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International Journal of Histopathol Interpret

Case Report

Primary Retroperitoneal DOG-1 Positive & P16 Negative Squamous Cell Carcinoma in a Male – A Rare Case Report

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How to cite: **Ahsan N, Sharma M., Primary Retroperitoneal DOG-1 Positive & P16 Negative Squamous Cell Carcinoma in a Male – A Rare Case Report.** ***Int J Histopathol Interpret 2024; 13(2):10-16.***

DOI: ***https://doi.org/10.56501/intjhistopatholinterpret.v13i2.1145***

Received:17/07/2024 *Accepted:24/07/2024* *Web Published:27/08/2024*

Abstract

Retroperitoneal neoplasms represent a rare subset of tumors, accounting for only 0.1–0.2% of all cancers. Among them, squamous cell carcinoma (SCC) arising in the retroperitoneal cavity is exceedingly rare, with limited understanding of its pathogenesis and clinical features. Here, a case of primary retroperitoneal squamous cell carcinoma is reported in a male patient who presented with complains of abdominal pain and recurrent diarrhea. On radiological imaging, a large, heteroechoic mass with necrotic components enveloping the celiac trunk in the retroperitoneal region was noted. Histopathological assessment of a core biopsy confirmed a malignant tumor with large atypical cells in clusters with moderate to marked nuclear pleomorphism, prominent nucleoli and abundant eosinophilic to clear cytoplasm. An immunohistochemical (IHC) panel, including markers such as Epithelial Membranous Antigen (EMA), PanCK, CK7, CK20, DOG-1, CD117, β-Catenin, SOX10, CD10, SMA, S100, CEA, TTF-1, CDX2, HMB45, p16, p53, p40 and p63 was systematically conducted for further characterization. Based on the Immunohistochemical (IHC) results, a myriad of differentials were ruled out and the diagnosis of primary retroperitoneal squamous cell carcinoma with DOG1 positivity and P16 negativity was established. Based on extensive research conducted on PubMed, Scopus, and Google Scholar, it appears that this case could potentially be the first documented instance of a male patient with primary retroperitoneal squamous cell carcinoma exhibiting positive DOG1 and negative p16.

Keywords: DOG-1, P16, Immunohistochemistry, Squamous cell carcinoma (SCC), Retroperitoneum

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INTRODUCTION

Retroperitoneal neoplasms are a rare but significant subset of tumors, constituting only 0.1–0.2% of all malignancies.[1] These tumors exhibit a wide spectrum of pathologies, including both benign and malignant lesions. Among the primary retroperitoneal tumors, liposarcoma, leiomyosarcoma, and malignant fibrous histiocytoma are predominant, while the remaining masses primarily originate from the nervous system.[2] Diagnosis of these neoplasms is often challenging due to their rarity, late presentation, and complex anatomical location, often in close proximity to vital structures in the retroperitoneal space. Squamous cell carcinoma (SCC) arising in the retroperitoneal cavity is exceedingly rare, with very limited understanding of its pathogenesis and clinical features. Here, we report a case of primary retroperitoneal squamous cell carcinoma in a male patient with DOG-1 positivity and p16 negativity.

CASE REPORT

A 63-year-old male presented to the outpatient department complaining of abdominal pain and recurring diarrhoea lasting for three months. He has been a chronic smoker, with no reported history of alcohol abuse, and no notable personal or family medical history. All laboratory investigations, including hemogram, liver function tests (LFT), renal function tests (RFT), and serum electrolytes, were within normal limits. Endoscopic ultrasonography, revealed a sizable, heteroechoic mass measuring 5.2x4.1 cm with necrotic components enveloping the celiac trunk in the retroperitoneal region.

Subsequent imaging via contrast-enhanced computed tomography (CECT) of the abdomen and pelvis confirmed these findings, delineating a 5.4x5.5x4.7 cm mass in the pre-aortic retroperitoneal space, characterized by a lobulated contour. Central areas of necrosis were evident, accompanied by surrounding fat stranding. This mass demonstrated encasement of the left gastric artery, celiac trunk, and trifurcations, along with infiltration into the lesser curvature of the stomach. Further assessment via positron emission tomography (PET) CT imaging validated these findings. All other organs, including the upper aerodigestive system, salivary glands, lungs, liver, gall bladder, pancreas, spleen, kidneys, adrenal glands, small and large bowel loops, urinary bladder, and prostate, were normal.

A core biopsy was done and submitted for histopathological assessment. Histopathological examination revealed a malignant tumor characterized by large atypical cells arranged in small clusters, separated by fibrous bands. These cells displayed moderate to marked nuclear pleomorphism, prominent nucleoli and abundant eosinophilic to clear cytoplasm. Few large bizarre cells were seen along with evidence of mitotic activity (Figure 1).

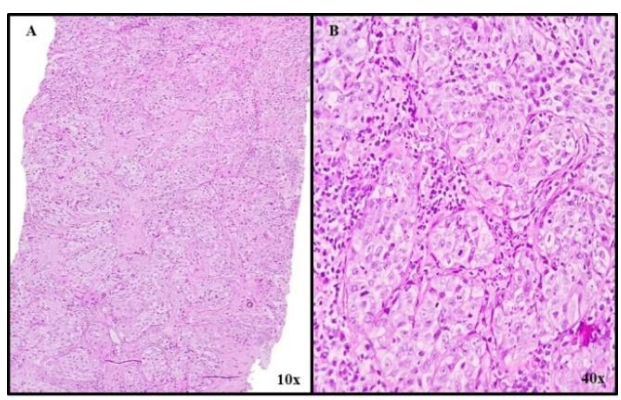

Figure 1: A Section shows atypical cells arranged in small clusters separated by fibrous bands (H&E, X100). **B** Section shows large atypical cells arranged in small clusters showing moderate to marked nuclear pleomorphism, prominent nucleoli, and abundant eosinophilic to clear cytoplasm. Mitotic activity is also noted (H&E, X400).

Based on the tumor's morphology and location, an extensive immunohistochemical (IHC) panel was systematically conducted to rule out the possibility of metastatic disease, assessing markers like Epithelial Membranous Antigen (EMA), PanCK, CK7, CK20, DOG-1, CD117, β-Catenin, SOX10, CD10, SMA, S100, CEA, TTF-1, CDX2, HMB45, p16, p53, p40 and p63 for further characterization and differentiation. The analysis revealed strong and diffuse positivity for epithelial markers like Epithelial Membranous Antigen (EMA), PanCK, CK7 and CEA suggesting an epithelial origin of the tumor (Figure 2). Since CEA was positive, immunohistochemistry for CDX2, TTF-1, and CK20 were conducted, all of which yielded negative results, ruling out the possibility of metastatic adenocarcinoma. To exclude metastatic epithelioid variant of Gastrointestinal Stromal Tumor (GIST), DOG-1 and CD117 were performed. While CD117 returned negative, DOG-1 showed strong and diffuse positivity (Figure 2), suggesting a potential diagnosis of metastatic acinar/acinic cell carcinoma of the pancreas, salivary glands and breast in correlation with histomorphology.

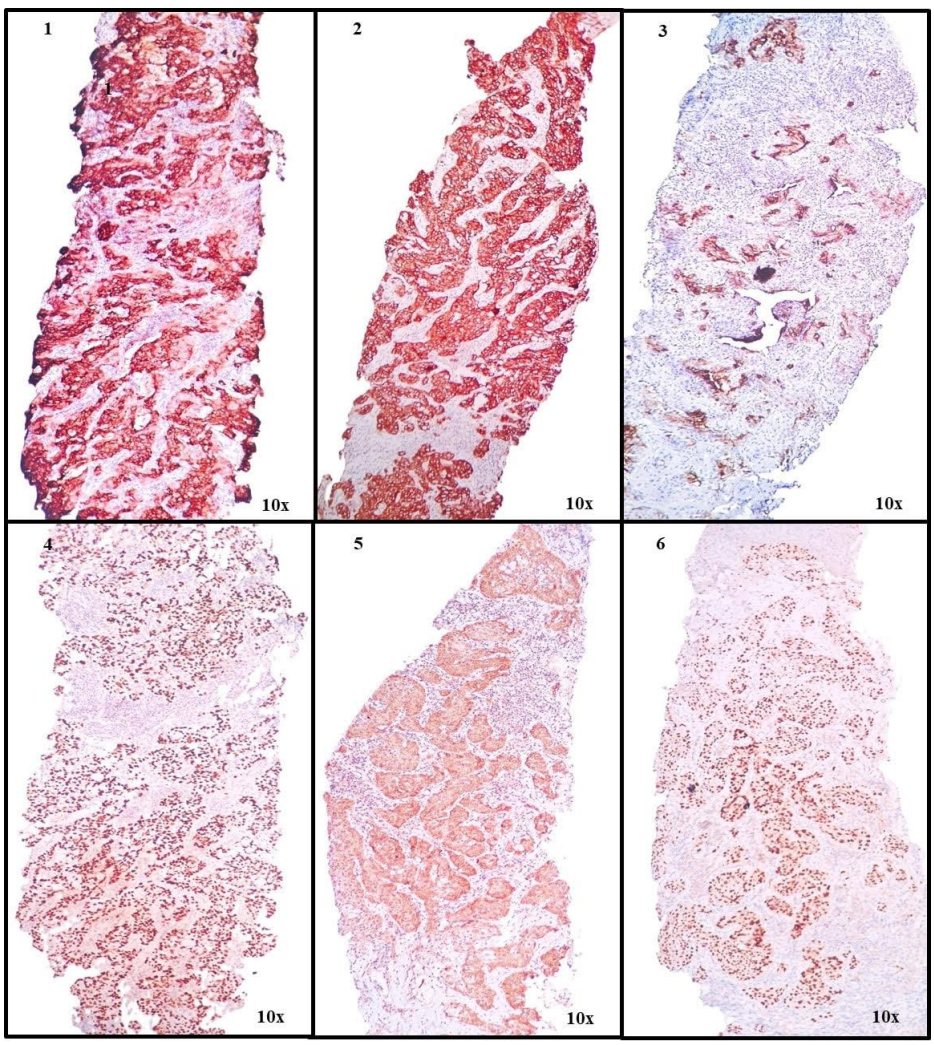

Figure 2: 1. Strong and diffuse membranous immunoreactivity for EMA (X100). **2.** Strong and diffuse membranous and cytoplasmic immunoreactivity for PanCk (X100). **3.** Focal membranous immunoreactivity for CEA (X100). **4.** Strong and diffuse membranous and cytoplasmic immunoreactivity for DOG-1 (X100). **5.** P40 shows Strong and diffuse nuclear immunoreactivity for P40 (X100). **6.** P63 shows Strong and diffuse nuclear immunoreactivity for P63 (X100).

Nevertheless, these possibilities were effectively ruled out by negative results of β-Catenin for pancreas, negative SOX10 for metastatic acinic cell carcinoma of the salivary glands and negative S100 for metastatic acinic cell carcinoma of the breast. Additionally, Chromophobe Renal Cell Carcinoma (RCC) was also contemplated due to similarities in histopathological features, but the absence of strong and membranous CD117 staining, along with negative CD10, contradicted this hypothesis. Given the tumour's retroperitoneal location, paraganglioma was ruled out, due to the absence of S100 positivity, and HMB45 staining to rule out Melanoma yielded negative results (Figure 3).

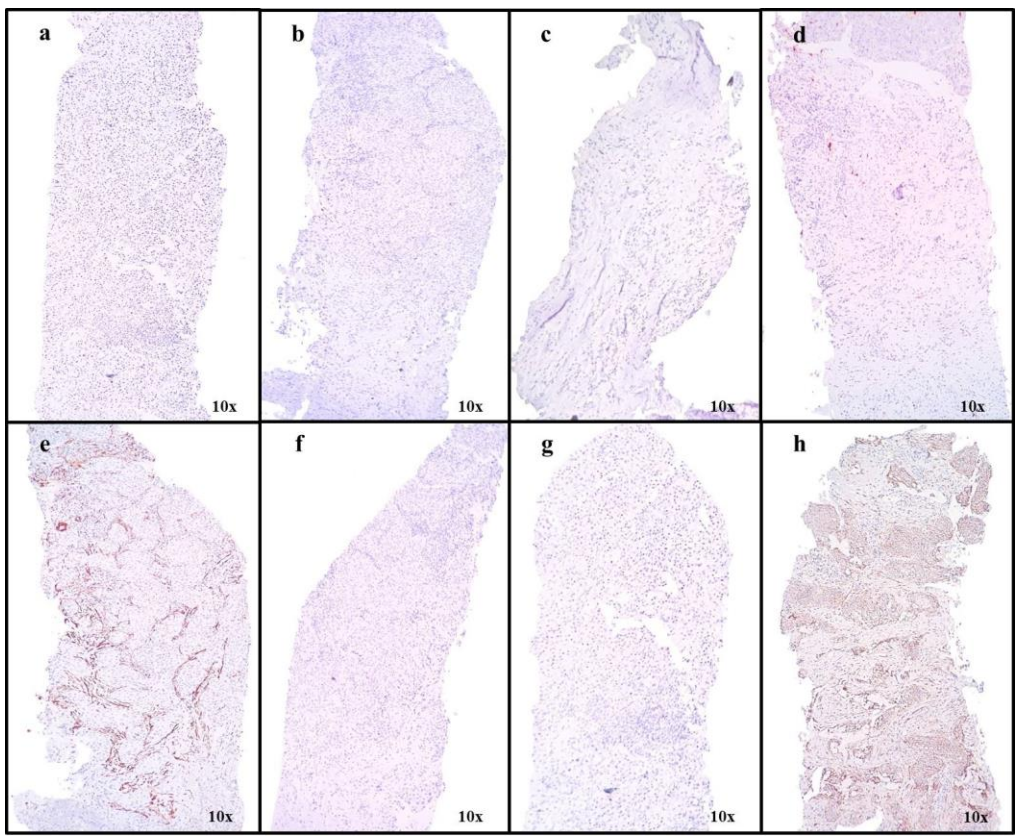

Figure 3: a. Tumor cells negative for P16 (X100). **b.** Tumor cells negative for CD117 (X100). **c.** Tumor cells negative for SOX10 (X100). **d.** Tumor cells negative for S100 (X100). **e.** Tumor cells negative for SMA (X100). **f.** Tumor cells negative for HMB45 (X100). **g.** Tumor cells negative for CD10 (X100). **h.**Tumor cells negative for β- catenin (nuclear immunoreactivity is considered positive) (X100).

Additionally, the positive expression of p40 and p63 (Figure 2), which are markers of squamous differentiation, indicated a tumor of squamous origin. Therefore, a diagnosis of retroperitoneal squamous cell carcinoma with DOG-1 positivity was offered. Considering the rarity of primary retroperitoneal squamous cell carcinoma, especially in males, the possibility of metastasis from oesophagus, and head and neck regions were also considered but ruled out based on negative contrast-enhanced computed tomography (CECT) and positron emission tomography (PET CT) reports. P16 was negative, ruling out HPV-associated squamous cell carcinoma, and p53 was normal. In light of these findings, the diagnosis was confidently established as a primary squamous cell carcinoma of the retroperitoneum with DOG-1 positivity and P16 negativity.

DISCUSSION

Squamous cell carcinoma (SCC) is an epithelial malignancy occurring in organs usually lined by squamous epithelium such as the skin, mouth, lips, esophagus, lungs, vagina, cervix, urinary tract and prostate.[3] SCC of the retroperitoneum is exceptionally rare, with only 14 cases reported so far, most originating in the pelvis.[4] Notably, all reported cases have been female. This case marks the first reported instance of a male presenting with primary retroperitoneal squamous cell carcinoma. While several causative factors contribute to squamous cell carcinoma (SCC), prominent ones include smoking, alcohol consumption, and HPV-16 infection, the latter is particularly significant in retroperitoneal squamous cell carcinoma, often indicating a favorable prognosis,[5] which was absent in this case. Yu Matsuzaka et al.'s[6] study on seven patients with primary retroperitoneal squamous cell carcinoma demonstrated that all five cases tested for p16 were positive. In contrast, our study showed a deviation from this trend, with p16 testing returning negative results indicating a poor prognosis. TP53, a key tumor suppressor gene in humans, is activated under stress conditions to safeguard genomic integrity. Despite its prevalence in all major squamous cell carcinomas (SCCs), TP53 mutations have not been associated with SCC aggressiveness.[7] The normal TP53 test result in this case indicates an absence of mutation, indicating a favorable outcome.

Most patients with retroperitoneal tumors present with abdominal swelling, early satiety, discomfort, and a palpable mass. Symptoms are vague and emerge late due to compression of retroperitoneal structures.[8] Cross-sectional imaging, including computed tomography (CT) and magnetic resonance imaging (MRI), has revolutionized the evaluation of retroperitoneal neoplasms, aiding in characterization, assessing extent, and planning treatment.[9] While imaging features can help differentiate between different entities, histological confirmation is necessary due to overlap in features and grading.

Upon histological examination and immunohistochemical analysis, several potential differentials were evaluated. Initially, a standard immunohistochemistry panel was conducted, revealing positive results for EMA, PanCK, CK7, and CEA, indicative of an epithelial-origin tumor. Given the prevalence of metastatic adenocarcinoma in the retroperitoneum and the positive CEA result; subsequent testing for CDX2, TTF1, and CK20 was carried out, all returning negative results.

The histomorphologic pattern prompted consideration of the epithelioid variant of Gastrointestinal Stromal Tumors (GIST). However, subsequent testing with DOG1 and CD117 revealed strong positivity for DOG1 and negativity for CD117, leading to its exclusion. Attention then shifted to tumors with similar histomorphology, location, and positive immunohistochemistry for EMA, PanCK, and DOG1, such as acinar/acinic cell carcinoma of the pancreas, salivary gland, and breast. Tests were conducted to rule out the possibility of pleomorphic acinar cell carcinoma of the pancreas, with negative results for β-Catenin. Subsequent negative results for SOX10 along with a positive p63 ruled out the likelihood of metastatic acinic cell carcinoma from the salivary glands. Furthermore, a negative result for S100 excluded the possibility of metastatic acinic cell carcinoma originating from the breast.

Additionally, metastatic chromophobe renal cell carcinoma was also considered due to histological similarities and positivity for EMA, CK7 and DOG1 but was excluded due to negative CD117 and CD10. Paraganglioma was contemplated based on the location, along with clustering of large cells with abundant eosinophilic cytoplasm and prominent nucleoli but was dismissed due to negative S100. The strong positivity for p40 and p63, markers associated with squamous differentiation and myoepithelial cells, suggested the possibility of Epithelial-Myoepithelial carcinoma. The support for this consideration lies in the strong positivity for EMA, DOG-1, p63, p40 all of which were observed in this case. However, the absence of SMA and S100, along with discrepancies in site and histomorphology, deterred further consideration of this diagnosis.

Eventually, based on histology along with the extensive immunohistochemistry panel and the location of the tumor, the diagnosis of primary retroperitoneal squamous cell carcinoma with DOG-1 positivity and P16 negativity was established. A study conducted by Jansen et al.[10] concluded that DOG1 can be highly expressed in a variety of tumor types. Besides GIST, which exhibited the highest DOG1 expression, high frequencies of DOG1 were also found in 11 additional tumor categories, such as squamous cell carcinomas and adenocarcinomas of the esophagus, pancreatic adenocarcinomas, squamous cell carcinomas of the oral cavity and vulva, endometroid carcinomas of the endometrium, adenomas and adenocarcinomas of the colorectum, and basal cell adenomas of the salivary gland. Notably, the study also highlighted that high-level DOG1 expression was associated with the absence of HPV infection in squamous cell carcinomas as seen in the indexed case, indicating a potential role in prognosis. Another study done by Fiorentino et al. [11] indicated that high expression of DOG-1 correlated with an unfavorable prognosis, increased tumor aggressiveness, and the occurrence of distant metastasis.

CONCLUSION

In summary, this case presents a rare instance of Primary Retroperitoneal Squamous Cell Carcinoma with DOG-1 positivity and p16 negativity in a male patient. Histological and immunohistochemical analyses are essential in establishing a definitive diagnosis in cases of retroperitoneal neoplasms. Further research is warranted to better understand the prognostic implications of DOG1 expression and non-HPV association in squamous cell carcinomas, particularly in rare anatomical locations such as the retroperitoneum.

Acknowledgement:
We gratefully acknowledge Mr. Subrata Das and Mr. Nilotpal Naskar for their prompt slide preparation and adept execution of IHC staining.

Financial support and sponsorship:
Nil

Conflicts of interest
There are no conflicts of interest

REFERENCES

1. Neville A, Herts BR. CT Characteristics of Primary Retroperitoneal Neoplasms. Critical Reviews in Computed Tomography. 2004; 45(4):247–70. DOI: 10.3109/10408370490506616. https://pubmed.ncbi.nlm.nih.gov/15554383/
2. Rajiah P, Sinha R, Cuevas C, Dubinsky TJ, Bush WH, Kolokythas O. Imaging of Uncommon Retroperitoneal Masses. Radiographics. 2011; 31(4):949–76. DOI: 10.1148/rg.314095132. https://pubmed.ncbi.nlm.nih.gov/21768233/
3. Yan W, Wistuba II, Emmert-Buck MR, Erickson HS. Squamous Cell Carcinoma - Similarities and Differences among Anatomical Sites. Am. J. Cancer Res 2011;1(3):275–300. DOI:10.1158/1538-7445.am2011-275. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3175764/
4. Pandey A, Kumar D, Gupta P, Khosla D, Periasamy K, Kapoor R. Primary retroperitoneal squamous cell carcinoma: a literature review. J . Cancer Res Clin Oncol. 2023; 149(13):12507-12512. DOI: 10.1007/s00432-023-04969-8. https://pubmed.ncbi.nlm.nih.gov/37353604/
5. Isbell A, Fields EC. Three cases of women with HPV-related squamous cell carcinoma of unknown primary in the pelvis and retroperitoneum: A case series. Gynecol. Oncol. Rep. 2016 Apr; 16:5–8. DOI: 10.1016/j.gore.2016.01.005. https://pubmed.ncbi.nlm.nih.gov/27331126/

6. Matsuzaka Y, Yamaguchi K, Koki Moriyoshi, Takao Y, Kenji Takakura, Konishi I. Primary retroperitoneal squamous cell carcinoma: a case report with review of the literature. Int. Canc. Conf.J.2019;8(2):61–5.DOI:10.1007/s13691-018-00354-2 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6498350/
7. Zhou G, Liu Z, Myers JN. TP53 Mutations in Head and Neck Squamous Cell Carcinoma and Their Impact on Disease Progression and Treatment Response. J. Cell. Biochem. 2016;117(12):2682–92. DOI: 10.1002/jcb.25592 https://pubmed.ncbi.nlm.nih.gov/27166782/
8. Wee-Stekly WW, Mueller MD. Retroperitoneal Tumors in the Pelvis: A Diagnostic Challenge in Gynecology. Front. Surg. 2014;1:7-9. DOI: 10.3389/fsurg.2014.00049 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4286971/
9. Brennan C, Kajal D, Khalili K, Ghai S. Solid malignant retroperitoneal masses—a pictorial review. Insights Imaging. 2014; 5(1):53–65. DOI: 10.1007/s13244-013-0294-0. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3948907/
10. Jansen K, Farahi N, Büscheck F, Lennartz M, Luebke AM, Burandt E, et al. DOG1 expression is common in human tumors: A tissue microarray study on more than 15,000 tissue samples. JPRP. 2021; 228:153663. DOI: 10.1016/j.prp.2021.153663 https://pubmed.ncbi.nlm.nih.gov/34717148/
11. Fiorentino V, Patrizia Straccia, Tralongo P, Musarra T, Pierconti F, Martini M, et al. DOG1 as an Immunohistochemical Marker of Acinic Cell Carcinoma: A Systematic Review and Meta-Analysis. Int. J. Mol. Sci. 2022 Aug 26;23(17):9711–1. DOI: 10.3390/ijms23179711 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9456024/

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