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CD117 expression in breast phyllodes tumors correlates with adverse pathologic parameters and reduced survival

Wai Jin Tan[1,2], Aye Aye Thike[1], Sie Yong Tan[1], Gary M-K Tse[3], Min-Han Tan[4], Boon Huat Bay[2] and Puay Hoon Tan[1,2,5]

[1]Department of Pathology, Singapore General Hospital, Singapore; [2]Department of Anatomy, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [3]Department of Anatomical and Cellular Pathology, Chinese University of Hong Kong, Hong Kong; [4]Institute of Bioengineering and Nanotechnology, Singapore and [5]Duke-NUS Graduate Medical School, Singapore

CD117 (c-kit) is a type III receptor tyrosine kinase encoded by the *KIT* gene. Deregulation of expression and mutations in the gene are implicated in various tumors. Reports of CD117 expression in phyllodes tumors have been controversial. We aim to investigate the protein expression of CD117 and mutations in the *KIT* gene in phyllodes tumors, and correlate the findings with pathological parameters and clinical outcome. A total of 272 cases were included in this study. CD117 expression was investigated by immunohistochemistry on tissue microarray sections. Toluidine blue staining was performed to indicate mast cells. Overall, 28 (10%) cases were CD117 positive. CD117 expression was significantly associated with tumor grade ($P<0.001$), increased stromal hypercellularity ($P=0.003$), stromal atypia ($P=0.01$), and stromal mitotic activity ($P<0.001$), permeative microscopic margins ($P=0.002$), and presence of hemorrhage ($P=0.001$). Expression was also associated with poorer overall survival ($P=0.003$). Nineteen cases were further selected for mutation screening through the Affymetrix OncoScan platform. No mutation of the *KIT* gene was found. Despite a lack of mutations in the *KIT* gene, CD117 protein expression is associated with unfavorable pathological parameters and poorer prognosis, suggesting an underlying role in the biology of phyllodes tumors.
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CD117 (also known as c-kit) is a type III receptor tyrosine kinase encoded by the *KIT* gene. It is characterized by an extracellular domain containing five immunoglobulin-like repeats (encoded by exon 9), a transmembrane domain, a juxtamembrane domain (exon 11), and two intracellular tyrosine kinase domains (exons 13 and 17). On binding of KIT ligand at the extracellular domain, CD117 is activated and this initiates various downstream signaling pathways mediating cell survival, migration, and proliferation depending on the cell type.[1] Since the *KIT* gene was identified in the 1980s as a proto-oncogene, it has been implicated in various tumors including gastrointestinal stromal tumors (GISTs),[2] colon cancer,[3] and melanomas.[4]

Correspondence: Dr PH Tan, MD, FRCPA, Department of Pathology, Singapore General Hospital, 20 College Road, Academia, Diagnostics Tower, Singapore 169856, Singapore.
E-mail: tan.puay.hoon@sgh.com.sg
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Phyllodes tumors are fibroepithelial neoplasms of the breast, characterized by a double-layered epithelial component arranged in leafy fronds formed by hypercellular spindle-cell stroma. They are classified into benign, borderline, and malignant grades on the basis of microscopic features of the stromal component as recommended by the World Health Organization (WHO) classification of tumors of the breast.[5] Reports of CD117 expression in phyllodes tumors vary in the literature, with some documenting overexpression of CD117 in malignant phyllodes tumors,[6,7] whereas others found negative or weak expression observed across all grades of phyllodes tumors.[8,9] Data on prognosis of CD117-expressing phyllodes tumors are scanty, with two studies reporting an association with tumor recurrence.[10,11] Investigations into *KIT* mutations in phyllodes tumors are even fewer, with two studies conducted in Asian cohorts revealing opposing findings.[11,12]

The objective of this study was to investigate protein expression and mutational status of CD117 in phyllodes tumors diagnosed in a single institution

in Singapore; and to correlate the findings with pathologic parameters and clinical outcomes.

Materials and methods

Patients and Tumors

Phyllodes tumors diagnosed at the Department of Pathology, Singapore General Hospital from January 2003 to December 2010 were included in this study. The study received approval from the Centralized Institutional Review Board. Tumors were classified into benign, borderline, and malignant on the basis of histological features according to the WHO classification of breast tumors as previously described.[13] Histological features included stromal hypercellularity, stromal atypia, tumor microscopic margins, stromal mitotic activity, and stromal overgrowth. Patient follow-up was retrieved from medical records.

Tissue Microarrays

Tissue microarrays were constructed using the Manual Tissue Arrayer MTA-1 (Beecher Instruments, USA). Hematoxylin and eosin-stained slides were reviewed and three representative areas of interest with a high density of stromal cells were circled. The corresponding regions were marked on archival formalin-fixed, paraffin-embedded tissue blocks. The representative areas were then punched with a 2-mm diameter core and arrayed on three recipient blocks. An array was constructed with a maximum of 40 cores and a tonsil core was used as an orientation marker.

Staining

Sections of 4 μm were fished onto charged slides (Microsystems Plus Slides, Leica, Germany). Immunohistochemistry was performed for CD117 using the BOND-MAX (Leica) automated system. Tissue sections were deparaffinized with Bond Dewax Solution, followed by antigen retrieval in ER solution 2 (pH 9.0) for 20 min at 100 °C. Then, sections were treated with anti-CD117 antibody (A4502, Dako, Denmark) diluted in the ratio 1:400 for 20 min. Visualization was developed using the Bond Polymer Refine Detection (Leica) system. GIST was used as positive control and lymphocytes acted as negative control. For assessment of staining, slides were scanned with the ScanScope System (Aperio, CA) and viewed with ImageScope (Aperio). CD117 immunohistochemical staining was assessed in the cytoplasm and cytoplasmic membrane of stromal cells by two independent observers. Percentage of reactive stromal cells was recorded excluding the mast cells. Positivity of CD117 was defined when 1% or more stromal cells were reactive, taking into account the results of all three microarrays.

To further confirm that the CD117-positive cases were not confounded by mast cells, tissue microarray sections containing the positive cases were subjected to toluidine blue stain. Toluidine blue staining was performed with 0.5% toluidine blue working solution. After deparaffinization in xylene and graded alcohol, tissue sections were incubated in 0.5% toluidine blue working solution for 6 min. Then, slides were immediately rinsed in changes of 95% alcohol and dipped in absolute alcohol for 1 min. Finally, sections were cleared with xylene and mounted with DPX mounting media. Bone marrow tissue was used as a positive control. Presence of mast cells was defined by its red-purple (metachromatic) appearance amidst the toluidine blue-stained background.

Mutation Analysis

Nineteen cases were selected for mutation analysis on the basis of a prior study that included cases with and without events of recurrence/death on follow-up.[14] Five to ten whole sections were cut at 10 μm each for each case. DNA extraction was performed using the Ambion RecoverAll Total Nucleic Acid Isolation Kit (Life Technologies, USA) according to the manufacturer's protocol. DNA was quantified with PicoGreen (Life Technologies) assay and subjected for the OncoScan FFPE Express 2.0 Service (Affymetrix, CA). It interrogated 16 commonly reported CD117 mutations (Table 1) including exons 11, 13, and 17 using the molecular inversion probe assay.

Statistical Analysis

Statistical analysis was performed with SPSS for Windows, version 18. Chi-square and Fisher's exact tests were used to analyze the associations between CD117 expression and clinicopathological

Table 1 Panel of *KIT* mutations included in the OncoScan assay

No.	*KIT mutations*	*Exon number*
1	D52N	2
2	W557R	11
3	V559A	11
4	V560D	11
5	L576P	11
6	F584S	11
7	P585P	11
8	K642E	13
9	V654A	13
10	T670I	13
11	I798I	13
12	D816Y	17
13	N822K	17
14	Y823D	17
15	V825A	17
16	E839K	17

parameters. Survival analysis was performed with Kaplan–Meier to estimate recurrence-free survival and overall survival, which were defined as the time from date of surgery to date of first relapse and death from phyllodes tumor, respectively, or to the last follow-up date for censored cases. Survival between groups was compared using the Log-rank test. A *P*-value of <0.05 was considered a significant result.

Results

A total of 272 cases of phyllodes tumor were diagnosed between January 2003 and December 2010—189 (70%) were benign, 60 (22%) were borderline, and 23 (8%) were malignant. The overall patient age range was 15–79 years (mean and median 43 years). Tumor size range was 8–250 mm (mean 51 mm, median 38 mm). Overall, 28 (10%) cases were positive for CD117—9 benign (5%), 14 borderline (23%), and 5 malignant (22%) tumors (Figures 1a and b). Care was taken to discount CD117-positive mast cells from being erroneously included among CD117-positive phyllodes tumors (Figures 1c and d). Proportion of positively stained stromal cells ranged from 1 to 5% with a mean of 1.4% and median of 1%. Table 2 shows clinicopathological features of phyllodes tumors in association with CD117 positivity. CD117 expression was significantly associated with borderline/malignant tumors ($P<0.001$). There was a significant association of CD117 positivity with increased stromal hypercellularity ($P=0.003$), stromal atypia ($P=0.01$), and stromal mitotic activity ($P<0.001$), permeative microscopic margins ($P=0.002$), and presence of hemorrhage ($P=0.001$).

A total of 248 patients were included for the follow-up analysis after discounting those lost to follow-up and those in whom follow-up was <3 months. There were 24 (10%) recurrences documented of which 18 were local and 6 were distant (Table 3). Mean and median times to recurrence were 27 and 21 months, respectively. Five deaths were documented—one benign, two borderline, and two malignant cases. The benign case recurred with

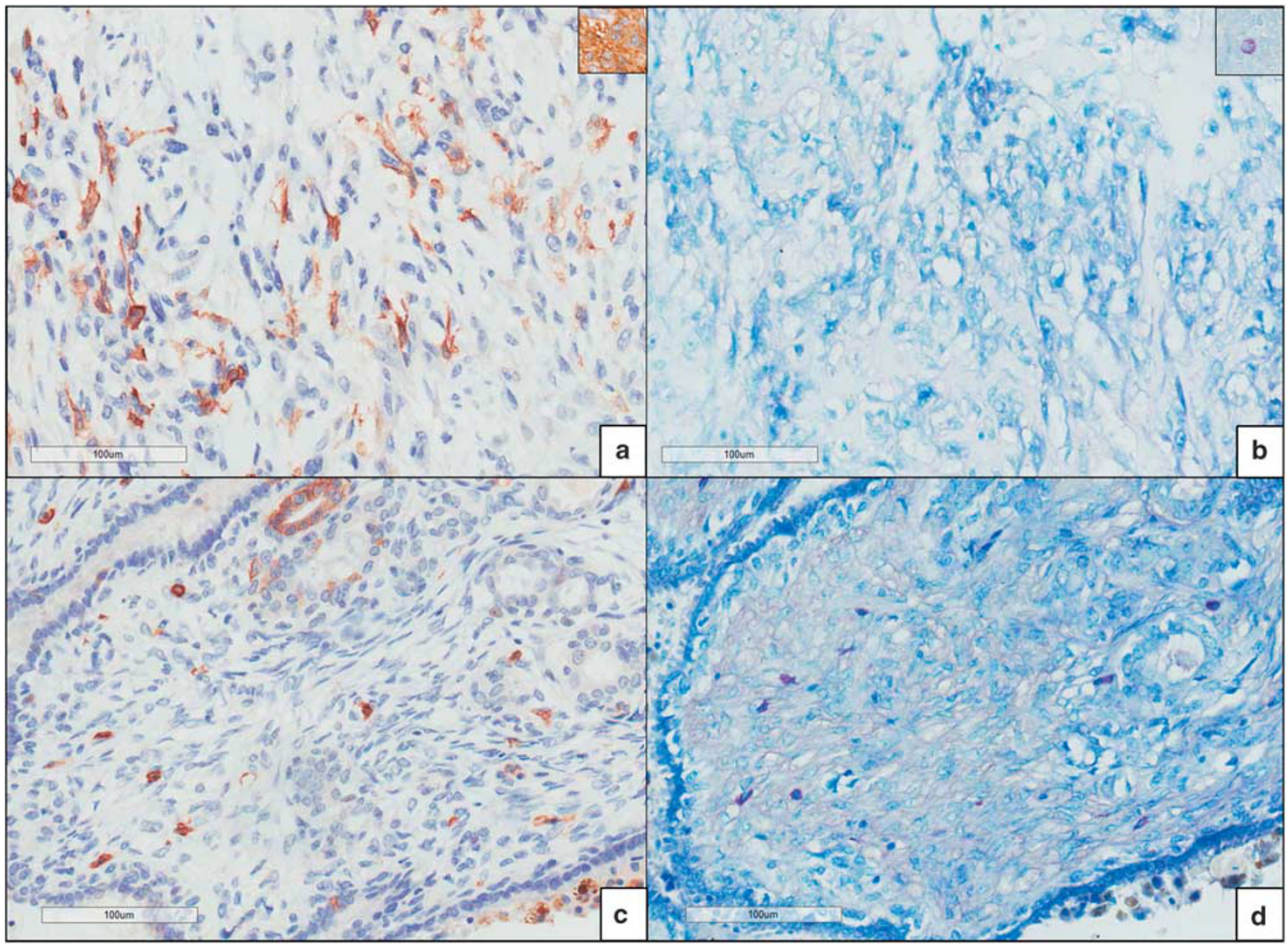

Figure 1 Example of a CD117-positive phyllodes tumor (**a**) with corresponding negative toluidine blue staining (**b**). Positive controls are shown in the top right inset. (**c**,**d**) An example of mast cells that are positive for both CD117 and toluidine blue staining. These cells are excluded in the assessment of CD117-positive stromal cells.

Table 2 Clinicopathological characteristics of phyllodes tumors in association with CD117 stromal positivity

Clinicopathological parameters	*CD117 negative,* n *(%)*	*CD117 positive,* n *(%)*	P-*value*
Age (mean 43 years, median 43 years, range 15–79)			
≤43 years	124 (91)	13 (9)	
>43 years	120 (89)	15 (11)	0.694
Tumor size (mean 51 mm, median 38 mm, range 8–250 mm)			
≤51 mm	175 (93)	13 (7)	
>51 mm	69 (82)	15 (18)	0.009[a]
Tumor grade			
Benign	180 (95)	9 (5)	
Borderline	46 (77)	14 (23)	
Malignant	18 (78)	5 (22)	<0.001[a]
Stromal hypercellularity			
Mild	142 (95)	7 (5)	
Moderate	87 (82)	19 (18)	
Marked	15 (88)	2 (12)	0.003[a]
Stromal atypia			
Mild	207 (92)	18 (8)	
Moderate	31 (82)	7 (18)	
Marked	6 (67)	3 (33)	0.01[a]
Stromal mitosis			
0–4	181 (95)	10 (5)	
5–9	39 (85)	7 (15)	
>9	24 (69)	11 (31)	<0.001[a]
Stromal overgrowth			
No	218 (91)	21 (9)	0.059
Yes	26 (79)	7 (21)	
Microscopic margin			
Circumscribed	192 (93)	14 (7)	
Permeative	52 (79)	14 (21)	0.002[a]
Pseudoangiomatous stromal hyperplasia			
Absent	236 (90)	26 (10)	
Present	8 (80)	2 (20)	0.275
Myxoid change			
Absent	85 (89)	11 (11)	
Present	159 (90)	17 (10)	0.679
Cystic change			
Absent	190 (88)	25 (12)	
Present	54 (95)	3 (5)	0.221
Necrosis			
Absent	217 (91)	21 (9)	
Present	27 (79)	7 (21)	0.062
Hemorrhage			
Absent	152 (95)	8 (5)	
Present	92 (82)	20 (18)	0.001[a]

[a]Denotes statistically significant results.

a borderline tumor with subsequent lung metastasis before death, whereas one patient with borderline tumor passed away from acute pancolitis, and the other patient with borderline tumor suffered lung metastasis leading to death. Details of the follow-up

Table 3 Details of 248 cases with follow-up

Diagnosis	*N*	*CD117 positive*	*Local recurrence*	*Distant recurrence*	*Death*
Benign	169	7 (4%)	12 (7%)	1 (1%)[a]	1 (1%)[b]
Borderline	57	14 (25%)	4 (7%)	1 (2%)	2 (4%)[c]
Malignant	22	5 (23%)	2 (9%)	6 (27%)[a]	2 (9%)[d]

[a]local recurrence preceded distant recurrence.
[b]recurred with a borderline tumor with subsequent lung metastasis prior to death.
[c]one patient passed away from acute pancolitis, and the other had lung metastasis prior to death.
[d]one patient had lung metastasis preceding death, the other died without recurrence.

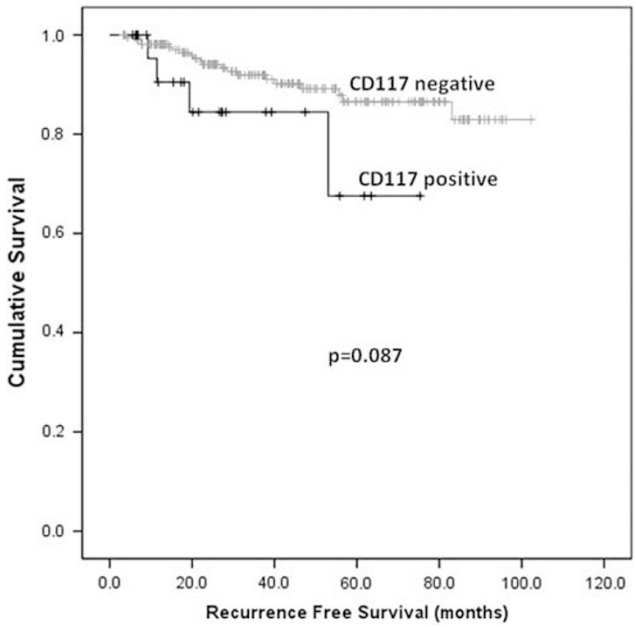

Figure 2 A trend of shorter recurrence-free survival was observed in patients with CD117-positive tumors.

were as previously described.[15] A trend of shorter time to recurrence for tumors expressing CD117 was observed (Figure 2) compared with tumors not expressing CD117 ($P=0.087$). In addition, we observed a higher percentage of CD117-expressing tumors in cases that metastasized (25%) compared with those without metastasis (10%), although this was not statistically significant. A worse prognosis was observed ($P=0.003$) for tumors expressing CD117 compared with CD117-negative tumors (Figure 3).

Nineteen cases subjected to mutation analysis comprised seven benign, seven borderline, and five malignant cases. Details of the cases such as CD117 expression, prognosis, and epithelium–stromal composition are shown in Table 4. CD117 mutations (as shown in Table 1) were absent in all the cases.

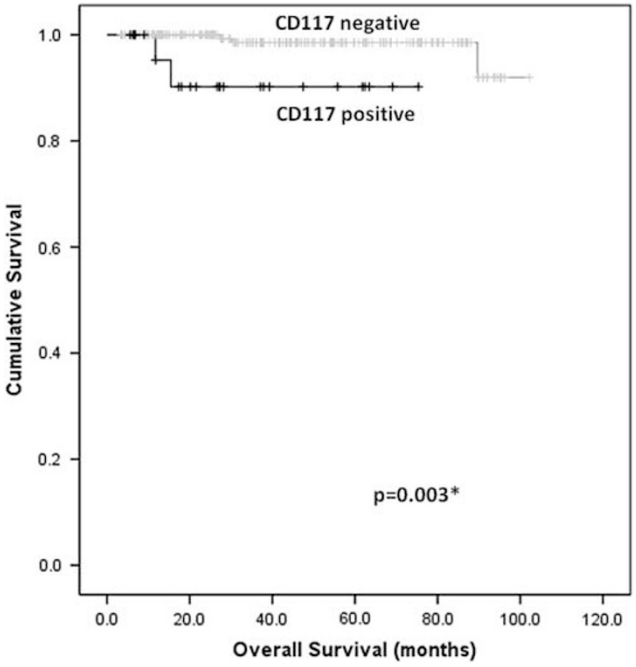

Figure 3 Patients with CD117-positive tumors experienced a worse overall survival compared to patients with CD117-negative tumors.

Table 4 Profile of tumors selected for mutation analysis via OncoScan

No.	*Diagnosis*	*CD117 staining status*	*Epithelial–stromal percentage*	*Prognosis*
1	Benign	Negative	35–75	No recurrence
2	Benign	Negative	40–60	No recurrence
3	Benign	Negative	30–70	No recurrence
4	Benign	Positive	15–85	No recurrence
5	Benign	Negative	40–60	No recurrence
6	Benign	Positive	20–80	Local recurrence
7	Benign	Negative	20–80	Local recurrence
8	Borderline	Negative	10–90	No recurrence
9	Borderline	Positive	50–50	No recurrence
10	Borderline	Negative	20–80	No recurrence
11	Borderline	Positive	30–70	No recurrence
12	Borderline	Positive	15–85	No recurrence
13	Borderline	Negative	20–80	Local recurrence
14	Borderline	Positive	10–90	Bone metastasis preceded death
15	Malignant	Negative	5–95	Lung metastasis
16	Malignant	Negative	0–100	Lung metastasis
17	Malignant	Negative	30–70	Lung metastasis
18	Malignant	Negative	0–100	Lung metastasis preceded death
19	Malignant	Positive	1–99	Death without recurrence

Discussion

Investigation of CD117 mutation status in phyllodes tumors was initiated in year 2000 by Chen *et al.*[12] with a study sample size of 19 cases. The authors found two point mutations Q556X and N564S, involving the juxtamembrane domain (exon 11). Mutations in this domain alter the autoinhibitory function of the receptor and lead to activation of the receptor even without the binding of a ligand. However, Jung *et al.*[11] who also studied an Asian population found no mutations in exon 11, as well as in exons 9, 13, and 17 (commonly reported regions of activating mutations). Our findings concur with the latter observation, where no activating mutations were found. Several other studies of non-Asian populations also reported no activating mutations, despite scant findings of silent mutations or mutations of unknown significance. Sawyer *et al.*[6] found a point mutation of L510M (exon 10) of unknown significance in one case. Carvalho *et al.*[7] and Bose *et al.*[8] reported a silent mutation of isoleucine 798 (exon 17) in two and one cases, respectively. Djordjevic *et al.*[9] found no mutations in two cases of CD117-positive tumors.

Despite a lack of activating mutations observed in the *KIT* gene, overexpression of CD117 protein has previously been reported in phyllodes tumors.[6,7] Several other reports have also shown an association of CD117 protein expression with increasing grade,[11,16] with a few detailing preferential expression of CD117 in the malignant phenotype.[6,7,12,17,18] However, there were also several groups that indicated no association between CD117 expression and tumor grade.[8,9,19] In this study, we observed CD117 expression to be associated with borderline and malignant grade tumors. Toluidine blue staining was performed to rule out possible confounding contribution of mast cells, as previously suggested by Djodjervic *et al.*[9] that the associations observed might have been a mast cell phenomenon. Toluidine blue was negative on cases that we defined as CD117 positive, reinforcing our initial observations.

The spectrum of results from the different groups could be attributed by the variable antibodies, staining protocols, and scoring criteria used (summarized in Table 5). There is no universal consensus currently as to which protocol and scoring criteria are the best. However, standardization of protocols between laboratories has been challenging and the antibodies used need to be optimized and validated individually.[20] In this study, we employed Dako A4502, an antibody that is validated for diagnostic use and was evaluated previously by other authors to have high sensitivity and specificity across different tumors.[21,22] As for scoring criteria, we used a 1% cutoff in view of the fact that CD117 is not normally expressed in breast stromal cells.[23] Hence, even a low percentage of protein expression could indicate an abnormal state. This is exemplified by our study in which cases that were CD117 positive on immunohistochemistry demonstrated a low percentage of positive cells. Although this may be partly due to the use of tissue microarrays that reflect only a small proportion of the entire tumor, we have previously shown that tissue microarrays provide a dependable replication of phyllodes tumors in terms of biomarker expression.[24]

Table 5 Summary of investigations of CD117 expression and mutation status in phyllodes tumors

Authors, reference	N	*Antibody and dilution*	*Scoring criteria*	*CD117 expression*	*Mutation status*	*Follow-up*
Chen *et al.*[12]	19	Chemicon clone K69 1:100	≥10%	Associated with malignant grade	Q556X (exon 11) and N564S (exon 11) in one case each	NA
Sawyer *et al.*[6]	30	Novocastra 1:20	Intensity ≥1	Associated with malignant grade	L510M (exon 10) in one case	NA
Tse *et al.*[16]	179	Novocastra 1:40	≥20% stromal cells of moderate-to-strong staining	Correlated with increasing grade	NA	Not correlated with recurrence
Carvalho *et al.*[7]	19	Novocastra 1:60	≥25%	Associated with malignant grade	Silent mutation Isoleucine 798 (exon 17) in two cases	NA
Tan *et al.*[10]	335	Dako A4502 1:250	Any unequivocal staining	Associated with tumor grade	NA	Expression correlated with recurrence
Esposito *et al.*[117]	16	Dako polyclonal 1:100	Combined immunoreactive score ≥1	Associated with tumor grade	NA	Not correlated with recurrence
Yonemori *et al.*[19]	41	Dako A4502 Dilution not specified	>10% of at least moderate intensity	None of the cases were positive	NA	No positive cases for correlation with six distant recurrences
Djordjevic *et al*[9].	47	Zymed 1:400	>0%	No correlation	Not detected in two CD117-positive tumors	NA
Bose *et al.*[8]	17	Dako 1:50	≥5%	No correlation	Silent mutation Isoleucine 798 (exon 17) in one case	NA
Jung *et al.*[11]	67	Dako polyclonal 1:300	>10%	Correlated with increasing grade	None detected in subset of 28 samples	Expression associated with recurrence
Noronha *et al.*[18]	33	Biocare clone Y145 1:100	≥20%	Differentially expressed in malignant grade	NA	NA

NA- Experiment not performed/Data not available.

We observed a trend of shorter recurrence-free survival in CD117-positive cases, despite not being statistically significant. This trend corroborates our previous findings where CD117 stromal positivity was correlated with recurrence.[10] In this study, we also observed a higher percentage of CD117-positive cases among tumors that metastasized despite not being significant statistically. In addition, a significant poorer survival outcome was observed in patients with CD117-positive tumors. The limitation with all of the above findings is the small number of events that were documented. Nevertheless, it is worthwhile to note that all these traits point to a poorer clinical outcome of CD117-expressing tumors, which suggest their underlying aggressive nature.

Investigations into CD117 protein expression and mutation status were largely motivated by the success of a tyrosine kinase inhibitor in patients with GISTs. There has been previous suggestion that the stromal component of phyllodes tumors bear some similarities to GISTs such as the spindled nature and spectrum of behavior from benign to malignant.[7] However, recent insights into the roles of CD117 in cancer shed important light on the different types of CD117-expressing tumors. Broadly, CD117-expressing tumors can be classified into two main groups:[25] (1) those characterized by gain-of-function (activating) CD117 mutations and derived from cells that normally express CD117. In these cases, CD117 has a central pathogenetic role in neoplasm initiation; (2) those with rare occurrence of CD117 mutations, in which tumors are composed of cells that normally do not express CD117. CD117 has a passive role in this group of tumors and its expression is acquired during tumor progression. This may explain the lack of mutations found in phyllodes tumors as compared with GISTs. GISTs arise from the oncogenic transformation of interstitial cells of Cajal that normally express high levels of CD117. Comparatively, the stromal component of phyllodes tumors, which likely arises from breast mesenchymal tissue, does not usually express CD117 under normal circumstances.

In conclusion, we report an association of CD117 protein expression with borderline/malignant tumors and with worse pathologic parameters. We also observed a worse prognosis in patients with CD117 immunohistochemically positive tumors despite the absence of activating mutations. The lack of activating mutations suggests that the therapeutic option of using a tyrosine kinase such as imatinib in patients with malignant phyllodes tumors is unlikely to be effective. Nonetheless, the associations observed with tumor grade and poorer prognosis are real phenomena that suggest a role of CD117 in the biological behavior of breast phyllodes tumors.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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