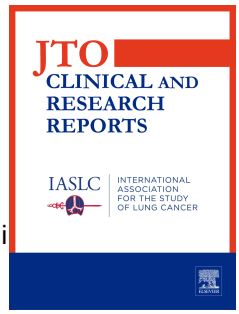

High levels of CD47 expression in thymic epithelial tumors

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Brief Report: High levels of CD47 expression in thymic epithelial tumors

Thomas Yang Sun,[a] Brandon Nguyen,[b] Simon B. Chen,[a] Yasodha Natkunam,[c] Sukhmani Padda,[d] Matt van de Rijn,[c] Robert West,[c] Joel W. Neal,[a] Heather Wakelee,[a] Jonathan W. Riess[b,*]

[a]Division of Oncology, Department of Medicine, Stanford University School of Medicine, 875 Blake Wilbur Drive, Stanford, CA, USA 94305
[b]Division of Oncology, Department of Medicine, University of California, Davis, Cancer Ctr So, Sacramento, CA, USA 95817
[c]Department of Pathology, Stanford University School of Medicine, 875 Blake Wilbur Drive, Stanford, CA, USA 94305
[d]Samuel Oschin Cancer Center, Cedars-Sinai Medical Center, 127 S San Vicente Blvd, Los Angeles, CA, USA 90048
*Corresponding author: Jonathan W. Riess, jwriess@ucdavis.edu

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ABSTRACT

Background:
CD47 is a tumor antigen that inhibits phagocytosis leading to immune evasion. Anti-CD47 therapy is a promising new immunotherapy across numerous tumor types but have not been tested in thymic epithelial tumors (TETs)—thymoma and thymic carcinoma. TETs are rare tumors which are difficult to treat, especially with PD-1/PD-L1 checkpoint inhibitors, due to the excessive rates of immune-related adverse events. This study investigated the levels of CD47 expression in TETs to explore the possibility of anti-CD47 therapy.

Methods:
A total of 67 thymic tumors (63 thymomas and 4 thymic carcinomas) and 14 benign thymus controls, and their clinical data were included. Samples were stained for CD47 expression (rabbit monoclonal antibody SP279, Abcam, USA) and scored for both intensity and H-score (intensity multiplied by the percentage of tumor involved). Intensity was defined as: 0 = none, 1 = weak, 2 = moderate, and 3 = strong. H-scores ranged from 0 to 300. Samples with an intensity score below 2 or an H-score below 150 were considered $CD47^{low}$, while the rest were $CD47^{high}$.

Results:
Compared to normal thymic tissue, TETs were more frequently CD47 positive and had significantly higher levels of CD47 expression. CD47 was positive in 79.1% of TETs compared to 57.1% of normal thymus. The level of CD47 expression was 16-fold higher in TETs (mean H-score 75.0 vs 4.6, $p = 0.003$). Multivariate analysis adjusted for age, sex, stage, resection status, and performance status showed that CD47-high tumors were highly correlated with WHO histology ($p = 0.028$). The most frequent $CD47^{high}$ tumors, in contrast to $CD47^{low}$ tumors, were types A (28.6% vs 7.5%) and AB (57.1% vs 13.2%), and the least frequent were B1 (7.1% vs 24.5%), B2 (0% vs 35.8%), B3 (7.1% vs 11.3%) and C (0% vs 7.5%).

Conclusions:
In contrast to normal thymus, TETs had significantly higher levels of CD47 expression. Tumor samples with high CD47 expression were mostly WHO types A and AB. This is the first study to explore CD47 expression in thymic cancers, and lends support for ongoing investigation of anti-CD47 macrophage checkpoint inhibitor therapy in these tumors.

INTRODUCTION

Thymic epithelial tumors (TETs), classified as either thymomas or thymic carcinomas (TC), are rare tumors of the mediastinum which affect roughly 1 in 100,000 patients.[1] For patients not amenable to curative surgical resection, systemic therapy is indicated with platinum-based chemotherapy regimens often used in the first-line setting. For patients who have subsequent relapsed or resistant disease, options are limited to either alternative chemotherapeutic agents or oral tyrosine kinase inhibitors with modest activity.[2] Underlying molecular aberrations are still poorly understood and no targeted therapies are available.

Over the past decade, immunotherapy targeting the CTLA-4 and the PD-1/PD-L1 axis have garnered tremendous success across a wide range of tumor types. Clinical activity has been noted with ICI in TETs[3,4]. However, the use of anti-PD-1/PD-L1 inhibitors is limited in these tumors, as high rates of severe and even fatal immune-related adverse events (irAEs) have been seen in TETs, including prohibitively high and severe irAEs in thymoma. PD-1 antibodies are occasionally administered with caution in thymic carcinoma, which also have higher rates of irAEs compared to other tumors[4]. TETs have been known to cause autoimmune sequelae on their own, and this predilection appears highly increased with the addition of T-cell targeted immunotherapy. One prospective trial of pembrolizumab found rates of grade 3 or higher adverse events to range from 15% (for thymic carcinomas) to as high as 70% (for thymomas), with some patients experiencing multiple autoimmune complications concurrently and several autoimmune toxicities seen in >50% of thymoma patients, limiting any further development in that patient population.[3]

The risks of conventional T-cell targeting checkpoint inhibition has prompted the search for alternative methods of immune activation. CD47 is a transmembrane protein expressed on tumor cells that when bound to its receptor SIRPα is an important innate immune checkpoint inhibiting macrophage phagocytosis.[5,6] Tumoral CD47 expression is a predictor of disease progression and inferior survival outcomes in multiple cancer types.[7] Anti-CD47 therapy serves as a macrophage checkpoint inhibitor and renders tumor cells susceptible to immune elimination, without causing significant autoimmune side effects.[8] It has shown promising activity in the relapsed/resistant setting in a number of CD47-expressing tumor types including non-Hodgkin lymphoma and myelodysplastic syndrome.[9,10]

Anti-CD47 therapy has not been tested in TETs, though in a phase 1/2 study of a peptide compound that blocks the CD47 immune checkpoint via expression of thrombospondin-1 (Tsp-1), the only a response was seen in a patient with thymoma (21). Maturation of T-cells occur in the thymus through positive and negative selection and thymomas can produce abnormal T-cell populations.[11] CD47 expression may prevent the clearance of abnormal T-cells and the homeostasis of T-reg cell populations.[6] As an initial step to exploring the potential role of anti-CD47 targeting in thymic epithelial malignancies, we conducted a study to quantify the levels of CD47 expression in these tumors compared to normal thymic tissue.

MATERIALS AND METHODS

A TET tissue microarray was constructed using formalin-fixed, paraffin-embedded tissue from 67 thymic tumors (63 thymomas and 4 thymic carcinomas) and 14 benign thymus controls with associated clinical data included as previously described.[12,13] Patients provided informed consent or a waiver of consent was obtained on an IRB approved protocol. Samples with an average of 3 cores each were stained for CD47 expression in epithelial cells (rabbit monoclonal antibody SP279, Abcam, USA) and scored for both intensity and H-score (intensity multiplied by the percentage of tumor involved). Intensity was defined as: 0 = none, 1 = weak, 2 = moderate, and 3 = strong. H-scores ranged from 0 to 300. Samples with an intensity score below 2 or an H-score below 150 were considered $CD47^{low}$, while the rest were $CD47^{high}$. The scoring pathologist (S.C.) was
blinded to clinical data and sample identity.

The Mann-Whitney test was used to compare the CD47 staining between TETs and controls. The fisher's exact test or chi-squared test was used to examine the relationship between staining and categorical variables. Multivariate linear regression analysis of CD47 H-scores adjusted for age, sex, performance status, WHO type, stage and resection status (Prism 9, Graphpad). Univariate survival analysis was performed with Mantel-Cox test, while multivariate survival analysis was done with a Cox regression model. Survival analyses were performed using Prism v9, Graphpad and R v4. Overall survival (OS) was measured from date of diagnosis to the date of death. Event-free survival (EFS) was measured from date of diagnosis for those patients without metastasis at diagnosis to the date of first recurrence or death from any cause. A two-sided p value less than 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

Samples from a total of 67 patients with TETs were included in this analysis (Table 1). The average age of the patients was 56 (range 2-86), with 51% men and 49 % women. All patients except one had ECOG performance status of 0-2 at diagnosis. The pathologic Masaoka-Koga stage was predominantly early stage I and II, 45% and 22% respectively. The most frequent histology types were AB, B1 and B2. Most patients had a R0 resection (67%). Just over a third of patients (37.3%) had a paraneoplastic syndrome (PNS), with myasthenia gravis being the most common (64%).

CD47 Expression in Thymic Epithelial Tumors

Samples were graded by both CD47 intensity and H-score (intensity multiplied by proportion of tissue staining), as reported previously (Figure 1).[1] Compared to normal thymic tissue, TETs were more frequently CD47 positive and had significantly higher levels of CD47 expression. CD47 was positive in 79% of TETs (≥1% by H-score), compared to 57% of normal thymus. Importantly, CD47 expression was significantly higher in TETs than in normal thymic tissue (Figure 2a-b). The mean intensity score was 1.36 for TETs compared to 0.57 for control ($p = 0.004$) and the mean H-score was 75.0 compared to 4.59 ($p = 0.003$). The level of expression, based on H-score, was on average 16-fold higher in TETs. The mean H-score for thymomas (75.33, n = 63) was not significantly different than that for thymic carcinomas (61.25, n = 4; $p = 0.77$).

Higher CD47 expression was associated with less aggressive WHO histologies

Tumors which exhibited high CD47 expression (20.9% with H-score ≥ 150, n = 14) were significantly associated with a lower Masaoka stage ($p = 0.032$). Most CD47-high tumors (78.6%, n = 11/14) were stage 1, compared to only 35.8% of CD47-low tumors (n = 19/53). There was a trend towards more complete resection (R0 resection) with CD47-high tumors ($p = 0.058$).

CD47-high tumors were more often characterized by less aggressive WHO histology types when compared to CD47-low tumors ($p = 0.0006$; Figure 2c, Table 1).[14] CD47-high tumors were of types A and AB 85.7% of the time (n = 12/14), compared to 20.7% of CD47-low tumors (n = 11/53). CD47-high tumors were most frequently type AB (57.1% in CD47-high vs 13.2% in CD47-low tumors) followed by type A (28.6% vs 7.5%). Tumors with the worst prognostic type C (n = 4) were exclusively CD47-low. A multivariate analysis adjusting for age, sex, performance status, stage and resection status confirmed the significant correlation between CD47-high status and a more favorable WHO type ($p = 0.0275$).

Type A and AB tumors had nearly equal proportions of CD47-high and CD47-low tumors: type A (50.0% CD47-high, n = 4/8), type AB (53.3%, n = 8/15). Types B1-C were almost exclusively CD47-low (B1: 7.1% CD47-high, n = 1/14; B2: 0%, n = 0/19; B3: 14.3%, n = 1/7; C: 0%, n = 0/4; Table 1).
As expected, EFS and OS were both worse for WHO types B3-C in this cohort compared to the other histologies. Median EFS was 1.7 years vs 7.7 years (HR 3.39, 95% CI 1.03-11.15, p = 0.0023), while OS was 5.25 years vs 22.2 years (HR 4.06, 95% CI 1.08-15.27, p = 0.0017). EFS and OS were not significantly different between CD47-high and CD47-low patients (EFS HR 0.54, 95% CI 0.17-1.71, p = 0.39; OS HR 0.83, 95% CI 0.27-2.51, p = 0.73). Multivariate survival analysis adjusting for age, sex, performance status, WHO type, and resection status did not reveal any significant correlation between CD47 and these survival outcomes, EFS (p = 0.81) and OS (p = 0.33).

Just over a third of patients in the cohort had a PNS (37.3%), with most (64%) having myasthenia gravis. Other paraneoplastic syndromes included pure red cell aplasia, Guillain-Barré syndrome, autoimmune enteropathy and lymphocytic myocarditis. Tumors which were $CD47^{low}$, when compared to $CD47^{high}$, more often had a PNS (52.4% vs 12.0%). However, multivariate analysis adjusted for WHO type did not show an independent association between CD47 status and PNS (p = 0.0948). $CD47^{low}$ tumors were most often WHO types B2 and B3 which in this cohort had the highest frequency of PNS.

DISCUSSION

To our knowledge, this study is the first report of CD47 expression levels in TETs. CD47 expression predicts worse outcomes in hematological and solid malignancies.[7,15] We found that most TETs were CD47 positive and expressed significantly higher levels of CD47 compared to the normal thymus. TETs which tended to have higher CD47 expression were those with a more favorable WHO histology, but this did not correlate with improved EFS or OS. This may have been limited by the sample size of the cohort. Prior studies in other cancer types have similarly failed to find a clear relationship between CD47 expression and survival outcomes, and further studies with larger cohorts remain to be done.[16–19]

The vast majority (85.7%) of tumors with high CD47 expression were WHO types A and AB, which unlike other types, are difficult to distinguish apart as they share a common histologic appearance (the occurrence of spindle epithelial cells) as well as specific genetic alterations.[20] It is yet unclear how their common tumor microenvironment selectively promotes higher CD47 expression.

Preclinical data has shown targeting CD47 leads to inhibition of tumoral growth and metastasis in a number of cancer types including breast and non-small cell lung cancers.[21,22] In the clinical setting, anti-CD47 monoclonal therapy has not been tested in TETs, although in a phase 1/2 trial of a peptide compound designed to achieve downstream inhibition of CD47, the only response was seen in a patient with thymoma, who also had high levels of CD47 expression.[23]

For patients with TETs who develop resistance to chemotherapy, and who already have a high incidence of autoimmune events, anti-CD47 therapy may be worth exploring as a novel immunotherapy given the different side effect profile of anti-CD-47 antibodies and anti-PD(L)1 antibodies given the high expression of CD47 on TET tumor cells, though we still need to be vigilant with observing for irAEs. We have initiated a clinical trial to test anti-CD47 blockade in TETs.

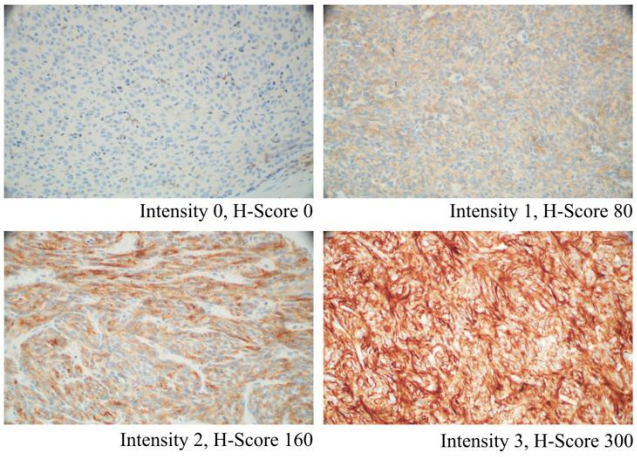
TABLE 1. Baseline Characteristics

Variable	All Cases (n = 67)	CD47 high* (n = 14)	CD47 low (n = 53)	p value (H-Score; Intensity)#
Age, mean (range)	56.0 (2-86)	59.1 (36-80)	55.2 (2-86)	0.44
Sex				0.95
Male	34 (50.7%)	7 (50.0%)	27 (50.9%)	
Female	33 (49.3%)	7 (50.0%)	26 (49.1%)	
ECOG Performance Status				**0.02**
0	33 (49.3%)	10 (71.4%)	23 (43.4%)	
1	28 (41.8%)	3 (21.4%)	25 (47.2%)	
2	5 (7.5%)	1 (7.1%)	4 (7.5%)	
3	1 (1.5%)	0	1 (1.9%)	
WHO Histology[a]				**0.0006; 0.0006**
A	8 (11.9%)	4 (28.6%)	4 (7.5%)	
AB	15 (22.4%)	8 (57.1%)	7 (13.2%)	
B1	14 (20.9%)	1 (7.1%)	13 (24.5%)	
B2	19 (28.4%)	0	19 (35.8%)	
B3	7 (10.4%)	1 (7.1%)	6 (11.3%)	
C	4 (6.0%)	0	4 (7.5%)	
Pathologic Masaoka Stage				**0.032; 0.023**
I	30 (44.8%)	11 (78.6%)	19 (35.8%)	
II	15 (22.4%)	2 (14.3%)	13 (24.5%)	
IIa	12	2	10	
IIb	3	0	3	
III	12 (17.9%)	1 (7.1%)	11 (20.8%)	
IV	10 (14.9%)	0	10 (18.9%)	
IVa	6	0	6	
IVb	4	0	4	
Paraneoplastic Syndrome	25 (37.3%)	2 (14.3%)	23 (43.4%)	0.063; **0.0014**
Myasthenia Gravis	16 (23.9%)	0	16 (30.2%)	
Pure Red Cell Aplasia	2 (3.0%)	0	2 (3.8%)	
Hypogammaglobulinemia	1 (1.5%)	0	1 (1.9%)	
Other[b]	6 (9.0%)	2 (14.3%)	4 (7.5%)	
None	42 (62.7%)	12 (85.7%)	30 (56.6%)	
Resection Status				0.058; 0.073
R0	45 (67.2%)	13 (92.9%)	32 (60.4%)	
R1	9 (13.4%)	1 (7.1%)	8 (15.1%)	
R2	13 (19.4%)	0	13 (24.5%)	

[a]A micronodular thymoma with lymphoid stroma was classified as type A; one classified as C as mixed B3/C.
[b]Other paraneoplastic syndromes were autoimmune enteropathy, dermatomyositis, Guillain-Barré syndrome, lymphocytic myocarditis, minimal change nephrotic syndrome and rheumatoid arthritis.
*CD47 high based on H-Score: ≥150; CD47 low based on H-Score <150

[#]$\chi 2$ or Fisher's Exact Test
Bolded values are two-sided p values less than 0.05 and are considered statistically significant.

A



B

CD47 Tumor Expression (N = 67)	**n (%)**
Intensity (mean ± SD)	0.57 ± 0.96
0	12 (17.9)
1	30 (44.8)
2	14 (20.9)
3	11 (16.4)
Percentage of Tumor Involved (mean ± SD)	35.74 ± 37.54
0-25	35 (52.2)
25-50	6 (9.0)
50-75	12 (17.9)
75-100	14 (20.9)
H-Score (mean ± SD)	74.49 ± 94.31
0-74	43 (64.2)
75-149	10 (14.9)
150-224	6 (9.0)
225-300	8 (11.9)

Figure 1. CD47 expression in thymic epithelial tumors. A, Representative immunohistochemical staining of CD47 (brown signal) in a tissue microarray with intensity and H-scores presented. Magnification, 400x. B, CD47 expression levels in 67 tumor samples.

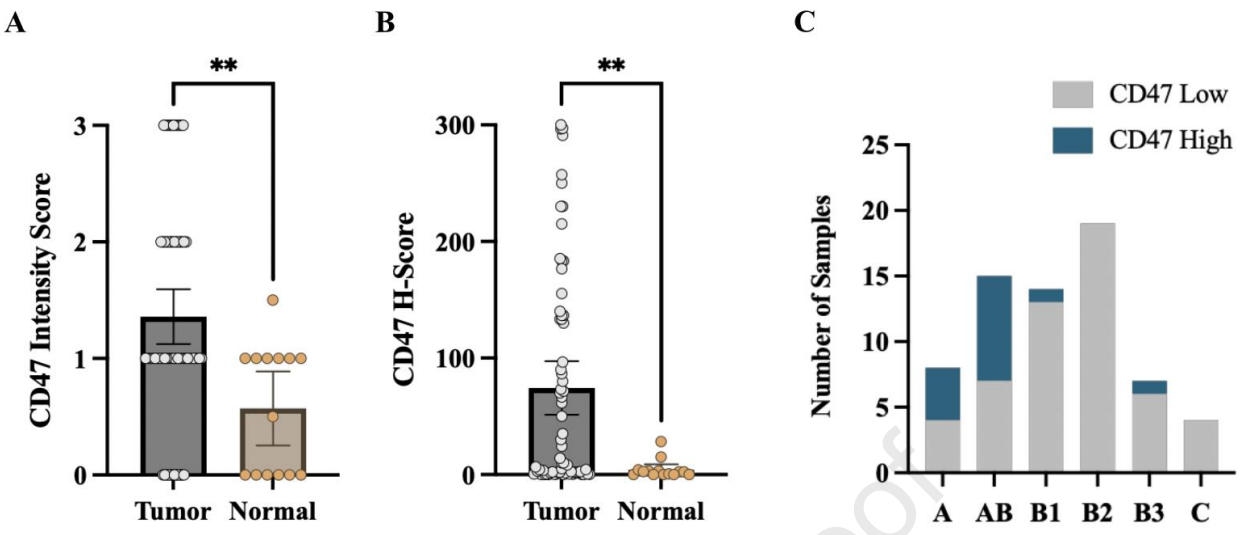


Figure 2. CD47 Expression Levels. A, CD47 staining intensity scores. P value was 0.004. B, CD47 staining H-scores (intensity multiplied by percentage of tumor cells involved). P value was 0.003. ** denotes a p-value of less than 0.01. Errors bars denote 95% confidence intervals. C, proportions of CD47-high and CD47-low tumors within each WHO histology type.

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Credit Statement

Thomas Yang Sun: writing-original draft preparation and subsequent revisions, data gathering, data analysis, investigation

Brandon Nguyen: data analysis, data gathering

Simon B. Chen: pathology review, manuscript review

Yasodha Natkunam: pathology review, tissue microarray creation, manuscript review

Sukhmani Padda: database curation, manuscript review

Matt van de Rijn: tissue microarray creation

Robert West: tissue microarray creation

Joel W. Neal: data gathering, manuscript review

Heather Wakelee: manuscript review, supervision

Jonathan W. Riess: conception, supervision, manuscript review, data analysis