcus pneumoniae* serotypes (>1.2 ug/ml) or (4) at least a fourfold response for protein antigens (tetanus) and at least a twofold response for polysaccharide antigens (*H. influenzae* and *S. pneumoniae*) [22, 23]. Primary immunodeficiencies (PIDs) were defined as defects in immune responses that are intrinsic to the immune system and not secondary to underlying disease processes or medications [22]. CVID was defined by the presence of hypogammaglobulinemia of two or more immunoglobulin isotypes (low IgG, IgM, or IgA), recurrent sinopulmonary infections, and impaired functional antibody responses as described above [24].

Results

One hundred and thirty three patients were identified with either hypogammaglobulinemia (ICD-9 code 279.00) or CVID (ICD-9 code 279.06). Sixty-five patients were identified with CVID of whom one also had monoclonal paraproteinemia (ICD-9 code 273.1). Sixty-seven patients were identified with unspecified hypogammaglobulinemia without CVID, of whom two had monoclonal paraproteinemia. An additional patient with hypogammaglobulinemia but without the associated ICD-9 code was identified with monoclonal paraproteinemia (ICD-9 code 273.1) with confirmed monoclonal gammopathy on SPEP testing. Of the 67 patients with unspecified hypogammaglobulinemia, 34 (50.7%) had evidence of SPEP testing and of those with SPEP testing 4 (11.8%) had monoclonal gammopathy on SPEP. Of the 65 patients with CVID, 33 (50.8%) had documented SPEP testing and of those with SPEP testing, 5 (13.2%) had monoclonal gammopathy on SPEP. Of the ten patients with monoclonal gammopathy, three were excluded for a history of lymphoma, one was excluded for Waldenstrom's macroglobulinemia, and one was excluded for a history of multiple myeloma, leaving five patients for review. Therefore, of the 133 patients evaluated for hypogammaglobulinemia, 68 were screened for monoclonal gammopathy and 5 (7.4%) were found to have MGUS (after excluding five patients secondary to hematological malignancies). The laboratory and clinical features of these patients are summarized in Table 1.

Table 1 Immunologic abnormalities, infectious history, and diagnoses

Case	Immunofixation/ concentration (mg/dl)	Ig level of polyclonal Ig with same isotype as M-protein (mg/dl)	Impaired specific antibody production	Significant infectious history	Diagnosis
1	IgG (880)	Normal (1370)	Yes	No	MGUS without PID
2	IgA (100)	Increased (511)	Yes	Recurrent pneumonia with bronchiectasis, recurrent sinusitis	MGUS and CVID
3	IgG (850)	Normal (1470)	Yes	Two lifetime episodes of pneumonia with mild bronchiectasis, 2–3 episodes per year of fever with cough and discolored nasal discharge	Uncertain, see text
4	IgG (NQ)	Decreased (568)	ND	No	MGUS without PID
5	IgA (NQ)	Decreased (8)	Yes	No	MGUS without PID

Ig Immunoglobulin, PID primary immunodeficiency, NQ not quantifiable, ND not determined

Case 1

A 41-year-old woman with a history of hypertension was referred for evaluation of possible food allergies after chronic diarrhea for 10 months, an 18-lb weight loss, and a low serum IgM with previous negative gastroenterologic work-up. Her prior infectious history included recurrent childhood sinusitis, bronchitis, otitis media, and “pneumonia” that was not documented by chest X-ray 18 months prior to her initial visit. Her family history was positive for atopy without immunodeficiency, hematologic malignancy, or autoimmune disease.

Previous laboratory examination showed the following serum protein levels: IgG 1,370 mg/dl (normal 650–2,000), IgM 25 mg/dl (normal 40–270), IgA 61 mg/dl (normal 50–500) and albumin 4,900 mg/dl (normal 3,500–5,800). SPEP showed a band in the gamma region that was quantitated to be 880 mg/dl. The SPEP was also notable for borderline polyclonal hypogammaglobulinemia. Immunofixation identified the band seen on SPEP as IgG kappa. Further evaluation of humoral immunity showed baseline levels of antibody titers against tetanus toxoid and *S. pneumoniae* to be non-protective (with 0/14 titers protective against *S. pneumoniae*). Repeat SPEP 3 months later showed a band in the gamma region that was quantitated to be 830 mg/dl, consistent with the previously identified IgG kappa and polyclonal hypogammaglobulinemia. Repeat immunoglobulin levels showed IgG of 829 mg/dL, IgM of 14 mg/dl, and IgA of 40 mg/dl, indicating almost no polyclonal IgG present. Humoral immune response to vaccination with Pneumovax showed partial response with protective antibody titers against only 6/14 *S. pneumoniae* serotypes. She developed protective IgG titers in response to vaccination against tetanus toxoid and *H. influenzae B*. A computerized tomography (CT) scan of her

chest done after non-related trauma showed no bronchiectasis, lymphadenopathy, or thymoma. The patient subsequently developed a toe infection but has had no significant recurrent sinopulmonary infections as an adult. She was diagnosed with MGUS and hypogammaglobulinemia in the absence of a defining PID and remained free of malignant transformation for over 3 years

Case 2

A 52-year-old female with a complex medical history was referred for evaluation of possible immunodeficiency. The patient had recurrent otitis and tonsillitis during childhood and a history of recurrent sinusitis and pneumonia requiring hospitalization and intubation as an adult. Her other past medical history included rheumatic fever at age 12, asthma, allergic rhinitis, obesity, diabetes mellitus type 2, physical abuse, bipolar disorder with multiple psychiatric hospitalizations and suicide attempts, hypertension, a cerebrovascular accident with no residual deficits, pancreatitis, and gout. She had no family history of immunodeficiency, hematologic malignancy, or autoimmune disease.

Immunoglobulin levels were IgG 455 mg/dl, IgM 15 mg/dl, and IgA 511 mg/dl. SPEP showed an abnormal band quantitated to be 100 mg/dl with immunofixation indicating that the band was IgA kappa. She had protective IgG titers after vaccination with tetanus toxoid (>7 IU/ml), and *H. influenzae B* (5.58 mcg/ml). She had a severely impaired IgG antibody response to Pneumovax with protective titers against only 2/14 *S. pneumoniae* serotypes. Chest CT showed a few patchy ground glass opacities in the periphery of both upper lobes with bronchiectasis in the right middle lobe. She received a diagnosis of CVID and MGUS. The patient declined treatment with intravenous immunoglobulin (IVIG) and was subsequently lost to follow-up.

Case 3

A 72-year-old female with a 16-year history of MGUS, remote history of breast cancer (status-post left-sided mastectomy), remote history of endometrial cancer (status-post hysterectomy), no prior chemotherapy, irritable bowel syndrome, osteoporosis, swallowing dysfunction, and gastroesophageal reflux presented for a second opinion regarding possible humoral immunodeficiency. She had previously been treated by an outside allergist/immunologist with IVIG for presumed specific antibody deficiency. She transferred care after a mild adverse reaction to IVIG.

Her infectious history consisted of 2–3 episodes yearly for the previous 10 years of cough with yellow-green nasal discharge and fever, which resolved with oral antibiotics, and two lifetime episodes of pneumonia, one of which was post-operative. Her history was complicated by the swallowing dysfunction. She had no family history of immunodeficiency, hematologic malignancy, or autoimmune disease. CT of her chest showed minimal reticulonodular thickening in the inferior right upper lobe and pleural parenchymal scarring with minimal bronchiectasis in the right middle lobe and significant dilatation of the thoracic esophagus.

Quantitative immunoglobulin levels checked 8 months after previous immunoglobulin replacement were IgG 1,470 mg/dl, IgM 38 mg/dl, and IgA 49 mg/dl. SPEP showed a monoclonal protein in the gamma region identified by immunofixation as IgG kappa. It accounted for 850 mg/dl of the total 1,240 mg/dl of gammaglobulins measured on the SPEP leaving under 400 mg/dl of total polyclonal immunoglobulins. Baseline IgG titers against *H. influenzae B* and tetanus toxoid were protective (0.37 mg/ml and 1.85 IU/ml, respectively). IgG titers against *S. pneumoniae* were not protective (0/7 serotypes protective). After vaccination with tetanus toxoid, *H. influenzae B*, and Pneumovax, her IgG titers to tetanus toxoid increased to 14.23 IU/ml, and her IgG titers to *H. influenza B* increased to 8 µg/ml, but she developed protective IgG titers to only 2/14 *S. pneumoniae* serotypes. She had no incremental protective response to *S. pneumoniae* following additional vaccination with Prevnar. A clear-cut diagnosis was not possible given her clinical history consistent with recurrent aspiration. Nevertheless, she had recurrent sinopulmonary infections in association with longstanding MGUS and more recently recognized hypogammaglobulinemia and impaired IgG antibody response to a thymic-independent antigen suggestive of CVID. She has been followed in our clinic for over 3 years with no evidence of hematologic malignancy. She has continued to present with episodes of bronchitis and sinusitis and variously has been treated with prophylactic antibiotics. She declined treatment with replacement immunoglobulin.

Case 4

A 69-year-old woman with a history of MGUS was referred for evaluation of hypogammaglobulinemia. SPEP showed evidence of decreased gamma globulins without monoclonal spike, with immunofixation showing an IgG kappa monoclonal protein that was not quantifiable. Quantitative immunoglobulin levels were IgG 568 mg/dl, IgM 89 mg/dl, and IgA 76 mg/dl. She had no significant infectious history, and no further humoral immune evaluation was undertaken. This patient had MGUS and hypogammaglobulinemia in the absence of a defining PID and did not suffer from recurrent bacterial infections. She was referred back to her primary care physician and had no further follow-up in our clinic.

Case 5

A 51-year-old male was referred for evaluation of severe panhypogammaglobulinemia diagnosed 6 years earlier. He had no other major medical problems or any significant history of infections. Family history was notable for a deceased mother and brother, both from multiple myeloma, a maternal aunt with MGUS, and a father who died from metastatic cancer of unknown primary site. Immunoglobulin levels were IgG 169 mg/dl, IgM 25 mg/dl, and IgA 8 mg/dl. SPEP showed two bands in the gamma region which reacted on immunofixation as IgA with concentrations below detectable limits. His work-up for multiple myeloma was negative. He developed protective IgG titers in response to vaccination with tetanus toxoid but did not develop protective titers in response to vaccination with *H. influenzae B* or Pneumovax. He was diagnosed with biclonal gammopathy of undetermined significance and hypogammaglobulinemia in the absence of a defining PID. Given his severe panhypogammaglobulinemia and lack of IgG antibody response to vaccination, he elected treatment with monthly IVIG replacement therapy. He has remained free of recurrent infections over the past 4 years.

Discussion

This report is highlighted by the finding of MGUS in 5 of 68 patients referred to our tertiary care clinical immunology practice over a 2-year period for hypogammaglobulinemia who were evaluated for monoclonal gammopathy. After excluding other causes of hypogammaglobulinemia in our series, we were left with two principal diagnoses, MGUS associated hypogammaglobulinemia in the absence of a defining PID (cases 1, 4, and 5) and CVID plus MGUS (case 2). In case 3, it was unclear whether the diagnosis was MGUS with hypogammaglobulinemia and recurrent sino-

pulmonary infections in the absence of a PID, MGUS complicated by recurrent aspiration, or MGUS and associated CVID.

Hypogammaglobulinemia (defined as a decrease in at least one of the non-monoclonal immunoglobulin heavy chain classes) has been previously reported in 26.4% of patients in a cohort of 1,247 MGUS patients [18]. Other studies have reported a similar frequency of hypogammaglobulinemia in MGUS patients ranging from 20% to 33% [15–17, 19]. However, levels of polyclonal immunoglobulins corresponding to the heavy chain isotype of the monoclonal protein generally are not reported in individual patients, indicating that actual polyclonal hypogammaglobulinemia is likely even more prevalent across the major immunoglobulin classes. Although the mechanisms leading to hypogammaglobulinemia in MGUS remain to be elucidated, impaired polyclonal immunoglobulin synthesis may be responsible based on studies carried out in hypogammaglobulinemic multiple myeloma patients [25–32].

CVID is a primary humoral immune deficiency characterized by a reduced serum level of IgG along with a reduced level of either or both IgM and IgA in association with recurrent sinopulmonary infections. To our knowledge, MGUS has not previously been reported in patients with CVID. Whereas CVID is known to be a risk factor for the development of B cell lymphoma, data linking it as a risk factor for the development of MGUS are lacking. In a series of 248 CVID patients, non-Hodgkin's lymphoma developed in 19 subjects (7.7%), Hodgkin's disease in three subjects, and Waldenstrom's macroglobulinemia in one patient. No patients had multiple myeloma, and no data on MGUS were reported [33]. In another series of 176 patients with CVID, the incidence of cancer at all sites combined was increased, which was due mainly to significant excesses of lymphoma and stomach cancer with no reported cases of multiple myeloma or MGUS [34]. It is certainly possible that multiple myeloma was not reported in these surveys because its presence usually disqualifies patients from being diagnosed with CVID. However, unlike myeloma patients, MGUS patients often have a serum level of monoclonal protein that falls within or below the normal range of the corresponding immunoglobulin heavy chain class. This fact, along with the absence of defining organ pathology in MGUS, raises the possibility that its diagnosis in patients presenting with hypogammaglobulinemia including those diagnosed with CVID could be missed unless a serum protein electrophoresis and serum immunofixation are performed. However, SPEP and immunofixation are not routinely performed in patients diagnosed with CVID. Despite an internal recommendation for SPEP testing in patients referred to our practice for evaluation of hypogammaglobulinemia, only about

half the patients identified by ICD-9 codes for hypogammaglobulinemia or CVID had this testing done.

Interestingly, MGUS is known to occur in association with several chronic inflammatory states including autoimmune, infectious, and inflammatory disorders [21]. This association raises the possibility that MGUS might actually occur secondarily to the chronic infectious and autoimmune processes that complicate some of the PID syndromes like CVID. This developmental sequence is consistent with the history obtained in case 2.

The risk of developing infections in patients with MGUS and associated hypogammaglobulinemia in the absence of a defining PID remains to be determined. Unlike multiple myeloma where the more frequently associated hypogammaglobulinemia is often attended by impaired IgG antibody responses to common bacterial vaccines and recurrent bacterial infections [25, 26], the picture is less clear in MGUS patients in whom the specific IgG antibody responses to such vaccines has not been systematically studied. The number of MGUS patients reported herein is too small to definitively address these questions. Nevertheless, in our study, hypogammaglobulinemia was associated with impaired antibody responses to bacterial vaccines, in the two patients with MGUS and no defining PID in whom these responses were assessed.

A limitation of our study is its retrospective nature that allowed for the absence of SPEP or immunofixation determinations on serum specimens from 49% of the patients evaluated. Thus, it is not possible to assign an accurate estimate of the frequency of MGUS in the hypogammaglobulinemic patients presenting to our tertiary ambulatory practice. Moreover, we cannot rule out bias favoring an association between MGUS and recurrent infections given the fact that most patients had either recurrent infections or hypogammaglobulinemia at the time of referral.

Our findings (case 4) indicate that even a SPEP is not sufficient to exclude the diagnosis of MGUS in patients with panhypogammaglobulinemia (low serum IgG, IgA, and IgM) since such patients may harbor an amount of monoclonal protein that falls below the detection threshold of this diagnostic tool.

In summary, the cases presented herein illustrate that MGUS is a potential coexistent serological abnormality in adult patients presenting with hypogammaglobulinemia. Two of the cases (cases 4 and 5) actually had reduced levels of the heavy chain isotype bearing the monoclonal protein and only one of the cases (case 2) had an elevated level of the heavy chain isotype corresponding to the monoclonal protein. Although, only two of the presenting patients with MGUS and hypogammaglobulinemia had a new diagnosis of MGUS, overall 7.4% of screened patients

were found to have MGUS, even some lacking an elevated amount of one of the heavy chain isotypes in their serum.

Further studies are necessary to establish an accurate prevalence of MGUS in patients discovered to have hypogammaglobulinemia. Given the still undefined clinical significance of this finding, routine screening of hypogammaglobulinemic patients for MGUS by community practitioners is not recommended. Nevertheless, screening of sufficient numbers of patients seen by clinical immunologists in large tertiary care practices could be expected to provide the data necessary to determine whether the clinical phenotype of patients with hypogammaglobulinemia and coexistent MGUS differs from that of hypogammaglobulinemic patients who lack this serological abnormality.

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