Clinical Biochemistry xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Review

IgE monoclonal gammopathy: A case report and literature review

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ARTICLE INFO

Keywords:
Immunoglobulin E
Myeloma
MGUS
Gammopathy

ABSTRACT

Immunoglobulin E (IgE) gammopathy is a rare disorder, accounting for just 0.1% of all patients with multiple myeloma (MM). Herein, we report a case of IgE monoclonal gammopathy without any biological and clinical symptoms, and we review 63 published cases in the literature. Demographic, biological and clinical presentations and features appear to be similar to those of other subtypes of MM, with a median age of diagnosis of 67 years. There is a slight excess of male patients, and incidence seems to increase with age. The prevalence of renal failure, anaemia and hypercalcaemia at diagnosis was computed to be at 26%, 44% and 18%, respectively, in patients with MM. According to the literature, IgE MM is more aggressive and associated with poorer survival. Nonetheless, cases that are prolonged have also been described.

1. Introduction

Immunoglobulin E (IgE) monoclonal protein is a rare finding. Since the first report in 1967, approximately 63 cases of IgE multiple myeloma (MM) have been described in the English literature [1]. Here, we identified an IgE monoclonal protein in a 62-year-old Caucasian male. This case has been compared with the previously reported cases of IgE myeloma published from 1967 to 2017. The objective of this work was to review the clinical and biological features of these rare myelomas and compare the data to our case report and the data recorded for common myeloma (IgG, IgA and light-chain myeloma).

2. Case report

A 62-year-old Caucasian male presented to the medical clinic complaining of a chronic left foot ulcer secondary to type 2 diabetes diagnosed 10 years before. His past medical history was significant in terms of peripheral arterial disease and neuropathy. As his ulcer was not healing despite multiple rounds of antibiotics treatment, he was admitted to the hospital for further evaluation and treatment. He was then referred to a vascular surgeon; an amputation was scheduled. As part of his evaluation before surgery, a comprehensive battery of laboratory tests was performed. This included a complete blood count, serum chemistry panel and serum protein capillary zone electrophoresis (CZE; Capillaries Sebia®). While reviewing the CZE results (Fig. 1), the laboratory personnel noticed a tiny restriction, i.e. a band of small magnitude, in the gamma region. Serum immunofixation electrophoresis (IFE; Hydragel 7 HR, Hydrasys, Sebia®) using anti-IgG, IgA, IgM, kappa (κ) and lambda (λ) antisera provided evidence of only one slight band that was ascribable to κ chains with no heavy chain. As the restriction seemed to belong to light chains only, further testing was carried out with IgE, IgD heavy chain, anti-free κ and anti-free λ light chain antisera. This second IFE exhibited a distinct slight band for IgE and the κ light chain (Fig. 2), thus confirming the presence of an IgE-κ isotype monoclonal protein. All other laboratory results were normal: total protein concentration in the serum was 65.8 g/L (reference range: 65–83 g/L) and albumin was 42 g/L (reference range: 35–52 g/L). There was no anaemia (haemoglobin = 15.3 g/dL; reference range: 13–17 g/dL), increase in serum calcium concentration (2.35 mmol/L; reference range: 2.15–2.60 mmol/L), rise in serum creatinine concentration (68 μmol/L; reference range: 39–110 μmol/L) or elevation in β2 microglobulin concentration (1.7 mg/L; reference range: 0.8–2.2 mg/L). Immunoglobulin concentrations were within the normal limits, except IgE. Serum IgE concentration was evaluated through immunoassay (ImmunoCAP, Phadia®); there was a significant increase at 679000 IU/mL (reference range: inferior to 140 IU/mL), which corresponded to a relatively small amount in gravimetric terms (1.62 g/L). The serum free κ-to-λ light chain ratio (Freelite, Binding Site®) was 1.78 (reference range: 1.17–2.93). Traces of a monoclonal immunoglobulin were detected with urine immunofixation (IFU). The bone marrow did not document plasma cell infiltration: plasmacytosis constituted 2% of the nucleated cells upon bone marrow aspiration. Moreover, there was no t (11;14) translocation. At the time of his presentation, this patient did not exhibit clinical and radiological features suggestive of MM.

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http://dx.doi.org/10.1016/j.clinbiochem.2017.09.015
Received 14 August 2017; Received in revised form 19 September 2017; Accepted 19 September 2017

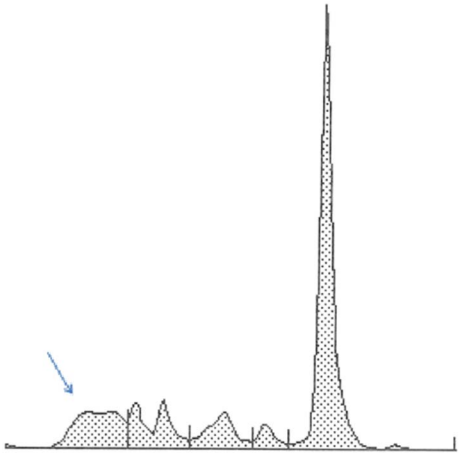

Fig. 1. Results of serum protein electrophoresis. Capillary electrophoresis showing a tiny restriction (arrow) in the gamma region.

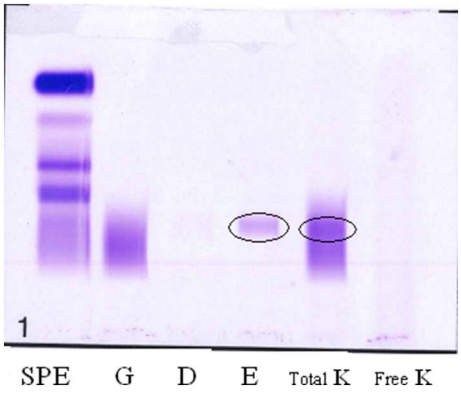

Fig. 2. Results of immunofixation. Serum immunofixation demonstrating a monoclonal IgE kappa component (circled in the photo).

Moreover, biological presentation was not typical. According to the International Myeloma Working Group (IMWG), biological presentation of MM includes clonal bone marrow plasma cells > 10% in bone marrow or the presence of biopsy-proven bony or extramedullary plasmacytoma and any one or more of these following features: hypercalcaemia, renal failure, anaemia and bone lesions (CRAB) and myeloma-defining events (MDEs).

To further explain, biological CRAB features refer to hypercalcaemia, which is defined as serum calcium 0.25 mmol/L higher than the upper limit of normal or superior to 2.75 mmol/L; renal insufficiency, with a creatinine clearance inferior to 40 mL per minute or with a serum creatinine superior to 177 µmol/L; and anaemia, specifically with a haemoglobin value of 2 g/dL below the lowest limit of normal or a haemoglobin value < 10 g/dL.

MDEs are defined as the presence of 60% or greater clonal plasma cells upon bone marrow examination and a serum-involved/uninvolved free light chain ratio of 100 or more, provided the absolute level of the involved light chain is at least 100 mg/L [2].

Three months later, the same battery of biological tests was performed. These explorations confirmed the presence of an IgE κ monoclonal immunoglobulin in serum, which did not appear as an M spike with protein electrophoresis. IgE κ monoclonal proteins in serum were seen to be diminished at 349800 IU/mL. These concentrations exceeded those observed in rare cases with allergic disease and were in the ranges described for MM and monoclonal gammopathy of undetermined significance (MGUS) (Table 1). The clinical, biological and radiological aspects of this case placed it in the category of idiopathic paraproteinaemia (MGUS or transient IgE). Regular follow-up was scheduled to evaluate peak progression and eventual transition to MM; the risk of progression to MM could not be ignored. As the patient was lost to follow-up in 2016, we do not have any information pertaining to his evolution. With this, the patient did sign an informed consent form to publish these data.

3. Discussion and review

MM constitutes between 10% and 15% of all haematological malignancies and 1% of all cancers. In this review, we focus on IgE variants [1,3–64].

With MM, IgE MM is the rarest subtype, accounting for just 0.1% of all patients. IgG and IgA multiple myelomas predominate corresponding to 52% and 21% of all myeloma forms. Light chains MM accounts for 16% of myeloma [65,72]. IgM and IgD variants are quite rare, with a prevalence of 0.5% and 2%, respectively.

As a consequence of rarity, knowledge surrounding IgE variants has been gathered from single case reports or small case series. The largest is that of Macro et al., which reviewed 35 published cases [3].

3.1. Epidemiology, incidence and presentation of IgE variants

Reviewing the 63 published cases from 1967 to 2017 shows that the median age of diagnosis was 67 years (range: 28–87) (Table 1) [1,3–64]. The sex ratio (M/F) was 1.29. κ light chains are reported in 63% of patients and λ light chains in 37%, leading to a κ/λ ratio of 1.7. Monoclonal IgE spikes or restrictions with electrophoresis were generally found in the gamma region (n = 36) and less frequently in the beta (n = 5) or alpha-2 region (n = 1). IgE concentrations were measured either by an IgE-specific immunoassay (n = 32) and/or by densitometric scanning of the electrophoresis (n = 41). There was great variability in serum IgE levels in the literature. With immunometric immunoassays, concentrations were estimated to be from 9.38 to 17.9 10^6 IU/mL (reference value < 140 IU/mL). Similarly, when the component was quantified by SPE, the levels of IgE in serum were between 0.5 and 63 g/L. A non-secretory IgE MM with an IgE level estimated at 9.38 IU/mL was also reported [63]. Hence, IgE could be present in just trace amounts. M-protein spikes were often small and could escape detection—CZE could reveal a small or absent monoclonal spike. In the case of a tiny restriction in the beta or gamma region, the laboratory technician should be vigilant and suggest repeating serum electrophoresis a few months later to see if the process resolves. An IFE can also be added, and if a patient presents a distinct band ascribable to light chains on serum or urine immunofixation, without a corresponding monoclonal IgG, IgA and IgM band, testing for IgD and IgE must be performed. Then, as described by Grimalt et al., Talamo et al. and Vignon et al., when quantification of serum IgE is conducted through immunoassays, there is the possibility of a prozone effect, i.e. an artefactual underestimation of the IgE concentration due to antigen excess [24,54,57]. Serial dilutions of the sample should be analysed to negate this interference.

Biological data (calcaemia, creatinine, haemoglobin and β_2 microglobulin) were not systematically available for all 63 published cases. Anaemia, renal failure and hypercalcaemia were defined according to IMWG criteria [2]. Approximately 44% of the patients (25/57) presented anaemia. Renal failure was observed in 10 out of 39 cases (26%) and hypercalcaemia in 18% of the population (7/38 cases). β2 microglobulin was > 3 mg/L in 10 of 16 cases [9,17,24,31–33,36,40,49]. In 2 cases, an elevated serum CA125 was reported; the mechanism and significance of this elevation is not fully understood [40,59]. The presence of the translocation t(11;14)(q13;q32) was determined in five cases and could be the hallmark of IgE myeloma [7,53,54,57]. This genetic aberrancy is not always evident, as stated by Li et al. [40]. As a result of the rarity of IgE MM, the prognostic significance of t (11,14) in the monoclonal expansion of IgE plasma cells necessitates further study. Hua et al. also documented an increase in Krebs von den Lungen-6