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An immunohistochemical study of laminin in basal cell carcinoma

Background: Laminins are components of the extracellular matrix that mediate cell adhesion, growth, migration, proliferation and differentiation. Basement membrane (BM) laminins, in particular, may play a role in enhancing carcinoma cell motility.
Aim: To evaluate the distribution pattern of laminin in basal cell carcinoma (BCC), as regards the basement membrane, cellular cytoplasm, peritumoral lacunae and surface epithelium and to correlate laminin distribution with different variants of BCC.
Patients and Methods: Skin biopsy specimens were obtained from 21 BCC patients for routine histopathological and immunohistochemical study. Laminin was evaluated qualitatively and semiquantitatively using monoclonal mouse antihuman antibody (Dako-Laminin, 4C7. Code No: MO638, which reacts with the terminal globular domain of the α5 chain)
Results: The majority of BCC cases showed patchy cytoplasmic distribution of laminin. The BM expression of laminin, in most cases, was well defined, fine and linear with irregular areas of thickening. Staining intensity was moderate in differentiated and mixed variants, weak in superficial spreading and absent in morpheic types.
Conclusion: Cytoplasmic and basement membrane laminin is important in the pathogenesis and invasion of BCC. Most laminin was in basement membrane zone (BMZ), and the more differentiated the tumor, the more cytoplasmic and BM staining it expressed.

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Laminins are basement membrane glycoproteins consisting of three polypeptide chains α, β and γ.[1] The functional properties of laminins include cell adhesion, proliferation, differentiation, growth and migration.[2] Laminins 5 and 1 are distributed mainly in the skin especially in basement membranes, where their biological functions involve anchorage and locomotion of cells.[3]

The role of basement membranes in carcinoma biology has not been clarified. On the basis of morphologic data, the loss of BM continuity has been associated with increasing malignancy.[4] Conversely, basement membranes are not degraded, but may be synthesized in some carcinomas. Various carcinoma cells are active in synthesizing new laminins.[5] Hence, it is probable that BM may not only be a barrier against invasion, but rather an active and dynamic structure.[6]

Basal cell carcinoma (BCC) is the most common malignancy in whites.[7] A continuous band of type IV collagen, type V collagen and laminin around nodular islands of BCC have been detected, indicating intact basement membrane. Occasional discontinuations have been observed with finger-like cytoplasmic projections extending into the stroma in these regions.[8]

The aim of the present study is to evaluate the distribution pattern of laminin in the following specific areas of BCC, namely; basement membrane, cellular cytoplasm, peritumoral lacunae and surface epithelium and to correlate this distribution to the different pathological variants.

Patients and methods

Patients and controls

Twenty-one patients with BCC presenting to the Dermatology out-patient clinic, Kasr EL-Aini hospital, Cairo, were the subjects of our study. All patients were subjected to the following: Personal history, history suggestive of risk factors as excessive exposure to sun or associated xeroderma pigmentosum (XP), history of present illness and family history. General examination and full dermatological examination were carried out for all patients; with determination of the clinical type of the presenting BCC. Twenty-five (6 postmortem normal skin and 19 specimens from tumor safety margins) served as control.

Methods

A 4-mm punch biopsy specimen was obtained from each of the 21 BCC patients for routine histopathological and immunohistochemical examination. The specimens were placed in 10% neutral buffered formalin, embedded in paraffin and 5 micron sections were prepared for:

Histopathology

Routine haematoxylin and eosin-stained sections were examined to determine histological type of the tumor.

Immunohistochemistry

A second slide was stained with mouse antihuman monoclonal antibody against the α chain of human laminin using a monoclonal Mouse Antihuman Laminin (Dako-Laminin, 4C7). Code No: MO638. Dako-Laminin 4C7 is a monoclonal mouse antibody, which reacts with the terminal globular domain of the α5 chain of laminin. The staining procedure was carried out according to the kit instruction manual. Many of the studies performed with 4C7 antibody should be seen as valuable sources for description of the distribution of α5 chain. However, it is not known whether 4C7 detects different splice variants of α5 chains. Although this particular detail is still unclear, it is evident that 4C7, that reacts with human, horse, guinea pig, rat and hamster tissues will be useful for many studies of the major α5 chain isoforms in many species.[9]

The staining of laminin was evaluated at the following areas

1. *Tumor proper:* Laminin staining was recorded within groups of tumor cells in two locations (Tables 1 and 2)

a. Central

b. Peripheral
Intensity was rated as follows:

- Mild (+): 25–50% of cells.
- Moderate (++): 50–75% of cells.
- Marked (+ + +) :>75% of cells.

c. Basement membrane (BM) pattern and intensity: Positive BM staining was continuous or patchy/discontinuous.
The intensity of staining was graded as: Absent:–, mild: +, moderate: ++, marked: + + +.

d. Overall pattern of tumor groups:

- A: Single +ve cells.
- B: Patchy staining (Focal).
- C: Zonal
- D: Diffuse.

2. *Lacunae*: These are peritumoral spaces between parts of cells nests and the adjacent stroma.
Positively stained lacunae were assessed by pattern of staining as follows:

- Patchy: Partial staining of lacunae on the stromal side.
- Continuous: Continuous staining of lacunae on the stromal side.

3. *Surface epithelium*: Estimation of laminin in surface epidermis when present completely or as remnants of epidermis overlying the tumor groups (data not shown in Tables).

Data management and statistical methods

The data were coded and analyzed using the Statistical Package for Social Sciences (SPSS) version 9.0. Data were summarized using the mean and standard deviation for quantitative data and percent for qualitative data. Differences between the studied groups were statistically assessed using the chi-square test for qualitative data and one-way analysis of variance (ANOVA) for quantitative data. The results were considered significant at p value <0.05.

Results

Patients

The study included 21 patients with BCC. Clinical data of all patients are summarized in Table 3.

Controls

Six normal postmortem skin samples, in addition to 19 safety margin samples from epidermis adjacent to the tumor were used. In general, staining of formalin-fixed tissues after protease treatment, results

Table 1. Patterns of laminin distribution in BCC lesions

Patient no.	Histological Type	Tumor		Along basement membrane		Lacunae	Overall pattern
		Central	Peripheral				
1	Superficial	+	+	+	d	Patchy	B
2	Solid pigmented	+	++	+	d	Patchy	B
3	Solid pigmented	++	++	+++	c	Patchy	B
4	Solid	+	+++	+++	d	Continuous	B
5	Solid+XP	++	++	+	d	Patchy	B
6	Morpheiform	++	++	–	–	–	B
7	Mixed	+	++	+	d	–	A
8	Mixed	+	+	+++	c	–	B
9	Solid pigmented	+	++	++	d	Patchy	B
10	Solid pigmented	+	++	++	d	Patchy	B
11	Superficial	+++	+++	+++	c	–	D
12	Mixed	+++	+++	+++	d	Patchy	D
13	Mixed	+++	+++	+++	d	Patchy	B
14	Superficial	+	++	+	c	–	B
15	Solid pigmented	+	+	+	d	–	B
16	Morpheiform	+	+	–	–	–	B
17	Solid pigmented	++	++	+	d	Patchy	B
18	Morpheiform	++	++	–	–	–	B
19	Mixed	+++	+++	+++	d	Patchy	B
20	Mixed	+++	+++	+++	c	Patchy	B
21	Superficial	+	++	+	d	–	B

BCC, basal cell carcinoma; XP, xeroderma pigmentosum.
Pattern: A, single +ve cells; B, patchy staining (focal); C, zonal; D, diffuse.
Basement membrane: c, continuous; d, discontinuous.
Staining intensity:—, absent; +, mild; ++, moderate; +++, marked.

in staining not only of the basement membrane, but also the cytoplasm of the epithelia, endothelia and smooth muscles (Dako kit manual). All controls revealed similar staining patterns. The epidermis showed weak diffuse or absent laminin staining, with basal keratinocyte accentuation by positive laminin expression (zonal pattern C). The stratum corneum did not show any stain uptake. The BM appeared as a continuous intensely stained fine line. Appendages as well as blood vessels were surrounded by a continuous linear strongly stained BM with laminin (Fig. 1).

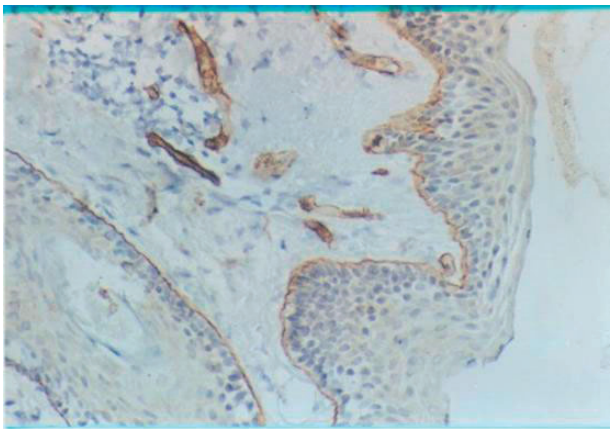

Fig. 1. Control specimen. The BM is continuous, linear and strongly stained. Blood vessels are very well defined by their intensely stained BM (laminin ×200). BM, basement membrane.

Distribution of laminin in different histological patterns of BCC Tables 1 and 2:

Comments

- The staining intensity varied in different areas of the tumor and within the same tumor cell nest. The majority of cases of BCC (18/21) had a patchy cytoplasmic laminin distribution (Tables 1 and 2 and Fig. 2–5).
- The laminin intensity correlated with tumor differentiation; the more differentiated the tumor, the more laminin it contained within its cells ($p = 0.033$) and its BM ($p = 0.000$). The mixed solid with adenoid or sebaceous differentiation showed the highest degree of laminin expression in the section as a whole, whilst superficial and morpheiform types were mildly stained. The peripheral basal cells of the tumor groups exhibited either similar or slightly more laminin than their central counterparts.
- Positive BM staining was a feature of most varieties of BCC (18/21) except for the morpheiform type, which was totally devoid of BM staining. It was weakly stained in superficial BCC ($p = 0.000$). In most cases the BM was well defined, fine and linear with irregular areas of

Table 2. Statistical results of laminin distribution in different histological types of BCC lesions (n = 21)

	Solid		Superficial		Mixed		Morpheiform		Total patients		
Item assessed	No.	Percentage	No.	%	No.	Percentage	No.	Percentage	No.	Percentage	p value
1-Central laminin per nest											
1 – +	5	45	3	27.3	2	18.2	1	9.1	11	100	0.033*
2 – ++	3	60	0	0	0	0	2	40	5	100	
3 – + + +	0	0	1	20	4	80	0	0	5	100	
Total	8	38.1	4	19	6	28.6	3	14.3	21	100	
2-Peripheral laminin per nest											
1 – +	1	25	1	25	1	25	1	25	4	100	0.269
2 – ++	6	54.5	2	18.2	1	9.1	2	18.2	11	100	
3 – + + +	1	16.7	1	16.7	4	66.7	0	0	6	100	
Total	8	38.1	4	19	6	28.6	3	14.3	21	100	
3-BM-staining											
1-Present	8	44.4	4	22.2	6	33.3	0	0	18	100	0.000*
2-Absent	0	0	0	0	0	0	3	100	3	100	
Total	8	38.1	4	19	6	28.6	3	14.3	21	100	
4-BM-intensity											
0-—	0	0	0	0	0	0	3	100	3	100	0.000*
1 – +	4	50	3	37.5	1	12.5	0	0	8	100	
2 – ++	2	100	0	0	0	0	0	0	2	100	
3 – + + +	2	25	1	12.5	5	62.5	0	0	8	100	
Total	8	38.1	4	19	6	28.6	3	14.3	21	100	
5-BM-pattern											
0-—	0	0	0	0	0	0	3	100	3	100	0.008*
1- Continuous	2	40	2	40	2	40	0	0	6	100	
2- Discontinuous	6	50	2	16.7	4	33.3	0	0	12	100	
Total	8	38.1	4	19	6	28.6	3	14.3	21	100	
6-Lacunae-staining											
1-Present	7	58.3	1	8.3	4	33.3	0	0	12	100	0.030*
2-Absent	1	11.1	3	33.3	2	22.2	3	33.3	9	100	
Total	8	38.1	4	19	6	28.6	3	14.3	21	100	
7-Lacunae-pattern											
0-—	1	11.1	3	33.3	2	22.2	3	33.3	9	100	0.130
1-Patchy	6	54.5	1	9.1	4	36.4	0	0	11	100	
2-Continuous	1	100	0	0	0	0	0	0	1	100	
Total	8	38.1	4	19	6	28.6	3	14.3	21	100	
8-Overall pattern											
1-A	0	0	0	0	1	100	0	0	1	100	0.488
2-B	8	44.4	3	16.7	4	22.2	3	16.7	18	100	
3-C	0	0	0	0	0	0	0	0	0	100	
4-D	0	0	1	50	1	50	0	0	2	100	
Total	8	38.1	4	19	6	28.6	3	14.3	21	100	

*p value: <0.05 significant.

BCC, basal cell carcinoma; BM: basement membrane.

–, absent; +, mild staining intensity; ++, moderate staining intensity; + + +, marked staining intensity. Pattern: A, single +ve cells; B, patchy staining (focal); C, zonal; D, diffuse

thickening and hazy at others. In only five cases did the BM display a complete ring around the tumor cells. In the remaining cases BM was discontinuous ($p = 0.008$), particularly adjacent to positively stained stroma within peritumoral lacunae (12/21 cases).

- Peritumoral lacunae staining was observed commonly in mixed and solid types 11/14, rarely (1/4) in superficial spreading and was absent in morpheiform BCC ($p = 0.03$).
- The epidermis covering groups of BCC cells in the dermis was observed in all sections to show weak diffuse cytoplasmic staining and absent BM-staining.
- In BCC lesions occurring in XP (one patient), features were observed as follows:

  i. Cytoplasmic staining pattern was mild patchy (B) type.
  ii. Basement membrane staining was discontinuous.
  iii. Peritumoral lacunae showed positive staining.

Table 3. Clinical data of BCC patients

Number of patients	21
Age (years)	Mean: 52 Range:11–76
Sex	Male: 11 (52.4%) Female: 10 (47.6%)
Disease duration	Mean:5 y Range:3 m–25 y
Risk factors [excessive sun exposure, xeroderma pigmentosum (XP)]	Present: 16 (76.2%)
Skin type	II: 1 (4.8%) IV: 16 (76.2%) V: 4 (19%)
Family history	3+ve (14.3%)
Site	Face: 17 (80.9%) Trunk: 4 (19%)
Clinical appearance	Ulcer: 9 (42.9%) Nodule/Tumor: 6 (28.6%) Papule/Plaque:6 (28.6%)
Diagnosis	Solid BCC (pigmented/non-pigmented/nodular):8 (38%) Superficial: 4 (19%) Mixed: 6 (28.6%) Morpheiform: 3 (14.3%)

BCC, basal cell carcinoma; m, month; y, year.

Discussion

Basement membranes are composed of complex proteins such as laminin glycoproteins.[3] Laminin may be expressed inside the cytoplasm of budding carcinoma cells, at the basement membrane, at the invasive front of the tumor as well as inside the stroma.[10] Some researchers have reported laminin deposits in one or two components of BCC such as BM,[11–14] BM and cytoplasm[15] and peritumoral lacunae.[16] Adding up to their work, our study elaborated its distribution in all these sites in addition to the surface epithelium and presented it in this study. Similar work could not be found in published literature. They used different types of laminin antibodies such as laminin antibodies specific for A, B1 and B2 chains of classic laminin, for the M chain of merosin and for the S chain of S-laminin in one study.[12] In another study, monoclonal antibodies as GB3 to laminin 5, K140 to the 125 KDa laminin β3 chain and polyclonal antibodies SE144 to the 100 KDa laminin γ2 chain, SE85 to the 150 KDa laminin α3 chain antilaminin were used.[15] Others used purified antibodies against laminin to localize basement membrane by indirect immunofluorescense.[16] RNA was isolated from papulonodular BCC, using reverse transcriptase-polymerase chain reaction utilizing primers specific for β3 chain of laminin.[13] To the best of our knowledge, our study was the first to use the monoclonal antibody 4C7 in staining of laminin α5 chain in BCC.

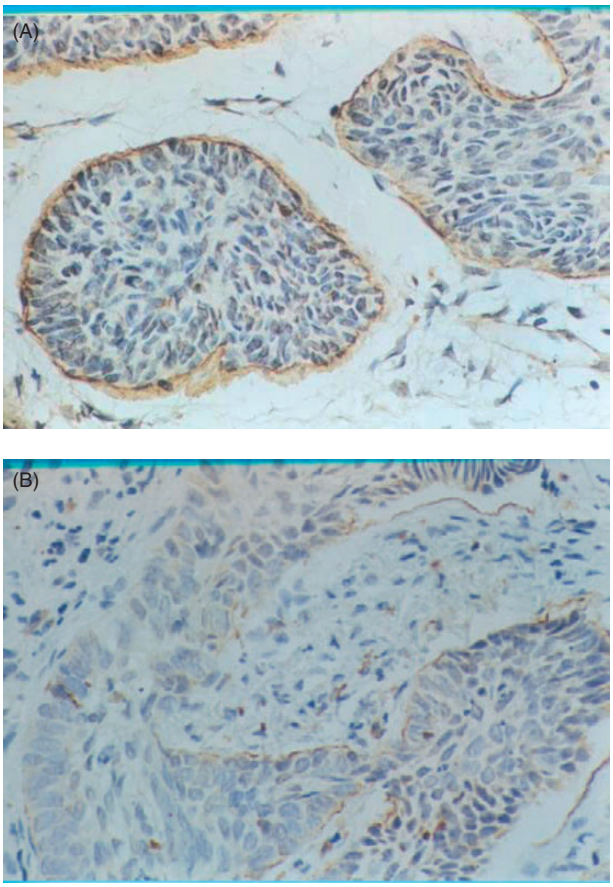

Fig. 2. Solid BCC. A) A case showing a complete linear BM of irregular thickness (Laminin ×400). B) High power of previous case of solid pigmented BCC showing two peritumoral lacunae with dense patchy stromal aspect staining. BM is positive but discontinuous (laminin ×200). BCC, basal cell carcinoma; BM, basement membrane.

In basal cell carcinoma (BCC) the zonal C pattern, which was seen in all control specimens was totally lacking; and pattern B (focal staining) was noted in the majority of cases. Such a loss in the zonal pattern may hence be an important signal of malignant transformation of keratinocytes.

The patchy distribution of laminin (which was the main pattern in our cases) may be attributed to the absence of the enzyme capable of ensuring the proteolytic digestion of BM proteins (including laminin) in cases of nodular BCC but not in other types of BCC, revealing distinct biological features for different histological types of the neoplasm. In addition, these patches may represent residual, undegraded cytoplasmic fragments resulting from apoptosis and cell death.

In the present work BM staining for laminin, was discontinuous in almost half of the BCC cases. It was well defined, fine and linear with irregular areas of thickening. Similar results where BM was

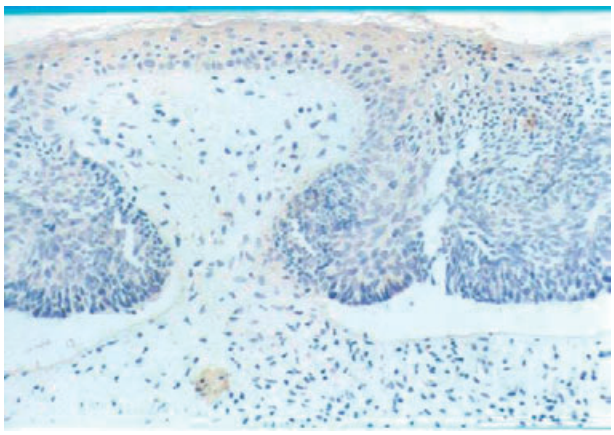

Fig. 3. Superficial BCC. The BM is negative in the three basaloid collections. Also apparent two negative peritumoural lacunae are present (laminin ×200). BCC, basal cell carcinoma; BM, basement membrane.

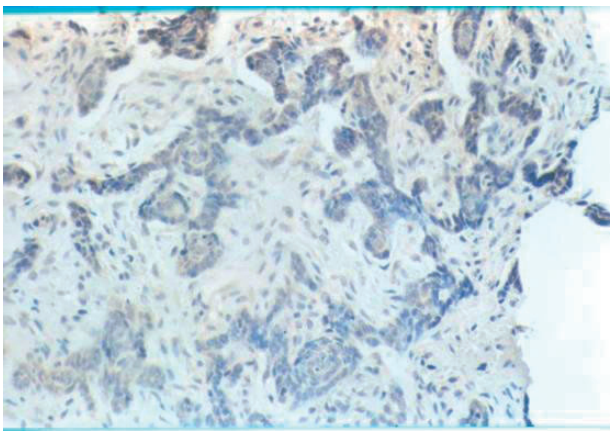

Fig. 5. Morpheiform BCC. Some groups of cells stained with antilaminin antibodies and showing negative BM staining but positive cytoplasmic staining for laminin (laminin ×200). BCC, basal cell carcinoma; BM, basement membrane.

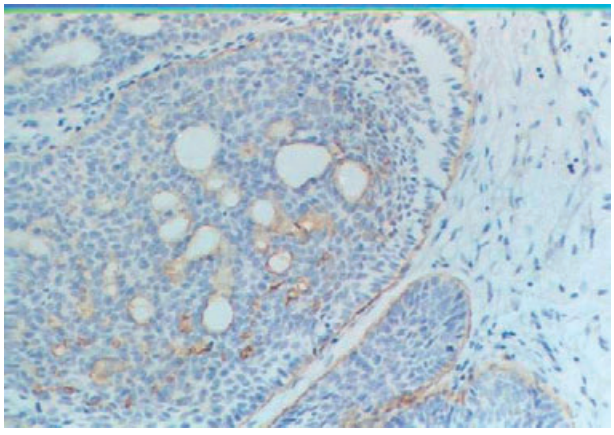

Fig. 4. Mixed BCC. The basaloid groups have a positive continuous linear BM and linear laminin delineating the duct like lumena (laminin ×200). BCC, basal cell carcinoma; BM, basement membrane.

markedly fragmented particularly in areas of diffuse infiltrative types of growth were reported by previous workers.[11–14] Aggressive BCC showed discontinuous staining for laminin and the non-aggressive BCC showed a continuous basement membrane.[18] Also a discontinuous basement membrane in BCC was demonstrated versus a continuous BM in non-tumorous areas.[19] Chopra et al. in 1998 found that there were decreased protein levels of BM components in BCC, which were explained at least partially, by the downregulation of BM mRNA species. These alterations would lead to structurally incompetent BM that facilitates the BCC ability to invade tissues.[13]

On the other hand, in one study continuous linear expression of laminin was demonstrated in BMZ around tumor islands and no apparent correlation between the histological pattern of BCC and the laminin staining pattern was found.[20]

We demonstrated weak and absent BM laminin expression in superficial and morpheiform variants respectively, whereas in differentiated, mixed variants and controls it was strong reflecting a clear correlation between intensity of expression and the clinical form/biological behavior. This expression in BCC cells of the genes coding for the basement membrane molecules, including laminin, suggests that their synthesis is a physiological characteristic of basal keratinocytes unrelated to cancer and whenever these cells lose this differentiation, they lose the ability for basement membrane proteins synthesis, including laminin.[17]

Moreover, a statistically significant correlation between laminin expression on the stromal side of the peritumoral lacunae and the clinical form/behavior being absent in morpheiform, rare in superficial and frequent in mixed and solid variants of BCC. Stromal retraction frequently occurring in BCC around tumor islands had been suggested to result from BMZ cleavage consequent to weakening of hemidesmosome anchoring filament adhesion device including laminin.[21] However, the fact that laminin is expressed refutes a major role in the lacunae appearance.

The molecular events underlying the progression of malignant tumors through the surrounding tissue are largely mediated by membrane bound adhesion molecules. Basal cell adhesion molecule (B-CAM), 90-kDa laminin receptor of the immunoglobulin superfamily, is strongly induced in BCC, and is most pronounced at the basal surface of the tumor nests. Interestingly, the only known B-CAM ligand, laminin, was markedly upregulated within corresponding microanatomical sites surrounding the

tumor nests, suggesting that both molecules may interact there.[21]

Laminin expression in BCC occurring in one XP patient is for the first time presented. This patient was an 11-year-old girl with skin type IV exhibiting ulcerative BCC (0.5×0.5 cm) on the right cheek of 1-year duration and it was solid BCC. The specimen was characterized by mild patchy cytoplasmic laminin expression, discontinuous on BM and patchy on stromal side of peritumoral lacunae.

Conclusion

Cytoplasmic and basement membrane laminin may play an important role in the pathogenesis and invasion of BCC. Laminin was predominantly expressed in the basement membrane region in BCC. Cytoplasmic and basement membrane laminin expression is relative to the tumor differentiation in BCC. Absence of laminin in BM and peritumoral lacunae in the morpheic forms may be associated with the aggressive behavior of that BCC variant.

Recommendations

Further studies are needed to investigate the significance of the various laminin staining patterns in early detection of BCC in predisposed patients. A possible value for laminin as a prognostic index for patients with BCC needs further assessment.

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