


Figure 1. Patterns of CD56 expression in eosinophilic vacuolated tumor and differential diagnostic tumors.

**Figure 2 - 845.**

**Conclusions:** Our findings support the utility of CD56 as an adjunct diagnostic tool in the workup of kidney tumors (along with CD117, cathepsin K, GPNMB, KRT7, KRT20, SDHB, and CD10) when EVT is a consideration in the differential diagnosis. Diffuse CD56 showed high sensitivity and moderate specificity for EVT. Importantly, the presence of diffuse CD56 excluded most types of RCC except a small subset of ESC RCC.

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## 846 | Eosinophilic Vacuolated Tumor with Worrisome Morphologic Features May Have Metastatic Potential

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**Background:** Eosinophilic vacuolated tumor (EVT) is described in the 2022 World Health Organization classification as an emerging renal tumor with *TSC1/TSC2/MTOR* mutation(s). Approximately 60 clinically indolent cases have been reported. However, we have encountered EVTs with potentially aggressive morphologic features. The frequency and clinical significance of these findings remain unknown and prompted the current study.

**Design:** Through multi-institutional collaboration, 36 EVTs resected between 2004 and 2025 were evaluated for worrisome morphologic features including invasion into large vessels, fat, the pelvicalyceal system, or lymphatic/small vessels, as well as increased mitotic activity, necrosis and large size (≥7 cm). EVTs were diagnosed using established diagnostic features, including eosinophilic cells with prominent cytoplasmic vacuoles and nucleoli plus immunohistochemistry (CD117, KRT7, KRT20, CD10 and/or cathepsin K). In a subset of EVTs, somatic tumor testing for *TSC1/TSC2/MTOR* variants was performed. Events (metastasis, recurrence, progression, and disease-specific death), treatment received, and clinical status at last follow-up were collected via review of the electronic patient records.

**Results:** Patient age ranged from 13 to 80 years (median 51). The M:F ratio was 1:1.8. EVTs were resected by partial (n=22) or radical (n=14) nephrectomy, with tumor size ranging from 1.1 to 15.5 cm (median 2.7). Eleven of 13 sequenced EVTs had a *TSC1* (n=2), *TSC2* (n=5) *or MTOR* (n=4) mutation. One additional patient had clinically suspected tuberous sclerosis. Seven of 36 (19.4%) EVTs had worrisome morphologic features (Table 1): 5 tumors measured ≥7 cm, 3 showed fat invasion (Figure 1), 2 had large vessel invasion (Figure 2), and 2 invaded lymphatic/small vessels. No increased mitotic activity or necrosis was identified. Median follow-up time for 17 patients was 12 months (range 1-67). One patient had regional lymph node (LN) metastases at nephrectomy with no progression on follow-up. Another patient with no nodal disease at presentation developed regional and distant LN metastases 9 and 24 months post nephrectomy, respectively. All patients were alive at last follow-up.

**Table 1. Clinicopathologic characteristics and clinical outcomes of eosinophilic vacuolated tumors with worrisome morphologic features**

| Patient | Age (years) | Gender | Specimen | Tumor size (cm) | Actionable molecular alterations | Worrisome morphologic features | Events | Post-nephrectomy treatment | Clinical status at last follow-up | Follow-up time (months) |
|---|---|---|---|---|---|---|---|---|---|---|
| #1 | 59 | M | Partial nephrectomy | 7.5 | *MTOR* mutation | • Large vessel invasion<br>• Extensive lymphatic/small vessel invasion<br>• Size ≥7 cm | • Regional lymph node metastases proven on biopsy (9 months after nephrectomy)<br>• Distant lymph node metastases on imaging (24 months after nephrectomy) | • Adjuvant chemotherapy<br>• Retroperitoneal lymph node dissection | Alive with distant lymph node metastases | 29 |
| #2 | 27 | F | Radical nephrectomy and retroperitoneal lymph node dissection | 7.0 | *MTOR* mutation | • Renal sinus fat invasion<br>• Size ≥7 cm | Regional lymph node metastases (at the time of nephrectomy) | None | Alive with no disease | 4 |
| #3 | 80 | M | Radical nephrectomy | 15.5 | None | • Perinephric fat invasion<br>• Renal sinus fat invasion<br>• Lymphatic/small vessel invasion<br>• Size ≥7 cm | None | None | Alive with no disease | 3 |
| #4 | 78 | M | Partial nephrectomy | 1.5 | N/A | Perinephric fat invasion | None | None | Alive with no disease | 12 |
| #5 | 50 | M | Partial nephrectomy | 1.9 | *MTOR* mutation | Large vessel invasion | None | None | Alive with no disease | 10 |
| #6 | 13 | F | Radical nephrectomy | 10.0 | N/A | Size ≥7 cm | None | None | Alive with no disease | 17 |
| #7 | 73 | M | Partial nephrectomy | 7.0 | None | Size ≥7 cm | None | None | Alive with no disease | 11 |

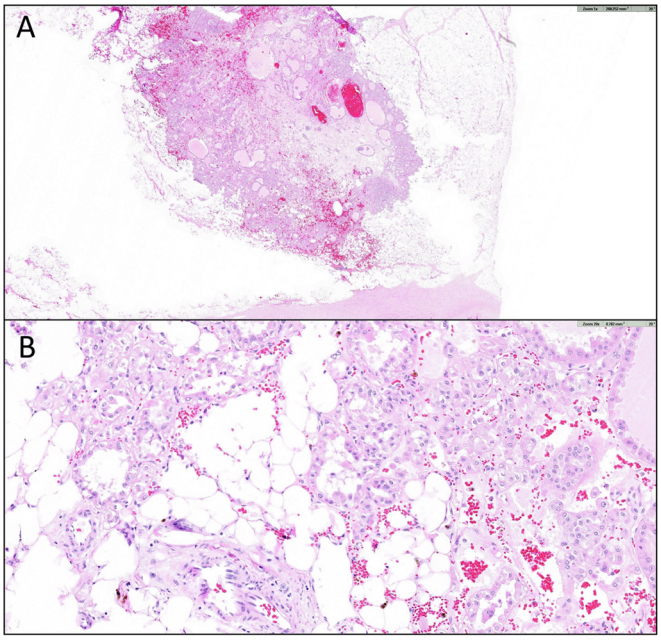



**Figure 1. Eosinophilic vacuolated tumor invading perinephric fat (patient #4).**
(A) 10x magnification. (B) 200x magnification.

**Figure 1 - 846.**

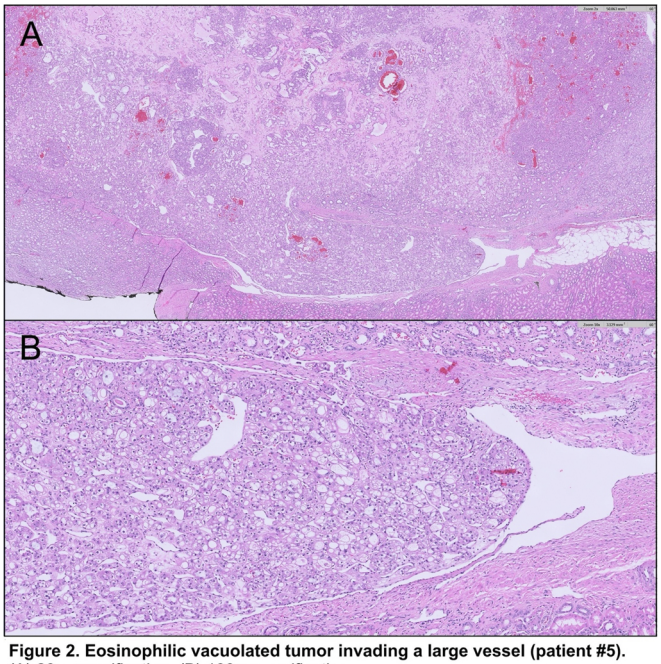



**Figure 2. Eosinophilic vacuolated tumor invading a large vessel (patient #5).**
(A) 20x magnification. (B) 100x magnification.

**Figure 2 - 846.**

**Conclusions:** Worrisome morphologic features including vascular invasion, fat invasion and/or large tumor size can be seen in up to one fifth of EVTs, some of which may be associated with metastatic potential, at least to local lymph nodes. The clinical significance of such findings warrants further validation with longer follow-up.

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## 847 | Prevalence, Clinicopathologic Associations and Prognostic Significance of HER2, Nectin-4 and Trop-2 Expression in Advanced or Metastatic Urothelial Carcinoma

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**Background:** Antibody drug conjugates (ADC) directed against HER2, Nectin-4 and Trop-2 have shown to improve overall survival in patients with metastatic or advanced urothelial carcinoma (UC) in phase II/III clinical trials. The current study aims (1) to characterize the immunohistochemical expression of HER2, Nectin-4 and Trop-2 in advanced/metastatic UC, and (2) to explore their clinicopathologic associations and prognostic significance.

**Design:** Tissue microarrays were constructed with advanced/metastatic UC tissue from 398 patients (3 cores/patient). HER2 expression was assessed using guidelines for gastric cancer. Nectin-4 and Trop-2 expression was analyzed using H-scores, classified as negative (0), low (<100), intermediate (100-200), or high (>200). Clinicopathologic features were compared based on HER2, Nectin-4 and Trop-2 expression levels using Mann-Whitney U and Chi-square tests, and recurrence-free survival (RFS) was evaluated using Kaplan-Meier curves and log-rank tests.

**Results:** Median age was 72 years (range 33-93). M:F ratio was 1:0.3. Median time to recurrence/last follow-up was 9 months (range 1-206). Clinicopathologic features and comparisons based on biomarker expression are summarized in Table 1. HER2 2+/3+ UC significantly correlated with concomitant CIS ($p=0.044$), nodal disease ($p<0.001$), and the luminal subtype ($p<0.001$). High Nectin-4 H-scores were associated with male sex ($p=0.014$), nodal disease ($p=0.038$), and the luminal subtype ($p=0002$). Compared to UC with Trop-2 H-score $\leq$200, UC with a high Trop-2 H-score were more frequently of pathological stage pT3 vs pT2 ($p=0.049$), and there was a strong association with nodal disease ($p=0.018$) and the luminal subtype ($p<0.001$). Co-expression of high HER2/Nectin-4/Trop-2 levels was seen in 84/398 (21.1%) UC (Figure 1). Up to three quarters of UC had high Trop-2 expression with HER2 0/1+ and Nectin-4 H-score <200. There was a lack of high HER2/Nectin-4/Trop-2 expression in 24/398 (6%) UC. High Trop-2 expression ($p<0.001$) and Nectin-4 H-scores <200 ($p=0.331$) correlated with higher RFS probabilities, while HER2 ($p=0.760$) did not stratify patients in terms of RFS (Figure 2).