Polyclonal Immunoglobulin E Levels Are Correlated with Hemoglobin Values and Overall Survival in Patients with Multiple Myeloma

Giorgia Maria Elena Matta,[1,2] Silvano Battaglio,[3] Cristiana DiBello,[1] Patrizia Napoli,[6] Cristina Baldi,[4] Giovannino Ciccone,[5] Marta Coscia,[1,2] Mario Boccadoro,[1] and Massimo Massaia[1,2]

Abstract

Purpose: Polyclonal IgG, IgA, and IgM immunoglobulins are often decreased in sera of patients with multiple myeloma (MM), whereas very few data are available on polyclonal IgE levels. We have determined IgE levels in a large series of MM patients at diagnosis and subjects with monoclonal gammopathy of undetermined significance (MGUS) and correlated IgE levels with survival and prognostic factors in MM.

Experimental Design: IgE were determined with a commercially available ELISA kit in 201 MM patients at diagnosis, 144 subjects with MGUS, and 77 age-matched controls.

Results: IgE levels progressively decreased from controls to MGUS and from MGUS to MM ($P = 0.001$). MM patients with IgE levels of >11.5 IU/mL (median) had a better survival than patients with IgE of <11.5 IU/mL ($P = 0.048$). The difference was even more significant when MM patients were divided according to clinical cutoff values. Patients with elevated IgE levels (>100 IU/mL) had from 2 to 3 years longer survival than those with low (<10 IU/mL) or intermediate values (10-100 IU/mL; $P < 0.01$). IgE levels were positively and negatively correlated with hemoglobin ($P = 0.006$) and β_2-microglobulin levels ($P = 0.007$), respectively. Univariate and multivariate analyses confirmed that high IgE levels are positive predictors of overall survival ($P = 0.03$ and 0.08, respectively) and strongly correlated with hemoglobin values.

Conclusions: Because IgE levels are dependent on Th_2 responses, these data open new perspectives in the interpretation of antitumor immune responses and pathogenesis of anemia in MM.

Polyclonal IgG, IgA, and IgM immunoglobulins are often decreased in sera of patients with multiple myeloma (MM) due to an increased catabolism and a decreased biosynthesis (1, 2). It is a matter of debate whether the extent of polyclonal IgG, IgA, and IgM hypo-γ-globulinemia has a prognostic significance in MM at diagnosis or predicts development of active MM in monoclonal gammopathy of undetermined significance (MGUS). By contrast, very little is known on serum levels of polyclonal IgE (2–4). In normal subjects, IgE synthesis is dependent on several factors, including the intrinsic properties and dose of antigen, the route of antigen delivery, the release of interleukin-4 from dendritic cells favoring the differentiation of naive Th_0 cells into Th_2 cells, the release of interleukin-4 and interleukin-13 from Th_2 cells, and the costimulatory interactions mediated by CD40/CD40 ligand between B and T cells (5–9). As a result, total IgE levels are highly variable in general population, depending on many factors, such as age, gender, race, atopy, genetics, immune status, season of the year, tobacco smoke, and concomitant diseases (10–15). Plotting the frequency distribution of IgE levels in a sample population on an arithmetic scale results in an overall distribution strongly skewed toward low values, with an isolated peak of very high IgE values. Replotting the same data on a logarithmic scale produces a Gaussian distribution (10, 11).

Our interest on polyclonal IgE in MM originated from the immune monitoring of a group of patients treated at our institution with autologous idiotype vaccines and granulocyte macrophage colony-stimulating factor as a consolidation therapy after high-dose chemotherapy and autologous stem cell transplantation (SCT) (16). The increase of eosinophils observed in the peripheral blood of these patients, very likely due to the delivery of granulocyte macrophage colony-stimulating factor, prompted us to determine IgE levels at the end of the vaccination study. We found an increase of IgE levels compared with prevaccination baseline values in 7 of 17 patients, and IgE were cross-reactive against the autologous monoclonal immunoglobulin in 6 of 7 patients (17).

Stimulated by these findings, we measured total IgE levels in a random sample of 93 MM patients in different phases of disease. Values were highly heterogeneous with either patients with undetectable levels or patients with high levels in the allergy range. Twenty-one patients showed IgE levels of >100 IU/mL, and six of them showed serum IgE levels of >1100 IU/mL. However, no clinical or anamnestic explanation, such as atopy, parasitosis, infections and tabagism, was documented in MM patients with elevated IgE levels. These findings prompted us to investigate total IgE levels in a large series of MM patients at diagnosis, and subjects with MGUS, and to correlate IgE levels with survival and prognostic factors in MM.

Materials and Methods

Study populations. Serum samples from MM patients and MGUS subjects were collected at our institution and stored in aliquots at -25°C until use. All MM sera were collected at diagnosis before any treatment. The MM series was composed of 201 patients (ages, 27-85 years; median, 59 years). Samples were collected at diagnosis, after informed consent, between May 1989 and September 2000. The clinical follow up of MM patients ended on 31 December 2005 (median follow up of survivors, 97 months; range, 63-199 months). Clinical features of MM patients at diagnosis are summarized in Table 1. Clinical records of MM patients with IgE levels of >100 IU/mL were carefully revised in search of any clinical or anamnestic evidence of allergy or intolerance. The MGUS series comprised 144 subjects (ages, 37-87 years; median, 62 years). Samples were collected between April 1989 and May 1999. The control group consisted of 77 healthy subjects (ages, 40-90 years; median, 57 years) kindly provided by the local blood bank after informed consent.

Table 1. Clinical features of MM patients at diagnosis

	No. patients	%
Total	201	100
Mean age, y (range)	59 (27-85)	
Female	96	47.7
M component		
IgG	126	62.6
IgA	40	20
IgD	1	0.5
Light chain	31	15.4
Nonsecretory	3	1.5
K	130	64.6
Salmon and Durie stage		
I	13	6.5
II	53	26.3
III	135	67.2
A (creatinine level < 2 mg/dL)	178	88.5
B (creatinine level > 2 mg/dL)	23	11.5
Mean Hb level, g/dL (range)*	10.9 (4.3-16)	
Mean β2M level, mg/dL (range) †	4.3 (0-16.7)	
Mean albumin level, mg/dL (range) ‡	3.8 (0.3-6)	
Treatment		
Conventional only	68	33.8
Autologous or allogeneic SCT	133	66.2
Thalidomide	67	33.3

*Hb level available in 197 patients.
† β2M level available in 158 patients.
‡ Albumin level available in 123 patients.

Serum levels and specificity of IgE. Total IgE levels were assessed with a commercially available ELISA kit according to the manufacturer's instructions (IEMA WELL, RADIM). Specific IgE against the four commonest allergens (i.e., *Dermatophagoides*, *Cynodon dactylon*, wheat, and cat dandruff) were determined with a commercially available ELISA kit (UniCAP, Pharmacia Diagnostics) and a standardized clinical instrument designed for this purpose (UniCAP 100).

Reactivity of IgE against autologous (Id+) or isotype-related allogeneic (Id-) monoclonal immunoglobulin was evaluated as previously reported in details (16, 17). Briefly, microplates were coated with mouse monoclonal anti-IgE antibody. Sera were dispensed into microwells and incubated for 1 h at room temperature. Id+ and Id- were isolated as previously reported (17). After extensive washing, purified Id+ or Id- was added in PBS + 2% FCS and incubated for 1 h at room temperature. After washing, alkaline phosphatase–conjugated goat anti-human IgA (IgA MM) or IgG (IgG MM) was added and incubated for 1 h at room temperature. The enzyme substrate solution was added after extensive washing and incubated for 10 min at 37°C. Absorption was evaluated at an absorbance of 405 nm with an ELISA microtiter plate reader (Titertek Multiskan Plus, Flow Laboratories).

Statistical analysis. Results are expressed as median or mean ± SE as indicated. Serum IgE levels were converted to $\log_{10}$ (log) for comparison between means. IgE levels equal to zero were ascribed a value of 0.05 IU/mL for logarithmic transformation. The Mann-Whitney rank sum test and one-way ANOVA on ranks were used to compare controls, MGUS, and MM. The Wilcoxon-signed rank test was used to compare IgE levels in the MGUS patients that progressed to MM. Correlations were assessed by Pearson's correlation coefficient. Overall survival was measured from the date of diagnosis to the date of death or end of follow-up. Overall survival curves were estimated by the Kaplan-Meier method and compared by the log-rank test. Univariate and multivariate survival analyses were done with the Cox model, and results expressed as hazard ratios (HR; 95% confidence interval). A P value of <0.05 was considered statistically significant. All data were processed with the SAS statistical software package (SAS Institute).

Results

Decreased serum IgE levels in MGUS subjects and MM patients. The arithmetic and logarithmic distributions of total IgE levels in controls, MGUS subjects, and MM patients are shown in Fig. 1 and Table 2.

In the 77 controls, IgE levels ranged from 2.0 to 384 IU/mL with a median of 38.2 IU/mL. The data set was skewed in the overall arithmetic distribution due to the large number of subjects with values lower than 50 IU/mL and an isolated peak of subjects with values higher than 200 IU/mL. When data were logarithmically transformed, they adequately fit a normal distribution. Thus, comparisons with MGUS subjects and MM patients were made using log-transformed data. The logarithmic mean of controls was 1.6 ± 0.06 IU/mL.

IgE levels in the 144 MGUS subjects ranged from 0 to 631 with a median of 14.3 IU/mL. The arithmetic distribution in MGUS subjects was similar to that of the controls, but, after logarithmic conversion, values were normally distributed only for subjects with detectable values. The MGUS data set showed a peak in the lower tail due to the subjects with undetectable values. The logarithmic mean of MGUS subjects was 0.95 ± 0.09.

IgE levels in the 201 MM patients at diagnosis ranged from 0 to 827 IU/mL with a median of 11.5 IU/mL. Sixteen MM patients displayed levels higher than 100 IU/mL without any anamnestic or clinical explanation for this increase. As in MGUS subjects, a large number of MM patients had undetectable IgE levels. The logarithmic mean of MM patients was 0.8 ± 0.07.
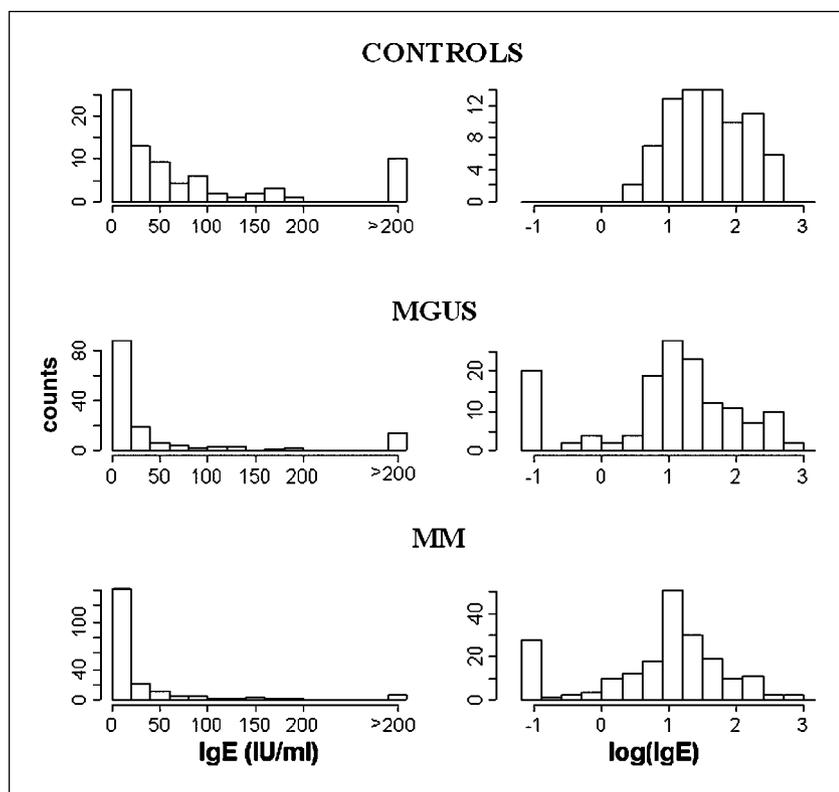
Fig. 1. Distribution of total IgE levels in controls, MGUS subjects, and MM patients at diagnosis. Arithmetic (*left*) versus logarithmic (*right*) distributions of total IgE levels in controls, MGUS, and MM at diagnosis. The differences are statistically significant between controls and MGUS and between controls and MM (both *P* < 0.001), but not between MGUS and MM (*P* = 0.21).

Differences were significant between controls and MGUS and between controls and MM (both $P < 0.001$), but not between MGUS and MM ($P = 0.21$; Fig. 1).

Sera from 33 MGUS subjects were also available at the time of their progression to overt MM. By performing a paired analysis, significantly lower IgE levels were observed after disease progression (logarithmic means: MGUS 1.33 ± 0.1, MM 1.17 ± 0.09; $P = 0.001$).

Altogether, these data indicate that IgE levels progressively decrease from controls to MGUS and, to a minor extent, from MGUS to MM at diagnosis. Because IgE levels are regulated by Th$_2$ cytokines, these data also suggest that disease evolution is associated with a shrinking ability to mount Th$_2$ immune responses.

IgE levels are regulated independently from monoclonal and polyclonal immunoglobulin. Total IgE levels were not correlated with monoclonal ($r = -0.14$, nonsignificant) or polyclonal ($r = 0.16$ and 0.36, nonsignificant) immunoglobulin levels in MM at diagnosis, whereas a statistically significant inverse correlation was detected between the monoclonal and polyclonal immunoglobulin levels ($r = -0.47$, $P < 0.05$). These data indicate that total IgE levels are not influenced by the amount of circulating monoclonal immunoglobulin and are regulated independently from other polyclonal immunoglobulins.

IgE levels are correlated with survival in MM patients. Ranges of normal IgE levels are very variable, and no consensus among laboratories has been reached to define normal and pathologic values. Initially, we selected the median (11.5 IU/mL) as the cutoff to evaluate any association between survival and IgE levels in MM at diagnosis. Survival curves were almost superimposable until 5 years of observation, when they diverged in favor of MM patients with IgE of >11.5 IU/mL

(15% versus 3% survivors at 10 years, $P = 0.048$; Fig. 2A). Next, we selected the arbitrary cutoff value commonly used by the central laboratory to discriminate normal samples from those with allergy risk (e.g., IgE, <10 or >10 IU/mL). The median survival was significantly lower in the former versus the latter (53 months versus 63 months, $P < 0.005$; Fig. 2B). When MM patients with IgE of >10 IU/mL were further divided into patients with intermediate (10-100 IU/mL) or high IgE levels (>100 IU/mL), the median survival was 53 versus 61 versus 89 months, respectively ($P = 0.016$; Fig. 2C). At 5 years, survivors were 45%, 51%, and 69% in the <10 IU/mL, 10 to 100 IU/mL, and >100 IU/mL groups. These data indicate that MM patients with elevated IgE levels have from 2 to 3 years longer median survival than those with low or intermediate values.

IgE levels are correlated with hemoglobin values in MM patients. Clinical variables [age, Salmon and Durie stage of disease, hemoglobin (Hb), creatinine, β2-microglobulin (β2M), and albumin levels] and treatments [conventional, autologous, or allogenic SCT and use of thalidomide] were evaluated in patients with IgE levels above or below the median (Table 3). The former had significantly higher Hb values and

Table 2. Arithmetic and logarithmic distributions of total Ige levels

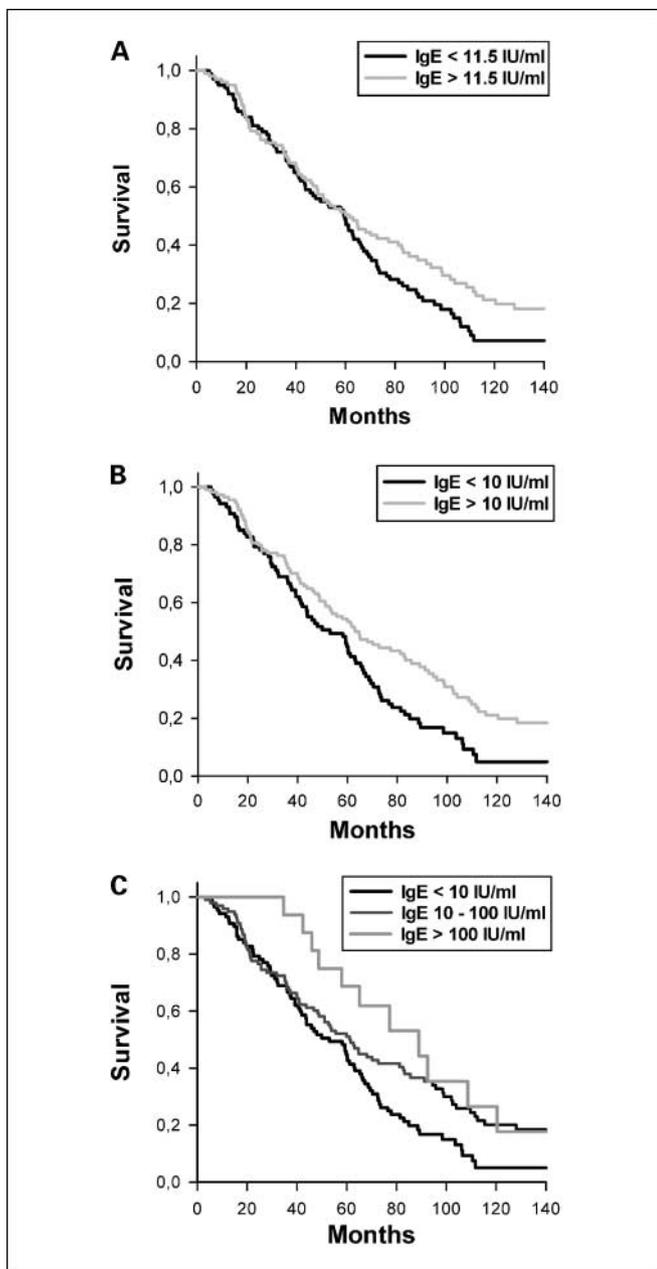|	Median (IU/ml)	Logarithmic mean
Controls	38.2	1.6 ± 0.06
MGUS	14.3	0.95 ± 0.09
MM	11.5	0.8 ± 0.07

Fig. 2. Overall survival of MM patients in relation to IgE levels. *A,* overall survival in MM patients with IgE levels below or above the median level (11.5 IU/mL; *P* = 0.048). *B,* overall survival in MM patients with IgE levels below or above 10 IU/mL (*P* < 0.005). *C,* overall survival in MM patients with IgE levels of <10 IU/mL, 10-100 IU/mL, and >100 IU/mL (*P* = 0.016).

lower β2M levels, whereas all the other variables were equally distributed. Because Hb is a favorable prognosticator, whereas β2M is a negative one, this finding fits very well with the good prognosis profile of patients with higher IgE levels. Moreover, β2M and Hb were the only variables statistically correlated with IgE levels (Hb: *r* = 0.19, *P* = 0.006; β2M: *r* = -0.21, *P* = 0.007).

The same results were observed when MM patients were divided according to the clinical cutoff value (10 IU/mL): all variables were equally distributed with the exception of Hb and β2M, which were significantly higher (*P* = 0.04) and lower (*P* = 0.008) in MM patients with IgE of >10 IU/mL (Supplementary Table S1).

These clinical, demographic, and treatment characteristics were analyzed by univariate and multivariate Cox models to determine which variables had an effect on survival and estimate adjusted HRs (Table 4). The median IgE value was selected to strengthen the robustness of these analyses. By univariate analysis, patients with IgE of >11.5 IU/mL have a 30% reduced risk of dying compared with patients with IgE of <11.5 IU/mL (HR 0.7, 95% confidence interval 0.52-0.97; *P* = 0.03). β2M, age, Hb, and treatment with SCT or thalidomide also confirmed their prognostic value (Table 3, left column).

The multivariate analyses showed that the IgE HR was maintained after adjustment for the other variables but with a lower level of statistical precision (HR 0.74, 95% confidence interval 0.53-1.0; *P* = 0.08; Table 3, right column). A stepwise selection procedure identified Hb as the most important variable affecting the IgE HR, thus confirming the correlation between Hb and IgE.

Discussion

This is the first study reporting polyclonal IgE levels in a large series of MGUS subjects and MM patients. To the best of our knowledge, it is also the first study reporting an association between IgE levels and Hb, and, even more interestingly, between IgE levels and survival in patients with hematologic malignancies. Thus far, an association between serum IgE levels and survival has only been reported in glioma patients (18). On average, total IgE levels were significantly lower in MGUS and MM than in controls, with a tendency to be lower in MM than in MGUS, even if the difference was not statistically significant. The arithmetic distribution of MGUS and MM data sets was similar compared with controls but more skewed toward low values. After logarithmic conversion, values were normally distributed for subjects with detectable values with a peak in the lower tail due to the subjects with IgE levels below the lower limit of the assay. Interestingly, none of the controls had IgE levels below the lower limit of detection, whereas 18 of 144 MGUS (12%) and 28 of 201 MM patients (14%) had undetectable serum IgE levels. The lower levels of IgE did not merely reflect retroinhibition of polyclonal immunoglobulin, a common finding in MM. Indeed, IgE levels were not correlated with monoclonal or polyclonal immunoglobulin levels, whereas a negative correlation was observed between the monoclonal immunoglobulin and polyclonal immunoglobulin other than IgE. Thus, IgE levels in MM are not influenced by the amount of circulating monoclonal immunoglobulin and are regulated independently from other polyclonal immunoglobulins.

We also had the possibility to make a side-by-side comparison in 33 MM patients whose sera were available before they developed active disease. This paired analysis showed that IgE levels were significantly lower after MM transformation, suggesting that further studies are required to determine whether IgE levels are different in MGUS subjects and MM patients.

The overall survival of MM patients was positively correlated with IgE levels at diagnosis. Patients with IgE above the median had a survival benefit, especially in the long term, as shown both by the significantly higher percentage of survivors at 10 years and by the 25% to 30% lower risk of death by univariate and multivariate Cox analyses. This survival benefit was even greater

Table 3. Comparison of clinical variables in MM patients with IgE levels of <11.5 IU/mL and >11.5 IU/mL (median)

	IgE		
	< 11.5 IU/mL	> 11.5 IU/mL	P
N	100	101	
Mean age, y	59.5 ± 1.15	59.2 ± 1.06	0.84
Stage, n (%)			
I	5 (5)	8 (7.9)	
II	25 (25)	28 (27.7)	0.59
III	70 (70)	65 (64.4)	
Mean Hb level, g/dL	10.63 ± 0.25*	11.28 ± 0.23 †	0.05
Creatinine, n (%)			
<2 mg/dL	87 (87)	91 (90.1)	0.50
>2 mg/dL	13 (13)	10 (9.9)	
Mean β2M level, mg/dL	4.96 ± 0.35 ‡	3.58 ± 0.19 §	0.01
Albumine, g/dL	3.8 ± 0.08‖	3.8 ± 0.06¶	0.68
Treatment, n (%)			
Conventional only	33 (33)	35 (34.6)	0.80
SCT	67 (67)	66 (65.3)	
Autologous	63	64	
Allogeneic	4	2	
First line	61	64	
Second line	6	2	
Thalidomide, n (%)	33 (33)	34 (33.6)	0.92

NOTE: Mean levels are expressed as mean ± SE.
*Hb available in 99 patients.
†Hb available in 98 patients.
‡β2M available in 81 patients.
§β2M available in 77 patients.
‖Albumin available in 65 patients.
¶Albumin available in 58 patients.

and occurred earlier if patients were subdivided according to the arbitrary IgE values used to predict the allergy risk. Notably, the median survival in MM patients with IgE of >100 IU/mL was 3 years longer than patients with low or intermediate values. Similar results have recently been reported in glioma (18). In this study, 115 patients were subgrouped according to normal (*n* = 70), borderline (*n* = 32), or elevated (*n* = 13) serum IgE levels. The very longest survivors (e.g., >40 months) were those with high IgE who lived, on average, 9 months longer than those with normal or borderline levels.

Differences in survival of MM patients did not reflect differences in demographics (age, sex), clinical variables (disease stage, creatinine, and albumine levels), or treatment, such as patients treated with conventional chemotherapy versus patients treated with high-dose chemotherapy and SCT or patients treated with thalidomide anytime during the course of the disease. The only variables that correlated with IgE levels were β2M and Hb. As expected, low serum IgE levels were associated with high β2M and low Hb values, further confirming the poor prognostic features of these patients.

The positive association between IgE levels and survival can be interpreted as an indication that (*a*) the immune system of MM patients with higher IgE levels is less deteriorated, including the ability to generate Th_2 responses and (*b*) Th_2 responses per se are not detrimental to disease progression. These conclusions are further supported by the longest survival observed in MM patients with IgE levels in the allergy range (i.e., >100 IU/mL) in whom an ongoing Th_2 response can be envisaged. This is quite unexpected because the wisdom is that Th_1 responses are mostly important to control tumor growth, whereas Th_2 responses play a deleterious role (19–21). However, epidemiologic data indicate that prior history of any allergy is associated with a reduced risk for pancreatic cancer (22), colorectal cancer (23), brain cancer (24, 25), childhood acute lymphoblastic leukemia (26), acute myelocytic leukemia (27), and chronic lymphocytic leukemia (28). Unfortunately, most of these studies are based on subjective questionnaires with self-reported allergies and study participants could have mistaken other morbidities for allergy. IgE represent a biological marker providing more specificity and reducing bias inherent in subjective questionnaires. Thus far, the only study addressing the issue of cancer incidence in relationship to serum IgE levels has been reported in glioma (29). In this study, the frequency of allergies and total IgE levels were inversely correlated with the occurrence of glioma, suggesting that individuals susceptible to allergies may have a higher capacity for tumor immunosurveillance, or, alternatively, allergies are correlated with other constitutional, environmental, or developmental factor(s) reducing the tumor risk. These results have recently been expanded by the same authors who have shown that glioma patients with elevated IgE levels have longer survival than patients with low or intermediate levels (18).

In the case of MM patients, elevated IgE levels were not associated with allergies, especially in MM at diagnosis. Clinical

Table 4. Univariate and multivariate analysis for IgE and prognostic factors in MM

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
IgE (>11.5 IU/mL)	0.71	0.52-0.97	0.03	0.74	0.53-1.04	0.08
Age*	1.03	1.02-1.05	0.0001	1.01	0.97-1.03	0.12
Stage III	1.25	0.9-1.75	0.18	1.05	0.73-1.5	0.8
Stage B	1.53	0.96-2.42	0.07	1.05	0.62-1.78	0.86
Hb level †	0.87	0.81-0.93	<0.0001	0.9	0.83-0.97	0.008
β2M (>3.5 mg/dL)	2.07	1.45-2.95	<0.0001	1.61	1.09-2.38	0.02
Albumin (>3.5 g/dL)	0.71	0.47-1.09	0.12	0.98	0.62-1.55	0.93
SCT	0.56	0.41-0.77	0.0004	0.64	0.44-0.92	0.02
Thalidomide	0.62	0.44-0.86	0.005	0.6	0.41-0.88	0.008

Abbreviation: 95% CI, 95% confidence interval.
*Age is expressed as continuous value, years.
† Hb level is expressed as continuous value, mg/dl.

records of all patients with IgE levels of >100 IU/mL were scrutinized in search of any clinical or anamnestic evidence of allergy, parasitosis, infections, or tabagism. Specific IgE levels against the four commonest allergens (e.g., *Dermatophagoides*, *C. dactylon*, wheat, and cat dandruff) were also assessed in 10 patients with IgE levels of >100 IU/mL with negative results. The clinical records of MM patients randomly studied after diagnosis were also examined for allergy when IgE levels were >100 IU/mL. Among 14 patients, one was found to be a heavy smoker, one was allergic to diclofenac, and one had asthma and was intolerant to penicillin. Specific IgE levels were also determined in six patients and found to be weakly detectable in three of them. Altogether, these data make unlikely that allergies play a protective role in MM. We also ruled out the possibility that IgE were directed against the monoclonal Ig, as previously reported in a series of MM patients receiving Id+ vaccines with granulocyte macrophage colony-stimulating factor as an immunoadjuvant (16, 17). After immunization, we have observed elevated IgE levels in 11 of 15 patients, without any evidence of allergic disease. In four patients, IgE were cross-reactive with Id+ and Id-, indicating that immunization occurred against epitopes localized in the constant region rather than the variable regions of autologous Id. As reported in prevaccine sera, also IgE from MM patients at diagnosis did not show any Id reactivity, ruling out their possible contribution to the natural anti-Id immunity previously described in MM (30).

An alternative hypothesis to explain a reciprocal influence between IgE and myeloma cells is through their specific cell surface receptors, namely the low-affinity (FcγRII, CD23) and the high-affinity (FcγRI) receptor for IgE. The former is strongly expressed by B cells playing a key role in the differentiation of germinal center B cells into plasma blasts (31). Interestingly, CD23 cross-linking by polymeric IgE or IgE immune complexes inhibits the proliferation and differentiation of B cells into plasma cells (32). CD23 is also expressed by stromal cells, and it can function as an adhesion ligand for CD21 expressed by myeloma cells (33). Interactions with stromal cells are a key factor to sustain the proliferation and survival of plasma cells (34). A similar interpretation has been proposed in glioma patients in which IgE may have antitumor activity via its direct activity on glioma cells or other resident cells within the central nervous system in proximity to the tumor (18).

Another interesting finding of our study is the strong correlation between IgE and Hb levels in MM patients at diagnosis, suggesting that IgE levels are influenced by the same factor(s) affecting Hb concentrations. Indeed, a stepwise selection procedure identified Hb as the most important variable affecting the IgE HR. Notably, it has been reported that erythropoietin positively regulates IgE production *in vitro* by T cell–dependent and monocyte-dependent mechanisms (35), but it is unknown whether Th$_2$ immune responses favor erythropoiesis better than Th$_1$ immune responses. Whatever the mechanism behind the association between IgE levels and survival is, this is also important in maintaining an effective erythropoiesis, as shown by the strong correlation between Hb concentrations and IgE levels. Anemia in MM has multiple causes, including decreased production of erythropoietin, insufficient responses to erythropoietin, bone marrow replacement by tumor cells, inhibition by cytokines like interleukin-6, tumor necrosis factor-α, and interleukin-1 (36–38), and apoptotic death of erythroid precursors by Fas+ myeloma cells (39). It is currently unknown whether elevated IgE levels and/or a Th$_2$-oriented immune response, including Th$_2$-derived cytokines, favor erythropoiesis compared with Th$_1$-oriented immune responses.

In conclusion, this is the first study reporting polyclonal IgE levels in a large series of MGUS subjects and MM patients. This is also the first study showing an association between serum IgE levels and survival in hematologic malignancies. Thus far, a similar association has only been reported in glioma patients (18). Because IgE levels are dependent on Th$_2$ responses (9, 40), these data open new perspectives in the interpretation of the immune responses playing a major role in antitumor responses and help to reconsider the mechanisms involved in the pathogenesis of anemia in MM.

Acknowledgments

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Giorgia Maria Elena Matta, Silvano Battaglio, Cristiana DiBello, et al.

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