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Elevated serum angiotensin converting enzyme levels as a reflection of bone marrow renin–angiotensin system activation in multiple myeloma

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Abstract

Introduction: Angiotensin converting enzyme (ACE) is a circulating enzyme that participates in the body's renin–angiotensin system (RAS) and is localized on the endothelial cell surface in the lung and other vascular beds. It catalyses the conversion of decapeptide angiotensin I to octapeptide angiotensin II. In the present study, we aimed to analyse the possible relationship between the levels of ACE in the context of RAS in multiple myeloma (MM) pathogenesis.

Materials and methods: The study was conducted on 25 MM patients (13 males, 12 females; median age 66 years, range 47–88) and 20 healthy controls. The clinical features of MM patients including demographics and laboratory findings were summarized. Serum ACE levels were measured by using commercially available kits.

Results: The serum ACE levels of MM patients and controls were 32.60±20.26 and 15.35±6.47 respectively. Serum ACE levels were significantly higher in MM patients compared with control groups ($p<0.001$).

Conclusions: Being an important component of RAS, circulating ACE might be associated with clonal proliferation of malignant plasma cells in the bone marrow microenvironment. Identification of the pathobiological activity of the local RAS in MM would enlighten the biologic basis and clinical management of haematologic disorders.

Keywords

Angiotensin converting enzyme, renin–angiotensin system, multiple myeloma

Introduction

Multiple myeloma (MM) is a mature clonal B cell neoplasm of the bone marrow (BM) with a complex array of clinical manifestations, including anaemia, bone lesions, hypercalcaemia, renal dysfunction and compromised immune function.[1] MM is thought to evolve most commonly from a monoclonal gammopathy of undetermined clinical significance that progresses to smouldering myeloma and, eventually, to symptomatic myeloma.[2] Although several genetic abnormalities that occur in tumour plasma cells play significant roles in the myeloma pathogenesis, BM microenvironmental changes were also proposed to be the cause of the malignant transformation.

The circulating renin–angiotensin system (RAS) is known to play a key role in regulating blood pressure, fluid volume, blood flow and electrolyte balance.[3,4] In addition to these physiologic effects, local tissue of the RAS has been described as present in tissues such as the kidneys, gonads, adipose tissue, liver, pancreas, biliary system and BM, from which it can elicit numerous, specific responses for individual tissue functions.[5-13] There is a considerable amount of data reporting the inevitable role of the RAS in a variety of inflammatory and haematologic disorders.[6,7,13-15]

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The demonstration of local RASs at tissue level has further implicated the importance of ACE in the pathobiology of a wide variety of diseases.

Angiotensin converting enzyme (ACE) is a membrane-bound glycoprotein which converts angiotensin I (Ang I) to angiotensin II (Ang II) and takes part in bradykinin degradation. It is considered a regulatory molecule in systemic and portal circulation in distinct disorders. An important component of the RAS and kallikrein-kinin system, ACE is involved in myelopiesis modulation mainly by cleaving tetrapeptide Acetyl-N-Ser-Asp-Lys-Pro (AcSDKP).[7] The aim of the present study was to assess circulating ACE concentrations in patients with MM. Clarification of the associations between ACE in the context of RAS and MM may help provide a better understanding of the enigmatic pathogenesis of MM. Moreover, elucidation of the pathological activity of the local autocrine/paracrine RAS-mediated regulation of monoclonal plasma cell proliferation is both pathobiologically and clinically important, since the angiotensin peptides represent a molecular target in the management of MM.

Materials and methods

This study included patients with MM in the haematology department of Ankara Diskapi Education and Research Hospital between October 2009 and June 2011. The study population included 25 MM patients and 20 healthy controls. The diagnosis of MM was reached by international diagnostic criteria.

Every patient was evaluated by serum and urine immunfixation electrophoresis. M protein was found in all patients. Then, bone marrow aspiration and biopsy was done. All patients had atypic plasma cell infiltration in 10% of the bone marrow (Figure 1). All patients had infiltration of end organ (symptomatic myeloma). All serum protein electrophoresis of the patients showed monoclonal M band. B2 microglobulin and albumin were studied in the serum of the patients. Staging (the International Staging System; ISS) was carried out according to the results.

All patients who participated in this study were newly diagnosed and none of them had been treated before. None of the patients with MM had any co-existing acute or chronic inflammatory diseases, such as hypertension, sarcoidosis, renal failure, diabetes mellitus or any other accompanying diseases that could influence ACE levels. None of the cases was receiving ACE inhibitors/angiotensin receptor blockers or any other drug that could affect the RAS. Twenty healthy controls were recruited from healthy adults with no history of acute/chronic inflammatory disorders or drug use. The staging of the patients with MM was done according to ISS. Serum ACE levels were measured and compared with healthy controls. The study was conducted in accordance with the guidelines of the Helsinki Declaration and written informed consent was obtained from each of the patients studied.

Collection of the serum

Five millilitres (ml) of venous blood was taken from each of the cases. All of the samples were centrifuged at 3000 *g* for 10 min to collect 2 ml serum sample. Subsequently, the sera were stored at -20ºC until assayed.

Biochemical analyses

The sera of the patients and controls were taken from storage and melted. Serum ACE activity was measured by monitoring the alteration in absorbance at 340 nm of the hydrolysis of furylacrylolylphenylalanylglycylglycine (FAPGG) to FAP and GG (Sigma-Aldrich, Poole, UK) on an analyser (Roche MIRA Analyser; Roche Diagnostic

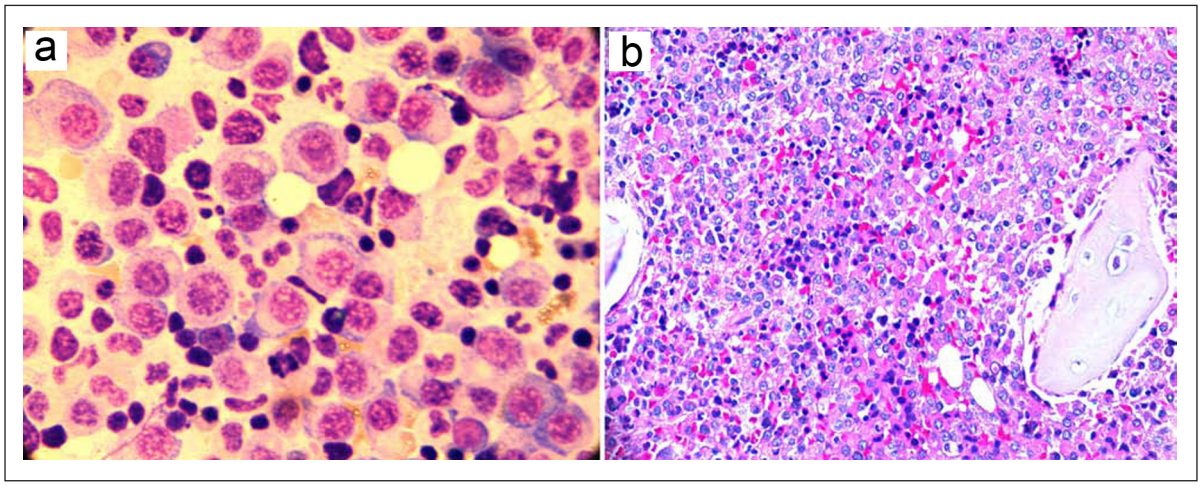

Figure 1. (a) Plasma cell infiltration in hypercellular bone marrow aspiration material (May Grunvald Giemsa; × 1000). (b) Plasma cell infiltration with significant mass in bone marrow biopsy material (H&E, × 400)

Systems, Welwyn Garden City, UK). ACE activity in the sample was determined by comparing the sample reaction rate to that obtained with the ACE calibrator. Peripheral blood samples were also taken from each patient for complete blood counts and biochemical analysis.

Statistical analyses

Data analysis was performed using Statistical Package for Social Sciences (SPSS) version 18 software (SPSS Inc., Chicago, USA). Continuous variables were tested for normality by the Kolmogorov–Smirnov test. Values were presented as mean ± standard deviations, or in the case of non-normally distributed data, as median and range. Comparisons of percentages between different groups of patients were carried out using the chi-squared test. All normally-distributed data were analysed using unpaired Student's *t* test. Data found to be non-normally distributed was analysed using the Mann–Whitney *U* test. A *p*-value of <0.05 was deemed statistically significant.

Results

Twenty five patients with MM and 20 control subjects were enrolled in the present study. The median age of patients with MM and control subjects was 66 (47–88) and 37.5 (21–64) years respectively. There were 13 males and 12 females in the MM group and 10 males and 10 females in the control group. Clinical characteristics and complete blood cell count values of the study participants are summarized in Table 1. According to the type of myeloma, 15 patients were detected as IgG (seven IgG kappa and eight IgG lambda), six were detected as IgA (two IgA kappa and four IgA lambda), and four as light chain type (two kappa and two lambda). With respect to routine biochemical tests among the study participants, there was an elevation in respect to serum urea, total protein and calcium levels. Sedimentation and CRP levels were also found to be elevated in patients with MM (Table 2).

The serum ACE levels of MM patients and controls were 32.60±20.26 and 15.35±6.47 respectively. Serum ACE levels were significantly higher in MM patients compared with control groups ($p<0.001$) (Figure 2). MM patients were also divided into three groups according to ISS classifications (Stage I: seven patients; Stage II: eight patients; Stage III: 10 patients). No significant correlation was found between these groups according to ACE levels (Figure 3). Likewise, the bone marrow plasma cell rates during the diagnosis showed no significant difference among these three groups. Plasma cell rates were found to be 45%, 49% and 51%, respectively.

Discussion

The present study demonstrated that patients with MM have increased levels of circulating ACE in comparison with the control group. The over-expression of this critical RAS component shed further light on the presence and pathologic functions of the local haematopoietic BM RAS in MM. Furthermore, increased ACE levels in the context of the RAS indicate a potential role of an RAS in disease pathophysiology.

MM is a neoplastic plasma cell disorder which arises from an asymptomatic premalignant proliferation of monoclonal plasma cells that are derived from post-germinal-centre B cells. Multistep microenvironmental and genetic alterations lead to the transformation of these cells into a malignant neoplasm.[2] Interactions between myeloma cells and BM cells or extracellular matrix receptors such as integrins, cadherins and cell-adhesion molecules increase tumoral growth, survival and migration and drug resistance. The adhesion of myeloma cells to haematopoietic and

Table 1. Characteristics and complete blood cell count values of study participants

	MM patients (*n*=25)	Control patients (*n*=20)	*p*
Median age, years	66 (47–88)	37.5 (21–64)	<0.001
Sex, M/F	13/12	10/10	0.894 (NS)
Blood pressure (BP)			
Systolic BP, mmHg	127±12	122±9	
Diastolic BP, mmHg	89±6	86±7	
ISS staging I (*n*=7)	7		
II (*n*=8)	8		
III (*n*=10)	10		
Haemoglobin, g/dl	10.5±1.2	14.6±1	<0.001
Leukocyte, /mm^3 × 10^3	6888±3200	7787±1993	0.279 (NS)
Platelet, /mm^3 × 10^3	257240±147008	275750±70738	0.608 (NS)
ACE, U/L	32.60±20.26	15.35±6.47	<0.001

Data is presented as median (range) or mean ± SD
MM: multiple myeloma; NS: not significant; ISS: International Staging System; ACE: angiotensin converting enzyme

Table 2. Biochemical parameters of study participants

	MM patients (*n*=25)	Control patients (*n*=20)	*p*
ALT (N: 0–49 U/L)	19 (9–58)	21 (12–66)	0.282 (NS)
AST (N: 0–34 U/L)	23 (13–71)	18.5 (13–41)	0.067 (NS)
ALP (N: 45–129 U/L)	119 (57–492)	68.5 (48–213)	0.004
GGT (N: 10–38 U/L)	24 (8–406)	22.5 (8–135)	0.982 (NS)
Urea (N: 19–48 mg/dl)	44.6±18	26.1±4.3	<0.001
Creatinine (N: 0.5–1.4 mg/dl)	0.97±0.30	0.87±0.16	0.162 (NS)
Calcium (N: 8.7–10.4 mg/dl)	9.4 (7.6–15)	9 (7.8–9.8)	0.022
Sedimentation (N: 0–20 mm/h)	92±27	11±6.8	<0.001
CRP (N: 0–8 mg/L)	5 (3.08–80.8)	3.06 (0.25–10)	0.001
Total protein (N:5.7–8.2 g/dl)	8.8±2	7.2±0.4	0.001
Albumin (N: 3.2–4.8 g/dl)	3.4±0.5	3.9±0.2	<0.001

Data is presented as median (range) or mean ± SD
MM: multiple myeloma; NS: not significant; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: g-glutamyl-transferase; CRP: C-reactive protein.

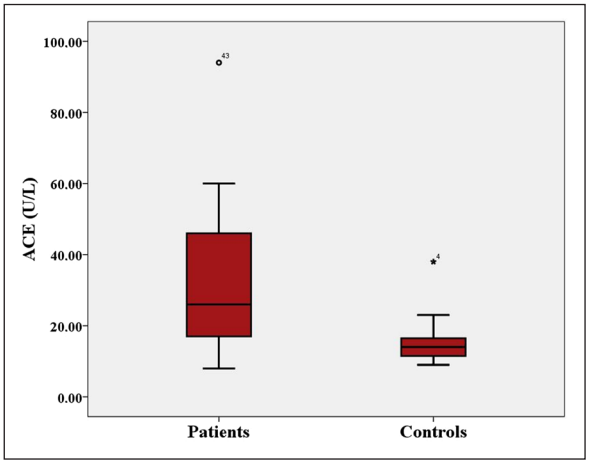

Figure 2. Serum angiotensin converting enzyme (ACE) levels in patients with multiple myeloma and controls.

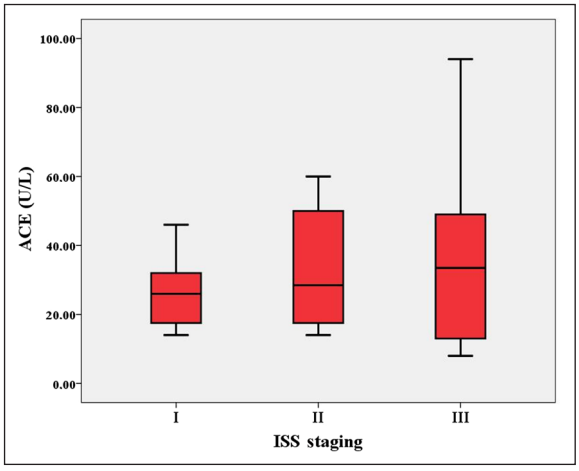

Figure 3. Serum angiotensin converting enzyme (ACE) levels in multiple myeloma patients according to the International Staging System (ISS) stagings.

stromal cells triggers the secretion of several cytokines and growth factors (e.g. interleukin-6, vascular endothelial growth factor, tumour necrosis factor, transforming growth factor β1, and interleukin-10). These cytokines and growth factors are produced and secreted by cells in the BM microenvironment, including myeloma cells, and are partially controlled by autocrine and paracrine fashions.[2,16] Being a signalling pathway, these cytokines and growth factors can serve as a point of crosstalk between the components of locally present BM RAS and pathobiological proliferation of malignant plasma cells. For this reason, based on the present study, it is reasonable to suggest that locally produced RAS elements, in the context of the local haematopoietic system, could be active in the pathobiological basis of neoplastic plasma cell disorders.

As a locally produced RAS component, ACE was shown to play a key role in haematopoietic disorders.[7,15,17] In physiological conditions, ACE regulates the plasma concentration of tetrapeptide AcSDKP, a reversible negative regulator of the proliferation of normal haematopoietic stem cells.[18] ACE inhibitors were shown to increase the levels of plasma AcSDKP by decreasing its hydrolysis, which was known to downregulate haematopoiesis through the inhibition of the proliferation of BM stem cells.[19] ACE inhibitors significantly modify the circulating haematopoietic progenitors in healthy subjects. A significant decrease via enalapril was observed in erythroid burst-forming units (BFU-Es) and the granulocyte-monocytic colony forming unit (CFU-GM) while increasing the mixed colony forming unit (CFU-mixed).[20] In a study by Rodgers et al.[21], it was shown that AT1a receptors are present in human CD34+CD38- cells, CD34+CD38+ cells, lymphocytes and stromal cells. They also demonstrated that Ang II increases the proliferation of haematopoietic

progenitor cells. The proliferative effect of Ang II was blocked by losartan (a specific AT1 receptor antagonist).[21] Based on this data, we think that elevated levels of ACE found in our study could be consistent with locally active RAS in the BM in MM.

In contrast to our findings, Rømer and Emmertsen[22] reported that serum ACE levels were depressed in MM and leukaemia patients. Although they were not able to give an explanation for the low serum ACE levels in patients whom they examined, they proposed that the greatest clinical value of serum ACE analysis could be as a supplement to other methods. Moreover, in a retrospective study by Buchler et al.[23] the outcome of patients with MM and hypertension that was treated with ACE inhibitors during high-dose chemotherapy was investigated. Although no data was given according to the serum ACE levels, the administration of ACE inhibitors during peripheral blood stem cell transplantation was reported to have adverse effects on the survival of patients with MM.

Angiotensinogen (AGT) is the precursor of Ang I, an inactive decapeptide that is converted into Ang II, the major effector of the RAS. Renin secreted from juxtaglomerular apparatus of the kidney cleaves the N-terminal end of AGT to generate Ang I. Ang I is then activated to Ang II by ACE, which is predominantly expressed in high concentrations on the surface of endothelial cells in the pulmonary circulation.[24] Ang II plays a pivotal role in the RAS mainly by two seven- transmembrane domain receptors, termed Ang II type 1 receptor (AT1R) and Ang II type 2 receptor (AT2R), showing a complex pattern of regulation and function.[25] The majority of Ang II effects are mediated by the AT1R. Whereas the AT1R induces angiogenesis, cellular proliferation and inflammatory responses, as well as being antiapoptotic, the AT2R appears to functionally antagonize many of these actions.[26-29]

The physiological malleability of the RAS can be achieved by alternative peptides and receptors. In this context, Ang II, the main effector peptide of RAS, increases haematopoietic progenitor cell proliferation by acting on AT1R present in the CD34+ haematopoietic stem cells.[21,30] Intracellularly generated Ang II in BM stem and progenitor cells could further contribute to the haematopoietic niche with autocrine/paracrine effects and to intracellular levels with intracrine effects.[7] In certain pathological-neoplastic conditions in the BM microenvironment and blood cell types of health and disease, the intracrine pathway may be the dominant mechanism of the effects of angiotensin peptides. Moreover, Ang II was shown to induce neovascularization in experimental systems by the expression of growth factors such as angiopoietin2, vascular endothelial factor, fibroblast growth factor, platelet derived growth factor and epidermal growth factor.[30] Angiogenesis is an essential process for tissue repair and development, participating in several pathologic conditions. In addition, the AT1R is demonstrated to be expressed in a great number of malignant neoplasms, and its blockade with ACE inhibitors and Ang II antagonists has shown an antineoplastic effect as well as inhibition of angiogenesis in tumoral experimental models.[30]

The autocrine and intracrine functions of the RAS are linked to haematopoiesis regulation by affecting production, proliferation and differentiation of the cells in both normal and malignant haematological processes.[31] The RAS regulates cellular growth in a variety of tissues including the BM and can exert considerable effects on erythropoietic progenitors and primitive pluripotential haematopoietic stem-cell populations.[17] Recent investigations have revealed several RAS elements and receptors on normal and neoplastic haematopoietic cells.[14,21,32,33] Strawn et al.[32] demonstrated the existence of ACE, Ang II, angiotensin type 1 and 2 receptors in rat unfractionated BM cells, haematopoietic lineage BM cells and cultured marrow stromal cells. In their study, ACE, renin and AGT mRNAs were reported to be present in BM cells and in cultured marrow stromal cells. Current literature supports the evidence that the effects of the RAS on the regulation of haematopoietic differentiation are various and diverse. ACE, Renin, AGT and/or AGTR1 are shown to be expressed in BM cells, human umbilical cord blood and $CD34^+$ haematopoietic stem cell (HSC); furthermore, Ang II peptide can regulate erythropoiesis by upregulating erythropoietin levels and/or by exerting mitogenic impacts on erythroid progenitors and $CD34^+$ HSC.[14,21,31,34,35] Unfortunately, there are no studies in the existing literature revealing the role of the RAS in neoplastic plasma cell disorders. Therefore, as disclosed in our study, elevated ACE levels in neoplastic plasma cell disorders, in the context of the RAS, could represent a starting point from which to reflect ongoing, locally enhanced RAS activity subject to pharmacological management with RAS modulators.

We recognize some limitations inherent in our study design. First of all, our patient and control groups differ in respect to blood haemoglobin levels. Although anaemia is a characteristic of MM, it is understandable that healthy controls that were recruited for this study do not have anaemia. Secondly, based on the fact that MM is generally seen in the elderly population, our control group is younger than the MM patients.

In conclusion, the possible relationship between the local haematopoietic RAS and neoplastic plasma cell disorders represents important new avenues for the search for MM pathogenesis. Further experimental and clinical studies should focus on determining the exact role of circulating and local RAS and ACE in the pathophysiology of the expanding spectrum of clonal proliferation of malignant plasma cells that will lead to better management of MM patients.

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Conflict of interest

The authors declare no conflict of interest

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