DETECTION AND LOCALIZATION OF LATENT MEMBRANE PROTEIN AND MATRIX METALLOPROTEINASE-9 IN PATIENTS WITH TRANSITIONAL CELL CARCINOMA (TCC) OF THE BLADDER

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Abstract.

Background: Transitional Cell Carcinomas (TCC) of the urinary bladder constituted a major health problem and can be a leading cause of death. Recently some studies link viral infection with bladder carcinoma as an important etiological factor. There are several proteolytic enzymes which are responsible for the degradation of the extra cellular components and have an essential role in tumor invasion and metastasis such as Matrix metalloproteinase-9 (MMP-9).

Objective: To investigated the correlation between latent membrane protein-1(LMP-1) and MMP-9 with tumorgenesis of transitional cell carcinoma of bladder.

Materials and methods: Fifty formalin fixed, paraffin embedded tissues with TCC of the bladder from Specialized Surgical Hospital in Baghdad were included in this study. In addition, ten healthy individual samples exposed to same procedure were considered as control group. Tissue blocks were sectioned on charged slides and used for the detection of LMP-1 and MMP-9.

Results: Latent membrane protein-1 localized by Immunohistochemistry (IHC) within the nuclei of cancer cell was detected in 22 cases (44%). While MMP-9 was detected in 32 cases (64 %) during used *in situ* hybridization (ISH). Statistical analysis was found significant differences between expressions of LMP-1, MMP-9 in TCC of the bladder.

Conclusion: The results of the present study suggested that EBV and MMP-9 may play an important role in tumor sections of TCC of the bladder or could facilitate its progression. Histopathological, epidemiological and molecular studies are necessary to confirm our observation in Iraqi populations.

Key word: Urinary bladder transitional cell carcinomas, Epstein Barr virus, Latent membrane protein-1, Matrix metalloproteinase-9, Carcinogenesis.

Introduction

Urinary bladder cancer is one of the most common cancers worldwide, with the highest incidence in industrialized countries (Tracey *et al.*, 2007). More than 90% of bladder cancers are transitional cell carcinomas (TCC) and about 5% are squamous cell carcinomas (SCC). There are also uncommon bladder cancers, such as adenocarcinoma and small cell carcinoma, which are responsible for less than 2% of all bladder cancers (De Vita *et al*., 2005).

Transitional Cell Carcinoma of the urinary bladder is the second most common tumor of the genitourinary tract. It is also the second most common cause of death from these cancers (Williams *et al*., 2001).

Many agents including radiation, chemicals and viruses, have been found to induce human cancer (De Villiers, 2003). Viral factors are the most important class of the infectious agents associated with human cancers (Mao *et al*., 2003). It is estimated that 17-20 % of worldwide incidence of cancers was attributable to a viral etiology (Cliffard *et al*., 2003).

Epstein Barr virus is one of the viruses that have some unclear and controversial points in its ability to trigger the development of certain tumors (Vokes and Liebowitz, 1997). Such as Burkett's lymphoma, nasopharyngeal carcinoma, Hodgkin's disease, gastric carcinoma and post-transplant lymphoprolifereative disease (Thornhill, 2008).

Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes which degrade the extracellular matrix (ECM) or components of the basement membrane. They have essential roles in tumor invasion and metastasis (Kanayama, 2001). In many physiological states or processes, degradation of extracellular matrix is very important and essential, for example, during

development, growth, and repair or remodeling of organ tissues (Ravanti and Kahari, 2000).

Zymographical analysis of the levels of MMP-9 and active MMP-2 showed a significant increase with tumor grade and invasiveness (Papathoma *et al*., 2000).

To our knowledge there is no Iraqi study had focused on the role of viral agent and MMP-9 in bladder cancer. This study is an attempted to take the first step in detection of these markers and study the relationship with different parameters such as age, gender, grade and pattern of growth and presence or absence of muscle invasion in transitional cell carcinoma of the bladder.

Material and Methods

Patients and tissue samples. Fifty patients with bladder carcinoma, 35 (males) and 15 (females), with an age ranged from 25 to 70 years, were included in this study, The patients samples were collected during the period from February-2009 till June-2009 from the archives of histopathology laboratories of Specialized Surgical Hospital in Baghdad.

The diagnosis of these tissue blocks were primarily based on the obtained histopathological records of bladder biopsy samples in the hospital laboratory. Confirmatory histopathological re-evaluation of each obtained tissue blocks was done by specialist pathologist. In addition ten apparently normal bladder autopsies, 5 (males) and 5 (female) of matched as control group. Formalin-fixed, paraffin embedded tissue blocks were sectioned (4µm) thickness, one section was stained with Haematoxylin and Eosin, the two sections were mounted on charged slides for IHC and ISH to be used for the detection LMP-1 and MMP-9.

Immunohistochemical staining was carried out using mouse monoclonal antibodies to EBV latent membrane protein (Cambridge Science Park. England Code No.: ab 78113). Slides were deparaffinized, and rehydrated in serially graded alcohol. Antigen retrieval was done by immersion of slides in citrate buffer pH: 6 at 95-99°C for 15 minutes. Endogenous peroxidase activity was blocked by 3% hydrogen peroxide for 10 minutes. Slides were washed in phosphate-buffered saline. Then treated with protein block, incubated at 37°C for 5 minutes and washed with PBS. Primary antibody was applied to cover slides and incubated for 1 hours in humidity chamber at 37°C (Primary Antibody was prepared at dilution 1:50). Slides were rinsed gently in PBS. The secondary antibody was added for 10 minutes at room temperature, followed by the addition of Streptavidine-HRP antibodies for 10 minutes at 37˚C. After washing, samples were stained with diluted liquid DAB for 15-45 minutes at room temperature, then counterstained with hematoxylin for 30 sec. Slides were washed well in running tap water, then dehydrated and mounting with permanent-mounting medium (DPX) then examined under light microscope first at 10 then at 400 magnification.

Immunoassaying was scored according to score system used by (Kraggerud *et al*., 1997) [Score 1, less than 10 %, Score 2, more than 10 % and less than 50% and Score 3, more than 50 %].

***In situ* hybridization procedure**. Slides were deparaffinized, dehydrated and treated with 20µl of freshly diluted 1X proteinase K solution. Slides were incubated at 37°C for 15 minutes. One drop of the biotinylated long cDNA probe for human MMP-9 (Maxim Biotech Cat. No.: IH-60028). Hybridization/ detection kit was used purchased from Maxim Biotech/USA Cat. Number IH-6001(IHD-0050) was placed on the tissue section in oven at 70˚C for 8-10 minutes. After that, slides were placed in a humid chamber and incubated over night at 37°C to allow hybridization of the probe with the target nucleic acid. Slides were soaked in 1X detergent wash at 37˚C until the cover slips fall, and then treated with RNase A solution and streptavidin-AP-conjugate. One to two drops of 5-bromo-4-chloro-3-indolyl phosphartel/nitro blue tetrazolium substrate-chromogen solution (BCIP/NBT) conjugate were placed on tissue section at room temperature for about 30 minutes; the latter was monitored by viewing the slides under the microscope. A blue colored will be formed at the site of the probe in positive cells. Slides were then counterstained using nuclear fast red stain and mounted with a permanent-mounting medium (DPX). Finally the examination and scoring were done under light microscope by a pathologist at power 400 according to score system used by (Blancato *et al*., 2004).

Statistical analysis: The statistical analysis was done using Chi-Square test for tables with frequencies percentages, range, mean and

standard deviation. Values were considered statistically significant when ($p<0.05$).

Results

Histopathpological assessment. Fifty formalin-fixed, paraffin embedded blocks with bladder carcinoma were graded according to world health organization (WHO) classification (Epstein *et al*., 1998). As follow: Grade I: well differentiated transitional cell carcinoma (n=4) (8%), Grade II: moderately differentiated transitional cell carcinoma (n=31) (62%) and Grade III: poorly differentiated transitional cell carcinoma (n=15) (30%).

Each carcinoma was also assessed according to the pattern of growth, as follows: papillary type (n=28) (56%) and solid type (n=22) (44%). According to the level of invasive in to these with muscle invasive (n=26) (52%) and these with no muscle invasive ion was seen in (n=24) (48%).

Immunohistochemistry results: The results of IHC demonstrated that 22 out of 50 cases (44%) were positive for LMP-1. Latent membrane protein-1 was not detected in healthy control group. The differences was ($P<0.01$) (table 1 and figure 1).

Table (1): Results of immunohistochemical detection of LMP-1 in the studied groups.

LMP-1 IHC tests results		Control group	TCC	Comparison of Significance	
				P-value	Sig.
Positive	Low	0	8	0.00	Highly Sig. (P<0.01)
	Intermediate	0	7		
	High	0	7		
	Total	0	22 (44%)		
Negative	N %	10	28 (56 %)		
Total	N %	10 (100 %)	50 (100 %)		

Chi-square used

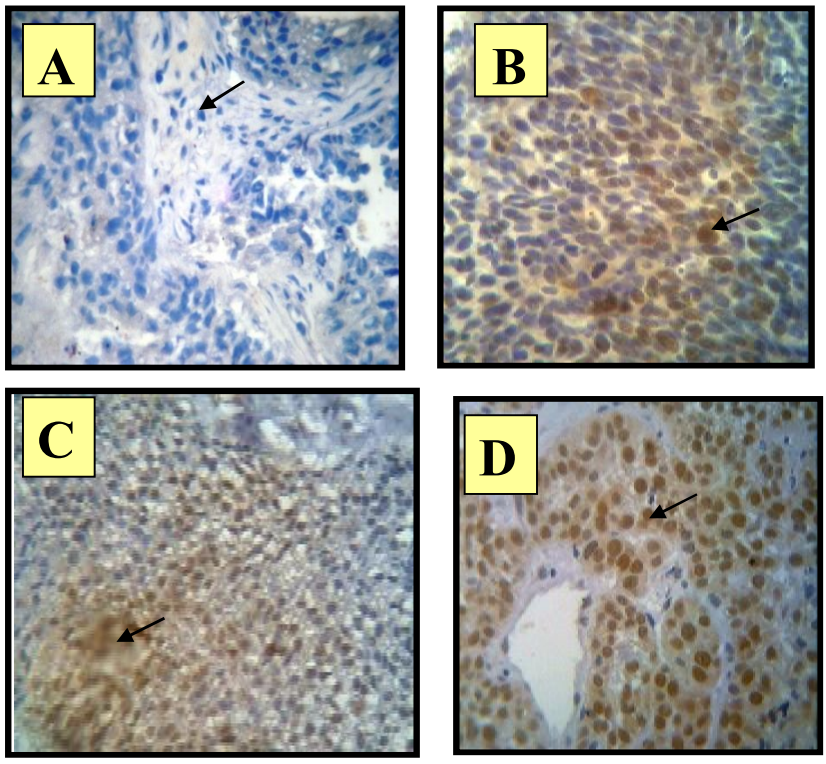

Figure (1): Immunohistochemical staining of LMP-1 (Magnification power X400), A- Moderately differentiated TCC, LMP-1 (negative expression) B- Moderately differentiated TCC, low LMP-1 (positive expression), C- Moderately differentiated TCC, intermediate LMP-1 (positive expression), D- Poorly differentiated, High LMP-1 (positive expression).

Table (2) demonstrates the association between expressions of LMP-1 with different variables. No significant differences was observed between IHC expression of LMP-1 and age, gender, grade, pattern of growth, and muscle invasive, based on Chi-square test of analysis.

Table (2): Association of LMP-1 expression and different parameters of patients with TCC.

Variables		LMP-1 positive	LMP-1 negative	Comparison of Significance	
				Chi^2-value	Sig.
Age	25-39	1 (4.5%)	3 (10.8 %)	0. 07	Non Sig. (P>0.05)
	40-54	2 (9.1%)	9(32.1%)		
	55-70	19 (86.4%)	16(57.1%)		
Gender	Male	16(72.7%)	19(67.9%)	0. 07	Non Sig. (P>0.05)
	Female	6(27.3%)	9(32.1%)		
Tumor grade	I	2(9.1%)	2(7.2%)	0. 28	Non Sig. (P>0.05)
	II	11(50%)	20(71.4%)		
	III	9(40.9%)	6(21.4%)		
Pattern of growth	Papillary	9(40.9%)	19(67.9%)	0.05	Non Sig. (P<0.05)
	Solid	13(59.1%)	9(32.1%)		
Muscle invasion	Invasive	13(59.1%)	11(39.3%)	0. 16	Non Sig. (P>0.05)
	Non invasive	9(40.9%)	17(60.7%)		

Chi-square used

***In situ* hybridization results**. The results of MMP-9 were showed that 32 positive cases (64%), while 18 negative cases (36%). Statistical analysis demonstrated a highly significant difference in MMP-9 expression among patients with transitional cell carcinoma of the bladder when compared with healthy control group P<0.01, table (3) and figure (2).

Table (3): The expression of MMP-9 in patients with TCC.

MMP-9 of ISH tests results		Control group	TCC	Comparison of Significance	
				P-value	Sig.
Positive	Low	0	19	0.01	Highly Sig. (P<0.01)
	Intermediate	0	10		
	High	0	3		
	Total	0	32 (64%)		
Negative	N %	10	18(36%)		
Total	N %	10 (100 %)	50 (100 %)		

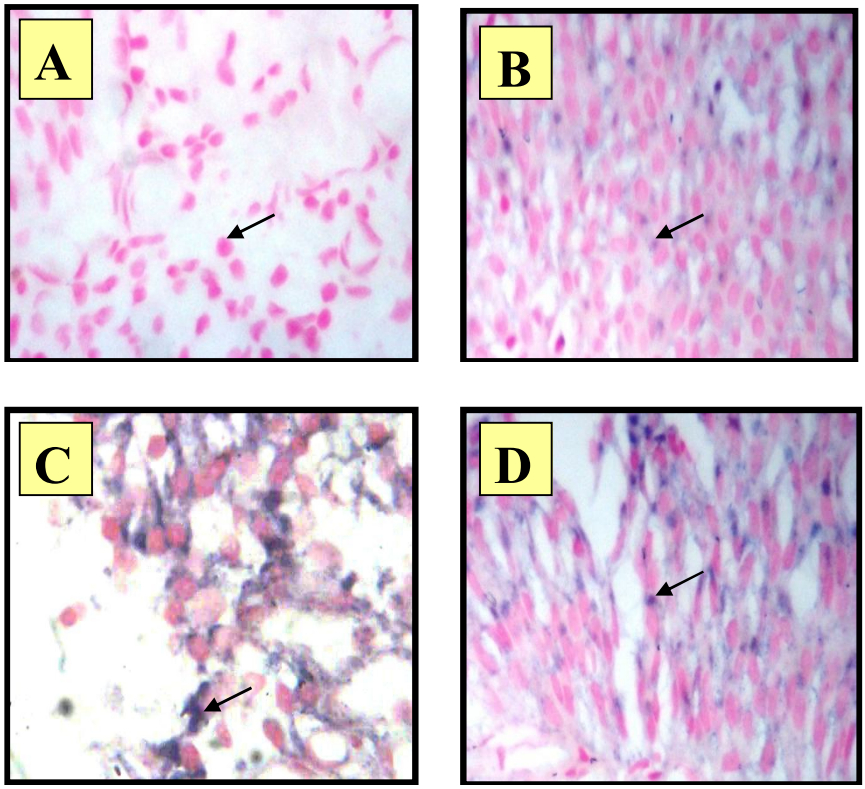

Figure (2): *In situ* hybridization for MMP-9 of patient with TCC of the bladder, stained by BCIP/NBT-Chromogen and counter stained with nuclear fast red (NFR), X400. A-Negative expression, B-low MMP-9 positive expression, C-intermediate MMP-9 positive expression, D-High MMP-9 positive expression.

Table (4) demonstrate the association of *in situ* hybridization expression of MMP-9 score, with different clinicpathological parameters. There were no significant differences between expression of MMP-9 and age, gender, grade, pattern of growth, and muscle invasive, based on Chi-square test of analysis.

Table (4): Correlation of MMP-9 scores and related with different parameters

Parameters		MMP-9 scores			Comparison of Significance	
		Low	Intermediate	High	p-value	Sig.
Age	25-39	0	1(10%)	1(33.3%)	0.37	Non Sig. (P>0.05)
	40-54	4(21.1%)	1(10%)	1(33.3%)		
	55-70	15(78.9%)	8(80%)	1(33.3%)		
Gender	Male	14(73.7%)	9(90%)	2(66.7%)	0.28	Non Sig. (P>0.05)
	Female	5(26.3%)	1(10%)	1(33.3%)		
Tumor grade	I	3(15.8%)	0	0	0.50	Non Sig. (P>0.05)
	II	12(63.3%)	6(60%)	1(33.3%)		
	III	4(21.1%)	4(40%)	2(66.7%)		
Pattern of growth	Papillary	11(57.9%)	5(50%)	1(33.3%)	0.80	Non Sig. (P>0.05)
	Solid	8(42.1%)	5(50%	2(66.7%)		
Muscle invasion	Invasive	10(52.6%)	3(30%)	2(66.7%)	0.59	Non Sig. (P>0.05)
	Non invasive	9(47.4%)	7(70%)	1(33.3%)		

Chi-square used

Discussion

Epstein-Barr virus-DNA and EBV-gene expressions have been shown in many malignant cells and considered to have a pathogenic role (Abe *et al*., 2008).

In this study we investigate the association between LMP-1 and bladder cancer by IHC. The results showed that LMP-1 was observed in 44% of patients with TCC of the bladder. This finding in agreement with the finding of Gazzaniga *et al*., (1998), who demonstrated that EBV genome in 34% using PCR. While Chuang and Liao (2004). Demonstrated that EBV-encoded RNA within both carcinoma cell and infiltrating lymphocytes in 21% only infiltrating lymphocytes in 7% and only carcinoma cells in 3% of bladder cancers obtained from Taiwanese population. Abe *et al*., (2008), reported that EBER-expressing lymphocytes were detected in the bladder carcinomas in 66.7% while negative results in normal urinary bladder specimens.

On the other hand the present study revealed that the prevalence of LMP-1 was found to be higher in males (72.7%) than females (27.3%) but statistical analysis not revealed significant differences between both of them, this may be related to the higher incidence rate of transitional cell carcinoma of the bladder in males than females.

In the present study we failed to find any association between LMP-1 expression and clinicopathological pattern such as age, grade, pattern of growth and muscle invasion, this suggest that EBV may act as a cofactor for development of TCC of the bladder. In addition, absence of EBV infection in normal bladder and low levels of infection in grade I may indicate that EBV infection plays a role in advanced cancer cases.

The current study had demonstrated that MMP-9 was over expressed in transitional cell carcinoma of the bladder. These results might possibly reflect the association between cellular expression of MMP-9 and bladder tumorgenesis. This was in agreement with the findings of (Grignon *et al*., 1996; Papathoma *et al*., 2000; Kanayama, 2001). As they found overexpression of this enzyme in TCC of the bladder. In comparison with other studies which are both enzyme are increased in malignant tissues compared to their benign counterparts (Iurlaro, 1999). Matrix metalloproteinases expression was rare in benign tumor, know that benign tumor have no metastasis and no invasion, so that no need for additional degradation of ECM and finally no need for exaggerated MMPs expression. In fact, analysis of both primary and

metastatic tumors demonstrated increased MMPs at the metastatic site had pointed out their role in tumor migration and spread (Sutinen *et al.,* 1998).

Matrexmetaloproteinase-9 is quite well examined in bladder cancer whether using tissue samples or serum or urine detection, it seems that high or elevated expression of MMP-9 enzyme correlates with clinical stage or histological grade of the tumor (Eissa *et al.,* 2007; Guan *et al.,*, 2003).

No significant association between MMP-9 expression and clinicpathological parameters, this result was in agreement with the findings of Özemir *et al.,* (1999), who pointed out no correlation was recorded between MMP-9 over expression and tumor grade. Mohammed *et al*., (2000), who measured the level of MMP-9 in serum by western blot technique and they revealed that serum level of MMP-9 was significant elevated compared to healthy normal and failed to detect any association with age, gender or even grade of the disease. Durkan *et al.,* (2003), demonstrated no correlation of MMP-9 with tumor grade, but instead, the MMP-9 levels when measured urine samples of bladder cancer patients by enzyme-linked immunoassay (ELISA) was observed correlated to be stage (Monier *et al.,* 2002).

In the present study most LMP-1 positive occurred within MMP-9 but this association was not significant and may be related to LMP-1, which is expressed in nasopharyngeal carcinoma (NPC), who has two essential signaling domains within the carboxyl terminus, termed C-terminal activation regions 1 (CTAR-1) and CTAR-2. Either signaling domain can activate the MMP-9 promoter and induce MMP-9 activity; however, LMP-1 deletion mutants lacking either CTAR-1 or CTAR-2 had a decreased ability to induce MMP-9 expression. The deletion of both activation regions completely abolished the induction of MMP-9 activity, while the cotransfection of both the CTAR-1 and CTAR-2 deletion mutants restored MMP-9 activity to levels produced by wild-type LMP-1.The NF-κB and activator protein 1 (AP-1) binding sites in the MMP-9 promoter were essential for the activation of MMP-9 gene expression by both CTAR-1 and CTAR-2. The induction of MMP-9 expression by LMP-1 and both CTAR-1 and CTAR-2 (Takeshita *et al.,* 1999)

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الكشف وتحديد موقع غشاء البروتين المستتر–1 و التعبير MMP–9 في المرضى المصابين بسرطان خلايا المثانة الانتقالي

الخلاصة:

خلفية الدراسة: يعد سرطان خلايا المثانة الانتقالي من المشاكل الصحية التي يعتد بها في العالم. موخرا بعض الدراسات اوحت بوجود علاقة بين فايروس الابشتاين بار و تطور سرطان المثانة.

هدف الدراسة: التحري عن العلاقة بين غشاء البروتين المستتر–1 و و التعبير MMP-9 وتطور سرطان.

المواد وطرائق العمل: جمعت خمسون قطعة من نسيج المثانة المحفوظ بالفورمالين والمطمور بشمع البرافين من مستشفى الجراحات التخصصي اضافة الى عشرة عينات من افراد طبيعيين عرضت لنفس الفحص واستخدمت كمجموعة سيطرة. العينات النسيجية قطعت ولصقت على شرائح زجاجية مشحونة بعدها استخدمت للكشف عن غشاء البروتين المستتر–1.

النتائج: حدد موقع غشاء البروتين المستتر–1 في الخلايا السرطانية باستخدام التقنية الكيميائية النسيجية المناعية وتم الكشف عنة في 22 عينة (44%). البيانات الاحصائية كشفت عن وجود علاقة احصائية معتمدة بين غشاء البروتين المستتر–1 وسرطان خلايا المثانة الانتقالي .

الاستنتاجات: اظهرت نتائجنا توافقا مع نتائج سابقة حول هذا الموضوع مما يزيد الاعتقاد بان فايروس الابشتاين بار قد يلعب دورا مهما في احداث سرطان خلايا المثانة الانتقالي او يساعد في اظهارة. الا انة يتوجب القيام بدراسات نسيجية وبائية وجزيئية لترسيخ هذا الاعتقاد ولتقييم مدى انتشار الاصابة بهذا لفايروس وعلاقتة مع سرطان المثانة بالمجتمع العراقي.

الكلمات المفتاحية: سرطان خلايا المثانة الانتقالي، فايروس الابشتاين بار، غشاء البروتين المستتر–1، التسرطن.

دیاری کردن و جیگیر کردنی (Latent Membrane Protein) و(Matrix Metalloproteinase-9) لەو نەخۆشانەی کە خانەی شیرپەنجەیي میزەلدانیان هەیە

پوختە

پێشینە: خانە شیرپەنجەیي کاتیەکان لە میزەلدان دادەنرێت بە کێشەیەکی تەندروستی گەورە و بەوهۆیەوە لەوانەیە مردن ڕوو بدات. هەندێ لە لێکۆڵینەوە نوێکان دەریانخستووە کەوا پەیوەندیەك هەیە لە نێوان تووش بوون بە ڤایروس و شیرپەنجەي میزەلدان. هەروەها چەندەها ئەنزیمی پرۆتۆلیتیکی کە بەر پرسیارە لە تێکشکانی پێکهاتووە دەرەکیەکان و ڕۆلێکی سەرەکی هەیە لە تووش بوون بە شیرپەنجەو خێراکردنی بلاّو بوونەوەی، هەروەك Metalloproteinase-9

ئامانج: بۆ زانینی پەیوەندی نێوان (MMP-9) (LMP-1) لەگەڵ خانە شیرپەنجەییەکان لە میزەڵدان.

ڕێگا و کەرەسە بەکارهێنراوەکان: (پەنجا) شانەی بە فۆرمالین چەسپ کراو بە TCC، لە میزەڵدانی نەخۆشەکان وەرگیرا لە هۆڵی نەشتەرگەری تایبەت لە نەخۆشخانەی تایبەت لە بغداد. هەروەها (10) شانەی بە فۆرمالین چەسپ کراو بە TCC لە میزەڵدانی کەسانی تەندروست وەرگیرا وەکو کۆمەڵەی کۆنترۆل. شانەکان ئامادە کران بە شێوەی تایبەت بۆ بە دەست هێنانی هەردوو (MMP-9) (LMP-1).

ئەنجام: بە دەست هێنانی (LMP-1) لەناوکی خانە شیرپەنجەییەکان بە ڕێگەی (بەرگری و کیمیای ژیانی شانەیی) لە 22 نەخۆش. بەلاّم بە دەست هێنانی(MMP-9) تەنیا لە 9 نەخۆش. جیاوازي دیارو بەلگەداری ئامارکاری تۆمارکرا لە دەردانی ئەم دوو ماددەیە لەلایەن میزەڵدان.

دەرئەنجام: ئەنجامی ئەم لێکۆڵینەوەیە دەریخست کەوا هەردوو (MMP-9) (EBV) لەوانەیە ڕۆلێکی گرنگ ببینن لە دەرخستنی خانە شیرپەنجەییەکان لە میزەڵدان و خێراکردنی بلاّو بوونەوەی. لێکۆڵینەوەی Histopathological, epidemiological and molecular studies پێویستە بۆ خەلکانی عیراق بۆ دڵنیا بوون لە بیر و بۆ چوونەکانمان.

ووشە سەرەکیەکان: خانە شیرپەنجەیي کاتیەکان لە میزەلدان، (MMP-9) ,(LMP-1), (EBV)، شیرپەنجە