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Research paper

The clinical spectrum of IgM monoclonal gammopathy: A single center retrospective study of 377 patients

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ABSTRACT

Objectives: We retrospectively evaluated the clinical features, serum levels of IgM, and prevalence of IgM related diseases in patients with serum immunofixation electrophoresis (sIFE) confirmed IgM monoclonal gammopathy at our center.
Methods: We included patients with sIFE confirmed IgM monoclonal gammopathy between January 2008 and December 2014 in this retrospective study. We evaluated clinical data, sIFE, serum IgM levels, and diagnosis.
Results: In total, 7107 patients had sIFE confirmed monoclonal gammopathy, with 377 (5.3%) patients having the IgM type. The median age was 62 years (range, 19–105 years). The median level of serum IgM is 8.3 g/L (range, 0.24–150 g/L). The diagnosis included monoclonal gammopathy of undetermined significance (MGUS, 157 patients, 41.6%), Waldenstrom macroglobulinemia (WM, 105 patients, 27.9%), B cell non-Hodgkin's lymphoma (69 patients, 18.3%), primary cold agglutinin disease (pCAD, 16 patients, 4.2%), primary amyloidosis (14 patients, 3.7%), cryoglobulinaemia (six patients, 1.6%), IgM MGUS associated neuropathy (five patients, 1.3%), multiple myeloma (three patients, 0.8%), and POEMS syndrome (two patients, 0.5%). Levels of serum IgM > 15.5 g/L were 80.6% sensitive and 89.2% specific for the diagnosis of WM. Kappa type light chain indicated the diagnosis of WM, pCAD, IgM MGUS associated neuropathy and cryoglobulinaemia, while lambda type light chain indicated POEMS and amyloidosis. There were 41/157 (26.1%) MGUS patients diagnosed with complications due to IgM-unrelated autoimmune diseases.
Conclusion: IgM monoclonal gammopathy contains a broad spectrum of diseases. Levels of serum IgM and the type of light chain can be used to help with differential diagnosis. The association between MGUS and some autoimmune diseases requires further investigation.

1. Introduction

The presence of IgM monoclonal gammopathy can occur in a broad spectrum of diseases, including Waldenstrom macroglobulinemia (WM), various B cell non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), primary amyloidosis (AL), monoclonal gammopathy of undetermined significance (MGUS), and so on. The clinical manifestations of IgM monoclonal gammopathy related diseases vary widely from quiet lesions to aggressive, and potentially lethal, diseases [1–3]. This rare condition is often misdiagnosed due to rarity and heterogeneity. To date, there is little information regarding IgM monoclonal gammopathy related diseases. The prevalence, clinical manifestations, serum level of IgM, and type of light chain in each type of IgM related disease has never been reported comprehensively. In the current study, we retrospectively evaluated the patients with serum immunofixation electrophoresis (sIFE) confirmed IgM monoclonal gammopathy in a single consecutive cohort. We focused on the clinical features, serum levels of IgM, and the prevalence of IgM related diseases.

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2. Methods

2.1. Patients

We included patients with sIFE confirmed IgM monoclonal gammopathy between January 2008 and December 2014 at Peking Union Medical College Hospital in this retrospective study. We collected clinical data, including age, sex, chief complaint, physical examination, sIFE, and routine laboratory analyses. Routine laboratory analyses included evaluation of complete blood count, levels of lactic dehydrogenase (LDH), levels of serum IgM. We also collected 18F Fluorodeoxyglucose positron emission tomography scans, thoracic and abdominal computed tomography (CT) scans, and ultrasound results. We obtained informed consent from all patients, and Peking Union Medical College Hospital Ethics Committee approved this study. We performed this study in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

2.2. Criteria for diagnosis

We diagnosed WM based on: (i) a lymphoplasmacytic bone marrow (BM) involvement; (ii) any level of IgM paraprotein; (iii) exclusion of other low-grade lymphoma; (iv) features attributable to tumor infiltration, e.g., constitutional symptoms, cytopenia(s), and organomegaly and/or symptoms attributable to the monoclonal proteins (eg, hyperviscosity syndrome, cryoglobulinemia, amyloidosis, or autoimmune phenomena such as peripheral neuropathy and cold agglutinin disease) [4]. If patients had no symptoms, we diagnosed them as smoldering WM (sWM) [4]. We diagnosed B cell NHL based on the World Health Organization classification [5].

We diagnosed MM based on clonal bone marrow plasma cells $\geq$10% or biopsy-confirmed bony or extramedullary plasmacytoma, and any end-organ damage related to the plasma cell proliferative disorder [6].

We diagnosed primary cold agglutinin disease(pCAD)based on: (i) cold induced hemolysis; (ii) monospecific direct antiglobulin test positive for C3d; (iii) cold agglutinin titer more than 1: 64; (iv) exclusion of infection or overt malignancy [7].

We diagnosed cryoglobulinaemia by the presence of typical organ involvement (mainly skin, kidney, or peripheral nerve) and circulating cryoglobulins [8].

We diagnosed primary AL histologically by demonstration of apple green birefringence after Congo red staining of tissue biopsies.

We diagnosed POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) based on the criteria from Dispenzieri et al. [9].

We diagnosed IgM MGUS associated neuropathy based on: (i) symmetrical, distal polyneuropathy with predominant sensory ataxia; (ii) IgM monoclonal gammopathy; (iii) anti-myelin-associated glycoprotein (MAG) antibodies or anti-GM1 antibodies positive; (iv) exclusion of cryoglobulinaemia, amyloidosis, or overt malignancy infiltration [10].

We characterized IgM-MGUS by having a serum IgM monoclonal protein but no morphological evidence of bone marrow infiltration by lymphoplasmacytic lymphoma, and no clinical features attributable to the IgM monoclonal protein [4].

2.3. Statistical analysis

We reported continuous variables as median and range. We analyzed the data using a chi-squared test. We evaluated the ability of the level of serum IgM to identify WM by using a receiver operating characteristic (ROC) curve. We performed statistical analyses using SPSS 21 software (IBM Corp. Released 2012. Armonk, NY: IBM Corp.). We considered a p-value of less than 0.05 statistically significant.

3. Results

3.1. General characteristics

In total, there were 7107 patients with sIFE confirmed monoclonal gammopathy between January 2008 and December 2014 at Peking Union Medical College Hospital, with 377 patients having the IgM type (5.3%). That included 233 male patients (61.8%) and 144 female patients (38.2%). The median age of patients was 62 years (range, 19–105 years); 38 patients (10.1%) were younger than 40 years, whereas 291 patients (77.2%) were more than 50 years old, and 98 patients (26.0%) were aged 70 years or older. Of the 377 consecutive patients identified in the database, 325 patients had serum IgM level results. The median level of serum IgM was 8.3 g/L (range, 0.24–150 g/L), 58 patients' levels of serum IgM were more than 30 g/L. As for the type of light chain, 255 patients were IgM kappa (67.6%), 121 patients were IgM lambda (32.1%), and one patient's IFE showed double clones (IgM kappa and IgM lambda).

3.2. Disease profiles

Based on the diagnostic criteria listed above, there were 157 patients diagnosed with MGUS (41.6%), 93 patients diagnosed with WM (24.7%), 12 patients diagnosed with sWM (3.2%), 69 patients diagnosed with B cell NHL (18.3%), 16 patients diagnosed with pCAD (4.2%), 14 patients diagnosed with AL (3.7%), 6 patients diagnosed with cryoglobulinaemia (1.6%), five patients diagnosed with IgM MGUS associated neuropathy (1.3%), three patients diagnosed with MM (0.8%), and two patients diagnosed with POEMS syndrome (0.5%). We outlined the main clinical characteristics of patients at diagnosis in Table 1.

3.3. Diagnostic value of the levels of serum IgM

Given the marked elevation of serum levels of IgM in WM and sWM patients, we evaluated its utility as a diagnostic biomarker in WM and sWM patients using ROC curve analysis. The area under curve was 0.92(95% CI 0.89–0.95)($P < 0.01$), and the best cut off value was 15.5 g/L. The levels of serum IgM >15.5 g/L were 80.6% sensitive and 89.2% specific for WM and sWM. We show the levels of serum IgM of different diseases in Fig. 1.

3.4. Specific light chain

As for the type of light chain, the kappa/lambda ratio was 3.8/1 in WM and sWM patients, 0.4 in AL patients, and 1.8 in MGUS patients. All the patients with pCAD were kappa light chain type, as well as patients with IgM MGUS associated neuropathy and cryoglobulinaemia, whereas patients with POEMS syndrome were all lambda light chain type.

3.5. B cell NHL

Among the 69 patients diagnosed with B cell NHL, 15 patients (21.7%) had chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), 12 patients (17.4%) had mucosa-associated lymphoid tissue (MALT), nine patients (13.0%) had splenic marginal zone lymphoma (SMZL), eight patients (11.6%) had diffuse large B cell lymphoma (DLBCL), four patients (5.8%) had mantle cell lymphoma (MCL), three patients (4.3%) had nodal marginal zone lymphoma (NMZL), two patients (2.9%) had follicular lymphoma