Soluble Major Histocompatibility Complex Class I Chain-related Antigen A Level in Chronic Allograft Dysfunction

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Introduction. Soluble major histocompatibility complex class I chain-related antigen A (soluble MICA) has recently been considered as an inhibitory molecule which is shed from tumors and protects them against natural killers and some subgroups of T cells' cytolysis. In transplantation, soluble MICA is also a foreign antigenic molecule that can induce allospecific responses. This study aimed to clarify its possible role in long-term kidney allograft outcome.
Materials and Methods. Thirty patients with biopsy-proven chronic allograft dysfunction (CAD) were pair-matched with kidney allograft recipients with 30 stable graft function. Fifteen healthy individuals were enrolled as controls. Soluble MICA antigen and anti-HLA antibodies were measured in their serum.
Results. There was no significant difference between CAD patients, stable recipients, and healthy volunteers in frequency or titer of soluble MICA; however, soluble MICA-positive patients were more frequent in the stable group was than the CAD group (43.4% versus 33.3%). In addition, a high level of soluble MICA was accompanied by enhanced humoral responses. No significant difference was found in anti-HLA antibodies production between the CAD and stable groups.
Conclusions. Our data suggest that soluble MICA, at least in a defined range, can protect the allograft against natural killers and T cell cytolysis; nonetheless, its excessive amounts might stimulate immune system to exert enhanced humoral response. In order to confirm the protective or detrimental role of soluble MICA in kidney transplantation, conducting larger studies is necessary.

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INTRODUCTION

The major histocompatibility complex class I chain-related antigen A (MICA) has recently been more noticed because of its involvement in transplantation, cancer, and autoimmunity as the new era's the most important clinical challenges.[1] This single-chain protein is produced by the *MICA* gene which is located 46.4 kilobases centromeric to human leukocyte antigen (HLA)-B and has molecular structure similar to HLA class I except lacking β-chain.[2] *MICA* is constitutively expressed on gastrointestinal epithelium but can be induced by cellular stress on permissive cell types like fibroblasts, keratinocytes, monocytes, and endothelial cells as they are expressed due to ischemia-reperfusion injury on endothelial cells.[3] Moreover, because of its polymorphic nature, including 93 alleles coding for 73 protein

molecules, MICA antigens are considered as important non-HLA antibody targets in various organ transplantations.[4] Therefore, some efforts have been developed to make MICA-matching and anti-MICA antibody detecting methods as routine surveillance test in clinic.[5,6]

Cell surface MICA as a ligand of natural killer group 2D (NKG2D) receptor on natural killer (NK) cells, γδ subgroups of T lymphocytes, and αβ subgroups of CD8+ T lymphocytes play a critical role in activating these cells and inducing enhanced cellular immunity against allograft.[7] On the other hand, soluble MICA can bind to NKG2D and induce receptor internalization and degradation, which diminishes NK and T cells cytolytic activity[8,9]; therefore, soluble MICA shedding from tumor cells protects them from NK cells immune surveillance, as shown in several malignancies.[10,11] In contrast, some researchers suggest that MICA alloreactive T cells may be primed to donor-derived soluble MICA antigens in the context of self major histocompatibility complex class I molecules and induce anti-MICA responses in allograft.[12]

Trying to clarify soluble MICA molecules role in transplantation outcome, many studies about different organs have been conducted and some controversial results are available, some suggesting soluble MICA's negative effect on allograft and some introducing it as a beneficial molecule in transplantation. For instance, it was shown in liver transplant recipients that patients who have more soluble MICA in their serum are at greater risk of developing biliary cast syndrome after transplantation[13]; on the contrary, in heart and transplantation fields, the results are quite different, since a group has explored that higher level of soluble MICA is significantly correlated with better outcomes.[14,15] In hematopoietic stem cell transplantation, a study has shown that elevated levels of soluble MICA are associated with the incidence of chronic graft versus host disease,[16] and in kidney transplantation, although the results were not significant, it was shown that recipients' soluble MICA in serum mildly decreases before acute rejection episodes.[17]

Chronic allograft dysfunction (CAD), pathologically known as nonspecific interstitial fibrosis and tubular atrophy (IFTA), is considered as the major cause of long-term allograft loss in kidney recipients.[18,19] Chronic allograft dysfunction manifests itself by a slow and progressive decrease in allograft function with high blood pressure and proteinuria and as a result of immunological or nonimmunological injuries it is described by pathological findings like interstitial fibrosis, tubular atrophy, glomerulosclerosis, fibrointimal hyperplasia, and arteriolar hyalinosis.[20] However, despite increasing prevalence of CAD, there is insufficient information available about immunologic factors precise contribution to this silent damage. Obviously, by determining soluble MICA's negative or positive impact on CAD, MICA would be a useful target for clinical manipulation and as an easily detectable molecule it can be an appropriate biomarker in designing noninvasive diagnostic tests. We aimed to clarify its possible role in long-term kidney allograft outcome.

MATERIALS AND METHODS

Patients enrolled in this study were 60 adults who had received their first kidney allograft at Labbafinejad Medical Center, 6 month to 5 years prior to the study. Thirty patients had CAD and 30 had stable allograft function. Fifteen healthy volunteers were also included as controls.

Patients with CAD were those who exhibited a progressive deterioration of kidney function with 15% or more irreversible rise in serum creatinine level and proteinuria more than 1 g/24 h.[21] All of them had undergone biopsy and IFTA pathologic lesions were reported in their biopsies according to the Banff updated classification.[20, 22] Eight patients showed IFTA grade 1, while 16 had IFTA grade 2 and 6 had IFTA grade 3. Five of them had C4d deposition together with antibodies detection in immunofluorescence staining of tissue. Twelve patients had arteriolar hyalinization in grades 1 and 2.

Patients with stable graft were selected according to their sex, age, and time posttransplant in order to be pair-matched with the CAD patients. Their results of clinical examination were normal, their serum creatinine levels were 1 mg/dL or less, they had proteinuria less than 0.5 g/24 h, and their glomerular filtration rate was greater than 80 mL/min. [21] They had no registered history of acute rejection episodes and did not have any diagnosed viral or bacterial infection within 1 month before enrollment. Since these patients presented no deterioration of graft function, and protocol biopsies

are not routine procedures in our transplantation centers, no biopsy was available for this group. Healthy volunteers were 15 age-matched healthy individuals without any renal or immunological disorders (ie, allergy, autoimmune disease, and immunodeficiency) and no family history of kidney diseases. Their serum creatinine level was 1 mg/mL or less and glomerular filtration rate was greater than 85 mL/min. The protocol was approved by Ethics Committee of Tehran University of Medical Sciences. All of the patients provided informed consent. Detailed clinical and demographic data of the three groups are shown in Table 1.

Soluble MICA levels in sera of the participants were measured using a human MICA enzyme-linked immunosorbent assay kit (Abcam, Cambridge, UK), following the manufacturer's instruction. Each assay was performed in duplicate. Results were expressed as pg/mL according to calibration curve drawn for standard dilutions. Enzyme-linked immunosorbent assay for screening anti-HLA class I and II antibodies was also performed according to manufacturers' instruction (AbScreen, HLA class I and II, Bio-Rad, Dreieich, Germany), and a screen greater than twice the mean of the negative controls was defined as positive.

Data were presented as mean ± standard deviation or mean ± standard error of mean, where appropriate. Nonparametric test Kruskall-Wallis test and 1-way analysis of variance test were used to compare data between the three groups of CAD patients, transplant recipients with stable graft, and healthy controls. The independent samples *t* test was used to compare paired groups. For analyzing nonquantitative variables, the chi-square and Fisher exact tests were used. The analyses were done using the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, Ill, USA). *P* values less than .05 were considered significant.

RESULTS

There was no significant difference in presence and amount of soluble MICA between the three groups of CAD patients, transplant recipients with stable graft, and healthy controls (Table 2); nonetheless, there was a lower frequency of soluble MICA among CAD patients in comparison with stable recipients (33.3% versus 43.4%). There was also an insignificant increase of soluble MICA in transplant recipients in comparison with healthy individuals (mean, 52.2 ± 11.34 pg/mL; 95%

Table 1. Characteristics of Patients With Chronic Allograft Dysfunction (CAD), Patients With Stable Graft Function (SGF), and Healthy Controls

Characteristic	Kidney Transplant Recipients		Controls
	CAD	SGF	
Number of participants	30	30	15
Age, y	39.40 ± 13.28	39.10 ± 12.25	38.33 ± 12.88
Sex			
Male	19	19	10
Female	11	11	5
Glomerular filtration rate, mL/min	34.36 ± 13.06	96.28 ± 14.11	109.03 ± 19.13
Time posttransplant, mo	41.00 ± 17.76	41.00 ± 17.76	
Immunosuppressant			
Cyclosporine, mycophenolate mofetil, steroids	22 (73.3)	26 (86.7)	…
Tacrolimus, azathioprine, steroids	5 (16.7)	3 (10.0)	…
Rapamicin, mycophenolate mofetil, steroids	3 (10.0)	1 (3.3)	…
Etiology of ESRD			
Diabetic nephropathy	5 (16.7)	3 (10.0)	…
Hypertension	6 (20.0)	7 (23.3)	…
Polycystic kidney disease	1 (3.3)	5 (16.7)	…
Infection	2 (6.7)	6 (20.0)	…
Urinary calculus	5 (16.7)	2 (6.7)	…
Vesicoureteral reflux	5 (16.7)	2 (6.7)	…
Chronic glomerulonephritis	3 (10.0)	0	…
Drug toxicity	0	3 (10.0)	…
Unknown	3 (10.0)	2 (6.7)	…

Table 2. Soluble Major Histocompatibility Complex Class I Chain-related Antigen A (MICA) in Patients With Chronic Allograft Dysfunction (CAD), Patients With Stable Graft Function (SGF), and Healthy Controls

	Kidney Transplant Recipients			
Soluble MICA	CAD	SGF	Controls	*P*
Positive in serum	10 (33.3)	13 (43.4)	6 (40.0)	.72
Serum concentration, pg/mL	41.8 ± 17.6 (0 to 378)	62.7 ± 14.3 (0 to 202)	44 ± 16.3 (0 to 163)	.47

confidence interval [CI], 29.6 to 74.9 versus mean, 44.1 ± 16.35 pg/mL; 95% CI, 9.0 to 79.1, respectively; *P* = .75). In stable recipients, soluble MICA levels were slightly higher than that in healthy individuals (*P* = .78). However, in CAD patients with a positive soluble MICA, it was interestingly usually either lower or higher than healthy volunteers (CAD group skewness, 2.81 ± 0.43 in comparison with 0.63 ± 0.43 in the stable group and 0.89 ± 0.58 in the healthy group; Figure 1).

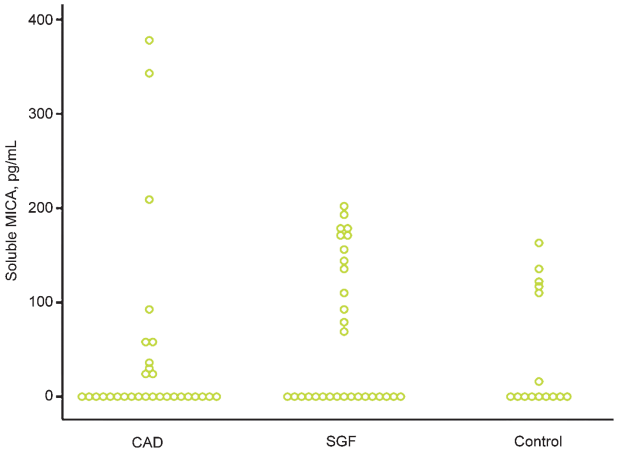

Figure 1. Soluble major histocompatibility complex class I chain-related antigen A (MICA) in patients with chronic allograft dysfunction (CAD), patients with stable graft function (SGF), and healthy controls.

Analysis of data in different pathologic grades of IFTA did not show any considerable differences between soluble MICA levels of these grades (Table 3); however, 3 patients with highest amounts of soluble MICA in their serum (209 pg/mL, 343 pg/mL, and 378 pg/mL) were in advanced stages of pathologic damage since 2 of them were in IFTA grade 2, and 1 was in grade 3.

The frequency of anti HLA I and II antibodies in serum of CAD and stable graft groups did not show any significant difference (*P* = .28 and *P* = .17, respectively). However, all of the four patients with both anti- HLA I and II antibodies were in the CAD group (*P* = .04).

Five of 30 patients with CAD showed C4d and antibody deposition in biopsy samples. Four of these five patients had both anti-HLA I and anti-HLA II antibodies in serum samples and one had only anti-HLA I antibody. Strikingly, 3 of 5 were positive for soluble MICA with soluble MICA levels of 22 pg/mL, 343 pg/mL, and 209 pg/mL (either low or high) and 2 of them had no detectable soluble MICA in their sera. Although there were no significant differences between transplant recipients positive and negative for soluble MICA in producing anti-HLA antibodies (Table 4), the analysis showed considerable odds ratios suggesting a harmful role for soluble MICA,

Table 3. Soluble Major Histocompatibility Complex Class I Chain-related Antigen A (MICA) in Patients With Chronic Allograft Dysfunction by Pathology Grade

	Interstitial Fibrosis and Tubular Atrophy			
Soluble MICA	Grade 1 (n = 8)	Grade 2 (n = 16)	Grade 3 (n = 6)	*P*
Positive in serum	2 (25.0)	6 (37.5)	2 (33.4)	.83
Serum concentration, pg/mL	12 ± 8 (0 to 60)	49 ± 26 (0 to 378)	61 ± 57 (0 to 343)	.80

Table 4. Human Leukocyte Antigen (HLA) Antibodies in Patients With Chronic Allograft Dysfunction (CAD), Patients With Stable Graft Function (SGF), and Healthy Controls

	Kidney Transplant Recipients			
HLA	CAD	SGF	Controls	*P*
Class I antibodies	12 (40.0)	8 (26.7)	2 (13.4)	.17
Class II antibodies	4 (13.4)	1 (3.4)	1 (6.7)	.36
Class I and II antibodies	4 (13.4)	0	0	.04

Table 5. Human Leukocyte Antigen (HLA) Antibodies in Patients With Chronic Allograft Dysfunction (CAD) and Stable Graft Function (SGF) by Presence or Absence of Soluble Major Histocompatibility Complex Class I Chain-related Antigen A (MICA)

	CAD		SGF			
HLA	MICA+	MICA-	MICA+	MICA-	P	Odds Ratio
Class I antibodies	7 (23.3)	5 (16.7)	3 (10.0)	5 (16.7)	.26	2.08
Class II antibodies	3 (10.0)	1 (3.3)	1 (3.3)	0	.07	7.58
Class I and II antibodies	3 (10.0)	1 (3.3)	0	0	.15	5.40

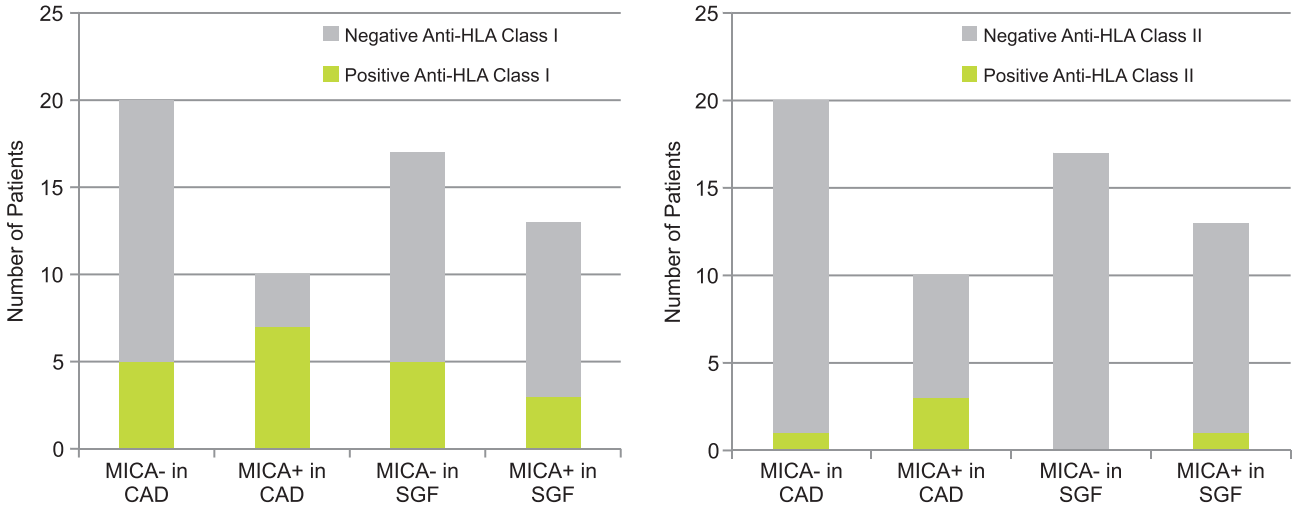

Figure 2. Human leukocyte antigen (HLA) antibodies in patients with chronic allograft dysfunction (CAD) and Stable Graft Function (SGF) by presence or absence of soluble major histocompatibility complex class I chain-related antigen A (MICA).

especially with anti-HLA II antibodies production (odds ratio, 7.58; Table 5). As shown in Figure 2, recipients positive for soluble MICA both groups of stable and CAD patients were at greater risk of developing humoral responses to allograft (Figure 2).

DISCUSSION

Recognizing soluble MICA as an immunosuppressive molecule which protects tumors from cytolytic activity of killer cells has made it subject of several tolerance induction surveys. However, this theory is still open to debate since MICA is presumed as a considerable alloantigen in organ transplantation and is able to evolve immune responses to allograft.

In present study, we evaluated the presence and serum level of soluble MICA in patients with stable graft function, patients with CAD, and healthy controls. Our data showed slightly increased levels of soluble MICA in allograft recipients in comparison with healthy people. In addition, although statistically nonsignificant, the number of soluble MICA-positive patients in the stable group was more than the CAD group. Related studies by Suárez-Álvarez and colleagues in heart transplantation showed similar results, as they represented significantly lower episodes of acute rejection among soluble MICA-positive recipients and their second study showed higher amounts of soluble MICA in serum of patients with stable graft.[14,15] In addition, Solgi and coworkers studying a group of kidney allograft recipients during the first year after transplantation found insignificant decreased levels of soluble MICA pre- and postoperatively in patients with rejection in comparison with the stable graft group.[17]

On the other hand, Zou and coworkers have studied soluble MICA in liver transplant recipients and found out a positive correlation between serum soluble MICA level and biliary cast syndrome after liver transplantation and showed that recipients who had high soluble MICA levels pre- and posttransplant had the worst outcomes.[13] This finding is in concordance with results of a survey conducted by Boukouaci and colleagues about chronic graft versus host disease prevalence in soluble MICA-positive patients. They suggested that stem cell transplant recipients with soluble MICA levels more than 80 pg/mL are at greater risk

of developing chronic graft versus host disease.[16]

Therefore, in published papers, there are 2 different explanations for soluble MICA's positive or negative impact on transplantation outcome. The first theory regards soluble MICA's inhibitory effect as an NKG2D ligand on NK and cytolytic T cells. The MICA molecules bind to NKG2D on cytolytic cells after shedding from endothelium and cause receptor blockage, internalization, and degradation. Diminished counts of activating receptors prevent killer cells from recognizing their target cells and results in protecting MICA expressing tissue from cellular attack.[8-11] The second explanation refers to increased expression of MICA molecules on endothelial cells in response to hypoxia or ischemia-reperfusion injury which predisposes them to host antibody-mediated attacks. Excessive prolonged expression of MICA on endothelial tissues results in shedding them into serum and these soluble MICAs as protein antigens after uptake by antigen presenting cells can be presented to allospecific T helper cells, stimulating them to induce humoral responses.[7,12] It is also possible that these two phenomena come about together and the final balance determines the outcome; therefore, it is not reasonable to refuse one and accept the other; especially when we are talking about different organs. Different donated tissues have various capabilities to express MICA and release it under stress situations due to their different vascularisation and blood supply, for instance, bone marrow and liver sinusoidal tissues are highly congested and presumed as primary and secondary lymphoid organs.

Moreover, all changes in serum soluble MICA can not be attributed to transplantation per se, since almost all recipients had a preliminary ailment causing organ failure which could be responsible for soluble MICA level fluctuations during pre and posttransplant periods as Kohga and colleagues has reported soluble MICA's excessive serum amounts in chronic liver disease.[23] These phenomena may explain higher rates of soluble MICA and its companion with poorer prognosis among stem cell and liver transplant recipients.

Another considerable finding in our study was variable levels of soluble MICA in soluble MICA-positive CAD patients' serum which were frequently either lower or higher than stable recipients' serum soluble MICA range (69 pg/mL to 202 pg/mL). Maybe CAD patients with scarce amounts of soluble MICA cannot escape NK and T cells allospecific cytolysis sufficiently and those who have greater levels of soluble MICA are in a hyper-immune state which makes them prone to express and release more MICA into serum and induce enhanced immunological response to tissue. In contrast, stable recipients who have rational levels of soluble MICA (69 pg/mL to 202 pg/mL) remain at a balanced state.

Analyzing correlation of soluble MICA levels with immune responses intensity, it was found out that 2 of 4 CAD patients with anti-HLA I and II antibodies had excessive amounts of soluble MICA in their serum (209 pg/mL and 343 pg/mL), while 2 others had no or very low amounts (22 pg/mL). In addition, although statistically inconsiderable, soluble MICA-negative patients had lower frequencies of anti-HLA I and II antibodies. These findings are in favor of suggesting soluble MICA molecule as an immune-stimulating antigen for humoral branch of immune system despite its inhibitory effect on cytolytic responses at least in a defined range.

In human renal transplant recipients, development of anti-HLA antibodies is usually associated with poor allograft outcomes. However, the precise role of these antibodies in progression of IFTA has not been determined.[24-26] Gerbase-DeLima and colleagues studying 512 kidney transplant recipients showed a frequency of 10.7% for anti HLA II antibodies in 3 years of follow-up and a relative risk of 3.29 for these antibodies companion with graft loss due to IFTA.[27] Nicknam and colleagues also evaluated 132 recipients and reported 19.7% anti HLA I antibody positivity. This study showed a significant relationship between these antibodies frequency and creatinine level among recipients in long term.[28] Recently Amirzargar and colleagues evaluated anti HLA antibodies presence in a group of recipients during a period of 4 years follow up and showed higher frequency of posttransplant HLA class II antibody in the absence of class-I antibody in failure group; furthermore, patients with posttransplant HLA class I and class II antibodies either alone or in combination showed significant lower 4 year graft survival.[29] Our study did not show any significant difference between anti-HLA antibodies frequency between CAD, stable function and healthy group, maybe due to

insufficient number of studied cases, involvement of multiparous females in studied groups and lack of anti-HLA antibodies specification tools , since we could not identify donor specific and non donor specific antibodies. Obviously it would be better by far to evaluate anti-MICA antibodies presence among soluble MICA-positive and soluble MICA-negative patients, which could not be performed due to equipment shortage.

CONCLUSIONS

The present study did not show any significant difference in the presence of soluble MICA in serum and its concentration between kidney transplant patients with CAD and those with stable allografts. However, soluble MICA-positive patients among stable recipients were more frequent than in the CAD group. Moreover, it was shown that excessive amounts of soluble MICA are accompanied by enhanced humoral responses. It is suggested to conduct larger studies to determine precise role of soluble MICA in transplantation.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Kirijas M, Spiroski M. MICA polymorphism, association with diseases and the role of anti-MICA antibodies in organ and stem cell transplantation. Macedonian J Med Sci. 2013;6:285-95.
2. Bahram S, Bresnahan M, Geraghty DE, Spies T. A second lineage of mammalian major histocompatibility complex class I genes. Proc Natl Acad Sci U S A. 1994;91:6259-63.
3. Groh V, Bahram S, Bauer S, Herman A, Beauchamp M, Spies T. Cell stress-regulated human major histocompatibility complex class I gene expressed in gastrointestinal epithelium. Proc Natl Acad Sci U S A. 1996;93:12445-50.
4. Sumitran-Holgersson S. Relevance of MICA and other non-HLA antibodies in clinical transplantation. Curr Opin Immunol. 2008;20:607-13.
5. Zou Y, Stastny P. Role of MICA in the immune response to transplants. Tissue Antigens. 2010;76:171-6.
6. Zou Y, Stastny P, Susal C, Dohler B, Opelz G. Antibodies against MICA antigens and kidney-transplant rejection. N Engl J Med. 2007;357:1293-300.
7. Zhang Y, Stastny P. MICA antigens stimulate T cell proliferation and cell-mediated cytotoxicity. Hum Immunol. 2006;67:215-22.
8. Jinushi M, Takehara T, Tatsumi T, et al. Expression and role of MICA and MICB in human hepatocellular carcinomas and their regulation by retinoic acid. Int J Cancer. 2003;104:354-61.
9. Groh V, Wu J, Yee C, Spies T. Tumour-derived soluble MIC ligands impair expression of NKG2D and T-cell activation. Nature. 2002;419:734-8.
10. Holdenrieder S, Stieber P, Peterfi A, Nagel D, Steinle A, Salih HR. Soluble MICA in malignant diseases. Int J Cancer. 2006;118:684-7.
11. Arreygue-Garcia NA, Daneri-Navarro A, del Toro-Arreola A, et al. Augmented serum level of major histocompatibility complex class I-related chain A (MICA) protein and reduced NKG2D expression on NK and T cells in patients with cervical cancer and precursor lesions. BMC Cancer. 2008;8:16.
12. Mizutani K, Terasaki PI, Shih RN, Pei R, Ozawa M, Lee J. Frequency of MIC antibody in rejected renal transplant patients without HLA antibody. Hum Immunol. 2006;67:223-9.
13. Zou Y, Yang X, Jiang X, et al. High levels of soluble Major Histocompatibility Complex class I related chain A (MICA) are associated with biliary cast syndrome after liver transplantation. Transpl Immunol. 2009;21:210-4.
14. Suarez-Alvarez B, Lopez-Vazquez A, Diaz-Pena R, et al. Post-transplant soluble MICA and MICA antibodies predict subsequent heart graft outcome. Transpl Immunol. 2006;17:43-6.
15. Suarez-Alvarez B, Lopez-Vazquez A, Diaz-Molina B, et al. The predictive value of soluble major histocompatibility complex class I chain-related molecule A (MICA) levels on heart allograft rejection. Transplantation. 2006;82:354-61.
16. Boukouaci W, Busson M, Peffault de LR, et al. MICA-129 genotype, soluble MICA, and anti-MICA antibodies as biomarkers of chronic graft-versus-host disease. Blood. 2009;114:5216-24.
17. Solgi G, Furst D, Mytilineos J, Pourmand G, Amirzargar AA. Clinical relevance of pre and post-transplant immune markers in kidney allograft recipients: anti-HLA and MICA antibodies and serum levels of sCD30 and sMICA. Transpl Immunol. 2012;26:81-7.
18. Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Allen RD, Chapman JR. The natural history of chronic allograft nephropathy. N Engl J Med. 2003;349:2326-33.
19. Ganji MR, Harririan A. Chronic allograft dysfunction: major contributing factors. Iran J Kidney Dis. 2012;6:88-93.
20. Solez K, Colvin RB, Racusen LC, et al. Banff '05 Meeting Report: differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy ('CAN'). Am J Transplant. 2007;7:518-26.
21. Chapman JR, O'Connell PJ, Nankivell BJ. Chronic renal allograft dysfunction. J Am Soc Nephrol. 2005;16:3015-26.
22. Haas M, Sis B, Racusen LC, et al. Banff 2013 meeting report: inclusion of c4d-negative antibody-mediated rejection and antibody-associated arterial lesions. Am J Transplant. 2014;14:272-83.
23. Kohga K, Takehara T, Tatsumi T, et al. Serum levels of soluble major histocompatibility complex (MHC) class I-related chain A in patients with chronic liver diseases and changes during transcatheter arterial embolization for hepatocellular carcinoma. Cancer Sci. 2008;99:1643-9.
24. Lee PC, Zhu L, Terasaki PI, Everly MJ. HLA-specific

antibodies developed in the first year posttransplant are predictive of chronic rejection and renal graft loss. Transplantation. 2009;88:568-74.

25. Morales-Buenrostro LE, Terasaki PI, Marino-Vazquez LA, Lee JH, El-Awar N, Alberu J. "Natural" human leukocyte antigen antibodies found in nonalloimmunized healthy males. Transplantation. 2008;86:1111-5.
26. Solgi G, Pourmand G, Mehrsai A, et al. Anti-HLA antibodies and kidney allograft outcomes in recipients with donor bone marrow cell infusion. Iran J Immunol. 2010;7:18-29.
27. Gerbase-DeLima M, Campos EF, Tedesco-Silva H, Machado PG, Franco M, Medina-Pestana JO. Anti-HLA class II antibodies and chronic allograft nephropathy. Clin Transpl. 2006;201-5.
28. Nicknam MH, Torkashvand A, Ghods A, et al. Evaluation of Anti- HLA Class I Antibodies in Chronic Rejection of Kidney Transplantation. Iran J Allergy Asthma Immunol. 2004;3:65-9.
29. Amirzargar MA, Amirzargar A, Basiri A, et al. Early post-transplant immune monitoring can predict long-term kidney graft survival: soluble CD30 levels, anti-HLA antibodies and IgA-anti-Fab autoantibodies. Hum Immunol. 2014;75:47-58.

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