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Research Article

Prognostic Significance of L1CAM Expression in Endometrial Carcinoma

Azza Mohamed Abdel Zaher[1], Shenoda Naser Ayad[1], Wafa Farghaly Aref[1] and Rabab Ahmed Moussa[1],

[1] Department of pathology, faculty of medicine, minia university

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Abstract

Background: Endometrial carcinoma (EC) is predominantly having a favorable prognosis. However, there is still need to identify prognostic biomarkers for improved categorization into high- or low-risk EC. There is ongoing debate about the predictive significance of L1CAM expression in EC. **Aim of the study:** to investigate the prognostic role of L1CAM in EC. **Methods:** This is a retrospective study included 52 randomly selected formalin fixed, paraffin embedded tissue blocks of endometrial carcinoma. Cases included 50 cases of endometroid EC and two cases of non-endometroid EC. Tissue sections were stained immunohistochemically with L1CAM antibody**. Results:** Regarding endometroid subtype cases, positive L1CAM expression was detected in 19 /50 (38%) cases. A significant positive association was found between positive L1CAM expression and higher tumor grade *(p = 0.01)*, advanced tumor stage *(p = 0.02)*, presence of LVI *(p <0.04),* post-menopausal state (*p*=0.02) and cervical stromal invasion (*p*=0.002). Additionally, positive significant association was found between L1CAM expression and higher risk groups *(p = 0.003).* No significant associations were found between L1CAM expression and patients' age, tumor necrosis, tumor site and tumor size (*p* = 0.7*, p* = 0.4, *p* = 0.4 *and p* = 0.2 respectively). Regarding both serous and clear cell types cases, high positive expression for L1CAM was detected. **Conclusion.** Our results suggest that L1CAM expression may help to detect EC patient group with poor prognostic features. L1CAM can be an additional tool of a considerable value for risk stratification in EC with potential therapeutic utility.

Keywords: Endometrial carcinoma, Risk stratification, L1CAM

Introduction

Endometrial Carcinoma (EC) is a malignant tumor of the epithelial lining of the endometrial cavity in the uterus, and it seriously threatens the health of women with high mortality rate [1]. It is regarded as one of the most prevalent cancer types among women globally and the most common cancer of the female genital tract[2]. Moreover it is the fifth most common cancer among women worldwide [3]. EC is the most common gynaecologic cancer in the developed countries and it ranked as the second common malignancy following cancer cervix in the developing countries [4]. It is considered that there are 319,500 cases of EC per year [5] and it is responsible for about 76,000 deaths per year worldwide [6].

EC is the third gynaecological cancer after ovary and cervix cancers, and it represents the 13th most known cancer in Egypt. Egypt, although having lower incidence of EC as compared with other Middle East countries, has shown an increase in the incidence over the last 12 years as it contributes to 31.4% of female genital tract

malignancies according to Cancer Pathology Registry, Cairo University and National Cancer Institute, with increased mortality rate and accounts for 1.6% of total cancers in female [7].

The majority of EC cases occurred in postmenopausal women, but a growing proportion of younger women are also being diagnosed with EC; specifically, approximately 25% of women with EC are

premenopausal, and 5% are diagnosed before the age of 40. All things considered, the peak incidence occurred between the ages of 60 and 70[8]. Low parity, nulliparity, early menarche, late age at menopause, age over 55, ovarian diseases like polycystic ovary syndrome (PCOS), tamoxifen therapy, chronic liver disease, obesity, and exogenous hormone use are some of the risk factors for EC [3].

Traditionally, EC has been categorised into a dualistic paradigm based on its clinical, molecular, and biological characteristics. Type I or endometroid ECs, which include 80% of cases, while type II or non-endometroid ECs are including papillary serous carcinoma, clear cell carcinoma, and carcinosarcoma [9].

Endometrial hyperplasia, obesity, hormone receptor positivity, and excess oestrogen have all been linked to type I (endometroid) carcinomas. Type I EC are moderately to well differentiated[10]. The majority of histologic types in type I EC are of lower grade, with a 5-year disease-free survival rate of more than 85% so women with type I EC had a favourable prognosis[11]. Type II includes less common serous, clear cell, undifferentiated carcinoma and carcinosarcoma-types and generally considered to be estrogen independent[12]. Type II EC were linked to poorly differentiated cancer and an atrophic endometrium [13]. The Cancer Genomic Atlas (TCGA) first introduced molecular classification of EC using whole genome sequencing in 2013, resulting in four distinct subtypes. These subtypes have been further studied clinically and found to translate into prognostic outcomes. Copy-number low: Nonspecific Molecular Profile (NSMP) subtype is defined by the lack of molecular subtype expression that defines each of the other three groups; prognostic outcomes are less clear within this subgroup, probably because of a high degree of population heterogeneity; further molecular stratification of the NSMP subgroup is required to better classify this group and aid in directing the proposal of adjuvant treatment. This understanding has led to additional research efforts on alternative molecular classifiers than what developed by the TCGAs [14]

L1CAM (also known as CD171) is one of the first neural adhesion molecules to be identified, it plays a crucial role in the maturation of the nervous system. L1CAM was discovered in 1984 as a novel cell surface antigen expressed in the mouse central nervous system [15]. Because it is crucial for neuronal migration, differentiation, nerve outgrowth, axon guidance, fasciculation of axons and dendrites, myelination, and synaptogenesis, L1CAM is involved in the development of the central nervous system [16].

L1CAM was shown to be expressed more frequently in both the primary tumor and the metastases of different kinds of cancers. By creating an immunosuppressive tumor microenvironment and increasing their resistance to endogenous death and drug-induced apoptosis, its expression gives cancer cells more survival [15] L1CAM was frequently linked to a poor prognosis and is expressed in a variety of solid malignancies. L1CAM has been demonstrated to maintain the aggressiveness of ovarian cancer (OC) tumors by promoting cell invasion, proliferation, and resistance to apoptosis. It is also necessary for the growth and spread of OC cells within the peritoneum. Lastly, there is now evidence linking L1CAM activation to OC chemoresistance [17]. A considerable risk of cancer-related mortality appears to be present in colorectal carcinomas with high expression of L1CAM, even at an early stage of the disease. Furthermore It had a connection to metastasis[18].

The prognostic importance of elevated L1CAM expression in EC is still up for debate. A minor non-endometrioid (serous, clear-cell differentiation) component, an unfavourable epithelial/mesenchymal transition, or a hidden aggressive neuroendocrine features may be connected to the identification of L1CAM in endometrioid endometrial cancer.[19]. It has been demonstrated that having a positive L1CAM is highly correlated with a poor prognosis and aggressive EC. Nonetheless, It has been shown that L1CAM expression was related to a bad prognosis, but only in women with endometroid EC and not in non-endometroid EC patients[20].

Material and Methods

Patients selection criteria:

This is a retrospective study included 52 formalin fixed, paraffin embedded EC tissue blocks. These tissue blocks were collected from Minia University's pathology department archive during the period between April 2021 and April 2023.

Cases included 50 cases of endometroid adenocarcinoma and two cases of non-endometroid EC. All cases have been examined for L1CAM expression. Two cases of non-endometroid type are excluded from the statistical analysis and interpreted separately.

The available clinicopathological data were obtained from the pathology reports of the cases and from patient's data files. These data include: Patient age, menopausal state, tumor size, site, grade, histological subtypes, lymphovascular invasion (LVI), tumor necrosis, tumor infiltration of the cervical stroma. Patients and tumor characteristics were listed in table (1). The histopathological classification of the tumors was performed according to the WHO 2014 classification of endometrial tumors[21]. Cases were graded according to 2009 FIGO grading criteria, using the 3-tier system. Then binary FIGO grading system was applied, in which FIGO grade1 and 2 tumors are categorized as low grade and FIGO grade 3 tumors as high grade [22].

Immunohistochemistry:

Five µm sections were prepared on positive charged slides for immunohistochemical staining using the primary antibody for L1CAM (Rabbit Monoclonal antibody 100 ul concentrated (1ul/ml). According to the manufacturer data sheet (BIOSS ANTIBDIES Company) utilizing the avidin biotin-peroxidase complex method with diaminobenzidine (DAB) chromogen detection system. Tissue sections were first deparaffinized and rehydrated on the positively charged slides. After that, the endogenous peroxidase was inhibited by submerging it in a 3% hydrogen peroxide solution and waiting 30 minutes for it to incubate. For antigen retrieval, the slides were submerged in a citrate buffer solution (pH 6) twice for ten minutes each at 750 W. The slides were treated by UV block to prevent non-specific background staining. Primary antibody L1CAM was then added, and tissue sections were incubated for 1 hour at room temperature (dilution 1:100). After removing the extra reagent, the slides were gently washed for five minutes with buffer solution. Subsequent biotinylated antibody was then applied and maintained on each slide for half an hour. DAB substrate and chromogen. The Positive control for L1CAM was human kidney tissue.

Interpretation of immunohistochemical staining:

L1CAM was expressed mainly in the cell membrane. Occasional weak cytoplasmic expression was detected in some cases. The percentage of positive tumor cells determined the score for L1CAM expression (score 0 = 0%, score 1 = 1–10%, score 2 = > 10–50%, and score 3 = > 50%). Tumors were identified as L1CAM positive if >10% (score 2 and 3) of the epithelial tumour cells exhibited membranous L1CAM staining. [23].

Statistical analysis:

Statistical analysis was conducted using the Statistical Package for Social Sciences (IBM SPSS software version 25), that used to analyze the data. Clinicopathological

characteristics will be described by descriptive analysis which includes the means, standard deviations (SDs), median. For qualitative data, the data were reported as both numbers and percentages, and either the Fisher`s exact test or the Chi-square test was used to assess them. A p-value of 0.05 or less was considered significant.

Results

In this study, regarding endometroid subtype cases, 19 out of 50 cases (38%) showed positive L1CAM expression, while 31 cases (62 %) showed negative L1CAM expression. Association between L1CAM expression and clinicopathological data for cases of endometroid type is shown in table (2).

As regard to tumor grade, a statistically significant association was found between L1CAM expression and tumor grade (p = 0.01). 12 /18 (66.7%) high grade EC cases showed positive L1CAM expression, while 7/32 (22%) low grade EC cases showed positive expression. Also, statistically significant association between L1CAM expression and myometrial invasion (p = 0.001) was detected, as 12/17 (70.6%) cases that showed infiltration more than half of the myometrium showed positive L1CAM expression. In addition, statistically significant association was found between L1CAM expression and LVSI ($p < 0.04$). 7 out of 11 cases (63.6%) that showed LVSI showed positive L1CAM expression while only 12 out of 39 cases (30.8%) without LVSI had positive L1CAM expression. Figure 1 (A-E). Furthermore, a statistically significant positive association was found between L1CAM expression and both menopausal state and cervical stromal invasion (p= 0.02, p= 0.002 respectively). No significant associations were found between L1CAM expression and patients' age, tumor necrosis, tumor site and tumor size (p = 0.7, p = 0.4, p = 0.4 and p = 0.2 respectively).

Regarding non-endometroid cases, there are two non-endometroid cases are included in this study. One case of serous subtype and one case of clear subtype. Concerning serous subtype case, patient characteristics showed post-menopausal state, tumor grade III, tumor stage III, invasion of less than one half of myometrial thickness, positive cervical stromal invasion, No lympho-vascular invasion, and absent necrosis. For L1CAM expression, this case showed high positive L1CAM expression (>50%). As to clear cell subtype case, patient characteristics showed post-menopausal state, tumor grade III and tumor stage IV, invasion of more than one half of myometrium, positive cervical stromal invasion, positive lympho-vascular invasion and presence of necrosis. For L1CAM expression, high positive L1CAM expression (>50%) was detected. Figure 2 (A&B).

In our study, risk stratification scheme according to (ESGO), (ESTRO/ ESP) guidelines for EC cases revealed that 17 cases were classified as low risk, 15 cases were classified as intermediate risk, 9 cases were intermediate to high risk, 7 cases were high risk, and two cases were advanced risk. A significant association was found between L1CAM expression and higher risk groups (p = 0.003). 85% and 100% of high risk and advanced risk group respectively were L1CAM positive, while only 17.6 % of low-risk groups were L1CAM positive, as shown in table (3).

Table (1): -The clinicopathological data for patients with EC (n=52): -

Clinicopathological features		**No =52**	**%**
Age range	**≤55 years**	25	(48%)
	> 55 years	27	(52%)
Menopausal State	**Pre-menopausal**	22	(42.3%)
	Post-menopausal	30	(57.7%)
Size of Lesion (cm)	**≤4.6cm**	31	(59.6%)
	> 4.6cm	21	(40.4%)
Site of lesion	**Fundus**	6	(11.5%)
	Body	35	(67.5%)
	Lower uterine segment	11	(21%)
Tumor histologic type	**Endometroid**	50	(96.2 %)
	Non-Endometroid	2	(3.8 %)
Tumor histologic grade	**Low grade**	32	(61.5%)
	High grade	20	(38.5%)
Myometrial invasion	**<50%**	33	(63.4%)
	≥50%	19	(36.6%)
Lympho-vascular invasion	**Absent**	39	(75%)
	Present	13	(25%)
Cervical stromal invasion	**Absent**	36	(69.2%)
	Present	16	(30.8%)
Tumor necrosis	**Absent**	27	(52%)
	Present	25	(48%)
Tumor stage	**Low stage**	37	(71%)
	High stage	15	(29%)

EC: Endometrial Carcinoma.

Table (2): - Association between expression of L1CAM and different clinicopathological variables in EEC studied cases.

Clinicopathological features		No. (%) =50	L1CAM Expression		*P*-value
			Negative Expression N=31 (62%)	Positive Expression N=19 (38%)	
Age groups	**≤55 years**	25 (50%)	15 (60%)	10 (40%)	0.7
	> 55 years	25 (50%)	16 (64%)	9 (36%)	
Menopausal State	**Pre-menopausal**	22 (44%)	18 (81.8 %)	4 (18.2 %)	**0.02***
	Post-menopausal	28 (56%)	13 (46.4%)	15 (53.6%)	
Size of Lesion (cm)	**≤4.6cm**	31 (62%)	16 (51.6%)	15 (48.4%)	0.2
	> 4.6cm	19 (38%)	15 (79%)	4 (21%)	
Site of lesion	**Fundus**	6 (12%)	5 (83.3%)	1 (16.7%)	0.4
	Body	33 (66%)	20 (60.6%)	13 (39.4%)	
	Lower uterine segment	11 (22%)	6 (54.5%)	5 (45.5%)	
Tumor histologic grade	**Low grade**	32 (20%)	25 (78%)	7 (22%)	**0.01***
	High grade	18 (80%)	6 (33.3%)	12 (66.7%)	
Myometrial invasion	**< 50%**	33 (66%)	26 (78.8%)	7 (21.2%)	**0.001***
	≥ 50%	17 (34%)	5(29.4%)	12 (70.6%)	
Lymphovascular invasion	**Absent**	39 (78%)	27 (69.2%)	12 (30.8%)	**0.04***
	Present	11 (22%)	4 (36.4%)	7 (63.6%)	
Cervical stromal invasion	**Absent**	36 (72%)	27(75%)	9 (25%)	**0.002***
	Present	14 (28%)	4 (28.6%)	10 (71.4%)	
Tumor necrosis	**Absent**	27 (54%)	18 (66.7%)	9 (33.3%)	0.4
	Present	23 (46%)	13 (56.5%)	10 (43.5%)	
Tumor stage	**Low stage**	37 (74%)	27 (72.9%)	10 (27.1%)	**0.02***
	High stage	13 (26%)	4 (30.8%)	9 (69.2%)	

Test of significance by Chi-square and Fischer exact tests, *p.*<0.05 is significant.
* Significant association.
EEC: Endometroid Endometrial Carcinoma.

Table (3): Correlation between L1CAM expression and risk groups according to (ESGO), (ESTRO/ ESP) in EEC studied cases:

			Risk group					p-value
			Low	Intermediate	Intermediate to High	high	Advanced	
L1CAM		**Total Count**	17	15	9	7	2	**0.003***
	Positive expression	**Count (%)**	3 (17.6%)	3 (20%)	5 (55%)	6 (85%)	2(100%)	
	Negative expression	**Count (%)**	14 (82.4%)	12 (80%)	4 (45%)	1 (15%)	0 (0%)	

* Significant association

EEC: Endometroid Endometrial Carc

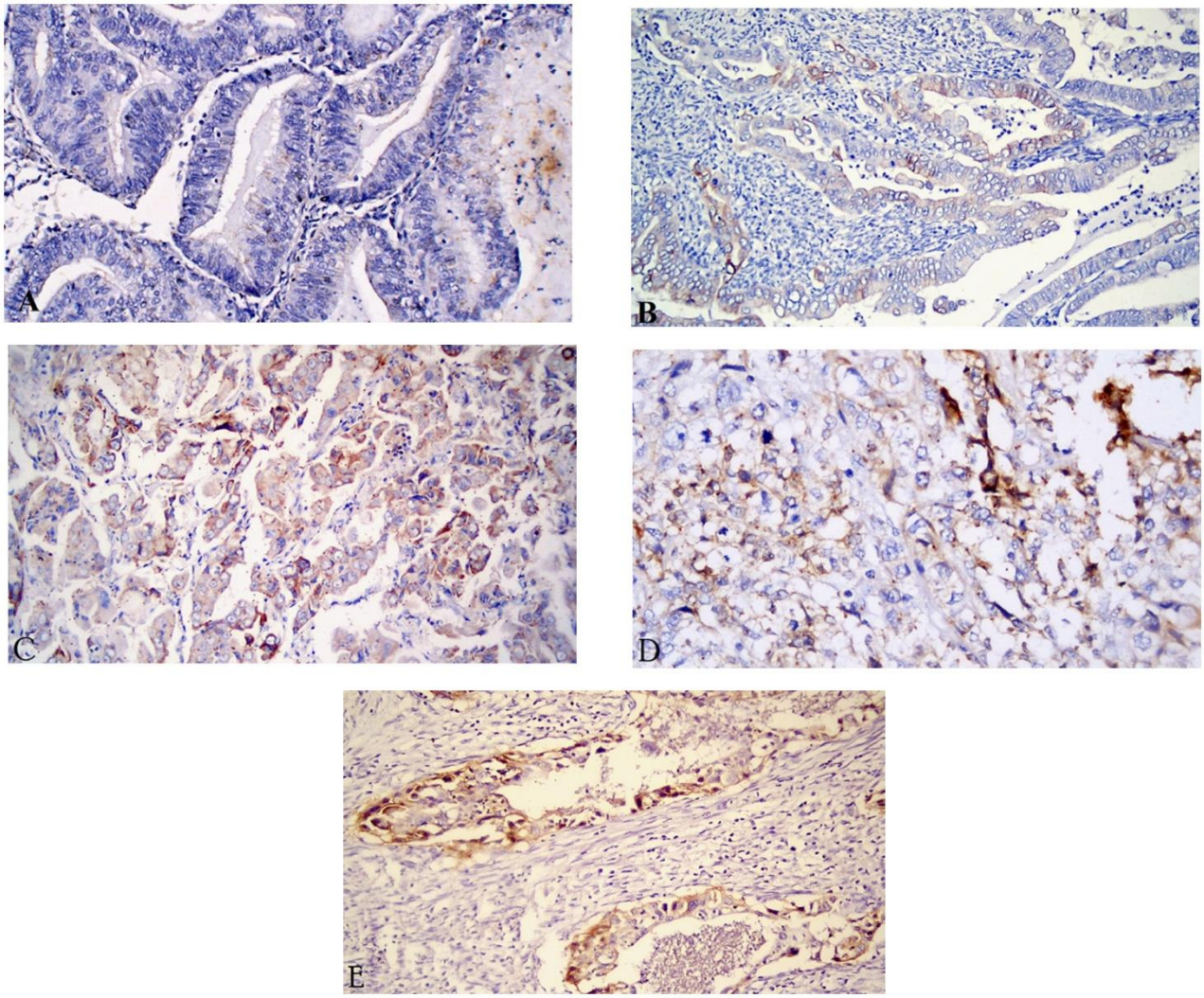

Figure 1: Microphotographs showing representative examples of immunohistochemical expression of L1CAM in endometroid type endometrial carcinomas. (A) Complete negativity of L1CAM expression in grade 1 endometrioid carcinoma with 0% cells positive x200; (B) low positivity of L1CAM expression in grade 1 endometrioid carcinoma x200; (C&D) strong positivity of L1CAM expression in grade 3 endometrioid carcinoma x200, x400 respectively; (E) LVI with positive L1CAM tumor clusters x200.

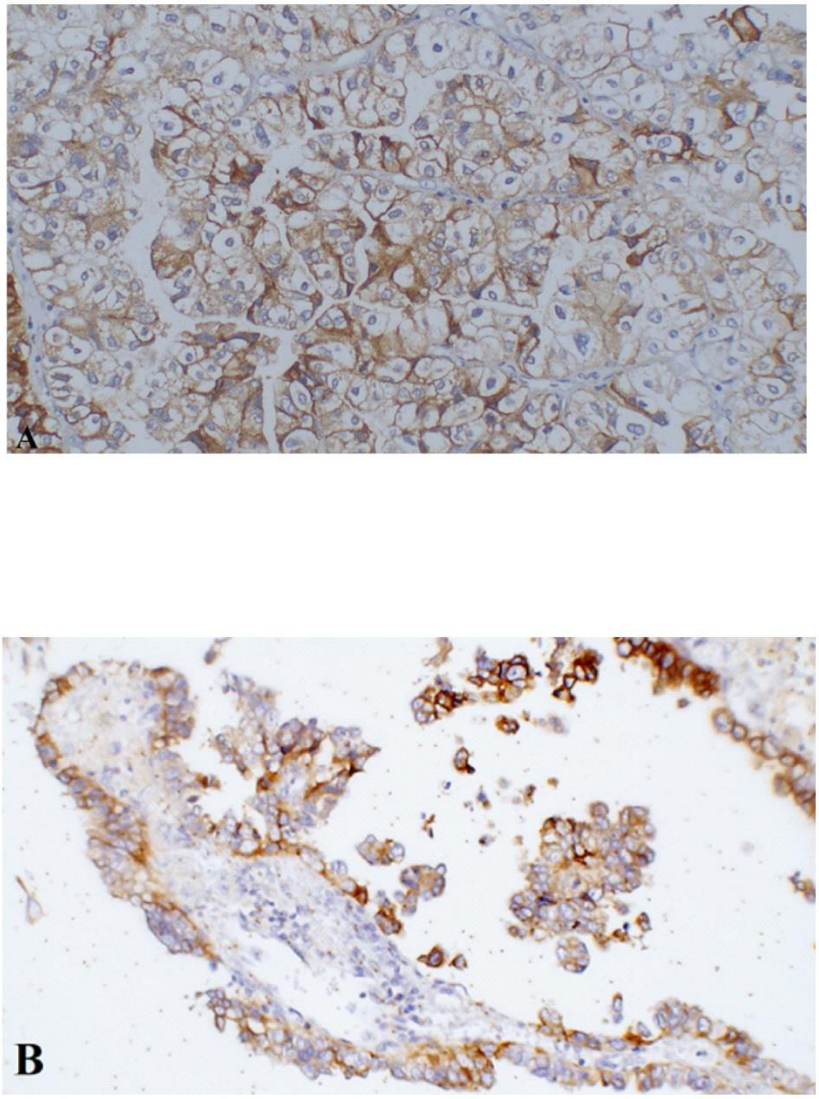

Figure 2: Microphotographs showing representative examples of L1CAM immunohistochemical expression in non-endometroid type endometrial carcinomas. (A) Strong diffuse membranous positivity of L1CAM expression in clear cell carcinoma with 100% cells positive x200; (B) Strong diffuse membranous positivity of L1CAM expression in serous carcinoma x200.

Discussion

Globally, the incidence of EC, one of the most prevalent gynecological tumors, is on the rise. In 2020 more than 417,000 women were diagnosed with uterine cancer worldwide[24]. L1CAM is a membrane glycoprotein which is frequently found in a range of solid cancers. The relationship between L1CAM expression and the prognosis of EC at various stages has been the subject of numerous studies undertaken to date, however, the prognostic significance of L1CAM in EC has remained controversial[20].

The current study included 52 cases of EC. Fifty cases were of endometroid type (96.2%) and only two cases were of non-endometroid type (3.8%). L1CAM immune-staining was found to be localized mainly in the cell membrane. Regarding endometroid type cases, 38% of cases showed positive

expression of L1CAM, this result was in concordance with two studies done by Klat et al., 2019 and Asano et al., 2020 who reported L1CAM positivity expression was 29.8%[25,26]. however, lower rate of expression was reported by Smogeli, 2021 who reported that 9% of studied cases had L1CAM-positive tumors. This differ-ence is due to different method of case selection, as all of their cases were of early FIGO stage and of low grade endometroid [27].

In this study, a statistically significant positive association between L1CAM expression and menopausal state (p =0.02). 53.6 % of cases with postmenopausal age showed positive L1CAM expression, while only 18.2% of premenopausal cases showed positive L1CAM expression. A study done by Abdol Manap et al., 2022 reported that premenopausal group of patients with negative L1CAM tends to present with a well differentiated grading of tumor compared to postmenopausal group [28]. These findings are correlated with a good prognosis and survival rate for the premenopausal group.

With respect to tumor grade, a significant positive association was found between L1CAM expression and tumor grade (p = 0.01). 66.7% high grade endometroid EC cases showed positive L1CAM expression, while 22% low grade endometroid EC cases showed positive expression. This was in accordance with the results of Gharib et al., 2020 who reported a significant association between L1CAM positive tumours with unfavourable factors such as tumor high grade [29]. Also, similar results reported by Kommoss et al., 2018 who reported that two thirds of grade 3 EC cases showed L1CAM expression, while only one third of grade I EC cases showed positive L1CAM [30]. In this study, a statistically significant association between myometrial invasion and L1CAM expression was demonstrated (p = 0.001). Twelve cases (70.6%) with infiltration more than half of the myometrium showed positive L1CAM expression, while only seven cases (21.2%) with infiltration of less than half of the myometrium were positive for L1CAM expression. This was in accordance with the results of Geels et al., 2016 who reported that 61.1% cases with positive L1CAM showed infiltration more than half of the myometrium, while only 38.9% cases with positive L1CAM were with myometrial invasion of less than half [31].

Concerning tumor stage, a significant association was detected between tumor stage and L1CAM expression (p = 0.02). In this study, high stage cases demonstrated 69.2% positive L1CAM expression, while low stage cases showed only 27.1% positive L1CAM expression. This was in accordance with results of Kommoss et al., 2018 who reported that 85.3% of cases with negative L1CAM expression were of stage I while 14.7% of cases with negative L1CAM expression were of stages II-IV [30].

Interestedly in this study, we demonstrated a significant positive association was found between L1CAM expression and LVI (p < 0.04). we noticed that 63.6% of cases with positive LVI showed positive L1CAM expression, while 30.8% of case without LVI had positive L1CAM expression. This was in accordance with the results of Visser, 2020 who found that L1CAM immunohistochemical reactivity in tumor cells was significantly associated with presence of LVI (P < 0.01). This study reported that 83% of L1CAM negative cases showed no LVI, while 12% of L1CAM negative cases showed LVI [32]. Our previous results are also in accordance Suh et al., 2014 who demonstrated that patients with positive expression of L1CAM had worse cancer-specific mortality and these findings were present in the patients with locally advanced (pT3-4) and/or positive lymph nodes disease [33].

In this study, no significant associations were found between L1CAM expression and patients' age, tumor size, tumor site and tumor necrosis (p = 0.7, p = 0.2, p =0.4 and p =0.4 respectively). For tumor size, our results were in accordance with study done by Pasanen et al., 2016 who reported that tumor size ≥2 cm was not significantly different between L1CAM-positive and

L1CAM -negative cases [34]. As regards patients age, a different result was reported by Zeimet et al., 2013 who demonstrated significant association between age older than 65 years and positive L1CAM [19]. This difference may be due to large number of cases investigated in this study (805) cases and ethnic or racial difference.

In this study, regarding risk classification of EC cases according to (ESGO), (ESTRO/ ESP) classification guideline, a significant correlation was found between L1CAM expression and higher risk groups (p = 0.003). Only 17.6% of low risk group cases showed positive L1CAM expression, while 20 % of intermediate risk group , 55% of high-intermediate risk group, 85% of high risk group and 100% of advanced risk groups respectively showed positive L1CAM expression, this was in concordance with Kommosset al., 2017 who reported that only 7.2% low risk cases were L1CAM positive, 9% of intermediate-risk cases were L1CAM positive and 18.5 % of high-intermediate-risk cases were L1CAM positive [35]. Similar results was reported by Nero et al., 2021 that demonstrated cancers with intermediate and high risks were more likely to have L1CAM positivity than those with low and intermediate risks (13.2 vs. 25.8%, respectively) [36]. A previous study done Wright et al., 2012 showed that low- and intermediate-risk EC cases have an excellent prognosis with a 10-year overall survival rate exceeding 80%, but a small subgroup of unexpected relapses will occur in this patient population and a potentially fatal tumor progression but until now, no available risk factor can predict this relapse. Additionally a study done by Zeimet et al., 2013 reported that although, 13.2 % of low-risk category cases showed positive L1CAM expression while 23.5% of intermediate risk are L1CAM expression. This study mentioned that despite of the excellent prognosis of (FIGO) stage I, type I EC patients (low and intermediate-risk EC cases), a number of these patients have developed recurrence and die from this disease[19,37]. Furthermore, Kommosset al., 2017 reported that tumor-related deaths of cases of low and intermediate-risk category was related to L1CAM positivity so, L1CAM status can play a key role in future in the planning of patient adjuvant treatment and follow-up so, if the tumor was L1CAM negative post-operatively, a longer follow-up intervals and more patient reassurance is recommended [35].

On the light of previous results, L1CAM can be an additional tool of a considerable value for risk stratification in EC. Inclusion of L1CAM expression in the ESMO-ESGOESTRO risk classification groups can be a useful tool to help with surgical staging and to determine which patients would benefit from a particular adjuvant treatment and patient monitoring; in the event that the tumor was L1CAM negative, this would provide extended follow-up intervals [38].

Regarding non-endometroid subtypes, we noticed that high L1CAM positive expression (>50%) was seen in both serous and clear cell subtype cases (2/2). Gharib and Amer, 2020 reported that positive L1CAM expression was detected in (22.4%) of patients and was significantly correlated with unfavorable prognostic factors such as non-endometroid type [29]. Also Asano et al., 2020 reported that non-endometrioid histology and L1CAM positive showed a strong correlation as 19/30 cases of non-endometroid were L1CAM positive, 6/7 cases of serous subtype and 4/5 of cases of clear subtype were L1CAM positive respectively[25]. However, in this study no statical association could be assessed as our included cases are only two cases.

It might be assumed that L1CAM drives the malignant progression in various tumors. It's still debatable if increased expression of L1CAM in EC instances has predictive significance. High expression of L1CAM in EC is expected to be more aggressive and linked to a worse prognosis. EC patients with high-risk disease typically receive adjuvant platinum-based chemotherapy (Pt-aCT). In vitro, inhibition of L1CAM significantly increased cell sensitivity to carboplatin so L1CAM is a promising candidate biomarker to affect decision

making in patients who are eligible for Pt-aCT. Moreover, Anti-It is anticipated that anti-L1CAM antibody therapy will result in tumor regression by preventing tumor growth [39].

For molecular point of view, a study done by Kommoss et al., 2018 reported important results indicating that L1CAM expression status may contribute significant predictive data to the molecular categorization of EC. The p53 wt/NSMP subgroup may be further stratified by L1CAM IHC, which identified carcinomas with a higher chance of a fatal outcome. It was also established that there was a high association between L1CAM expression in EC and mutation-type p53 immuno-staining. recommending the inclusion of L1CAM IHC in a more simple, clinically useful molecular classifier for EC [30]. Furthermore, a study done by Chalia et al., 2021 reported that correlation with MMR status, L1CAM positive is not mutually exclusive. Applying L1CAM immune-staining to all endometrial cancers may help determine the best plan of treatment for patients who test positive for L1CAM. This is especially true for MMR-positive cases that fall into the NSMP group [40].

When combined with other previous researches, the current study showed a strong association between L1CAM expression and several unfavorable EC prognostic factors, such as higher tumor grade, advanced stage, myometrial invasion, LVI, and higher prognostic risk groups. This highlights the critical role that L1CAM plays in the genesis, progression, and dissemination of tumors. Therefore, in EC, integrating molecular risk factors as L1CAM with clinicopathologic variables improves risk stratification and may have potential therapeutic benefits.

Conclusion

The present study had highlighted the important role of L1CAM in EC tumorigenesis, progression. Among the clinic-pathological parameters investigated, we found a positive significant association with higher tumor grades, advanced stage, myometrial invasion and LVSI specifically. Collectively, our results suggest that L1CAM expression may help to detect EC patient group with poor prognostic features. L1CAM can be a promising prospective biomarker that affect decision making in these patients as Anti-L1CAM antibody therapy.

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