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Role of Beta 2 microglobulin in systemic lupus erythematosus

Abstract

Aim: This is a prospective study reporting on the safety and feasibility of an iodinated hydrogel tissue fiducial marker (IH TFM) for image guided radiation therapy in the treatment of muscle invasive bladder cancer.

Materials and Methods: From September 2015 to July 2017, four patients diagnosed with muscle invasive unifocal transitional cell carcinoma (TCC) bladder cancer were included in the study. Under general anaesthetic, patients underwent cystoscopic injection of IH into their tumour base. Patients subsequently underwent image guided RT. The total prescription was 64.0 - 66.0 Gy in 2.0Gy per fraction. Daily online cone-beam CT (CBCT) matching to IH TFM were performed throughout the course of radiation therapy (RT) to verify the extent of daily treatment shifts. IH volume, its stability and visibility were also evaluated.

Results: The volume of IH TFM remained consistent over the course of bladder radiotherapy. IH TFM match recorded the largest variations in the supero-inferior (SI) and antero-posterior (AP) directions with the largest geometrical shift of 5 mm was recorded. If bony landmark was used, a margin of up to 17.4 mm in the AP direction would be required to ensure adequate clinical target volume (CTV) coverage. In this study, we found IH TFM to be well tolerated and feasible, with no major adverse events noted as a result of injection.

Conclusion: This study demonstrates that IH TFM can be safely injected into the bladder mucosa and can be considered as a fiducial marker for bladder cancer.

Keywords: Bladder cancer, radiation therapy, iodinated hydrogel, tissue fiducial marker, bladder sparing

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect virtually any organ in the body, with the kidney being one of the most frequently involved and a crucial determinant of patient prognosis.[1,2] Lupus nephropathy (LN), the renal manifestation of SLE, is associated with significantly increased morbidity and mortality. Despite advances in treatment, early diagnosis and effective monitoring of kidney damage remain major challenges in clinical practice.[3,4] Traditional biomarkers such as serum creatinine are often only elevated when significant kidney damage is already present, limiting their usefulness for early detection and prognostic assessment.[5]

Beta-2 microglobulin (B2M) is a low molecular weight (11.8 kDa) protein that is part of the major histocompatibility complex class I, present on the surface of almost all nucleated cells. It is continuously released into the bloodstream, freely filtered by the glomerulus, and almost completely reabsorbed and catabolized in the proximal renal tubules.[6,7] Due to this metabolic profile, serum and urinary B2M has been studied as a potential biomarker of renal function and as an indicator of immune cell proliferation and activation.[6,7]

In the context of SLE, it has been postulated that serum B2M could serve as a dual biomarker: on the one hand, reflecting the overall immunological activity of the disease due to the activation and turnover of immune cells.8 and on the other hand, indicating renal damage, particularly tubular damage, which is a common feature of lupus nephritis.[9] However, the distinction between its role as a marker of systemic activity versus its direct involvement in renal damage, especially when compared to other established biomarkers, is not always clearly defined.[8,9]

The present study aimed to evaluate the role of serum B2M in patients with SLE, analyzing its correlation with markers of renal function such as creatinine and cystatin C (CsC), and with markers of disease activity such as complement components C3 and C4. Our hypothesis is that serum B2M will show a stronger correlation with indicators of renal damage than with markers of general immunological activity, suggesting its greater utility as a biomarker of renal involvement in SLE.

Materials and methods

Study design and population: An observational, descriptive, cross-sectional study was conducted in a sample of 35 patients diagnosed with SLE. Patients were consecutively recruited from the National Reference Center for Rheumatic Diseases (CRNER) of the "10 de Octubre" Clinical and Surgical Teaching Hospital, between June 2023 and December 2023.

Patients with concomitant diseases that could alter serum B2M levels, such as lymphoproliferative diseases, multiple myeloma, diabetes mellitus, or severe acute infections, were excluded to avoid bias in the interpretation of the results.

Sample collection and measurements: Demographic data (age and sex) were collected from each patient, and peripheral blood samples were obtained by venipuncture. These samples were centrifuged at 3000 rpm for 10 minutes to separate the serum and immediately analyzed using a fully calibrated and certified Roche Cobas 311 biochemical multianalyzer. In all cases, the manufacturer's instructions for the reagents used in the analytical determinations were followed. The creatinine reagent was sourced in Spain (Immunoassay Center). The reagents for B2M, C3, C4, and CsC were sourced abroad (Roche Diagnostics, Indianapolis, United States).

The variables analyzed were:

Serum B2M: Quantified by immunoturbidimetry. A cutoff of 2.2 mg/L was established to define elevated levels.

Serum creatinine: Measured using the kinetic Jaffé colorimetric method. The cutoff point for elevated creatinine was 113 µmol/L.

Serum CsC concentrations: Determined by immunoturbidimetry following the manufacturer's protocol. A cutoff point of 0.95 mmol/L was used.

Complement C3 and C4: Quantified by immunoturbidimetry. The cutoff points for low levels, indicative of immunological activity, were 0.9 g/L for C3 and 0.1 g/L for C4.

Statistical analysis: Quantitative data were presented as mean and standard deviation (SD) or median and interquartile range (IQR), according to the distribution assessed using the Shapiro-Wilk normality test.

Categorical variables were presented as frequencies and percentages.

To evaluate the correlation between serum B2M and kidney damage variables (creatinine and CsC), as well as with disease activity variables (C3 and C4), the following statistical tests were used:

Pearson's correlation coefficient (r): This was used to evaluate the strength and direction of the linear relationship between continuous variables with a normal distribution.

Spearman's correlation coefficient (ρ): This was used to evaluate the strength and direction of the monotonic relationship between continuous variables, especially useful when the data did not follow a normal distribution or in the presence of outliers.

In the correlation analysis between serum B2M and the clinical variables evaluated, the Pearson and Spearman correlation coefficients were used to obtain a comprehensive and robust view of the existing relationships, considering the distribution characteristics of the data.

A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using PSPP statistical software (version 1.6.0). The results were presented in tables with correlation coefficients and corresponding p-values.

Ethical considerations

All participants provided written informed consent. The study was approved by the Ethics Committee of the "10 de Octubre" Clinical and Surgical Teaching Hospital.

Results

Descriptive characteristics of the study population:

The study population consisted of 35 patients with SLE. The mean age was 46.6 ± 13.5 years. The majority of patients were female (32/35) (91.4%). Table 1 presents the descriptive statistics for all quantitative variables included in the study:

Table 1 Descriptive statistics for the quantitative variables of the study population (n=35)

Variable	Mean (SD)	Median (IQR)	Minimum	Maximum
Age (years)	46,6 (13,5)	48 (38 - 56,5)	21	74
Cystatin C (mmol/L)	1,20 (0,50)	1,01 (0,94 - 1,28)	0,65	3,27
Creatinine (µmol/L)	99,8 (30,4)	94 (81,5 - 109,5)	51	187
Serum B2M (mg/L)	2,81 (2,07)	2,24 (1,54 - 3,51)	1,01	12,02
C3 (g/L)	1,07 (0,26)	1,10 (0,88 - 1,25)	0,43	1,76
C4 (g/L)	0,21 (0,10)	0,20 (0,15 - 0,29)	0,05	0,41

SD, standard deviation; IQR, interquartile range

Correlation of serum B2M with kidney damage variables

The results of the correlations between serum B2M and kidney damage markers are presented in Table 2. A strong and highly significant positive correlation was observed between serum B2M and CsC. In contrast, B2M showed a marginally nonsignificant correlation with serum creatinine.

Table 2 Correlation between serum B2M and kidney damage markers (n=35).

Variable	Spearman Correlation Coefficient (ρ)	p-value (Spearman)
Serum creatinine	0,33	0,053
Cystatin C	0,84	< 0,001

Correlation of serum B2M with immunological activity variables

The results of the correlations between serum B2M and immunological activity markers are presented in Table 3. No statistically significant correlations were found between serum B2M and C3 or C4 levels. The observed correlations were weak and did not reach statistical significance.

Table 3 Correlation between serum B2M and immunological activity markers (n=35).

Variable	Pearson Correlation Coefficient (r)	p-value (Pearson)
C3	-0,19	0,28
C4	-0,11	0,53

Discussion

This study evaluated the value of serum B2M as a biomarker in patients with SLE, distinguishing between its ability to reflect kidney damage and its correlation with the immune activity of the disease. These findings consistently indicate that serum B2M is strongly and significantly related to markers of kidney damage, particularly CsC, and to a lesser extent, creatinine. In contrast, no significant correlations were observed between serum B2M and complement components C3 and C4, conventional indicators of immune activity in SLE. Elevated B2M in SLE can be explained by two main mechanisms. First, B2M is

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an essential component of the major histocompatibility complex class I, present in all nucleated cells, and its serum concentration reflects the rate of cell turnover, especially of activated T and B lymphocytes.[9,10]

In SLE, the abnormal activation and proliferation of these immune cells increases the synthesis and release of B2M, which has been associated with immunological activity and autoantibody production.8 However, in our study, the lack of significant correlation with C3 and C4 indicates that serum B2M does not directly reflect complement system activity or overall immunological activity as measured by these parameters. This is consistent with some studies suggesting that B2M should be interpreted in conjunction with other markers to assess SLE activity.[8] Second, B2M is freely filtered by the glomerulus and almost completely reabsorbed and catabolized in the proximal renal tubules. Therefore, tubular or glomerular dysfunction, characteristic of lupus nephritis, can elevate serum and urinary B2M levels.[8–10]

The strong relationship observed between serum B2M and CsC, a sensitive and early marker of renal function, supports this hypothesis and suggests that B2M may be an excellent indicator of glomerular filtration rate and, by extension, of overall renal damage, in line with recent literature that positions B2M as a promising marker for the detection of renal dysfunction in patients with SLE.[9–11]

The correlation with creatinine was weak, which could indicate a less linear relationship or the influence of outliers, or the differential sensitivity of B2M in detecting renal abnormalities that are not as evident with creatinine, a less sensitive marker in the early stages of kidney damage, which is consistent with the literature.[9–12]

Previous studies have reported that elevated B2M levels are associated with a higher frequency of lupus nephritis and progressive kidney damage in SLE, and that B2M can predict renal outcome and response to treatment.[11,13,14] Furthermore, elevated B2M has been linked to complement C4 consumption, but not always with C3, which could reflect specific mechanisms of immune activation in kidney damage. In the present study, although no significant correlation with C4 was observed, the trend and previous evidence suggest that B2M may be involved in local immune processes in the kidney.[8,15]

The failure to find a significant relationship between serum B2M and C3 and C4 levels is a crucial aspect of the results obtained. While some studies have suggested that serum B2M may be elevated in active SLE due to immune cell proliferation,[8,15,16] the data suggest that in this sample, its elevation is more strongly linked to kidney involvement than to systemic immune activity measured by complement.

This could imply that B2M is a more specific biomarker for lupus nephritis or SLE-associated kidney damage, rather than a general marker of disease activity, which can manifest in a variety of organ-related forms. Other markers of disease activity, such as double-stranded DNA (anti-dsDNA) or clinical activity índices[8,17] (e.g., SLEDAI), may show a different correlation with B2M, but these variables were not evaluated in the present study.

B2M's ability to reflect renal tubular damage makes it a particularly valuable biomarker. In SLE, nephritis may involve not only the glomerulus but also the renal tubules, often subclinically or in early stages.[9,13,14] The almost complete reabsorption of B2M in the proximal tubules means that any alteration in tubular integrity or function can lead to increased urinary excretion or serum levels due to impaired catabolism.9,13,14 Our findings, correlating serum B2M with markers of renal function, reinforce its usefulness for monitoring renal involvement in SLE.

The clinical utility of B2M as a biomarker in SLE lies in its ability to detect kidney damage in early stages, even before conventional markers are altered, allowing for timely interventions and potentially improving renal prognosis. However, its interpretation should be cautious, as elevated B2M levels are not specific to SLE and can be observed in other inflammatory, infectious, or neoplastic diseases.

Limitations

This is a cross-sectional study; longitudinal studies would be necessary to evaluate the predictive value of serum B2M in the progression of kidney damage or treatment response in patients with SLE.

Finally, other markers of SLE activity (such as anti-dsDNA or SLEDAI) and renal histopathology were not evaluated, which could have provided a deeper understanding of the observed relationships.

Conclusion

The results of this study suggest that serum B2M is a promising biomarker of kidney damage in patients with SLE, showing a strong and significant correlation with CsC, although weak with creatinine. In contrast, no significant correlation was found with the immune activity markers C3 and C4. These findings reinforce the usefulness of serum B2M for the detection and monitoring of kidney damage in SLE, beyond its role as an indicator of general systemic disease. Incorporating serum B2M into the biomarker panel for the evaluation of patients with SLE could contribute to more accurate and timely management of kidney complications.

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None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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