The role of cytokines and adhesion molecules in the evolution of monoclonal gammopathy of undetermined significance into myeloma

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The aim of this study was to evaluate the influence of some cytokines on the evolution of monoclonal gammapathies. Fifty-one patients with multiple myeloma (MM) divided into 3 groups according to disease stage (MM1, MM2, MM3), 60 with monoclonal gammapathy of undetermined significance (MGUS) and 50 healthy controls (C) were studied. The levels of sCD138 (Syndecan-1), TGF-β₁, sVCAM-1, IL-13, Fas/APO-1, IL-6, β₂-microglobulin (β₂-M) and C-reactive protein (CRP) were assayed. Seven of the 60 cases of MGUS (11.6%) evolved into MM3 during the 5-year follow-up; these cases were studied in order to identify any changes in the cytokine network.

β₂-M and CRP concentrations increased significantly through C, MGUS and the three stages of MM. TGF-β₁, sVCAM-1, Fas/APO-1 and IL-6 levels were significantly higher, while IL-13 concentration was significantly lower, in MGUS and in MM than in C (p<0.001). The level of sCD138 was significantly lower in MGUS than in C and significantly higher in MM than in C (p<0.001). On the other hand, TGF-β₁ concentration was significantly higher, while IL-6 and sCD138 concentrations were significantly lower, in MGUS than in MM (p<0.001). Only sCD138 was significantly higher in MM3 than in MM1 and in MM2 (p<0.001), while the concentrations of all the other cytokines did not differ significantly between MM1, MM2, and MM3. There were no significant differences in cytokine values between MGUS which evolved into MM3 and MM1 (p>0.05).
and MGUS which did not evolve. Moreover, in the 7 cases of MGUS which did evolve into MM3, the cytokine levels were not significantly different between the start of the study and at the end of the follow-up. We conclude that syndecan-1, like the better recognised βββββ2-M, CRP and IL-6 markers, has a prognostic value for the evolution of monoclonal gammopathies.

**Key words:** MGUS, myeloma, cytokine, IL-6, syndecan-1

**Introduction**

Monoclonal gammopathies are lymphoproliferative diseases characterised by the production of immunoglobulins or only light or heavy chains, known as "M component", by a neoplastic B-cell clone. Gammopathies are classified on the basis of their degree of malignancy and their M component.

Monoclonal gammopathy of undetermined significance (MGUS) is characterised by being asymptomatic and having a modest M component (<3 g/dL), with bone marrow infiltration <10% and a low proliferative activity, without other alterations typical of multiple myeloma (MM). The risk of progression of MGUS to multiple myeloma or related disorders is about 1 percent per year.

MM is typically characterised by osteolytic lesions, the presence of Bence-Jones protein and kidney failure, while plasma cell infiltration of bone marrow is variable. The mechanisms of neoplastic transformation and evolution of monoclonal gammopathies have been studied by many authors, who have predominantly focused their attention on an involvement of programmed cell death, on anomalies of cell adhesion mechanisms and on the role of cytokines.

The aim of this study was to evaluate the cytokine network in patients with MGUS and MM and to identify any changes in cytokine concentrations in patients developing a MM from MGUS in order to establish whether the cytokines are involved in this evolution.

**Materials and methods**

**Patients**

Fifty-one patients (27 males, 24 females) with MM, 60 (32 M, 28 F) with MGUS and 50 healthy adult subjects (29 M, 21 F) were studied.
The 51 patients with a diagnosis of MM had a mean age of 62 ± 3.1 years.

The diagnosis of MM was made on the basis of the presence of following criteria: a) M-component in serum (IgG >3.5 g/dL or IgA >2 g/dL) and/or in urine (κ or λ chains >1 g/24 hr); b) osteolytic lesions; c) plasma cell bone marrow infiltration ≥10%. These patients were further divided into 3 groups according to their stage of MM, as defined by Durie and Salmon's criteria:

- **Stage I**: (13 patients, group MM1) - Hb >10 g/dL, normal calcium concentration, absence of radiological bone lesions, M component: IgG <5 g/dL or IgA <3 g/dL, Bence-Jones protein <4 g/24h;
- **Stage II**: (4 patients, group MM2) - patients not included in stage I or III;
- **Stage III**: (34 patients, group MM3) - Hb <8.5 g/dL, hypercalcaemia, extensive skeletal injuries or pathological fracture, M component = IgG >7 g/dL or IgA >5 g/dL, Bence-Jones protein >12 g/24h.

The 60 patients with MGUS had a mean age of 69 ± 4.3 years and the typical characteristics of the pathology.

Patients with MGUS or MM and contemporary HCV or HIV infection were excluded from the study because viral and bacterial infections can cause physiological clonal development of immune cells and thus interfere with the determination of cytokine concentrations.

Fifty healthy, sex-matched subjects (22 - 49 years) were also tested as the control group (C).

**Study protocol**

This study had two phases: at enrolment, cytokines were assayed in the sera of all patients and controls. β2-M and CRP were also assayed as indicators of disease.

After a follow-up of 5 years, 7 of the 60 patients initially characterised as having MGUS were studied again because, in the meantime, their pathology had evolved into stage III MM.

Table I - Serum cytokine levels in patients with monoclonal gammopathy of undetermined significance (MGUS), in patients with multiple myeloma (MM) and in healthy controls (C). Data are shown as mean ± SEM

<table>
<thead>
<tr>
<th></th>
<th>MGUS</th>
<th>MM</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>n° of subjects</td>
<td>60</td>
<td>51</td>
<td>50</td>
</tr>
<tr>
<td>TGF-β1 (ng/mL)</td>
<td>95.2 ± 12.1 § #</td>
<td>56.4 ± 2.8 §</td>
<td>4.7 ± 0.4</td>
</tr>
<tr>
<td>sVCAM-1 (ng/mL)</td>
<td>2456.5 ± 62.2 §</td>
<td>2413.9 ± 39.3 §</td>
<td>685.8 ± 68.9</td>
</tr>
<tr>
<td>sCD138 (ng/mL)</td>
<td>55.1 ± 18.8 § #</td>
<td>186.3 ± 6.7 §</td>
<td>76.4 ± 0.5</td>
</tr>
<tr>
<td>Fas/APO-1 (IU/mL)</td>
<td>20.6 ± 1.9 §</td>
<td>18.9 ± 0.5 §</td>
<td>8.7 ± 0.4</td>
</tr>
<tr>
<td>IL-13 (pg/mL)</td>
<td>0.9 ± 0.04 §</td>
<td>0.86 ± 0.02 §</td>
<td>1.5 ± 0.02</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>24.1 ± 0.5 § #</td>
<td>28.9 ± 0.7 §</td>
<td>6.1 ± 0.3</td>
</tr>
</tbody>
</table>

§ = p < 0.001 versus C; # = p < 0.001 versus MM

Camarillo, CA, USA), interleuchina 6 (IL-6) (Quantikine HS human IL-6, R&D System Inc., Minneapolis, MN, USA), Fas/APO-1 (CD95) (Oncogene Research Products Fas/APO-1 Assay, Calbiochem, San Diego, CA, USA), Syndecan-1 (SDC1/sCD138) (BioSource Cytoscreen Syndecan, BioSource International) and the soluble form of the vascular cell adhesion molecule (sVCAM –1) (Parameter human sVCAM-1, R&D System Inc) [valori normali < 714 ng/mL]. I livelli di β2-M sono stati dosati con tecnica MEIA [valori normali < 714 ng/mL]. I livelli di β2-M sono stati dosati con tecnica MEIA (Microparticle Enzyme Immunoassay) (AxSYM β2-Microglobulin, Abbott Japan, Tokyo, Japan) [v.n. = 0.66 – 2.25 mg/L]. La CRP è stata determinata mediante dosaggio nefelometrico [v.n. = 0 – 5 mg/L].

**Analisi statistica**

I dati sono espressi come media ± SEM (Errore Standard Medio). È stata eseguita l'analisi della varianza ad una via (ANOVA) seguita dal test di Newman-Keuls per l'analisi tra i gruppi e dal t-test di Student per i dati appaiati. Il livello di significatività è stato posto al 5% (p <0.05).

**Risultati**

I nostri risultati mostrano che i livelli sierici di TGF-β1, sVCAM 1, Fas/APO-1 e IL-6 erano significativamente più alti, mentre quelli dell'IL-13 più bassi, nei pazienti con MGUS o affetti da MM rispetto ai controlli (p <0.001); inoltre i livelli sierici di sCD138, comparati col gruppo di controllo, erano significativamente bassi nella MGUS e alti nel MM (p <0.001) (Tabella I). D'altra parte, il TGF-β1 era significativamente più alto, mentre l'IL-6 e il sCD138 risultavano significativamente più bassi nella MM rispetto al MM (p <0.001) (Tabella I).

TGF-β1, sVCAM 1, Fas/APO-1, IL-13 and IL-6 non presentavano delle differenze statisticamente significative nei tre stadi di MM (Figura 1). Al contrario, i livelli sierici di...
**Assays**

Serum levels of tumour growth factor-beta 1 (TGF-β1) (Biotrak human TGF-β1 ELISA system, Amersham International plc, Little Chalfont, Buckinghamshire, UK), interleukin 13 (IL-13) (BioSource Cytoscreen human interleukin-13, BioSource International, Camarillo, CA, USA), interleukin 6 (IL-6) (QuantiKine HS human IL-6, R&D System Inc., Minneapolis, MN, USA), Fas/APO-1 (CD95) (Oncogene Research Products Fas/APO-1 Assay, Calbiochem, San Diego, CA, USA), Syndecan-1 (SDC1/sCD138) (BioSource Cytoscreen Syndecan, BioSource International) and the soluble form of vascular cell adhesion molecule (sVCAM–1) (Parameter human sVCAM-1, R&D System Inc) [normal range <714 ng/mL] were determined by a solid phase sandwich enzyme linked-immunosorbent assay (ELISA).

β2-M levels were measured with a microparticle enzyme immunoassay (MEIA) (AxSYM β2-microglobulin, Abbott Japan, Tokyo, Japan) [normal range = 0.66 – 2.25 mg/L]. CRP was measured by a nephelometric assay [normal range = 0 – 5 mg/L].

**Statistical analysis**

Data are shown as mean ± SEM. ANOVA followed by the Newman-Keuls test for intergroup analysis and Student’s t-test for paired data were used. The level of statistical significance was set at 5% (p <0.05).

**Results**

Our results showed that serum levels of TGF-β1, sVCAM-1, Fas/APO-1 and IL-6 were significantly higher, while the level of IL-13 was significantly lower in the patients with MGUS or MM than in the controls (p <0.001); moreover, compared with its level in the control group, the serum level of sCD138 was significantly lower in MGUS and significantly higher in MM (p <0.001) (Table I). On the other hand, TGF-β1 concentration was significantly higher, while IL-6 and sCD138 concentrations were significantly lower, in MGUS than in MM (p <0.001) (Table I).

The levels of TGF-β1, sVCAM-1, Fas/APO-1, IL-13 and IL-6 were not significantly different between cases of MM1, MM2, and MM3 (Figure 1). In contrast, the serum level of syndecan-1 was significantly higher in MM3 than in MM1 and in MM2 (p <0.001) (Figure 1).

β2-M and CRP concentrations increased from their lowest levels in the healthy control subjects, intermediate levels in patients with MGUS, through to the highest levels Syedcan-1 nel MM3 erano significativamente più elevati rispetto a MM1 e MM2 (p<0,001) (Figura 1).

Le concentrazioni di β2-M e CRP mostravano livelli crescenti a partire dai controlli, attraverso i pazienti con MGUS fino ai tre stadi di MM. In particolare la β2-M era statisticamente più elevata nella MGUS rispetto ai controlli (p <0,001), nell'MM1 rispetto a C e MGUS (p <0,001), nell'MM2 rispetto a C e MGUS (p <0,001) e rispetto a MM1 (p<0,05), nell'MM3 rispetto ai C e MGUS (p <0,001) e MM1 (p<0,01) (Figura 2). La CRP era significativamente aumentata nella MGUS, MM1, MM2 e MM3 se comparata con i controlli (p <0,001); inoltre la CRP era significativamente più alta nel MM2 (p <0,01) e nel MM3 (p <0,001) rispetto alla MGUS (Figura 2).

Dopo un follow-up di 5 anni, abbiamo rivalutato i 60 pazienti inizialmente affetti da MGUS. Per 53 lo stato della malattia non era cambiato, mentre 7 su 60 (11,6%) sono stati riclassificati come affetti da MM allo stadio III. Abbiamo paragonato i livelli di citochine ottenuti dai risultati iniziali in questi 2 gruppi di pazienti per individuare un eventuale marcatore predittivo di evoluzione. I nostri dati mostravano differenze non statisticamente significative tra questi 2 gruppi (Figura 3). Inoltre, abbiamo paragonato i valori di citochine nei 7 pazienti evoluti a MM3, valutati al momento dell'arruolamento nello studio ed alla fine del follow-up, allo scopo di stabilire se esista una relazione tra evoluzione patologica e modificazione nei livelli di una o più citochine. Non è stata riportata nessuna differenza statisticamente significativa, sebbene il sCD138 fosse significativamente elevato nelle MGUS evolute a MM3 rispetto alle MGUS non evolute (p <0,05) (Figura 3).

**Discussione**

Lo scopo di questo studio è stato quello di indagare l'esistenza di un possibile coinvolgimento di TGF-β1, sVCAM-1, Syndecan-1 (sCD138), Fas/APO-1 (CD95), IL-13 e IL-6 nell'evoluzione di patologie linfoproliferative da bassa (MGUS) ad alta invasività (MM).

L'alterazione dell’assetto citochinico riveste, probabilmente, un importante ruolo nella patogenesi delle malattie linfoproliferative e delle gammapatie monoclonali10. Per tale motivo, lo studio delle citochine e di altre molecole, come i fattori di crescita12, le molecode di adesione9 e quelle coinvolte nell'apoptosi6, può dare preziose informazioni sulla fisiopatologia, diagnosi e prognosi di questi disordini.

Nel nostro studio, in accordo con la letteratura, la β2-M e la CRP sono risultati importanti indici prognostici, essendo i loro valori in costante incremento dai controlli allo stadio...
Figure 1 - Serum cytokine levels in 51 patients with multiple myeloma (MM): 13 patients had stage I disease (MM1), 4 patients had stage II (MM2) and 34 patients had stage III (MM3). Data are shown as mean ± SEM.
Figure 2 - Serum levels of β₂-microglobulin and C-reactive protein in 50 healthy controls (C), 60 patients with monoclonal gammopathy of undetermined significance (MGUS) and 51 patients with multiple myeloma (MM): 13 patients had stage I disease (MM1), 4 patients had stage II (MM2) and 34 patients had stage III (MM3). Data are expressed as mean ± SEM.
Figure 3 - Serum cytokine levels in 60 patients with monoclonal gammopathy of undetermined significance (MGUS) in follow-up for 5 years. The 1st column shows initial values in the 53 patients whose MGUS did not evolve during the follow-up. The 2nd and 3rd columns show levels at enrolment and at the end of the follow-up, respectively, in 7 patients whose MGUS evolved into stage III multiple myeloma (MM3). Data are shown as mean ± SEM.
in the three stages of MM. In particular, the level of $\beta_2$-M was significantly higher in MGUS patients than in controls (p <0.001), in MM1 patients than in controls and MGUS patients (p <0.001), in MM2 patients than in controls, MGUS patients (p <0.001) and MM1 patients (p <0.05), and finally, in MM3 patients than in controls, MGUS patients (p <0.001) and MM1 patients (p <0.01) (Figure 2). CRP was significantly higher in patients with MGUS, MM1, MM2 and MM3 than in controls (p<0.001); moreover CRP was significantly higher in MM2 (p<0.01) and MM3 (p<0.001) patients than in patients with MGUS (Figure 2).

After a follow-up of 5 years, we re-evaluated the 60 patients initially diagnosed as having MGUS. The state of disease had not changed in 53 of them, whereas the other 7 (11.6%) had developed stage III MM. We compared the cytokine levels obtained at enrolment in these two groups of patients in order to identify possible markers predictive of evolution. Our data showed that there were no significant differences between these two groups at enrolment (Figure 3). Furthermore, in the 7 patients whose MGUS evolved into MM3, we compared the cytokine levels assayed at the time of enrolment into the study and those at the end of the follow-up in order to establish whether there is a relationship between pathological evolution and modification in one or more cytokine levels. No significant modifications were recorded, although the level of sCD138 was significantly higher in MGUS that had evolved into MM3 than in MGUS which did not evolve (p<0.05) (Figure 3).

**Discussion**

The aim of this study was to investigate whether TGF-$\beta_1$, sVCAM-1, syndecan-1 (sCD138), Fas/APO-1 (CD95), IL-13 and IL-6 are involved in the evolution of pathologies from low (MGUS) to high invasiveness (MM). Alterations in the cytokine network probably have an important role in the pathogenesis of lymphoproliferative diseases and monoclonal gammopathies\(^\text{10}\). For this reason, the study of cytokines and other molecules, such as growth factors\(^\text{11}\), adhesion\(^\text{12}\) and apoptosis\(^\text{13}\) molecules, can give precious information about the pathophysiology, diagnosis and prognosis of these disorders.

In accordance with previously published data, we found that both $\beta_2$-M and CRP were important prognostic indices, their levels increasing from lowest in controls to highest in patients with stage III MM. In fact, many authors have classified MM patients into 3 risk groups (low, intermediate and high) on the basis of CRP and $\beta_2$-M serum levels\(^\text{13-15}\).
In particular, serum CRP concentration reflects IL-6 activity; in fact this cytokine stimulates hepatocytic synthesis of acute phase proteins, such as CRP. For this reason serum CRP level is a highly significant prognostic factor, independently of serum β_2-M level.

IL-6 is a pleiotropic cytokine that stimulates haematopoietic progenitor cells and promotes differentiation of human B cells. We found significantly higher levels of IL-6 in patients with MGUS and MM than in healthy subjects. It has been demonstrated that IL-6 is the major growth factor for MM, acting in either an autocrine or a paracrine fashion. In fact IL-6 and IGF-I, the major growth factor for MM, acting in either an higher levels of IL-6 in patients with MGUS and MM than resistance in MM cells.

In addition, IL-6 may both inhibit activity (associated with cell growth, survival and drug secretion) and up-regulate telomerase activity (associated with cell growth, survival and drug resistance in MM cells). In addition, IL-6 may both inhibit Fas-induced apoptosis and modulate stress-activated protein kinase (SAPK) activity.

In this study, serum levels of Fas/APO-1, which belongs to the family of type-1 membrane proteins that transduce apoptotic signals, were significantly higher in MGUS and in the three stages of MM than in controls (Table I and Figure 1). Fas ligand concentration is significantly elevated in both Fas receptor-negative MM and in Fas receptor-positive MM with the secretion of Fas splicing variants; it, therefore, represents the expression of myeloma cells escaping host immune surveillance.

TGF-β_1 is produced in MM by both tumour cells and bone marrow stromal cells and can positively regulate IL-6 secretion. In fact, our data demonstrate that TGF-β_1 concentrations are higher in both MGUS and MM than in controls (Table I). Some authors suggest that TGF-β_1 has a dual role: it inhibits normal B-cell proliferation and Ig secretion and promotes neoplastic growth, probably through IL-6 and by the fact that tumour cells are resistant to its inhibitory effects.

VCAM-1, expressed on bone marrow stroma, belongs to the family of cell adhesion molecules (CAM) and is a ligand for the integrin VLA-4, which mediates attachment, and consequently localisation, of myeloma cells to MM stroma. We found increased levels of sVCAM-1 in all our patients (Table I): in both groups the sVCAM-1 concentrations exceeded 3.5 times the values observed in controls and the upper limit of the normal range. There are reports of a statistical relationship between sVCAM-1 and various elements of the cytokine network (IL-2, sIL-2R, sIL-6R, TNF-α, sICAM-1) and β_2-M, so soluble forms of adhesion molecules probably play a role in the stadi trovati aumentati in tutti i nostri pazienti (Tabella I): in entrambi i gruppi il sVCAM-1 superava di 3,5 volte il valore osservato nei C ed il limite superiore dei valori di riferimento. È stato dimostrato che esiste una correlazione tra sVCAM-1 e vari elementi del network citochinico (IL-2, sIL-2R, sIL-6R, TNF-α, sICAM-1) e con la β_2-M, perciò le forme solubili delle molecole di adesione probabilmente possono giocare un ruolo nella patogenesi del MM, ma a tutt’oggi la loro peculiare attività non è stata ancora chiarita. In aggiunta, l’espressione di VCAM-1 nelle cellule endoteliali è regolata dall’IL-13, una citochina multifunzionale elaborata dai linfociti T attivati. Sulla base dei nostri risultati, il Syndecan-1 sembra un valido indice prognostico dell’evoluzione a MM. Infatti, la sua concentrazione è più alta nel MM rispetto alla MGUS e rispetto ai soggetti sani (Tabella I); inoltre, nell’ambito dei soggetti con MM, i più elevati valori di Syndecan-1 sono stati registrati nei pazienti allo stadio III (Figura 1). Questa molecola è espressa sulle cellule linfoidi B nei vari stadi di differenziazione. Il CD138 è un proteoglicano eparan-solfato transmembrana, capace di legare numerose molecole: componenti della matrice extra-cellulare (come il collagene di tipo I, la fibronectina e la trombospondina), citochine e fattori di crescita (come TGF-β_1 e FGF-2). Il Syndecan-1 regola varie funzioni cellulari (adesione, proliferazione ed apoptosi) e probabilmente gioca un ruolo nell’oncogenesi. Nei pazienti con MM, il CD138 è espresso, nel midollo osseo, solo sulle cellule mielomatose e, nel sangue periferico, sulle plasmacellule maligne. I nostri risultati mostrano che la MGUS evolvente a MM presenta alte concentrazioni di sCD138 rispetto alla MGUS non evolvente, anche se questa differenza non è statisticamente significativa a causa della grande dispersione dei dati e, di conseguenza, per un ampio errore standard (Figura 3). D’altra parte, i livelli sierici di Syndecan-1 sono significativamente più elevati nel MM originatosi dalla MGUS rispetto alla MGUS non evolvente (Figura 3). I dati osservati possono essere spiegati dal fatto che le cellule mielomatose apoptotiche perdono rapidamente il Syndecan-1. Infine, alti livelli di Syndecan-1 sono associati con un’alta percentuale di plasmacitosi midollare ed elevati livelli di β_2-M; per tale motivo, esso costituisce un parametro prognostico indipendente e potrebbe essere utile nella classificazione prognostica del MM. In conclusione, al di là dell’ormai noto ruolo della β_2-M, della CRP e dell’IL-6, possiamo affermare che il Syndecan-1 potrebbe avere un valore prognostico nell’evoluzione delle gammapatie monoclonali, sebbene non sia ancora chiaro se un’aumentata concentrazione di Syndecan-1 nel MM risulti critica per lo sviluppo della
pathogenesis of MM although their particular activities have not yet been clarified. In addition, VCAM-1 expression in endothelial cells is regulated by IL-13, a multifunctional cytokine produced by activated T cells\(^9\).

On the basis of our results, syndecan-1 seems to be a valid prognostic indicator of the evolution to MM. In fact, its concentration in MM was higher than in MGUS and in healthy subjects (Table I); moreover, within the subsets of MM, the highest levels of syndecan-1 were recorded in patients with stage III disease (Figure 1). This molecule is expressed on lymphoid B cells at various stages of differentiation\(^9\). CD138 is a transmembrane heparan sulfate proteoglycan\(^3\) able to link numerous molecules: extracellular matrix components (such as type I collagen\(^3\), fibronectin\(^3\) and thrombospondin\(^3\)), cytokines and growth factors (such as TGF-\(\beta\), and FGF-2\(^3\)). Syndecan-1 regulates various cell functions (adhesion, proliferation and apoptosis) and probably plays a role in oncogenesis\(^6\). In MM patients, CD138 is expressed, in bone marrow, only on myeloma cells\(^37\) and, in peripheral blood, on malignant plasma cells\(^38\). Our results show that the concentration of sCD138 in cases of MGUS evolving into MM was higher than in the not evolving cases although this difference was not statistically significant because of a large dispersion of data and, consequently, a large SEM (Figure 3). Nevertheless, serum syndecan-1 levels were significantly higher in MM that had evolved from MGUS than in not evolving MGUS (Figure 3). These observations can be explained by a rapid lost of syndecan-1 by apoptotic myeloma cells\(^39\). Finally, high levels of syndecan-1 are associated with a high percentage of bone marrow plasmocytosis and \(\beta_2\)-M levels\(^8\); indeed, syndecan-1 is an independent prognostic parameter and should be useful in the prognostic classification of MM\(^4\). In conclusion, besides confirming the well known role of \(\beta_2\)-M, CRP and IL-6, the results of our study suggest that syndecan-1 levels may have a prognostic value for the evolution of monoclonal gammopathies, although it is not yet clear whether the increased serum level of syndecan-1 in MM is critical for the development of disease or whether it is a secondary characteristic related to the pathological progression of the disease.

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Cytokines and monoclonal gammopathies

Riassunto

Scopo di questo studio è stato quello di valutare l'influenza di alcune citochine nell'evoluzione delle gammapatie monoclonali. Sono stati studiati 51 pazienti affetti da mieloma multiplo (MM), suddivisi in 3 gruppi in base alla stadiazione (MM1, MM2, MM3), 60 pazienti con gammapatia monoclonale di significato non determinato (MGUS) e 50 soggetti di controllo in apparente buona salute (C). Abbiamo testati i livelli sierici di sCD138 (Syndecan-1), TGF-\(\beta\), sVCAM-1, IL-13, Fas/APO-1, IL-6, \(\beta_2\)-Microglobulina (\(\beta_2\)-M) e proteina C reattiva (CRP). In un follow-up di 5 anni, la MGUS è evoluta a MM in 7 pazienti su 60 (11,6%); questi sono stati ri-esaminati per evidenziare un eventuale modifica nell'assetto citochinico. Le concentrazioni della \(\beta_2\)-M e della CRP mostravano livelli significativamente crescenti dai C, ai MGUS ed ai 3 stadi di MM. I livelli di TGF-\(\beta\), sVCAM-1, Fas/APO-1 e IL-6 erano significativamente più alti, mentre quello dell'IL-13 più basso, nei pazienti con MGUS e con MM rispetto a C (p<0,001). sCD138 era significativamente più basso nei MGUS e più alto nei MM, a paragone con C (p<0,001). D'altronde, il TGF-\(\beta\) era significativamente più alto, mentre l'IL-6 e il sCD138 erano significativamente più bassi, nei MGUS rispetto ai MM (p<0,001). Nei pazienti con MM al 3\° stadio, solo il Syndecan-1 era significativamente elevato rispetto agli altri stadi (p<0,001), mentre tutte le altre citochine non mostravano delle differenze significative tra i 3 stadi di malattia. Tra gli MGUS evoluti a MM3 e gli MGUS stabili, non evoluti, non abbiamo trovato differenze significative nei valori delle citochine. Inoltre, nei 7 pazienti con MGUS evoluta a MM3 non c'erano modificazioni significative nei livelli citochinici registrati all'inizio dello studio ed alla fine del follow-up. Al di là del ruolo già conosciuto della \(\beta_2\)-M, della CRP e dell'IL-6, possiamo concludere che anche il Syndecan-1 ha un valore prognostico per l'evoluzione delle gammapatie monoclonali.

Parole chiave: MGUS, mieloma, citochine, IL-6, syndecan-1

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Cytokines and monoclonal gammapathies


