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Letter to the editor

An IgE multiple myeloma: Contradictory findings in clinical laboratory testing

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ABSTRACT

Background: IgE multiple myeloma is a rare kind of plasma cell disorder, characterized by an aggressive clinical course, where laboratory testing plays a fundamental role for the correct diagnosis in order to start a targeted therapy. In the present paper it is described a case of IgE myeloma where contradictory findings between immunometric and separative techniques were found.
Materials and methods: Serum and 24 h urine samples were tested using electrophoresis and immunofixation electrophoresis employing IgE antiserum and IgE were quantified using an immunometric method.
Results: Serum immunofixation evidenced a monoclonal band ascribable to IgE lambda and IgE serum concentration was 1,364,00 kU/L. Urine electrophoresis evidenced a band compatible with IgE, and urine concentration was 2715 kU/L. On the contrary in the immunofixation of the urine sample no band reacting with IgE antiserum was found.
Conclusions: Considering that the immunometric method measured IgE in urine sample and the electrophoresis of urine sample evidenced a band compatible with IgE, the explanation could be that during renal filtration or because of some characteristics related to urine matrix, the immunoglobulin IgE could had been modified in the site recognized by the antiserum used in immunofixation, and not in the one used in the immunometric method.
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IgE multiple myeloma (IgE-MM) represents a rare kind of plasma cell disorder [1], associated to an aggressive clinical course, and indeed less than 50 cases have been described so far [2]. Therefore, most of the published papers describe single case reports, focusing on clinical conditions and different therapeutic approaches [3–5]. Here contradictory findings in serum and urine samples collected from a patient suffering from an IgE-MM are described.

A 64-year old man was referred to the attention of a hematologist for worsening macrocytic anemia (Hb 94 g/L, MCV 111 fL), refractory to iron and folate supplementation, over the past 6 months. He was symptomatic for weakness and dyspnea on exertion. He also presented with left lumbosciatica exacerbation and pain on the lower right side of his rib cage that worsened when coughing.

Other biochemical findings evidenced a mild increase in serum calcium concentration (2.65 mmol/L; reference range 2.15–2.55 mmol/L), and creatinine concentration of 200 μmol/L (reference range 62–106 μmol/L).

Serum protein electrophoresis (Capillarys, Sebia) evidenced a monoclonal peak in gamma zone, corresponding to 36 g/L, being total serum proteins 94 g/L (colorimetric method, Roche Diagnostics). Immunotyping (Capillarys Immunotyping Sebia, France), carried out using anti IgG, IgA, IgM, kappa and lambda antisera, evidenced both the disappearance of the monoclonal peak in gamma zone and of the entire beta1fraction when anti-lambda antiserum was used (Fig. 1A). Serum immunofixation electrophoresis (Hydragel 7 HR, Hydrasis, Sebia) was then performed using anti IgD and anti IgE heavy chain and anti kappa and anti lambda light chain antisera. Two bands were evidenced: the wider one, in gamma zone, ascribable to IgE lambda and the smaller one, in beta zone, ascribable to lambda chains only (Fig. 1B). Serum IgE concentration was 1.364.000 kU/L (ThermoFisher, Uppsala, Sweden), kappa and lambda free light chains (Freelite Binding Site kit applied to BNII nephelometer Siemens) were 4.8 mg/L and 7980 mg/L respectively (reference interval 4.52–22.33 mg/L and 4.84–21.88 mg/L [6]).

The bone marrow biopsy documented a massive monotypic (lambda light chain restricted) plasma cell infiltration, consistent with multiple myeloma. A diagnosis of IgE myeloma was, therefore, done.

A 24 hour-urine sample was then collected and tested for urinary electrophoresis using neutral buffered SDS-agarose gel (Hydragel proteinurie, Sebia) where proteins are separated by their molecular

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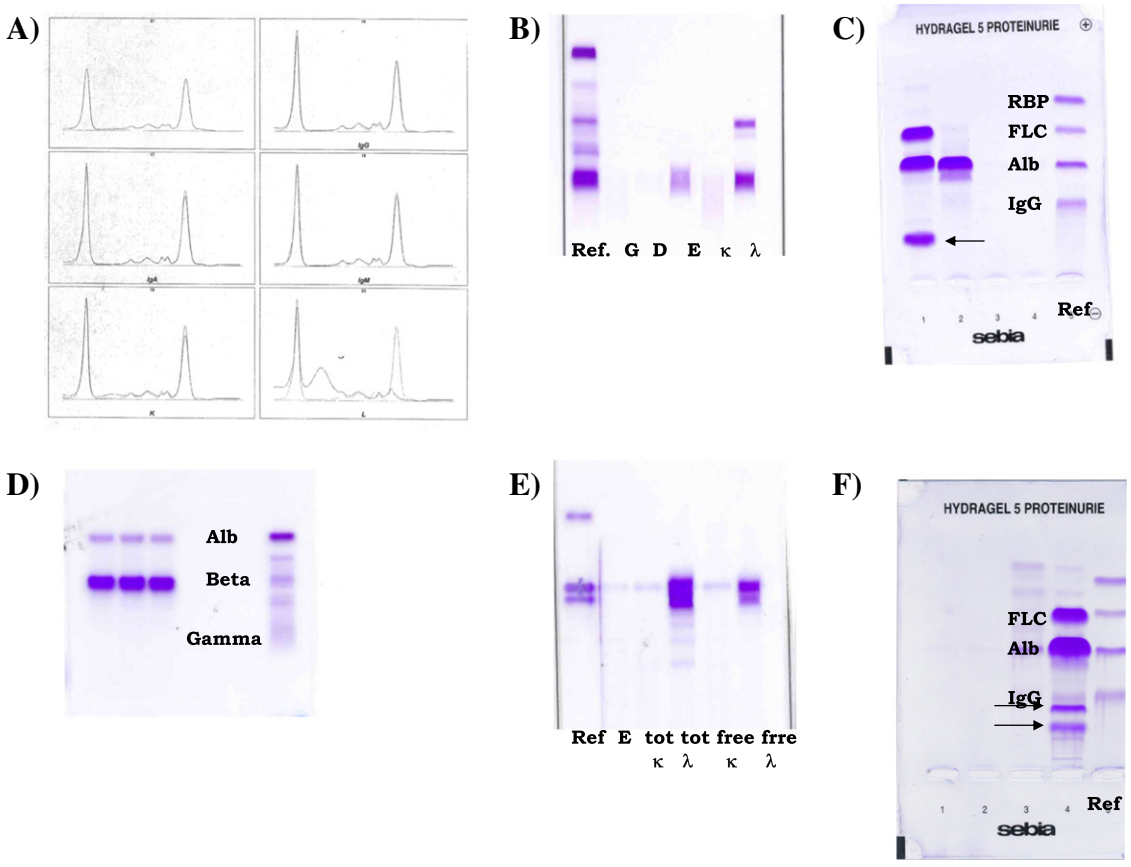

Fig. 1. A) Serum immunotyping carried out using anti IgG, IgA, IgM, kappa and lambda antisera; B) serum immunofixation electrophoresis employing antisera anti heavy chains G, D, E and light chains κ and λ; C) line 1: urinary electrophoresis in SDS-buffered gel of a 24 hour urine sample of the patient; D) lines 1,2,3 urinary electrophoresis in alkaline buffered agarose gel; E) agarose gel high resolution immunofixation on a 24 hour urine sample; F) line 4: mixed serum and urine samples electrophoresis in SDS-buffered gel (RBP = retinol binding protein, FLC = free light chains, Alb = albumin, IgG = immunoglobulin G).

weight. This electrophoresis evidenced 3 fractions: the fastest one corresponding to free light chains; the intermediate one corresponding to albumin; the slowest one with a mobility indicative of proteins with molecular weight greater than IgG (Fig. 1C), such as IgE or alpha-2 macroglobulin. The presence of alpha-2 macroglobulin was excluded because it was undetectable (BNII nephelometer Siemens). Conversely, performing urinary electrophoresis using alkaline buffered agarose gel (Hydragel kit, Sebia), where the migration occurs on the basis of the electric charge, only 2 fractions were evidenced: the smaller one attributable to albumin and the wider one localized in beta-gamma zone (Fig. 1D). In order to characterize this latter band, a higher resolution electrophoresis immunofixation was performed on native (Fig. 1E) and concentrated urine samples using and anti-IgE, total kappa, total lambda, free kappa and free lambda antisera. The beta-gamma band was split in two distinct bands, evidenced using anti total lambda and anti free lambda chains antisera (Bence-Jones proteinuria), but not using anti IgE antiserum. This result did not match with the urine IgE concentration of 2715 kU/L found using ImmunoCap.

IgE in urine sample could come only from serum, suggesting that it was synthesized from myeloma. The strangeness is that the serum IgE, well evidenced in immunofixation, was not detected in urine sample, even if the same procedure and the same antiserum were employed.

By performing an electrophoresis with neutral buffered SDS-agarose gel, mixing urine and serum patient samples (ratio 50:1), 2 different bands were detected in the area corresponding to proteins with high molecular weight (Fig. 1F), one of which corresponding to the one previously detected in the urine sample (Fig. 1C). The hypothesis could be that both of them belong to IgE, one from urine sample, and the other from serum sample, and that during renal filtration or due to some characteristics related to urine matrix (e.g. pH, protease activity) the site of IgE recognized by the antiserum used in immunofixation could had been modified. The consideration that this structural modification was due to alkaline pH during electrophoresis is not consistent, being serum electrophoresis performed in alkaline buffer too. Furthermore, the site recognized by the antiserum used by ImmunoCap could not have been modified, considering that this immunoassay was able to recognize the IgE both in serum and urine samples, even if they were not functionally related to allergic process.

All these findings underline the need to perform the immunofixation procedure using IgE and IgD antisera when monoclonal peak seems to belong to light chains only, in order to correctly classify the kind of myeloma and therefore starting the adequate therapy.

In this case, therapy consisted in 4 cycles of chemotherapy which involved a very good partial response (<10% bone marrow plasma cells without monotypic restriction; no detectable serum monoclonal component; persistence of positive Bence-Jones proteinuria, lambda). The patient became asymptomatic except for drug-induced neuropathy and he was undergone to high dose chemotherapy followed by autologous peripheral blood stem cell reinfusion.

In conclusion, while not affecting diagnostic and clinical management of the patient, the contradictory findings in the urine sample of this patient suggest that different techniques may provide different, and sometimes conflicting results, which should have been overlooked.

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