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SHORT COMMUNICATION

Nectin-4 and Trop-2 expression in collecting duct carcinoma: new promising therapeutic targets

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Background: Collecting duct carcinoma (CDC) is a rare and aggressive renal malignancy with limited therapeutic options and no established biomarker-driven strategies. Given its morphologic and embryologic overlap with urothelial carcinoma, we investigated the expression of Nectin-4 and Trop-2, targets of antibody—drug conjugates (ADCs) with proven activity in urothelial cancer.

Patients and methods: Tumor samples from 59 patients with CDC who were enrolled in the multicenter CICERONE study (NCT05372302) were centrally reviewed by expert genitourinary pathologists. Immunohistochemical analyses for Nectin-4 and Trop-2 were carried out on formalin-fixed, paraffin-embedded tissue. Tumors were considered positive when >10% of cells showed membranous and/or cytoplasmic staining.

Results: Nectin-4 expression was detected in 41% of cases, with variable staining intensity, while Trop-2 expression was observed in 89% of tumors, frequently showing strong and diffuse staining. No substantial associations were found between marker expression and clinicopathologic features.

Conclusions: Nectin-4 and Trop-2 are frequently expressed in CDC, supporting a biological overlap with urothelial carcinoma. Although these findings do not imply clinical efficacy, they provide a rationale for prospective evaluation of ADC-based strategies in this rare malignancy, including ongoing clinical trials investigating enfortumab vedotin-based combinations.

Key words: collecting duct carcinoma, enfortumab vedotin, Nectin-4, renal carcinoma, Trop-2

INTRODUCTION

Collecting duct carcinoma (CDC) is a rare and highly aggressive renal malignancy, accounting for ∼1% of renal tumors.[1] It is characterized by substantial diagnostic complexity and a meaningful risk of histological misclassification. Originating from the ureteric bud-derived collecting system, CDC displays embryologic, morphologic, and clinical features that partially overlap with upper tract urothelial carcinoma (UC),[2] underscoring the importance of centralized pathology review in expert centers. Therapeutic options for metastatic CDC remain limited and are largely extrapolated from small prospective studies,[3,4] retrospective series, or other renal cancer subtypes; outcomes remain poor, and no biomarker-driven therapeutic strategies are currently available for this disease. In UC, antibody—drug conjugates (ADCs) targeting Nectin-4 and Trop-2 have demonstrated clinically meaningful activity,[5,6] profoundly reshaping the treatment landscape of UC. Whether these targets are expressed in CDC has not been systematically evaluated. We therefore assessed Nectin-4 and Trop-2 expression in a centrally reviewed CDC cohort to explore potential biological overlap with UC warranting further investigation.

PATIENTS AND METHODS

Tumor samples from 59 patients with CDC enrolled in the multicenter CICERONE study were analyzed. CICERONE is a multicentric effort aimed at improving the biological characterization of CDC and supporting the development of

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biomarker-driven therapeutic strategies. All cases underwent mandatory centralized histopathologic review by expert genitourinary pathologists to confirm the diagnosis. Immunohistochemical analyses were carried out on formalin-fixed, paraffin-embedded tissue sections using validated antibodies against Nectin-4 and Trop-2 on an automated platform. Tumors were considered positive when >10% of neoplastic cells showed membranous and/or cytoplasmic staining. Staining intensity was categorized as weak (10%-30%), moderate (30%-50%), or strong (>50%). Descriptive statistics were used to summarize clinicopathologic characteristics and immunohistochemical findings.

CICERONE study was approved by the Ethics Committee of Fondazione IRCCS Istituto Nazionale dei Tumori di Milano (approval No. INT 12_21). All participants provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki.

RESULTS

The study included 59 tumor samples from patients diagnosed with CDC. The median age of the study population was 63 years (range, 20-90). Tumor specimens were obtained from nephrectomy or nephroureterectomy samples. Histologically, most tumors showed tubular growth patterns with desmoplastic stroma, consistent with typical CDC morphology. Necrosis was observed in 68% of cases, and features such as angioinvasion and perineural infiltration were frequently identified, reflecting the aggressive nature of this disease. Nectin-4 expression was detected in 24 of 59 CDC samples (41%). Among positive cases, strong expression was observed in 10%, moderate expression in 16%, and weak expression in 15%. Staining was predominantly cytoplasmic, with membranous localization observed in a minority of cases. Trop-2 expression was identified in 52 of 59 samples (89%), frequently showing strong and diffuse membranous and cytoplasmic staining across tumor cells. No nuclear staining was encountered in both Nectin-4 and Trop-2 positive cases. The pattern of the positive pathway in our series reduced the interobserver variability, which is usually observed when the type of expression is dichotomic (cytoplasmic versus membranous). No significant associations were observed between Nectin-4 or Trop-2 expression and standard clinicopathologic features, including tumor size, necrosis, or histological patterns. Representative immunohistochemical findings are shown in Figure 1.

DISCUSSION

In this centrally reviewed CDC cohort, we observed Nectin-4 expression in ∼40% of cases and near-ubiquitous expression of Trop-2. These findings reinforce the concept that CDC shares biological features with UC, extending beyond histological resemblance to include expression of therapeutically relevant surface antigens.

The identification of Nectin-4 expression in a substantial subset of CDC tumors is particularly noteworthy. Although anti-Nectin-4 ADCs such as enfortumab vedotin have transformed the treatment landscape of UC, the predictive value of Nectin-4 expression itself remains uncertain even in that setting. Therefore, our data should be interpreted cautiously and do not imply clinical efficacy. Rather, they provide a biological rationale for further investigation of anti-Nectin-4—

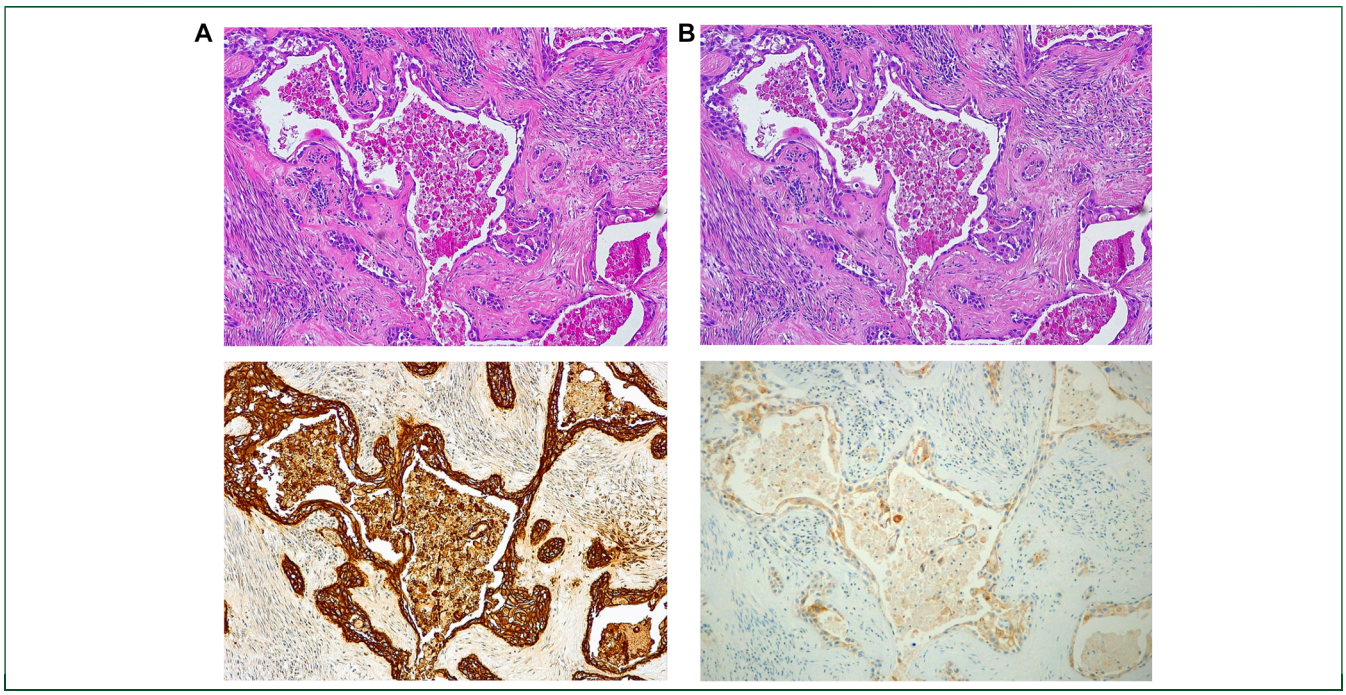

Figure 1. Representative immunohistochemical expression of Trop-2 and Nectin-4 in collecting duct carcinoma. (A) Hematoxylin and eosin-stained section (top) and corresponding immunohistochemical staining showing strong membranous and cytoplasmic expression of Trop-2 in tumor cells (bottom). (B) Hematoxylin and eosin-stained section (top) and corresponding immunohistochemical staining demonstrating moderate Nectin-4 expression in tumor cells (bottom).

based strategies in CDC, especially considering its phenotypic and embryologic similarities to urothelial malignancies.

Trop-2 expression was observed in the majority of cases, in line with its known widespread expression across epithelial tumors. Although this finding further supports the biological overlap with other tumor types, its therapeutic implications in CDC remain less specific, given the ubiquitous nature of Trop-2 expression.

Given the rarity of CDC and the lack of biomarker-driven therapeutic options, these data support the need for prospective clinical investigation of ADC-based strategies. In this context, a phase II study is currently evaluating enfortumab vedotin in combination with pembrolizumab in patients with metastatic CDC (REPRINT, NCT06302569).

This study has several limitations, including its descriptive nature and the absence of correlation with clinical outcomes. However, the use of centralized pathology review strengthens the validity of the findings, particularly in a disease known for diagnostic challenges. Moreover, the relatively large cohort for such a rare tumor represents an additional strength.

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DISCLOSURE

The authors have declared no conflicts of interest.

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