

CORRESPONDENCE

IgE-type multiple myeloma with the late development of IgA2 kappa and plasma cell leukaemia

Sir,

IgE-type myeloma is a rare haematological condition. Previously only around 40 cases have been described.^{1,2} Two recent cases were reported from Australia and China.^{3,4} Here we report what is believed to be the first published case of IgE-type myeloma from New Zealand.

Our patient was a 76-year-old woman who presented with several months of lethargy and bilateral rib pain. There were no symptoms suggestive of underlying allergy or hyperviscosity. Clinical examination revealed significant pallor and right lower rib tenderness. Initial laboratory investigations showed haemoglobin (Hb) 102 g/L (reference range 115–154), mean corpuscular volume (MCV) 100 fl (82–99), mean corpuscular haemoglobin (MCH) 33 pg (27–33), white blood cell count (WBC) $5.7 \times 10^9/L$ (4.1–11.7) and platelet $233 \times 10^9/L$ (110–400); plasma creatinine 90 $\mu\text{mol/L}$ (40–100), corrected calcium 2.47 mmol/L (2.10–2.55); plasma total protein 111 g/L (64–83), albumin 44 g/L (35–47); immunoglobulin G (IgG) 6.4 g/L (6–15), IgA 0.7 g/L (0.8–4), IgM 0.6 g/L (0.4–2.4); serum β_2 -microglobulin 3.4 mg/L (<2.4).

Serum protein electrophoresis and immunofixation (Sebia Hydrasys system; Sebia, France) revealed a large, diffuse mid gamma IgE kappa band, measured at 29.6 g/L by densitometry. Electrophoresis of concentrated urine revealed two far gamma free kappa light chain bands, their combined quantity measured at 12 mg/mmol creatinine. A full skeletal survey demonstrated asymptomatic radiolucencies in the skull and left distal humerus. A bone scintiscan revealed foci of increased tracer uptake in the ribs bilaterally. Sestamibi whole body scan revealed moderate diffuse uptake in the vertebral column, sternum and clavicles. Myeloma staging confirmed a Durie-Salmon stage IIIA (from bone lesions) and International Staging System stage I.

Bone marrow examination revealed extensive infiltration by mostly well differentiated plasma cells (55% of bone marrow cellularity). Occasional binucleate plasma cells were identified. The three haematopoietic lineages were mildly depressed. Interphase nuclear *in situ* hybridisation (FISH) studies on bone marrow aspirate material revealed no 13q14 deletion at the D13S319 and RB-1 loci (Abbott Molecular, USA). FISH at 14q32 IGH@ (Abbott Molecular), specifically looking at t(11:14) CCND1 and t(4:14) FGFR3 loci demonstrated a signal pattern consistent with no gene rearrangement.

After two cycles of monthly treatment with melphalan and prednisone together with intravenous Zoledronic acid, the patient's rib pain resolved, the total globulin fell to 38 g/L and the IgE band reduced to 9.7 g/L. M-band quantitation remained at 9.2 g/L after four cycles of chemotherapy. Treatment was changed to 2-weekly intravenous cyclophosphamide, which did not achieve any further reduction in the M-band level. The patient maintained a good quality of life for more than 14 months

(European Cooperative Oncology Group performance score 0).⁵ Renal function and calcium remained normal throughout this period. Some 17 months from diagnosis she developed secondary plasma cell leukaemia (peripheral blood plasma cell count $0.31 \times 10^9/L$). At the time, the IgE band declined further to 3.2 g/L but a new far gamma free kappa and a new mid gamma IgA kappa band emerged (Fig. 1). She was then treated with oral thalidomide and pulsed oral dexamethasone to which she responded briefly before deteriorating further. She died from disseminated infection some 23 months from diagnosis.

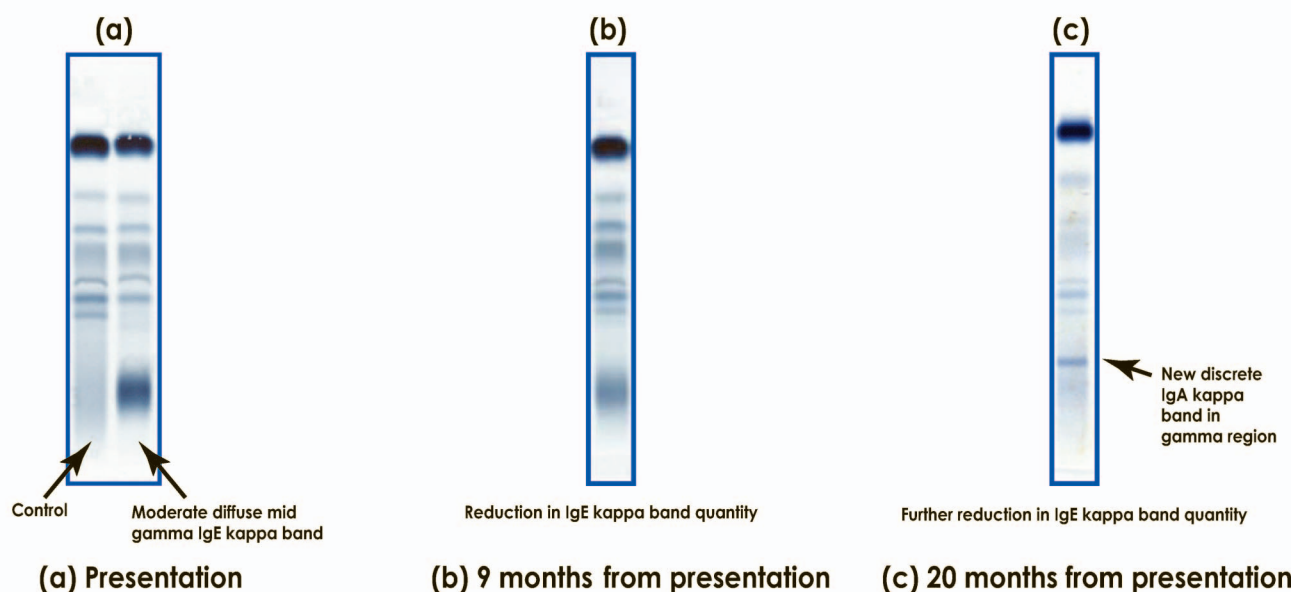
The new IgA kappa M-band was subsequently identified as predominantly of IgA₂ subtype (IgA subclass quantification radial immunodiffusion kit; Binding Site Ltd, UK). A dramatic rise of serum IgA₂ from the early phase of the patient's condition when the level was 125 mg/L (reference interval 60–610 mg/L) to a level of >4165 mg/L occurred during the later part of her illness. IgA₁ production was suppressed from the time of diagnosis and became further suppressed as the disease progressed [270 mg/L falling to 184 mg/L (600–2940 mg/L)].

The μ - ϵ switch region in this patient was examined at the DNA level midway in her clinical course, when the plasma cell leukaemia and the new IgA₂ band were detected. Polymerase chain reaction (PCR) was performed to amplify the μ - ϵ switch region⁶ with subsequent DNA sequencing being performed. We then carried out PCR using oligomers flanking the μ - α_2 switch site, cloned the product into a DNA vector and performed DNA sequencing on the cloned vector. A 'residual' molecular footprint of the ϵ switch region was not found at the μ - α_2 switch site. Molecular studies on the light chain region were not performed.

IgE-type multiple myeloma prevalence is estimated at <0.1% of all plasmacytomas. It usually presents late (mean age 62 years) with a slight male predominance.⁷ Features noted in higher frequency when compared to other myeloma subtypes include anaemia, Bence Jones proteinuria, osteoblastic bony lesions and progression to secondary plasma cell leukaemia. Protein electrophoresis usually detects the IgE type M-band in the γ region but sometimes the M-band is found at the β or α_2 regions.⁷ With the raised IgE level, hyperviscosity syndrome and mast cell activation reactions have been rarely reported.^{1,4} IgE-type myeloma generally runs a more malignant course than non-IgE myeloma with a mean survival 12.5 months⁷ or 19 months in those without renal failure.⁸

Hypodiploidy, chromosome 13 abnormalities and IGH@ gene rearrangement (chromosome 14q32) have been described in multiple myeloma patients and are typically associated with a poorer prognosis.⁹ From a small series of patients with myeloma variants, including IgM, IgD, non-secretory myeloma and two IgE subtype patients, a much higher (83%) incidence of the t(11:14) was found compared with the more common IgG and IgA subtypes.¹⁰ However, our patient's bone marrow did not reveal chromosome 14 IGH@ loci (11:14) rearrangement or chromosome 13 deletion.

Serum protein electrophoresis pattern over time



Serum immunofixation pattern over time

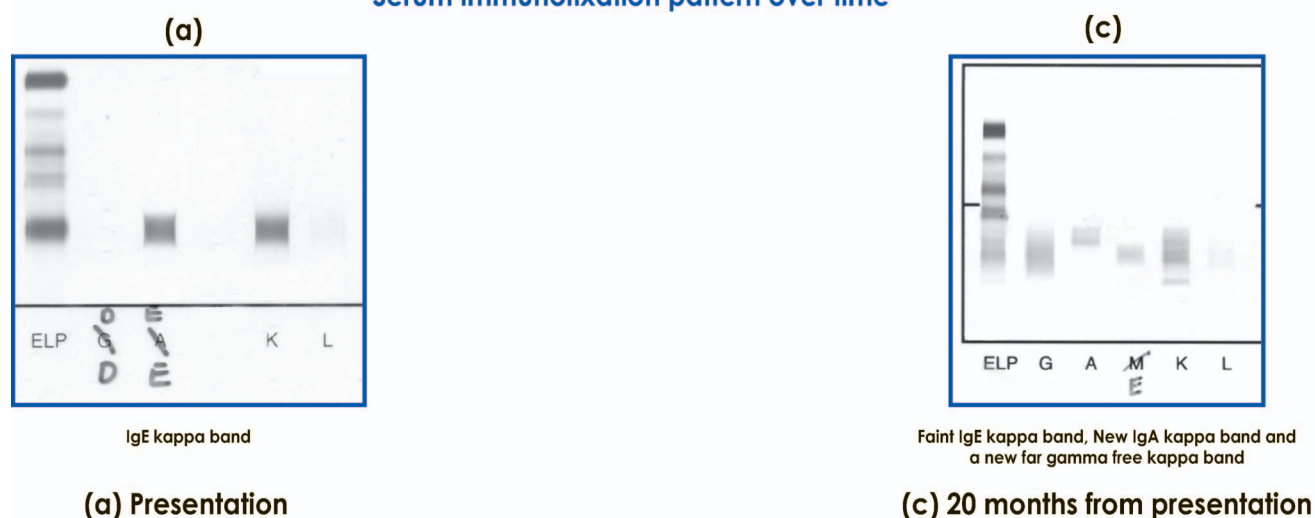


Fig. 1 Progression of the IgE and IgA kappa bands.

The emergence of IgA₂ kappa type clone in our patient was intriguing. IgE bi- or triclinal gammopathies in association with other heavy chains (G, A or M) have rarely been described.¹ In a previous report of a myeloma patient with co-secreting IgA₁ kappa and IgE kappa,¹¹ the investigators described how the IgE type plasma cells dominated over IgA₁ type plasma cells as the disease progressed. They concluded that both IgE and A tumour cell populations shared a common parental myeloma-related cell. In that case, it was unclear as to whether the event was via a pre-switched IgM to IgA or IgE (thought not as likely) or from a post-switched B cell that sequentially switched from IgA to E. This IgA₁ to E shift differed from our case which demonstrated the late

appearance of an IgA₂ clone which progressed rapidly, overtaking the diminishing IgE type clone.

From our DNA analysis, where the absence of a 'residual' molecular footprint of the ϵ switch region at the μ - α 2 switch site was found, the implication is that sequential switching of ϵ to α 2 leading to IgA₂ expression did not occur at the DNA level. However, it still leaves open the possibility of a true biclonal gammopathy at the pre-switched IgM level with parallel switch to IgA or IgE, with the existing IgA₂ clone simply overwhelming the IgE clone at the latter part of the illness. This hypothesis may be partly supported by our finding that the serum IgA₂ was not suppressed to below its lower reference limit even at the early phase of our patient's illness, in contrast to the finding of suppressed IgA₁

production throughout the illness as we would have expected from the effect of IgE-type myeloma.

An *in vitro* finding from a human IgE myeloma derived cell line may shed some light on another possible mechanism.¹² After the myeloma cell line had been cultivated for more than 12 years, the investigators found newly expressed IgA₂ accompanied by a lower rate of IgE production. Similar to our finding, they failed to demonstrate a recombinatory isotype switch from the ϵ to the $\alpha 2$ locus at the DNA level. The authors hypothesised that after long-term cultivation, a regulator which normally regulates isotype expression through RNA splicing or termination was altered, causing the $\alpha 2$ expression. Thus, it is possible that chemotherapy treatment on our patient might have exerted selection pressure on plasma cells in causing differential splicing of RNA via an altered regulator.

Proper identification of rare myeloma variants like IgD or IgE requires laboratory scientists to be alerted to unmatched light chain bands in routine serum immunofixation and take appropriate action to retest using IgD and IgE-type heavy chain antisera.

Weldon Chiu*

Humphrey Pullon§

See-Tarn Woon†

Paul Oei‡||

Roy The†

Rohan Ameratunga†

*Departments of *Clinical Biochemistry, †Virology and Immunology, and ‡Cytogenetics, Labplus, Auckland City Hospital, Auckland, §Department of Haematology, Waikato Hospital, Hamilton, and ||IGENZ Ltd, Auckland, New Zealand*

Contact Dr W. Chiu.

E-mail: weldonc@adhb.govt.nz

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Gelatinous transformation of the bone marrow as a late morphological change in imatinib mesylate treated chronic myeloid leukaemia

Sir,

Gelatinous transformation of the bone marrow is a well recognised pathological manifestation in people with cachexia consequent to malignancy, chronic infections or anorexia nervosa.¹ However, with the advent of imatinib for the treatment of chronic myeloid leukaemia, there appears to be an emerging new cause for this manifestation.

A 44-year-old male nurse was referred to the Haematology Department with characteristic peripheral blood, bone marrow and cytogenetic features of chronic myeloid leukaemia (CML) in chronic phase. He was completely asymptomatic at diagnosis. Initial full blood examination showed haemoglobin, white cell and platelet count of 120 g/L, $202.0 \times 10^9/L$ and $516 \times 10^9/L$, respectively. The film showed a full spectrum of myeloid left shift, including 1% blasts and 3% basophils. Bone marrow biopsy at diagnosis was markedly hypercellular with an increased myeloid to erythroid ratio and numerous micromegakaryocytes (Fig. 1A). Cytogenetic and molecular studies confirmed the presence of Philadelphia chromosome and BCR-ABL transcripts, respectively. Initial therapy was imatinib mesylate (IM) 400 mg orally daily, resulting in a complete haematological response. The dose of IM was increased to 600 mg daily at 3 months from diagnosis due to a sub-optimal molecular response defined by BCR-ABL/BCR transcripts falling from 1269.91% to 312.51%. Both doses of IM were well tolerated and the patient remained well.

At 11 months after diagnosis, repeat bone marrow biopsy confirmed complete cytogenetic remission and a major molecular response (BCR-ABL/BCR 0.06%). Although the full blood count was within normal limits and the aspirate appeared normocellular, the trephine was markedly hypocellular with minimal haemopoietic tissue (Fig. 1B). Fat cell atrophy was absent and no necrosis was seen. Pigment laden macrophages staining with both haemosiderin and lipofuscin were prominent. The marrow space was replaced by an amorphous eosinophilic staining ground substance on haematoxylin and eosin (H&E). These abnormal areas stained positively with Alcian blue, confirming gelatinous transformation (Fig. 1C).

On review at 14 months, the patient remains well and is in complete haematological remission.

Gelatinous transformation of the bone marrow is characterised by replacement of normal haemopoietic tissue and fat cells by an amorphous material consisting mostly of hyaluronic acid and is demonstrated by staining with Alcian blue. A variant without fat cell atrophy is described in acute myeloid leukaemia post-chemotherapy without the accompanying clinical conditions listed