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A, B AND H ANTIGENS IN BRENNER TUMORS

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ABSTRACT

We investigated the presence of A, B and H blood groups in 43 Brenner tumors using the red cell adherence test (RCA) with the purpose of seeing if the histogenesis of this tumor was related to the coelomic or germinal epithelium. The RCA test gives a positive reaction when the tissue under study contains the corresponding isoantigens and negative when they are absent. The only RCA positive structures of the normal ovary are the coelomic epithelium, rete ovari and the mesonephric tubules. The results obtained in the Brenner tumors differed greatly: the epithelial nest gave a positive reaction in 23.2% of the cases and 39.5% were negative. The reaction was plus and minus (+−) in the same nest in 16.2% of the cases and in 20.9% was positive, negative and plus-minus in different nests of the same patient. We analized the different possible origins of the tumor according with the results of the test discarding the germinal or coelomic epithelium as the only one origin of it. We suggest that perhaps the multiple different responses of the test are more in accord with the multiple origin that Greene gives to the tumor. Finally we analized the possibility

of the tumor beeing rather a Teratoma coming from the germinal cell which differentiates into ectodermic structures giving the typical cellular nests of the Brenner tumor.

INTRODUCTION

We demonstrated previously the presence of the A, B and H blood group antigens in the germinal epithelium (3). We believe that all the benign neoplasms arising from coelomic mesothelium contain the corresponding antigens, and that these antigens are lost in the malignant and benign (4), and in other similar non published studies done on mucinous cysts with the same results.

The histogenesis of the Brenner tumor is a highly controversial subject. Its origin has been attributed to the granulosa-theca cells by Brenner in his original papers, because frequently the epithelial nest of the neoplasms shows a structure similar to the cumulus oophorus. Another early theory states that the neoplasms originate from an embryonic structure called the Walthard Rest, because of morphologic similarities of the nucleus (coffe-bean) of the two.

Mayer 1932 (7) and Plaut 1933 (9), assumed that the Brenner tumors originate from the germinal epithelium of the ovary.

Greene 1952 (5), proposed a probable multiple origin of the tumor: Rete ovarii, stroma, surface epithelium of the ovary and mucinous cystadenoma. Woodruff (11), suggested that some Brenner tumors may arise from pre-existing mucinous neoplasms. Taking into consideration the possible origin of the Brenner tumors from the germinal epithelium, we decided to study this tumor with the red cells adherence test (RCA), to see if the Brenner tumor behaved the same as the other neoplasms that arise from the coelomic epithelium.

MATERIALS AND METHODS

Fifty-one cases of Brenner tumors from the files of the Mayo Clinic were available for the study. The age of the patients varied from 33 to 78 years. All the original slides were reviewed by us. Blocks of 43 of 51 cases were available for serial sections.

On three of the slides, from each block, the blood group of the patients was determined using the red cell adherence (RCA) test (2). Two consecutive slides were then used. In one, the RCA test was done according to

the blood group of the patient, the other was stained hematoxylin and eosin (H and E) to do a comparative inmunopathologic study in each case. The results of the RCA test could be positive (+) or negative (–). A positive reaction occurs when the tissue under study contains the corresponding isoantigen of his blood group, which we confirmed when we added antiserum to the antigens, then, a suspension of 1% of red cells of the patients same blood group was used as an indicator to visualize the antigen-antibody reaction that took place in the tissue. A negative reaction occurs when the tissue under study does not contain the iso-antigen, therefore the antigen-antibody reaction does not take place and the indicator red cells do not adhere. Other technical details in relation are available in a previous publication (3, 6).

RESULTS

Slides of the 43 cases of Brenner tumors included in this study, stained with hematoxylin and eosin showed typical nest cells of variable shapes and sizes. The cells resembled stratified squamous epithelium, which in some cases presented a nucleus of coffe-bean appearance. Occasionally the nest showed a cavity, usually centrally located (Insular cysts), and contained degenerated cells that appeared like keratin plugs.

Some of the neoplasms had both epithelium cell nests and cystic structures, most of them microscopic of varying sizes and shapes. Some of these cysts were lined with flat epithelium, others by columnar epithelium and some appeared mucous secreting, occasionally with cilia. Few cases had a high percentage of the epithelial nests replaced by cysts, some of them with secretion in the lumen and some empty. Surrounding the epithelial nest there was abundant connective tissue stroma formed by spindle shaped cells, occasionally with patchy calcification. Three of the 43 cases (6.9%) of Brenner tumors were associated with mucinous cysts, and 20% with serous cysts.

The response to the RCA test of the 43 cases of Brenner tumors varied from one case to the other. The variation had no relation to size and shape of the epithelial nests nor to nuclear morphology, neither with the presence nor absence of cystic structures, nor even where the cysts predominated. In summary, we found: a) cases of Brenner tumors where the epithelial nests were positive to the RCA test which is represented by an epithelial nest completely covered by indicator red cells (Fig. 1). b) The cases in which we call a plus and minus (+–) reaction, the epithelial nest showed areas covered by indicator red cells (positive result) and other areas in the same nest without indicator red cells, (negative result) (Fig. 2). c) Cases where all the epithelial nests were completely negative (Fig. 3).

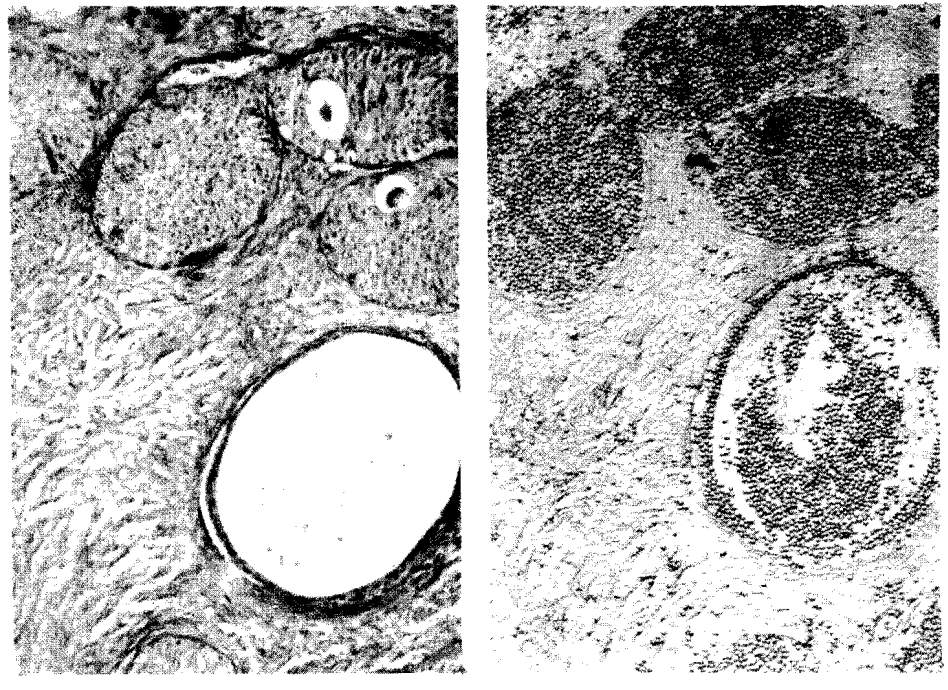

Fig. 1A.– Hematoxylin and eosin. Typical stroma and epithelial cell nest. A cyst is shown lined with several layers of flat epithelium. Fig. 1B.– RCA test, the epithelial nest gives a positive reaction. The cyst epithelium and secretion are also positive. The stroma gives a negative reaction (original magnification 100X).

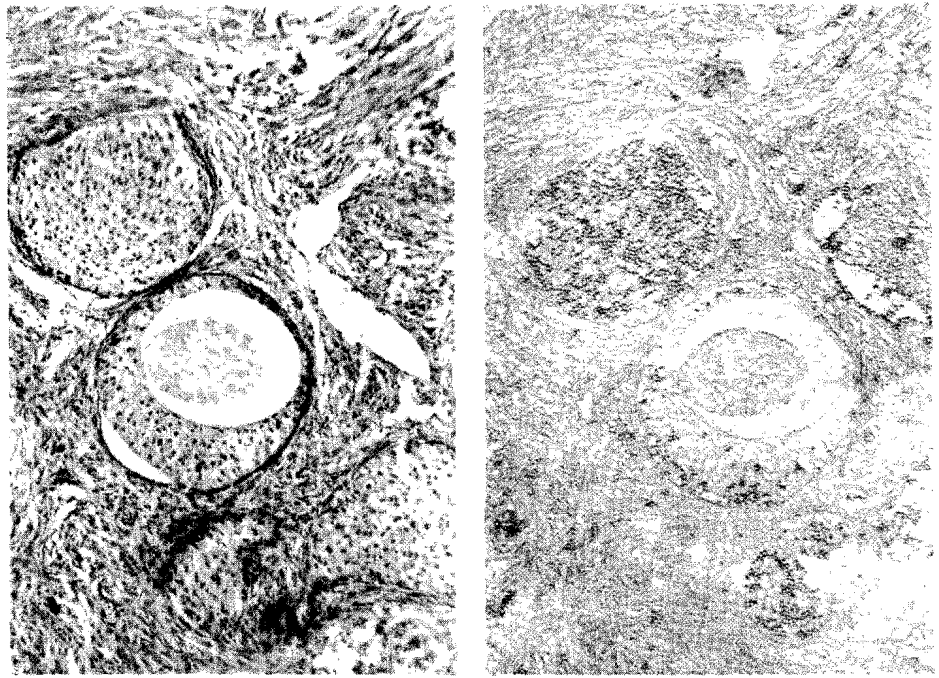

Fig. 2A.– Hematoxylin and eosin. Epithelial cell nests of Brenner tumors. One nest showing an insular cyst. Stroma with a blood vessel. Fig. 2B.– RCA test. Epithelial nest giving a plus and minus reaction. Stroma negative, blood vessels endothelium positive (original magnification 100X).

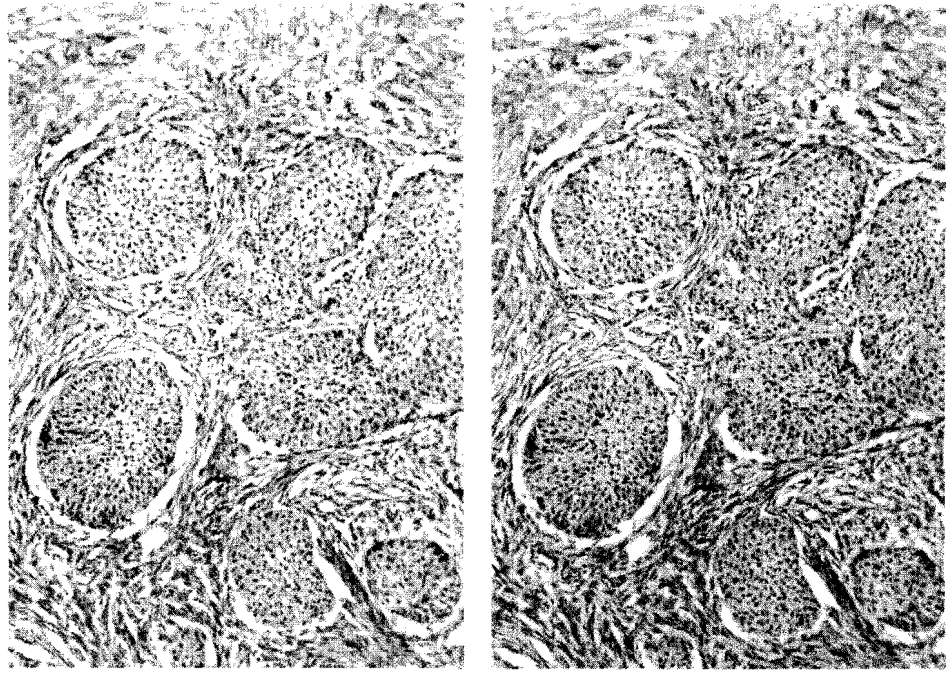

Fig. 3A.– Hematoxylin and eosin. Typical Brenner tumor. Fig. 3B.– RCA test. Epithelial cell nests giving a negative reaction (original magnification 100X).

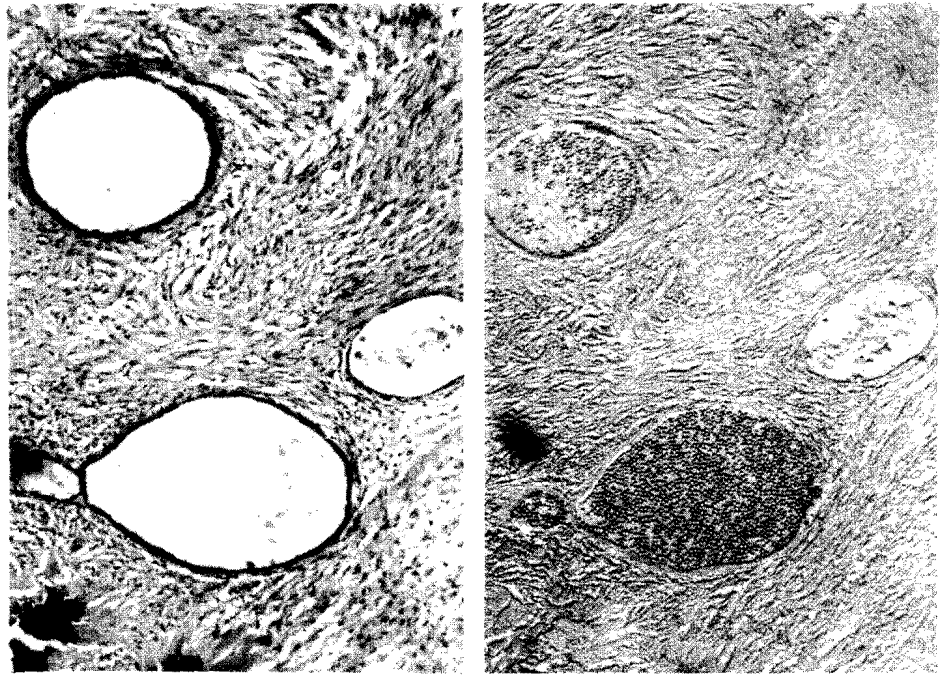

Fig. 4A.– Hematoxylin and eosin. Three cystic structures of a Brenner tumor lined by a flat epithelium. Typical fibrotic stroma.
Fig. 4B.– RCA test. Giving a combined reaction, one cyst positive, one plus and minus and the other negative (original magnification 100X).

d) Cases in which we observed a combined response in the same patients: Positive, negative and plus minus nest (Fig. 4) (Table I).

The findings of the typical epithelial nests, as described above, were also seen in cystic Brenner tumors. We had some cases where the cysts were positive, others negative, and some plus and minus (Fig. 1-4-5). Results of the RCA test were always negative in the connective tissue surrounding the epithelial nests, and only the endothelium of the blood vessels gave a positive reaction (Fig. 2). These findings agree with the RCA reaction response of connective tissue and vascular endothelium of the entire body. That is, the former never contains isoantigen present in the person's serum. Therefore, all tissues studied contained incorporated controls (2). The vascular endothelial cells always contain the iso-antigen and will give a positive reaction. This is a form of positive control. Connective tissue is always negative because it does not contain the iso-antigen, thus, providing an incorporated negative control.

DISCUSSION

A high percentage of Brenner tumors are benign, and this lesion gives a variable response to the RCA test: positive, negative, and plus-minus, which does not agree with our hypothesis that benign neoplasms, arising from a tissue that normally contains the corresponding A, B and H iso-antigens, should always give a positive response. Malignant variants of the Brenner tumors have been described, but they are rare (1).

If one considers the germinal epithelium as the only origin of this neoplasm, according to the hypothesis presented in this study, the response of the benign Brenner tumor to the RCA test should always be positive, since the coelomic mesothelium, along with the rete ovarii and the mesonephric tubules are the only RCA positive ovarian tissues (3) because, normally, they contain the corresponding A, B and H blood group antigens of the female (3). The fact that we found a variable response to the RCA test in Brenner tumors, we cannot consider that the germinal epithelium is the only origin of this neoplasm. The cysts that are seen in Brenner tumors, resemble the germinal inclusion cysts morphologically, but do not in the RCA reaction, since germinal inclusion cysts always give a positive reaction (3).

Perhaps the different responses of the Brenner tumor in the RCA test are more in agreement with the theory of diverse origins proposed by Greene for this neoplasm. Thus, Brenner tumors which originate from the germinal epithelium and rete ovarii should give a positive reaction

Fig. 5A.– Hematoxylin and eosin. Brenner tumor showing cystic changes in one of the cellular nests. The cyst is lined by columnar epithelium. A typical nest is seen on the top. Fig. 5B.– RCA test. Positive reaction on the epithelium of the cyst. The typical nest gives a RCA negative reaction (original magnification 100X).

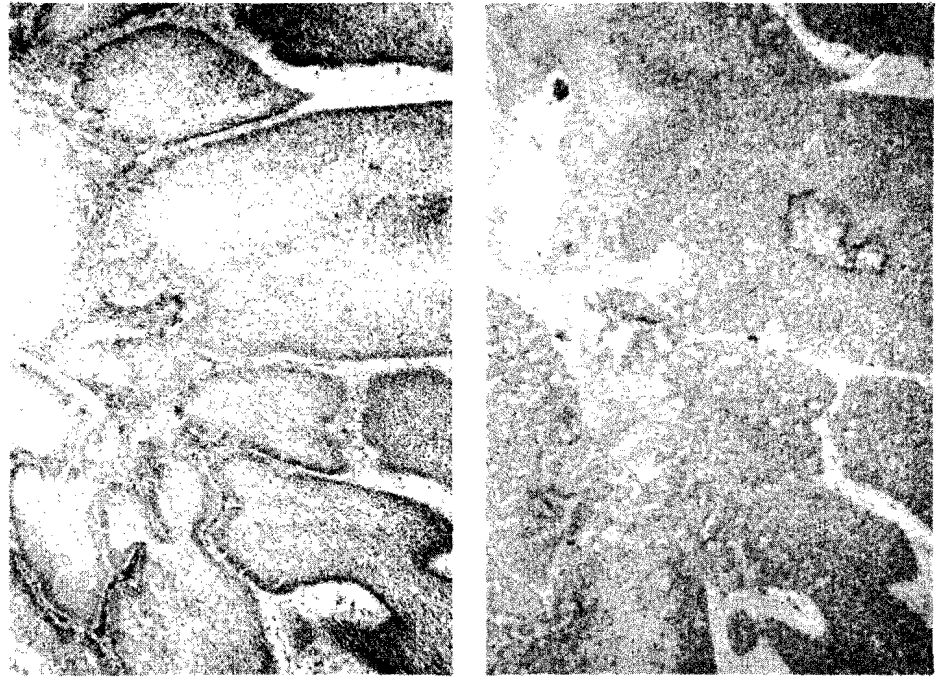

Fig. 6A.– Hematoxylin and eosin. A proliferating Brenner tumor with accumulation of epithelial cells resembling the disposition of a carcinoma. Fig. 6B.– RCA test. Positive reaction. The acumulus of epithelial cells (original magnification 40X).

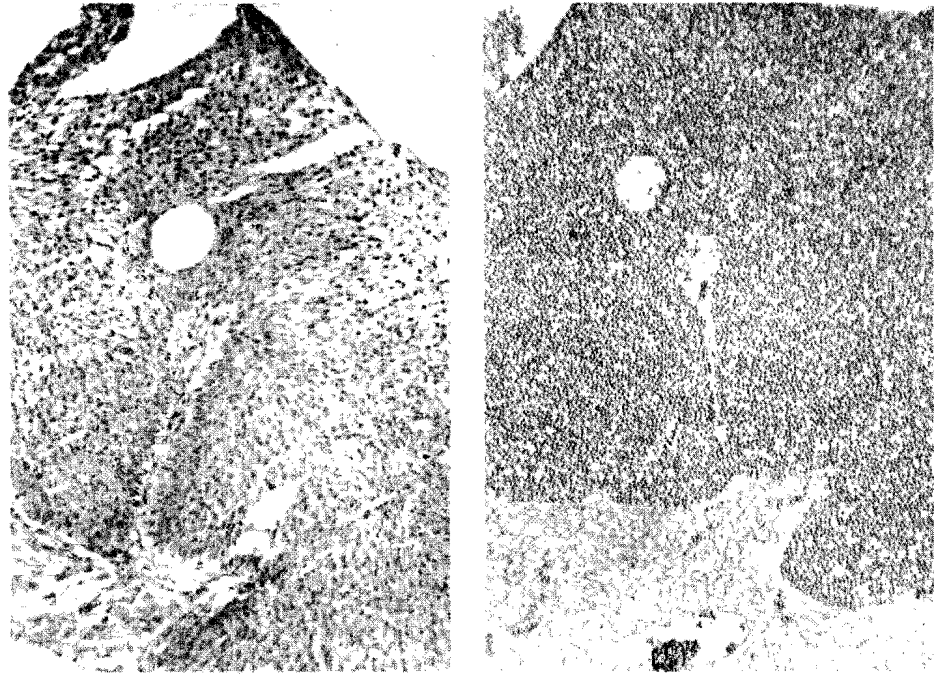

Fig. 7A.– Hematoxylin and eosin. Stroma of Brenner tumor with papillomatous growth of epithelial cells. Fig. 7B.– RCA test. Positive reaction on the epithelial cells (original magnification 100X).

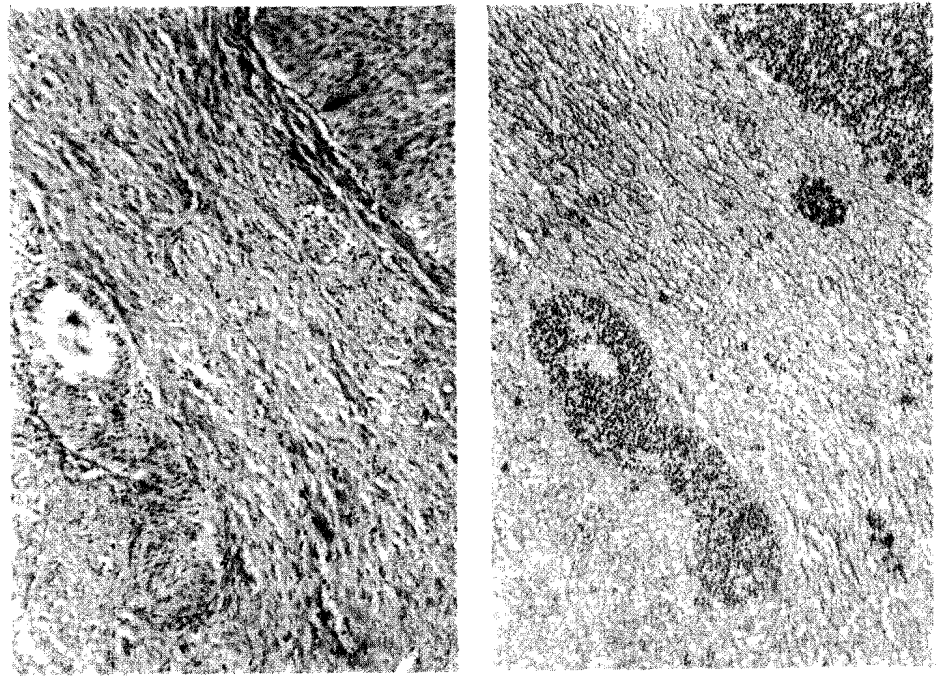

Fig. 8A.– Hematoxylin and eosin. Brenner tumor, same as Figure 7, showing a typical epithelial cell nest. On the top right, a portion of the papillomatous growth; a blood vessel seen. Fig. 8B.– RCA test. Positive on epithelial cells and in blood vessels (original magnification 100X).

in the epithelial nest. The Brenner tumors that originate from pseudo mucinous cystadenomas would also give a positive RCA response, because these cysts arise from the coelomic epithelium; however, only 3 of the 43 Brenner tumors studied here were associated with mucinous cysts and we did not find evidence of transition among them. Finally, the Brenner tumors that arise from the ovarian stroma would give us a negative RCA response, because, as we have already said, the ovarian stroma, as well as the connective tissue from any part of the body, does not contain iso-antigens (2).

Another possible origin of the Brenner tumor could be the germ cells. In this case, the germ cells would differentiate only into ectodermal structures, such as the epithelial nests, typical of the Brenner tumors, as well as cysts structures lined by a single layer of flat epithelium, stratified epithelium, ora secretory epithelium resembling nasal cavity and sinus epithelium.

If we consider that the Brenner tumor is a teratoma, we could explain its variable RCA responses in one of the following manners, based on the investigations of A, B and H iso-antigens in the human fetus, by Rudolf Stejskal, Patsy H. Lill and Israel Davidsohn: first the cells that form the epithelial mass in the Brenner tumor could be represented by the periderm cells, or the superficial layer of the intergumentary ectoderm that appear from the second month of intrauterine life. These periderm cells give a positive RCA response (10) because they contain isoantigens. The Brenner tumors formed by periderm cells could represent those that give RCA positive response. On the other hand, the Brenner that give RCA negative response, would be formed by the epidermis proper, which in the intergumentary of a 2 month embryo, gives a negative response. Furthermore, the Brenner tumors, whose epithelial cells give RCA positive-negative response, would be formed by a mixture of periderm and epidermis proper.

The second possible explanation of the variable responses of the Brenner tumor to the RCA technique, is that the cell formation is represented morphologically by cells with aspects of differenciated squamous epithelium would demonstrate functionally the same difference of reactivity with RCA technique observed in the stratified epithelium of a fetus in the third or fourth month of gestation, that is, the squamous epithelium that covers the mucous membrane gives an RCA positive test in all of its layers. On the other hand, the epithelium that covers the skin is only RCA positive in the stratum corneum and the stratum desquamativum. In accordance with this explanation, the Brenner tumors that give an RCA positive response, would be the epithelial nests that had differentiated

TABLE I

RCA TEST RESPONSE IN BRENNER TUMORS

Number	Blood Group	Positive (+)	Negative (−)	Pos. & Neg. (+) (−)
1	O	X		X
2	B			X
3	O		X	
4	B	X		
5	A		X	
6	O		X	
7	A	X		
8	O		X	
9	A		X	
10	O		X	
11	A		X	X
12	O	X	X	X
13	A	X		
14	A			X
15	A	X		
16	A			X
17	A		X	
18	O		X	
19	A	X		
20	A		X	
21	A		X	
22	A			X
23	A			X
24	A			X
25	O		X	X
26	A			X
27	B		X	
28	B	X		
29	O		X	
30	O	X	X	X
31	O	X	X	X
32	A	X		
33	A	X		
34	AB			X
35	B		X	
36	A		X	
37	O		X	
38	O	X		X
39	O	X		
40	A	X		
41	O		X	
42	A		X	
43	O	X	X	X

23.2% of the Brenner tumor study gave a positive (+) RCA reaction
39.5% gave a negative result.
16.2% gave a plus and minus reaction and 20.9% a combined reaction in the same tissue +, − and (+ and −).
48.6% of the cases belong to blood group A.
37.2% belong to blood group O.
11.6% belong to group B, and 2.2% to blood group AB.

into a squamous tissue of the type that covers the mucous membrane (10). The Brenner tumors that give RCA negative response would be represented by epithelial cells of the type that covers the skin. The Brenner tumors with a positive negative response are composed of a mixture of the two.

Among the cases of Brenner tumors that were studied, we found one characterized by marked proliferation of the squamous cells of a papillary aspect. This would correspond to what is termed proliferating Brenner tumors (8). The RCA test in this case was positive (Figs. 6, 7) which makes us thing that we are dealing with a Brenner tumor that is formed by epidermoid cells functionally similar to the cells that cover the mucous membrane in the 4th month of intrauterine life. Furthermore, we do not think that this proliferation constitutes a malignant Brenner tumor resembling an epidermoid carcinoma, because it gives a positive RCA test as has been demonstrated in the literature (2, 3) that malignant tumors loose the iso-antigens that are normally present in tissues from which they originated and the benign neoplasms preserved them.

Acknowledgment

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RESUMEN

Detección de antígenos A, B y H en tumores de Brenner. *Gaskin-Urdaneta, A. (Departamento de Patología, Facultad de Medicina, Universidad del Zulia. Apartado Postal 1575. Maracaibo, Venezuela), Davidsohn, I.* **Invest Clín** *22(1): 13-28, 1981.*– Investigamos la presencia de los grupos sanguíneos A, B y H en 43 tumores de Brenner utilizando la prueba de adherencia de la célula roja (RCA) con el propósito de observar si la histogénesis de este tumor está relacionada al epitelio celómico o germinal. La prueba RCA dá una reacción positiva cuando el tejido bajo estudio contiene los correspondientes isoantígenos y negativa cuando están ausentes. Las únicas estructuras que en el ovario normal dan RCA positiva son el epitelio celómico, el rete ovari y los túbulos mesonéfricos. Los resultados obtenidos en el tumor de Brenner variaron grandemente: los acúmulos epiteliales dieron una reacción positiva en 23,2% de los casos y 39,5% fueron negativos. La reacción fué positiva-negativa (+–) en el mismo acúmulo en 16,2% de los casos y en 20,9% fué positiva, negativa y positiva-negativa en acúmulos diferentes del mismo paciente. Se analizaron los diferentes orígenes posibles del tumor de acuerdo con los resultados de la prueba descartando el epitelio germinal o celómico como su único origen. Sugeri-

mos que quizás esta múltiple respuesta del tumor de Brenner ante la prueba RCA está más de acuerdo con el múltiple origen que a esta neoplasia le ha adjudicado Greene. Finalmente se analiza la posibilidad de que el tumor sea más bien un teratoma proviniendo de la célula germinal la cual se diferencia a estructuras ectodérmicas dando lugar a los acúmulos celulares típicos del tumor de Brenner.

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