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Case Report

CDX2 Expression Predicts Fluoropyrimidine Sensitivity Across Rare Non-GI Tumors: A Three-Case Series

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Simple Summary

CDX2 is a protein normally found in intestinal cells and is widely used by pathologists to help determine the origin of tumors. However, CDX2 may also carry important therapeutic information. In this study, we describe three patients with rare metastatic cancers of the prostate, salivary gland, and sinonasal tract whose tumors strongly expressed CDX2, indicating an intestinal-like phenotype. Standard treatments were ineffective or not well established in these cases. Based on CDX2 expression, patients were treated with chemotherapy typically used for colorectal cancer. All three experienced substantial clinical and radiologic improvement. These cases suggest that CDX2 may serve not only as a diagnostic marker but also as a practical biomarker to guide treatment selection across different cancer types, particularly in rare tumors where evidence-based systemic options are limited.

Abstract

Caudal type homeobox 2 (CDX2) is an intestine-specific transcription factor that serves as a diagnostic marker of enteric differentiation and may also reflect tumor behavior and therapeutic susceptibility. Emerging evidence suggests that CDX2 expression may predict sensitivity to fluoropyrimidine-based therapy independent of tissue of origin. We report a retrospective case series of three patients with metastatic adenocarcinoma (aggressive variant prostate, minor salivary gland, and intestinal-type sinonasal tract) exhibiting strong CDX2 nuclear expression. In all cases, tumors were refractory to or lacked established standard systemic therapy. Treatment decisions were guided by the CDX2-positive enteric phenotype, leading to the initiation of fluoropyrimidine-based regimens. Response was assessed using PET-CT and MRI. All three patients achieved marked metabolic and clinical responses, including a sustained complete metabolic response in the prostate cancer case and durable disease control in the salivary gland and sinonasal tumors. These findings highlight CDX2 as a clinically actionable biomarker that may identify tumors intrinsically susceptible to fluoropyrimidines regardless of anatomical origin. CDX2 immunohistochemistry is widely available and inexpensive, and may complement genomic profiling in rare malignancies or in settings where standard treatment algorithms are limited.

Keywords: CDX2; fluoropyrimidine; rare cancers; phenotype-driven therapy; immunohistochemistry

Introduction

Caudal type homeobox 2 (CDX2) is an intestine-specific nuclear transcription factor encoded by the human homolog of the *Drosophila* caudal homeobox gene (1). It plays a central role in establishing and maintaining intestinal epithelial identity during embryonic development and throughout adulthood (2). Experimental models have shown that CDX2 is indispensable for gut morphogenesis, differentiation, and the regulation of cellular proliferation (3, 4). In normal human tissues, CDX2 expression is localized to epithelial nuclei of the small intestine, colon, and appendix (5), with additional expression in pancreatic ductal and centroacinar cells (6). Ectopic expression in gastric mucosa can induce intestinal metaplasia, underscoring its ability to drive enteric differentiation beyond the intestine (7).

In malignancy, CDX2 is most prominently expressed in colorectal adenocarcinomas, where more than 90% of cases show nuclear positivity (8), establishing it as a sensitive diagnostic marker of colorectal origin. However, CDX2 expression is also found in gastric and pancreatobiliary adenocarcinomas, and even in tumors arising outside the gastrointestinal (GI) tract, including those of the sinonasal tract, lung, ovary, prostate, and bladder (9). This distribution indicates that CDX2 reflects a broader enteric differentiation program rather than a strictly site-specific phenotype.

Growing evidence suggests that CDX2 marks enteric differentiation and also reflects tumor behavior and therapeutic susceptibility. CDX2-positive tumors retain enterocyte-like programs, including pathways relevant to fluoropyrimidine response. In our recent CDX2-positive cancer of unknown primary (CUP) cohort, fluoropyrimidine-based therapy produced higher response rates and longer progression-free and overall survival than non-fluoropyrimidine regimens, independent of site-suggestive immunophenotypes (10). These findings support CDX2 as a phenotype-driven biomarker identifying tumors intrinsically sensitive to fluoropyrimidines and less responsive to taxanes, regardless of anatomic origin. Here, we describe three cases of metastatic adenocarcinoma of the prostate, salivary gland, and sinonasal tract in which CDX2 expression suggested enteric differentiation and guided fluoropyrimidine-based treatment. These cases underscore the growing diagnostic and predictive significance of CDX2 across diverse primary sites.

Case Presentation

Case 1

A 75-year-old never-smoker male patient with a history of high-risk prostate cancer treated with SBRT and leuprolide presented in January 2023 with a rising PSA of 3.9. CT scan showed a presacral mass and bilateral pulmonary nodules. Given radiologic progression of his prostate cancer, he started docetaxel; however, subsequent imaging demonstrated further progression involving the presacral lesion, pelvic lymph nodes, and pulmonary nodules.

A biopsy of the pulmonary nodules revealed a poorly differentiated carcinoma positive for AE1/AE3, CK7, p16, SATB2, and CDX2. Tumor cells were faintly positive for NKX3.1, synaptophysin, and INSM1, with a Ki-67 index >90%. The tumor was negative for TTF-1, CK20, p40, PSA, PSAP, AR, ERG, chromogranin, GATA3, uroplakin II, and SOX10. Molecular testing demonstrated microsatellite stability, a tumor mutational burden of 0, and copy number loss of RAD51C, PTEN, and TBL1XR1. No common colorectal cancer-associated mutations were detected.

PET-CT on April 5, 2023, confirmed FDG-avid disease in the presacral region, bilateral lungs, left inguinal and right iliac chain lymph nodes, and right penile crus (**Figure 1A**). PSMA-PET revealed a concordant uptake in the same regions. Colonoscopy was negative.

The patient was subsequently evaluated in the CUP clinic at Mayo Clinic. The overall findings, including the patient's history, persistent NKX3.1 expression, and diffuse PSMA uptake, favored a dedifferentiated prostate carcinoma with divergent enteric morphology. Given CDX2 positivity and prior progression on docetaxel, a histology-driven approach was adopted using FOLFOX (leucovorin, 5-fluorouracil [5-FU], and oxaliplatin). After six cycles, FDG PET-CT demonstrated a

complete metabolic response (**Figure 1B**), sustained on the 3-month restaging scan. He was subsequently maintained on 5-FU and leucovorin.

Four months after initiating maintenance therapy, he developed imbalance; brain MRI revealed multiple enhancing lesions. The dominant lesion was resected and followed by whole-brain radiation, confirming metastatic adenocarcinoma with identical morphology. Extracranial disease remained in complete response.

Given concern for CNS sanctuary progression, irinotecan was added to 5-FU due to its superior CNS penetration, and PET-CT three months later again showed no FDG-avid disease. As his performance status declined, systemic therapy was transitioned to olaparib monotherapy based on the RAD51C mutation, with capecitabine reserved for later use if progression occurred. Serial MRI and PET-CT demonstrated ongoing complete metabolic and CNS responses until July 2025, when new CNS lesions developed. He underwent right suboccipital craniotomy followed by postoperative radiation; extracranial disease remained in remission. He later elected hospice care but is alive at manuscript submission (January 2026).

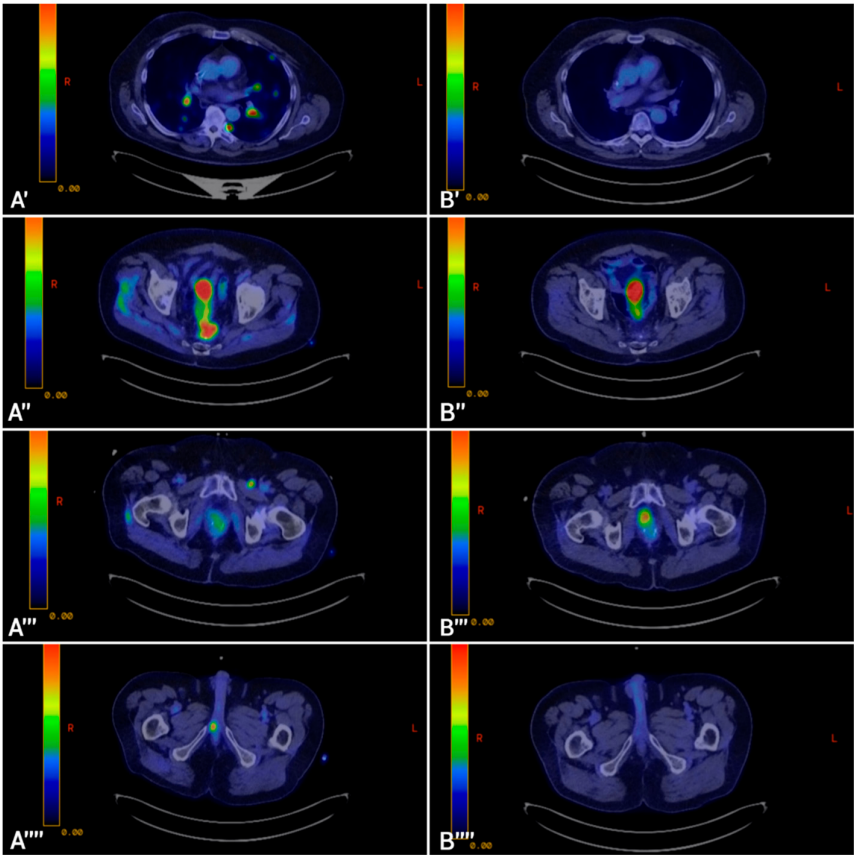


Figure 1. A: (A'–A''') Pre-treatment PET-CT images demonstrating FDG-avid disease involving multiple sites: (A') Bilateral pulmonary nodules, (A'') Pelvic mass in the presacral region, (A''') Pelvic lymph nodes, (A''') Right penile crus. B: (B'–B''') Post-treatment PET-CT images showing complete metabolic response with no FDG-avid disease in the corresponding sites: (B') Bilateral lungs, (B'') Pelvic region, (B''') Pelvic lymph nodes, (B''') Penile crus.

Case 2

A 61-year-old never-smoking male with no significant past medical history presented in November 2023 with right-sided tongue and ear pain. CT imaging revealed levels II and III cervical lymphadenopathy. Ultrasound-guided fine-needle aspiration of a right cervical lymph node showed

metastatic adenocarcinoma with mucinous features. Immunohistochemistry demonstrated strong positivity for CDX2 and CK20, focal positivity for CK7, and negativity for ER, HER2, SATB2, SOX10, and TTF-1. A staging PET-CT revealed FDG-avid right cervical lymphadenopathy and mild asymmetric uptake in the right palatine tonsillar region, with no evidence of distant metastasis (**Figure 2A**).

Evaluation in the Head and Neck Oncology Clinic at Mayo Clinic favored a diagnosis of minor salivary gland adenocarcinoma with enteric differentiation and regional nodal metastases. Surgical resection would have required near total glossectomy, severely impacting quality of life; therefore, non-surgical management was prioritized in alignment with the patient's preference for organ preservation.

Given the tumor's CDX2 positivity, chemotherapy with FOLFOXIRI (leucovorin, 5-FU, oxaliplatin, and irinotecan) was initiated. Soon after starting treatment, the patient experienced a remarkable clinical improvement, allowing discontinuation of around-the-clock oxycodone. Irinotecan was later omitted due to GI toxicity, and chemotherapy continued as modified FOLFOX with dose adjustments.

The patient then transitioned to concurrent chemoradiation, with FOLFOX administered at radiosensitizing doses. Three months after completion of chemoradiation, restaging with PET-CT demonstrated no evidence of active disease, with decreased enhancement at the primary site and reduction in nodal size (**Figure 2B**). Serial MRIs over subsequent months showed stable post-treatment changes without progression. The patient has now been without evidence of active disease for two years, maintaining good functional status with preserved speech and swallowing.

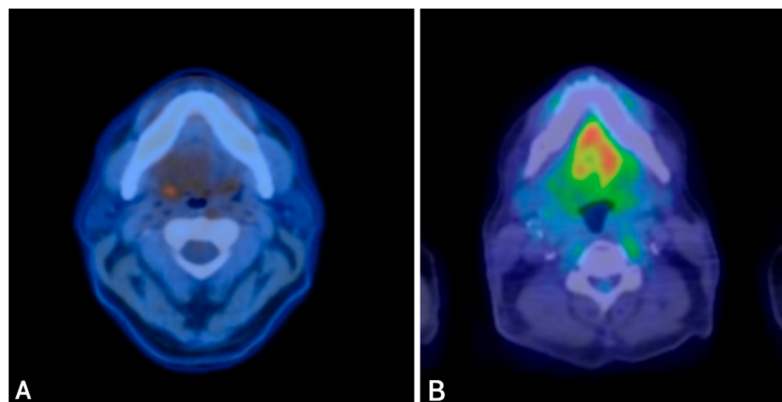


Figure 2. A. Pre-treatment PET-CT images demonstrating FDG-avid right cervical lymphadenopathy and mild asymmetric uptake in the right palatine tonsillar region B. Post-treatment PET-CT images showing no evidence of active disease, with decreased enhancement at the primary site and reduction in nodal size.

Case 3

A 48-year-old never-smoker male with no significant past medical history presented in July 2023 with recurrent, refractory epistaxis. ENT evaluation revealed a left nasal cavity mass. Biopsy demonstrated intestinal-type adenocarcinoma positive for CK7, CK20, and CDX2, with a CPS of 10 and HER2 2+. CT of the sinuses revealed an extensive left paranasal sinus mass without nodal or distant metastases. At an outside institution, the patient underwent endoscopic craniofacial resection of the anterior cranial fossa, followed by adjuvant proton beam radiation, completed in May 2024.

Three months later, surveillance imaging showed local recurrence. Repeat endoscopic resection demonstrated discordant margins, which persisted after a second re-resection. Pembrolizumab was started, but after three doses PET-CT showed progression with FDG-avid sinonasal, orbital, vomer, right cervical nodal, and pulmonary involvement (**Figure 3A**).

The patient was referred for a second opinion to the Head and Neck Oncology Clinic at our institution. He reported persistent sinonasal pressure requiring Norco every five hours and diplopia

interfering with daily activities. Given strong CDX2 expression consistent with enteric differentiation, FOLFOXIRI chemotherapy was initiated.

After three months, restaging PET-CT showed markedly decreased sinonasal uptake, improved nodal disease, and near-complete resolution of pulmonary nodules (**Figure 3B**). Clinically, the patient experienced significant pain relief (2/10 from 7/10) and complete resolution of diplopia.

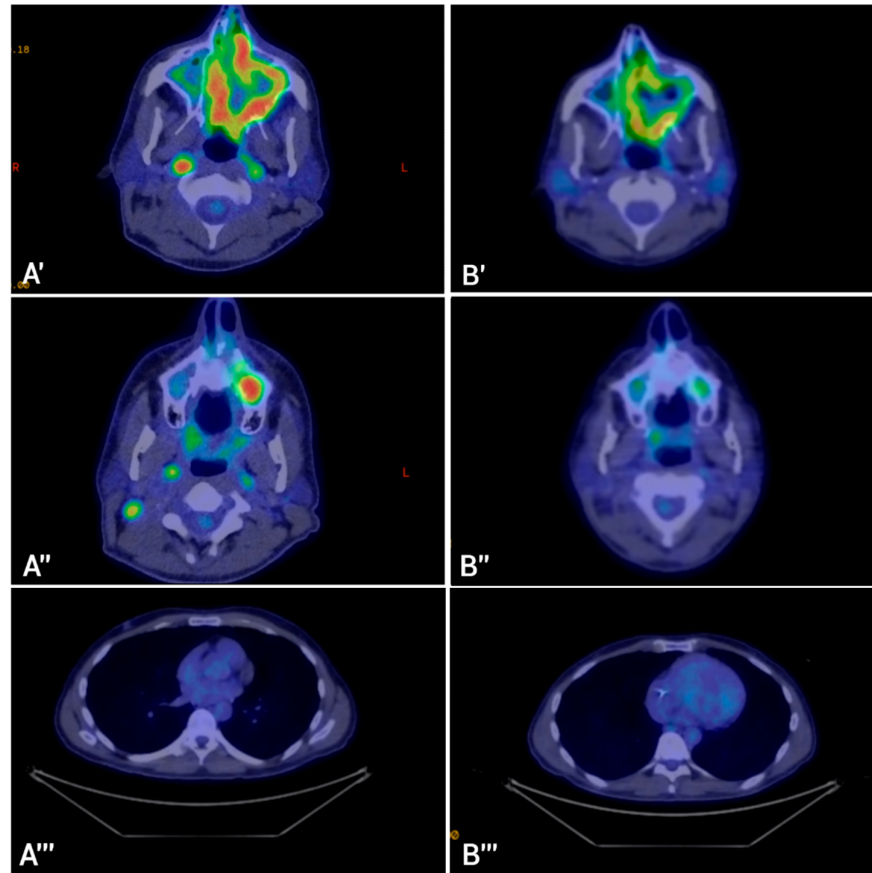


Figure 3. A: (A'–A''') Pre-treatment PET-CT images demonstrating FDG-avid disease involving multiple sites: (A') Left maxillary sinus mass (A'') Right cervical lymph nodes (A''') Right pulmonary nodules. B: (B'–B''') Post-treatment PET-CT images showing partial metabolic response in the left maxillary sinus mass and right cervical lymph nodes and near-complete resolution of pulmonary nodules: (B') Left maxillary sinus mass (B'') Right cervical lymph nodes, (B''') Right pulmonary nodules.

Discussion

In this series, CDX2 functioned not only as a marker of enteric differentiation but also as a clinically actionable biomarker that informed therapy across three rare, biologically distinct malignancies. In each case, diffuse strong CDX2 expression indicated an intestinal phenotype and prompted the use of fluoropyrimidine-based chemotherapy, typically reserved for colorectal cancer. All three patients achieved meaningful metabolic responses, supporting the hypothesis that CDX2 may identify tumors intrinsically sensitive to GI-type regimens regardless of anatomic origin.

These cases illustrate how CDX2 can guide treatment in settings where conventional therapeutic strategies are limited. Case 1 exemplified aggressive variant prostate cancer (AVPC), a subtype associated with poor prognosis and limited responsiveness to androgen-directed therapies. Standard systemic options for AVPC typically include platinum–taxane combinations (11), and cabazitaxel would ordinarily represent the next-line therapy after docetaxel failure (12). Instead, CDX2 positivity

suggested an alternative phenotype-driven vulnerability, and the patient achieved an exceptional and durable extracranial response to fluoropyrimidine-based therapy.

Similarly, Case 2 involved a CDX2-positive minor salivary gland adenocarcinoma, for which no universally accepted systemic standard exists. Historically, multi-agent regimens such as cyclophosphamide–doxorubicin–cisplatin achieve objective response rates in the range of 20–30% with modest durability (median 5–9 months) (13, 14). Randomized data are scarce; in one small phase II trial, vinorelbine–cisplatin improved response over vinorelbine alone but at the cost of increased toxicity (15). Against this backdrop, the marked radiologic and clinical improvement observed with fluoropyrimidine-based therapy underscores the potential value of CDX2-guided therapy selection in tumor types lacking effective systemic options.

Case 3, a recurrent intestinal-type sinonasal adenocarcinoma, further supports this concept. Systemic therapy for advanced sinonasal malignancies is not standardized and is often extrapolated from regimens used for head and neck squamous cell carcinoma, including pembrolizumab-based combinations (16) and platinum doublets frequently incorporating a taxane (17). This patient progressed rapidly on pembrolizumab but experienced a pronounced metabolic response and symptomatic improvement with a histology-driven, fluoropyrimidine-based approach. Such responses reinforce the notion that CDX2 positivity reflects a biologic program more aligned with intestinal epithelium than with head and neck carcinoma.

A unifying conceptual model emerges from these findings: CDX2 expression appears to mark a transcriptional program that preserves key enteric features—dampened Wnt/ β -catenin activity (18), favorable thymidylate synthase dynamics (19), and intact apoptotic signaling (20)—that collectively create a phenotype intrinsically susceptible to fluoropyrimidines, independent of tissue origin. In this framework, CDX2 functions not merely as a diagnostic marker but as a surrogate for an actionable cellular state, one that remains therapeutically meaningful even in tumors arising outside the gastrointestinal tract. This phenotype-driven vulnerability offers an important complement to genomic profiling, particularly for rare malignancies in which conventional treatment algorithms are limited or ineffective.

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