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Age related neoplasm in experimental animals

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Abstract

The albino rats are commonly recognized as tumor-resistant and appreciable research interest because of the scarcity of reports and article papers on neoplasm tumors. In this regard, we have encountered ten male and female spontaneous cases of tumor investigated in the veterinary medicine college, experimental animal house. Liver and kidney neoplasms were observed in the animals, ages 2-2.5 years. Tumor masses were measured grossly, giving different shapes and sizes. Histopathological analyses of these tumors revealed degenerative changes represented by cystic alteration, basophilic cell infiltration, reduced cytoplasm, permanent hyperchromatic nuclei, necrosis mass, papillary projection, metaplasia of epithelial lining, nest of cancerous cell, and tubules of tumors cell, in addition to clumpy chromatin with irregular nuclear membranes as well. The neoplastic cell had a positive immunoreactive. The correlation coefficient between BCL2&PAX8 showed significant differences; IHC scoring was done based on the observations of cell reactivity in each field as follows: negative and positive represented by weak reaction as five cytoplasmic positive cells per field, moderate IHC reactivity was 10-15cells positive, furthermore, intense positive staining where more than 15 cytoplasmic positively cell per field. Our results suggest that spontaneous aged-related neoplasms represented by renal and hepatocellular carcinoma were at stages 3 and 4 in the liver and kidney. Our study's conclusion revealed numerous markers of primary hepatic and renal cell carcinoma, yet a specific marker cannot be used to identify all types of cancer. The study and investigation of these markers will significantly impact the early detection, prognosis, and treatment of cancer.

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Introduction

Senility is a complex biological process that counts on the interaction of multiple genes, cellular activity pathways, and the environmental condition's risk factors. It leads to piecemeal damage of physiology function, an increase in chronic degenerative diseases, and several neoplastic and non-neoplastic diseases (1-3); the fact that aging is a progressive process means that its causes persist throughout adulthood and that aging rats can be identified at any age, Rats with benign tumors that have the tumor removed usually live a full allowing for the separation of young from adult in the animal kingdom (4). Generality rodent neoplasms are aging -concerning, and there is little information on their prevalence in the first year. The occurrences and development of cancer are the consequences of the interplay between the exogenous factors, such as physical, chemical, and biological, as well as intrinsic factors, such as genetic defects, including editing of genes, viruses, and homologous recombination. All these factors can collaborate to develop an animal malady model (5-8). Tumor genesis is also related to immune system cancer problems such as metabolism dysregulation (9,10). In this study, we looked into and analyzed the expression of particular proliferative protein markers in naturally rodent neoplasms of mixed breeds in the laboratory animal house,

Veterinary Medicine faculty at the University of Mosul. Targeting particular proliferative protein markers in rodents, rats, and other rodents could enhance therapy trials (11,12). It is interesting to learn if BCL2 and PAX8, which are typically employed in human Neoplasia, have any reaction to spontaneous rodent cancer cases. The B-cell lymphoma 2 (BCL2) is a member of the protein family that contains important regulators with both pro and anti-apoptotic functions (13). These regulators are kept in a precise, delicate equilibrium in healthy cells. They can permanently enable cells to avoid apoptosis and produce malignancy (14) or lead cells to go toward cell iinjury (15,16) irreversibly. BCL2 member families have been found and categorized according to their function and domains categorized into three subgroups (pro-survival represented by BCL-XL &BCL2 & and apoptotic (17). The paired box class of transcription factors includes PAX8.it has a significant function in kidney development and differentiation as well as in renal cell proliferation; it is highly expressed in kidney development and multiple organs system (18); the expression of PAX gene is limited to specific cell lineages (PAX 2,8) which are expressed in nephric ducts and PAX8 is expressed in the thyroid gland, as well epithelial neoplasm has been found to express these genes (19).

This study evaluated the immunohistochemistry expression of various proliferation markers in spontaneous aged-related neoplasms such as PAX -8&BCL2.

Materials and methods

Animals

Ten male and female Sprague Dawley rats, 2-2.5 to -2.5 years old, that showed the growth of tumor mass were kept in pairs in the typical filter topped cages with controlled temperatures (20-24°C),12 cycles of 24 hours of light and darkness (12h per each one) and 50%of humidity. Standard feed and tap water were ad libitum. Body weights were measured weekly, beginning on the first day of the tumor mass growth; in the current work. At the Veterinary Teaching Hospital of Mosul University College of Veterinary Medicine, samples of neoplasm tissue were surgically collected.

Ethical Approve

All procedures were approved by the College of Veterinary Medicine, University of Mosul, and accommodated with an ethical committee acceptance number UM.VET.2022.048.

Processing of tissue and staining

Animals were sacrificed by euthanasia, and affected tissue was removed and fixed in NPF 10%. Following fixation, tissue samples were sliced, sectioned, and embedded in paraffin wax and then stained with routine hematoxylin and eosin stain (H&E) (20); samples were certified by the council-veterinary pathology.

Immunohistochemistry analysis

Deparaffinization, hydration, and blocking by endogenous peroxidase were applied to the tissue section. Solution of Dako Retrieval Target, pH=6 (Dako, Carpinteria, CA) was used to retrieve the Ag in a pressure cooker set at 94-95C for 22 min, then gradually cooled for 19-20 min. The tissue slices were treated with anti-PAX8 and BCL2, mice polyclonal Ab (Protein Tech Group, Chicago, IL; dilution 1:50) for 29-30 minutes at room temperature. An enzyme-conjugated polymer complex designed for automatic strainers by Ventana was used to detect the staining reaction (21); for antibody reaction detection and immunoreactive assessment, the section was examined under low &high power of magnification (50 and 200 μm); positive measures included renal cell carcinoma and hepatocellular carcinoma they frequently served as built-in control section and often seen in the tissue section that was begin tested. Cytoplasmic staining part per field was classified as (negative and positive).

Results

Renal cell carcinoma

Multiple metastases of tumor tissue were detected in different organs; these lesions were found in 10 cases of aged male and female rats. Grossly, these tumors' mass varies in size and shape (soft and movable texture) (Figures 1 and 2). Some kidney organs showed cystic growth (Figure 3); more hemorrhage patches were also found (Figure 4). Histologically, the kidney section showed cells organized in irregular shape, internal hemorrhage, cystic alterations, basophilic cells surrounded by a basal membrane, cells clear scant cytoplasm, and some sections revealed permanent hyperchromatic nuclei (Figure 5). Area of necrosis seen as well, thickening of basement membrane as a result of uncontrolled hyperplasia(proliferation), proteinaceous eosinophilic materials detected and filled the kidney parenchyma (Figure 6), papillary projection in the lumen of tubules epithelium, pleomorphic cells (undifferentiated, some cells show clear cytoplasm which might another type of clear cell Renal cell carcinoma. Congested blood vessels and fibrous capsules surround the mass, forming a separated lobe. The heterogeneity of this tumor gives many different architectures and properties (Figures 7 and 8). Gender, age of rats per day, tumor mass origin, and volume, in addition to the stage of tumor mass were evaluated also (Table 1).

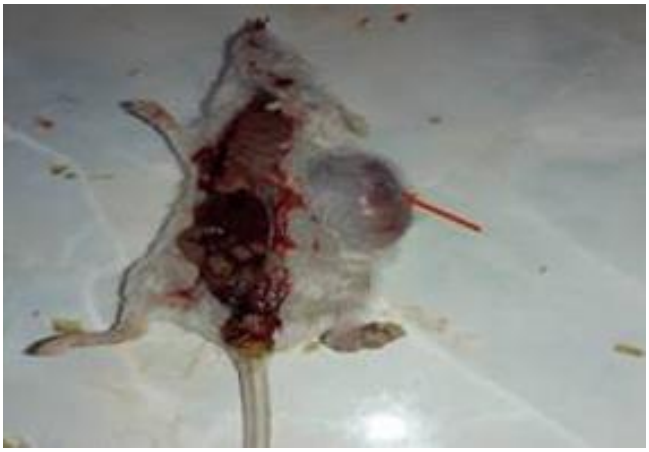

Figure 1: A photograph of a rat showed an irregular tumor mass in the abdominal cavity.

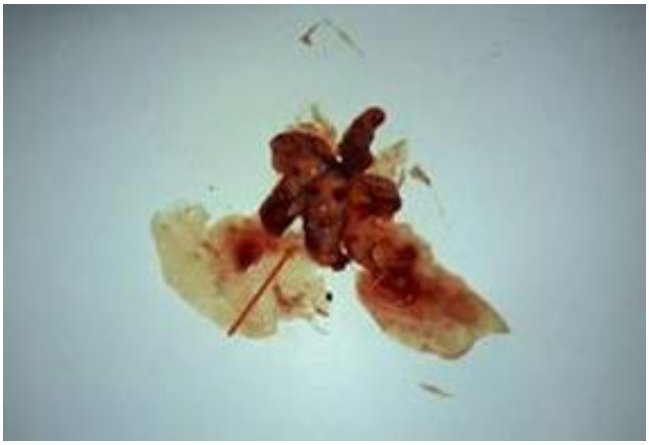

Figure 2: A photograph of the rat showed an irregular tumor mass on the left part of the body.

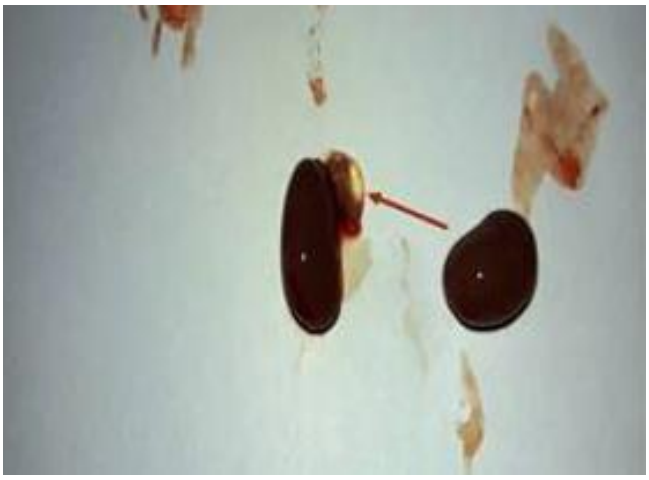

Figure 3: Photograph of rat kidney showed cystic alterations.

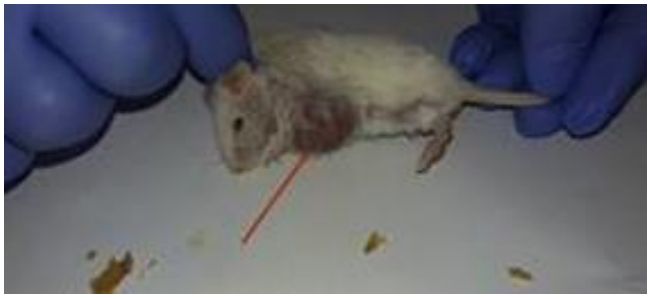

Figure 4: A photograph of rat liver showed a tan color, deposed growth, and multiple hemorrhage patches.

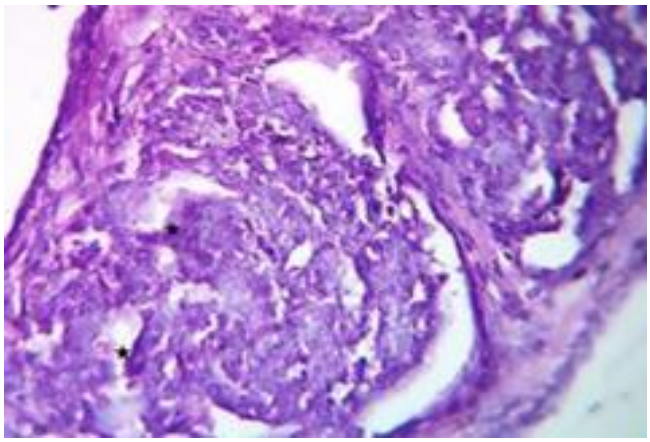

Figure 5: Internal hemorrhage (arrow), basophilic cells (A), surrounded by a basal membrane, cells show clear scant cytoplasm (head arrows), some sections reveal permanent hyperchromatic nuclei (star), thickening of basement membrane (B). H&E stain, 100X.

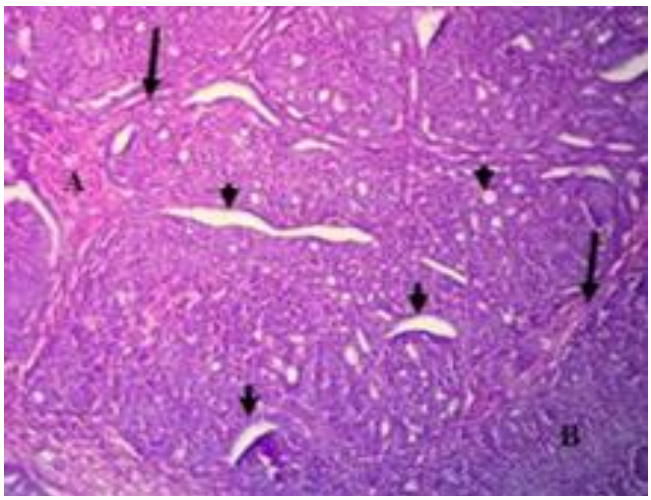

Figure 6: Fibrous capsule surrounds the mass, forming a separated lobe (arrows), and cystic alterations (head arrows), focal hemorrhage (a), mass necrosis (B). H&E, 40X.

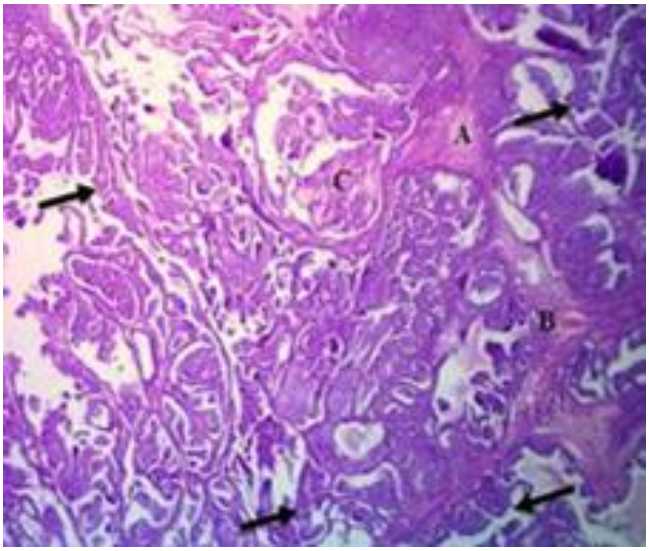

Figure 7: Fibrous tissue capsule (A), papillary projections (arrow). congested blood vessels (B), metaplasia of epithelial lining renal tubules (C). H&E, 40X.

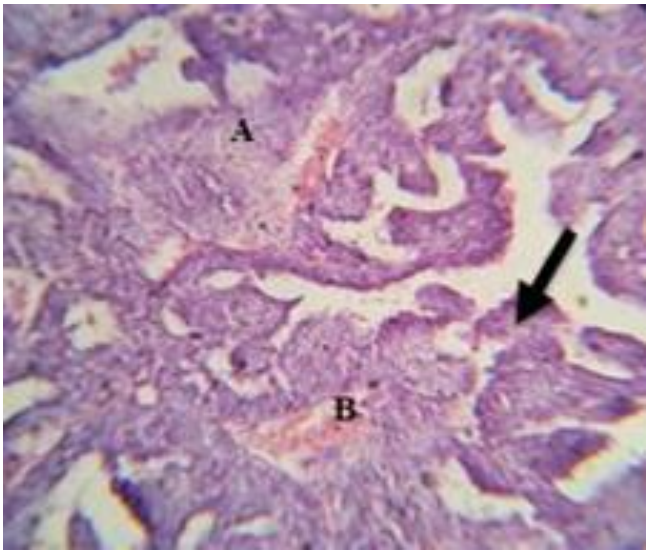

Figure 8: Fibrous tissue capsule (A), papillary projections (arrow), congested blood vessels (B). H&E, 100X.

Hepatocellular neoplasms

Clinical pathological features of the tumor, types of cancers, and grade in each affected section are shown in table 2. Renal cell carcinoma and hepatocellular carcinoma share several morphological characteristics. The hepatocellular carcinoma mass showed a tan with deposed growth and multiple hemorrhagic spots (Figure 9). Microscopically, cancerous hepatocyte nests and irregular trabeculae were seen in (Figure 10). Trabeculae that have thickened and nests with central necrosis are characteristics of cancerous tissue (Figures 11). Hepatocellular carcinoma involves the development of sizable glands that are composed primarily of eosinophilic protein. One layer of hepatocytes lines the glandular-like structures. Clear cells are arranged in nests with intervening stromal and blood vessels, large tumor cells with pleomorphic nuclei, prominent nucleoli, and abundant granular eosinophilic cytoplasm. The acinar pattern is well recognized. The acinar pattern surrounds small nests and tubules of tumor cells marked nuclear pleomorphic and hyperchromatic. Clumpy chromatin and irregular nuclear membranes are appreciable (Figures 12 and Table 2).

Table 1: Characteristic of tumor

Gender	Age/days	Tumor site	Volume of Tumor ($mm^{3)}$	Stage
Male	720	Peritoneal	24	3
Female	850	Kidney	36	4
Male	740	Liver	18	4
Male	790	Thoracic cavity	20	3
Female	840	Liver	28	2
Male	885	Kidney	33	4
Female	860	Kidney	29	4
Male	884	Peritoneal	30	3
Male	885	Liver	33	4
Male	900	Thoracic cavity	36	3

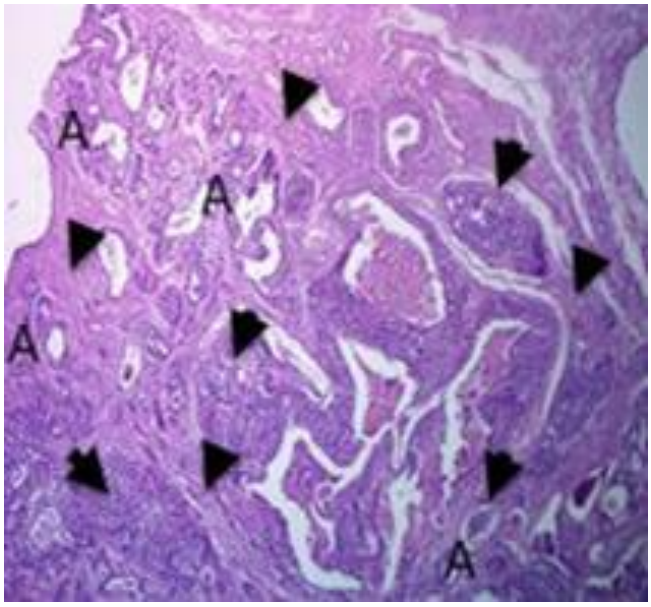

Figure 9: Cancerous hepatocyte nests (arrows) and irregular trabeculae (arrows head), one layer of hepatocytes lines the glandular-like structures (A). H&E, 40X.

Table 2: Clinical pathological features for both renal cell carcinoma and hepatocellular carcinoma

Section	Type of cancer	Lesion	Grade
A & B	RCC&HCC	Circulatory disturbance	III
C & D	RCC&HCC	Growth disturbance	III
E & F	RCC&HCC	Necrosis	IV
G & H	RCC&HCC	Tumor properties	IV
I & J	RCC&HCC	Pro-inflammatory changes	II

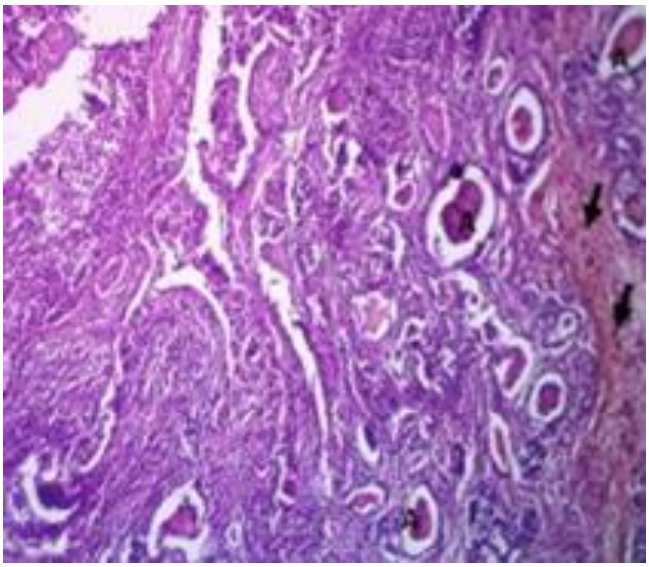

Figure 10: Trabeculae that have thickened and nests with a central necrosis (A), acinar pattern surrounds small nests and tubules of tumor cells (arrow). H&E, 100X.

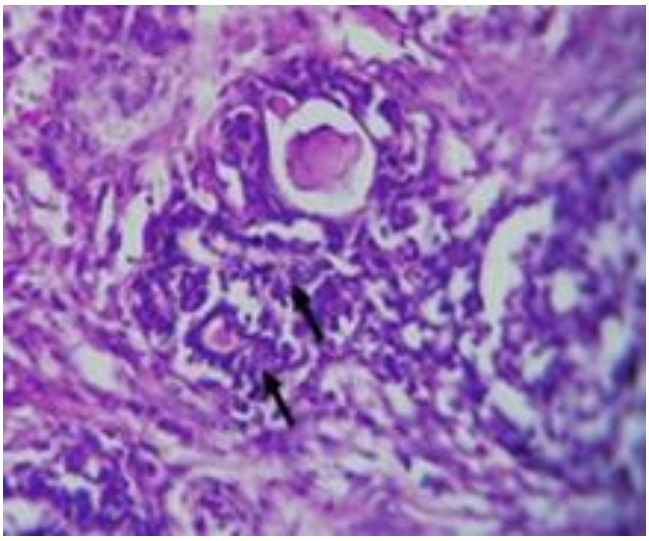

Figure 11: Trabeculae that have thickened and nests with a central necrosis (arrow), H&E, 400X.

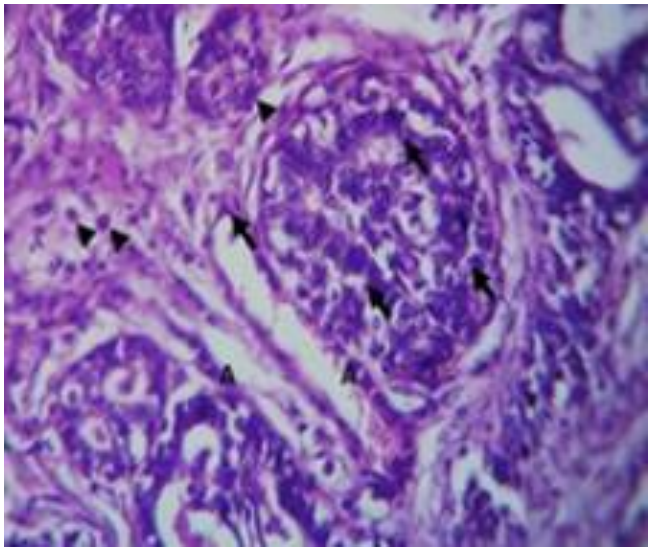

Figure 12: Marked nuclear pleomorphism and hyperchromasia (arrows), clumpy chromatin and irregular nuclear membranes are appreciable, abundant granular eosinophilic cytoplasm (arrows ahead), tubules of tumor cells (A). H&E, 400X.

Immunohistochemical reaction

Regarding the IHC investigated, the data reflect different results; all sections revealed positive immune reactions on both BCL2 and PAX8 in the kidney and liver. The criteria were divided into negative and positive grades, and the positive was divided into three stages (+ represented less than five cytoplasmic positivity cells per field while ++ reactive was between 10-15 cells per field. The +++ IHC reaction was more than 15 cytoplasmic cells per field. Respectively. Figures 13-28 shows the correlations between pro-apoptotic and anti-apoptotic proteins in table 3. Both significant correlations and highly significant correlations between pro-and anti-apoptotic proteins are found.

Table 3: Shows the correlation between BCL2 and PAX8 in the liver and kidney section

Proteins markers	Kidney PAX8	Kidney BCL2	Liver PAX8	Liver BCL2
Liver BCL2				1
Liver PAX8			1	0.950^{*}
Kidney PAX8	1		0.974^{**}	0.973^{**}
Kidney BCL2	0.999**	1	0.974^{**}	0.973^{**}

*indicates that there is a significant correlation between the two traits at ($p \leq 0.05$). **refers to highly significant correlation between the two traits at ($P \leq 0.01$).

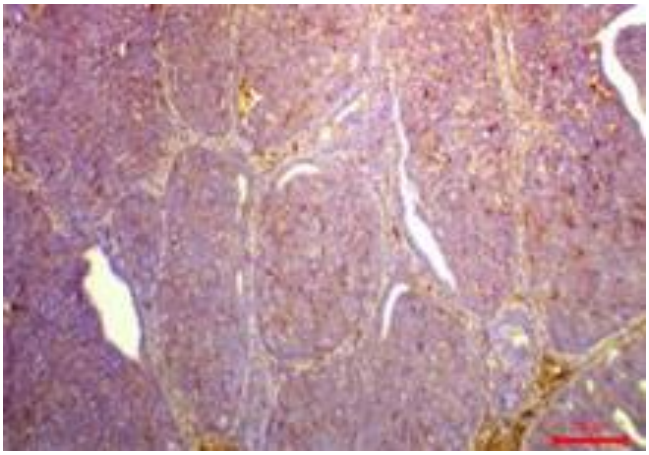

Figure 13: Negative expression of BCL2 protein inside hepatic cells. 100X.

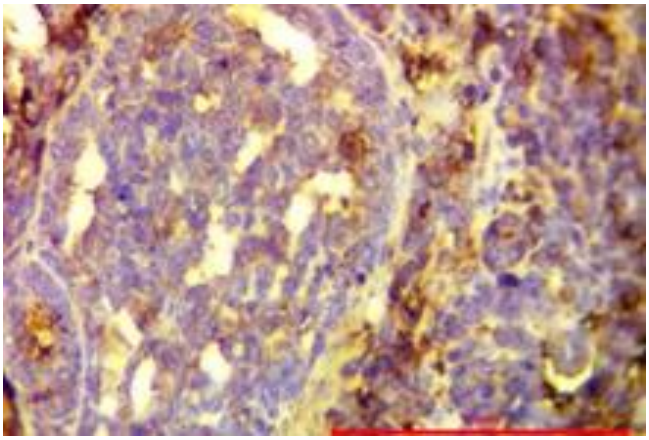

Figure 14: Positive + expression of BCL2 protein inside hepatic cells. 100X.

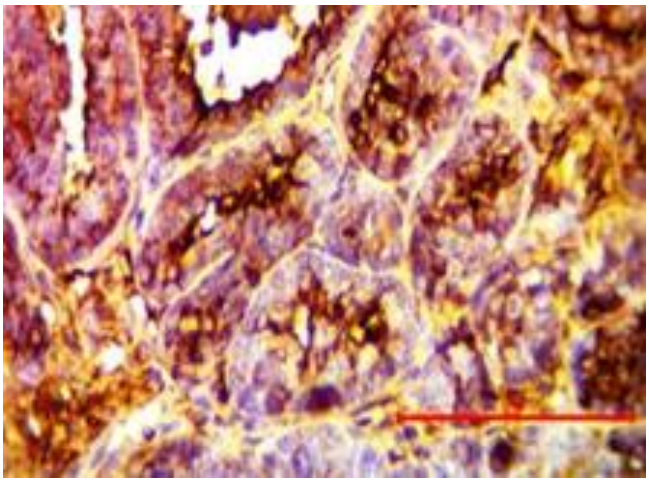

Figure 15: Positive ++ cytoplasmic expression of BCL2 protein inside cytoplasm of hepatic cells. 400X.

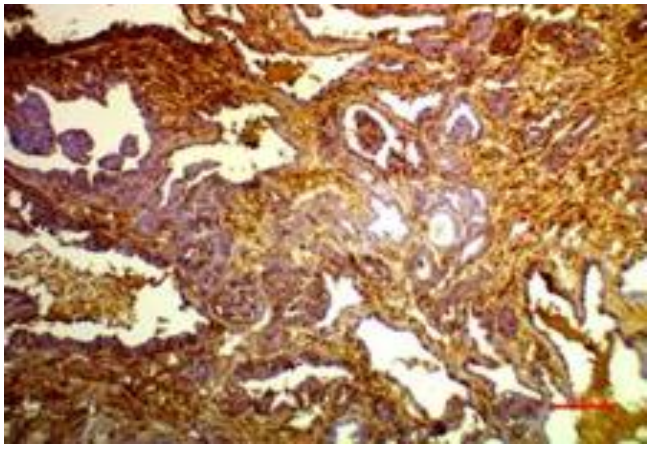

Figure 16: Positive +++ cytoplasmic expression of BCL2 protein inside hepatic cells. 400X.

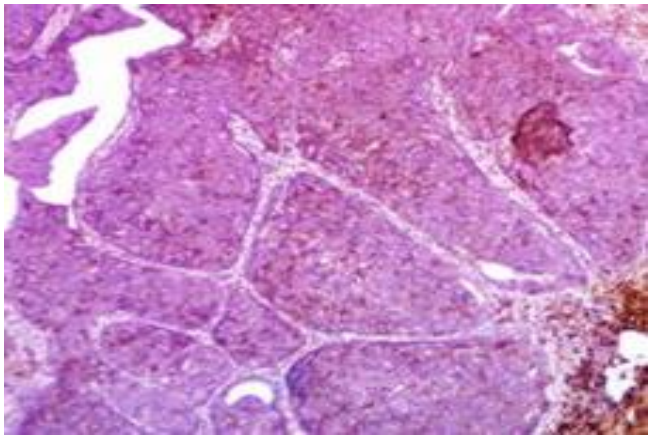

Figure 17: Negative expression of PAX8 protein inside hepatic lobules. 100X.

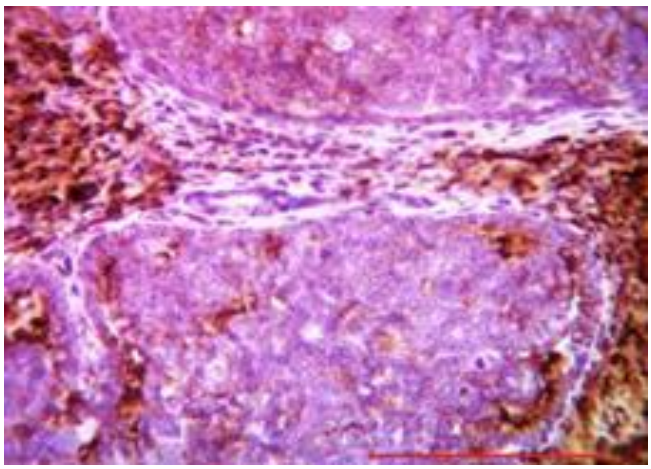

Figure 18: Positive + expression of PAX8 protein inside hepatic lobules. 400x.

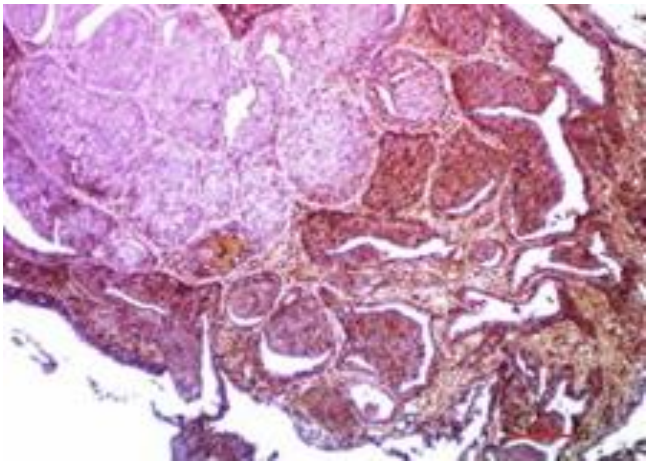

Figure 19: Positive +++ expression of PAX8 protein inside hepatic lobules. 400x.

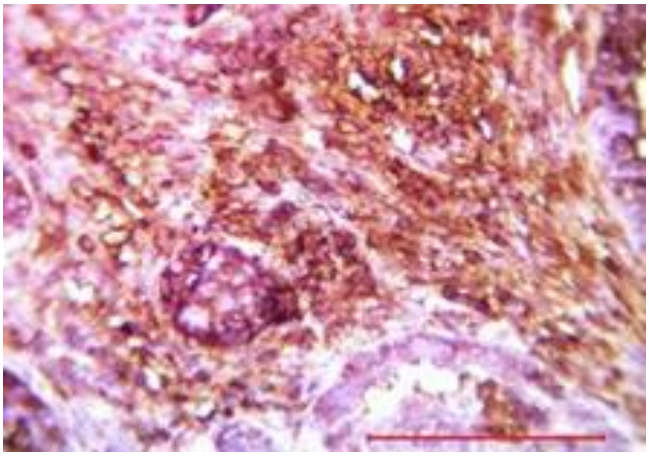

Figure 20: Positive ++ expression of PAX8 protein inside hepatic lobules. 400x.

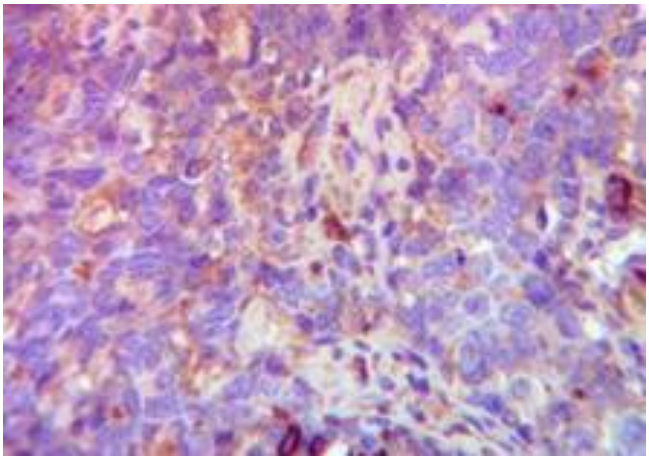

Figure 21: Negative expression of BCL2 protein inside renal cell. 400x.

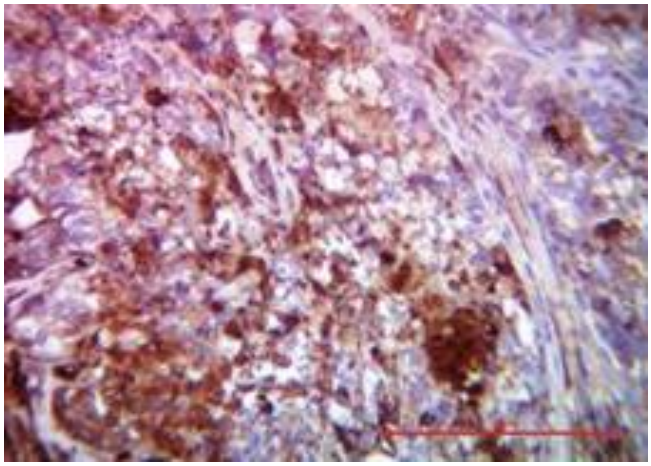

Figure 22: Positive + expression of BCL2 protein inside renal cell. 400x.

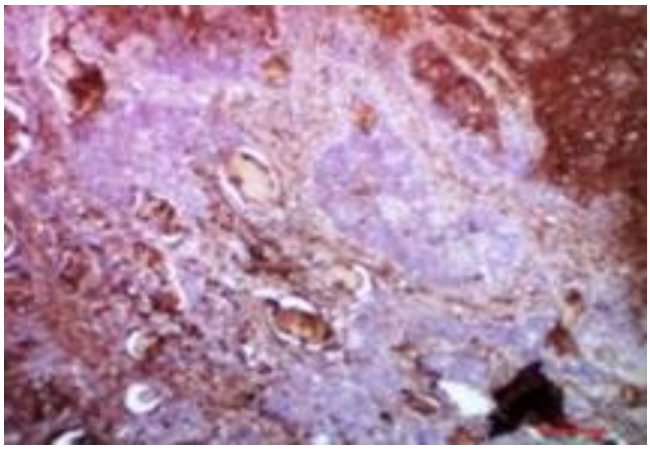

Figure 23: Positive ++ expression of BCL2 protein inside renal cell. 400x.

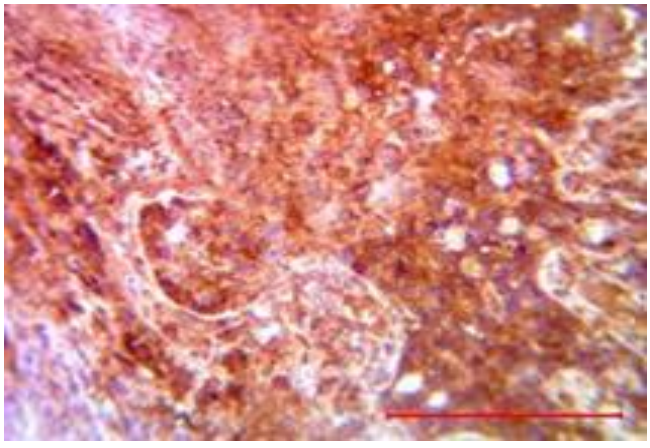

Figure 24: Positive +++ expression of BCL2 protein inside renal cell. 400x.

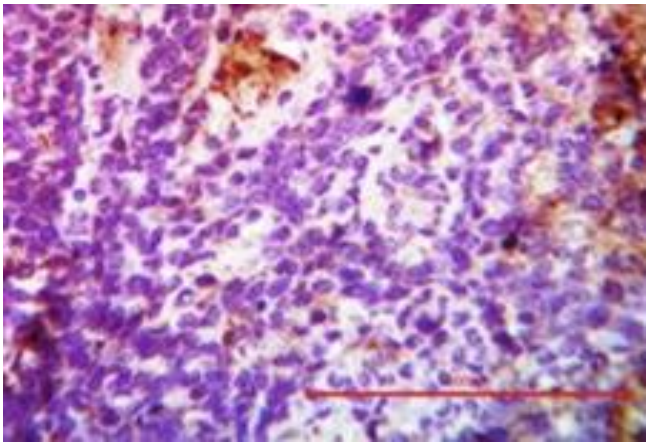

Figure 25: Negative expression of PAX8 protein inside renal cell. 400X.

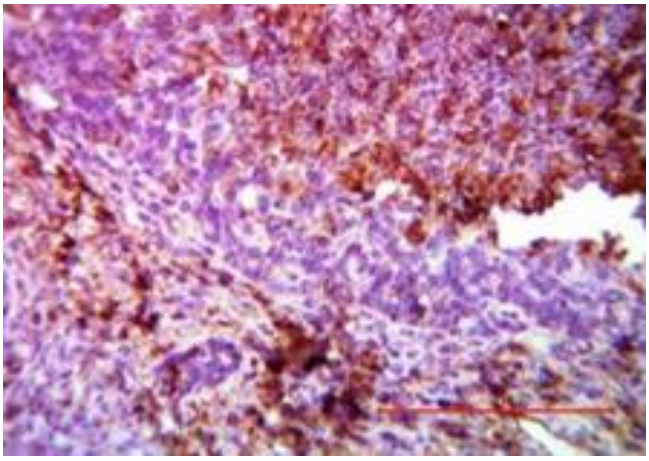

Figure 26: Positive + expression of PAX8 protein inside renal cell. 400X.

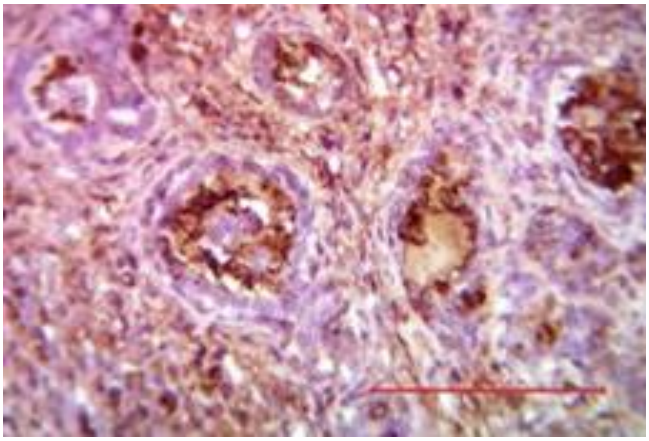

Figure 27: Positive ++ expression of PAX8 protein inside renal cell. 400X.

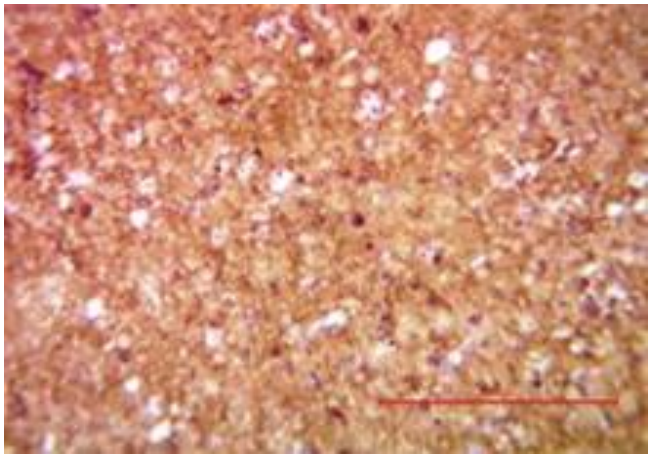

Figure 28: Positive +++ expression of PAX8 protein inside renal cell. 400X.

Discussion

This study aims to appreciate clinically relevant diseases that spontaneously metastasize. Only a small percentage of preclinical trials evaluating novel experimental therapies at this time mimic the stages of original tumor growth, surgical excision, and eventual spontaneous metastatic dissemination; spontaneous tumors are considered the most important manifestation of biological characteristics in laboratory animals (22-24), our results showed that naturally occurring tumors in is a rare event in experimental animals until they were comparatively old age, the incidence rate of spontaneous cancer did not begin to rise significantly until 2-2.5 years of age. However, the spontaneous cancer rate surpasses 25-30% in experimental animals; thus, as in the human population, cancer incidence in experimental animals increases with age. We think that the experimental animals represent a paradigm system for studying the influence of hereditary and environmental condition factors (25) on the occurrence of cancer, which should assist in clarifying the epidemiology of cancer in human beings (26). Our results showed that the most spontaneous tumors occurred in rats between 2 and 2.5 years of age, and these results agreed with PENG and Fletcher (27) and Son and Gopinath (28). Our results showed the presence of spontaneous tumors in 10 cases displaying fibrous capsule, papillary projection, and metaplasia, and these contributed to physiology and weights of the body, amount of food intake and environmental condition (29,30) the subepithelial nodular lesions, cancerous hepatocyte nest, glandular like structures, trabecular in addition to pleomorphism and hyperchromasia and thickening of the basement membranes of loops resemble immunological complex observed in New Zealand black mice (31), at a much younger mice, as well in a diabetic mutant (32) and inbred strain of mice and aging mastomys (33). Apoptosis is a modified state of a normal cell and a

crucial manifestation of physiological function (34). Tumors are illnesses of aberrant apoptosis and pathological prosoplasia and hyperplasia (35). The aberration of apoptosis and the gene that controls it contribute to tumor growth (36,37). The mortuus acceptor route, which causes apoptosis, is the primary cause of tissue cell destruction (38). BCL2 is a type of anti-apoptotic gene. Through inhibiting apoptosis of cancerous cells, promoting cancer cell proliferation, and proliferous survival cells, these gene cause several kinds of carcinogenesis. In addition, we discover that SK-RC-45 monolayers block BCL2 expression in Jurkat cells and activate T lymphocytes, which is consistent with the tumor lines capacity to cause apoptosis in those cells. BCL2 overexpression did, however, consistently shield the lymphocytes from tumor-mediated apoptosis in our experiments in our study. The capacity of overexpressed BCL2 to protect Jurkat cells from cytochrome C release and the activation of the caspase cascade is likely, which protects from apoptosis (39,40).

It is unclear whether this has to do with different Abs employed in Western blot analysis or a different mechanism. The expression of PAX8 in the metastatic disease has not been comprehensively assessed. However, this matter is essential for several reasons. Determination of cellular lineage, an interesting but often diagnostically irrelevant task in the study of primary neoplasms, becomes critical for metastatic tumors, particularly those of unknown tumors of primary origin or those diagnosed as multiple primary cancers. This task becomes crucial for metastatic tumors; PAX8 expression in the metastatic context has not been systematically evaluated (41,42). In addition, there might be a difference in the antigenic profiles of malignancies of their related primary tumor. The result of the current study demonstrated that PAX8 has equivalent tumor marker sensitivity for primary and metastatic cancer (43,44). The total PAX8 expression for metastatic renal cell carcinoma was higher than that of the primary tumors.

Conclusion

This work concluded that the malignant form was more frequently seen in males than females, and the IHC marker represented by BCL2 and PAX8 positively represented such tumors.

Acknowledgements

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Conflict of interest

There is no conflicting interest in this research.

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علاقة العمر بحدوث الأمراض السرطانية في الحيوانات المختبرية

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الخلاصة

تشتهر الفئران من نوع البينوا بكونها مقاومة للأمراض السرطانية، وذات اهتمام بحثي ملموس نتيجة ندرة التقارير والمقالات الخاصة بالأورام. تم اكتشاف حدوث الورم بصورة طبيعية في ١٠ حالات لذكور وإناث الفئران التابعة لبيت الحيوانات المختبرية في كلية الطب البيطري بجامعة الموصل، تم ملاحظة الورم داخل الكبد والكلية للحيوانات التي تراوحت أعمارها بين السنتين الى السنتين والنصف، كما تم قياس هذه الكتلة الورمية بشكل عياني والتي أظهرت أحجام وأشكال مختلفة، بينما اظهر الفحص النسجي التغيرات المرضية المتمثلة بالتنكس الحاوي على التغيرات الكيسة، ارتشاح الخلايا القاعدية، هيولي مختزل، نواة مفرطة اللون، كتلة نخرية، بروز نمو حليمي الشكل، فرط تنسج الخلايا الظهارية ونمو الخلايا السرطانية بشكل أعشاش بالإضافة الى كروماتين متكتل مع نواة غير منتظمة الشكل .اظهر التعبير الكيمائي التفاعل السالب و الموجب وتراوحت شدة هذا التفاعل بين الضعيف الذي كانت شدته اقل من ٥ خلايا هيوليه *PAX8،BCL2* لكل حقل، والتعبير المتوسط كانت شدته بين ١٠-١٥ خلية هيوليه لكل حقل، بينما كانت درجة التعبير الكيمائي الموجب القوي اكثر من ١٥ خلية هيوليه لكل حقل، نستنتج من نتائج الدراسة الحالية أن هناك علامات عديدة لسرطان الخلايا الكبدية والكلوية الأولية، ومع ذلك لا يمكن استخدام علامة محددة لتحديد جميع أنواع السرطان، وسيكون للدراسة والتحقيق في هذه العلامات التأثير الكبير في الكشف المبكر بالإضافة الى تشخيص وعلاج السرطان.