Papillary cystadenocarcinomas (PCAs) are rare low-grade salivary gland tumors historically characterized by cystic structures with frequent papillary projections, and lined by cuboidal, columnar, or mucus-secreting cells. This entity was first included in the World Health Organization (WHO) classification in 1991, and further reclassified as cystadenocarcinoma in 2005. In the more recent 2017 classification, cystadenocarcinoma and mucinous adenocarcinoma have become diagnoses of exclusion and are lumped under adenocarcinoma, not otherwise specified (NOS). Such revisions in classifications and potential confusion are further confounded by historical synonyms, including mucous-producing adenopapillary carcinoma, low-grade papillary adenocarcinoma, and malignant papillary cystadenoma.

While classically regarded as a low-grade malignancy, PCAs with clinically and histologically high-grade features have been reported, reflecting the often-underrecognized morphological diversity of this entity. An association with lymph node metastases and recurrence may exist. We present an intermediate-grade PCA case with hopes of increasing recognition of the rare possibility of high-grade features in an often-regarded low-grade malignancy.

**CASE REPORT**
A 51-year old male presented with progressive right facial fullness that had developed over four years with recent facial pain and serosanguinous drainage. Systems review was negative for fever, fatigue, weight loss, or facial weakness. There was no history of trauma or radiation. Physical examination was notable for a palpable 4 cm right parotid mass. Cranial nerve VII was intact bilaterally and there were no palpable lymph nodes.
Contrast-enhanced computed tomography of the neck demonstrated a 3.3 × 2.8 × 3.2 cm peripherally enhancing cystic and solid mass with enhancement of the periphery and internal septa located in the superficial lobe of the right parotid gland (Figure 1). The patient received a right superficial parotidectomy and selective right neck dissection involving the level II and III lymph nodes.

Gross pathology demonstrated a unilocular cystic mass (Figure 2). Histopathology demonstrated a large cyst lined by either papillary projections or a single layer of cuboidal cells with mild to moderate atypia and surrounding solid tumor nests with focal cribriform pattern (Figure 3a–c). No mitosis or necrosis was identified. A focus of lymphovascular invasion (Figure 3d) and multiple foci of stromal invasion (Figure 3b) were noted. Perineural invasion was not identified. There were two foci of invasion into the subcutaneous fibroadipose tissue (Figure 3e). One of 12 nodes was positive for metastatic carcinoma without extranodal extension (Figure 3f). We rendered a diagnosis of intermediate-grade PCA in agreement with two additional pathologists.
PCA was first included in the 1991 WHO classification scheme of salivary gland neoplasms and was lumped under the category of adenocarcinoma, NOS in the more recent 2017 WHO classification. Papillary was dropped from the name in the 2005 WHO classification, as the intracystic papillary projections were not always a prominent feature. The Armed Forces Institute of Pathology originally described PCA as demonstrating prominent cystic features and frequent papillary growth that otherwise lacked features of cystic variants of more common salivary gland malignancies. It is often considered the malignant counterpart to the non-Warthin benign cystadenoma, and given the former’s bland nuclear features and lack of atypia, histological differentiation from cystadenoma may often be challenging and largely depends on identifying stromal invasion.

The rare incidence, terminological revisions, and challenging histological differentiation contribute to the often poorly characterized nature and limited understanding of PCA. The largest study of PCAs was published in a series of 57 cases. All tumors demonstrated cystic components and stromal invasion, and approximately 75% of cases demonstrated intraluminal cystic papillary projections. Most cases demonstrated minimal atypia and low mitotic rate (0-1/10 high power field (hpf)), consistent with low-grade features. Of the parotid gland cases, lymph node metastasis was rarely observed and only seen in one case. The tumor in our case demonstrated stromal invasion and predominantly mild with focal moderate nuclear pleomorphism cytologically. The presence of regional lymph node metastasis in our case may have been related to the higher-grade histological features, such as the extra-parenchymal subcutaneous tissue and lymphovascular invasion, which were similarly observed in another case. Moreover, while most cases have been considered low-grade, scattered reports of clinically aggressive

**DISCUSSION**

**Figure 3:** (a) The tumor consisted of predominantly a large cystic space lined by either papillary projections or a single layer of cuboidal cells and surrounding tumor nests (hematoxylin and eosin (H&E) stain, magnification = 2 ×). (b) Infiltrative growth of tumor nests of varying sizes into the fibrotic stroma with hemorrhage (H&E, magnification = 10 ×). (c) Intracystic papillary projections with fibrovascular cores, micropapillary structures without a fibrovascular core, and relatively solid sheets of tumor cells. Neoplastic epithelial cells (insert) demonstrate focal moderate nuclear pleomorphism with prominent nucleoli (H&E, magnification = 20 ×; insert, 40 ×). (d) A focus of tumor with lymphovascular invasion (H&E, magnification = 20 ×). (e) A focus of tumor arranged in cribriform pattern involving the subcutaneous tissue (H&E, magnification = 20 ×). (f) One lymph node positive for metastatic carcinoma with calcification (H&E, magnification = 20 ×).
and histologically high-grade features have been reported [Table 1]. Although there is no universally advocated grading system, high-grade PCAs tend to demonstrate locally aggressive features, cytologic atypia, high mitotic rate, necrosis, and the absence of papillary features [Table 2]. For example, a high-grade PCA demonstrated a mitotic rate of 15–20/10 hpf and nuclear pleomorphism, which were associated with four large metastatic lymph nodes, extranodal extension, and postoperative recurrence (albeit in a setting of not receiving adjuvant radiation therapy). Accordingly, another study classified PCAs into well- and poorly-differentiated subtypes, and observed an association between differentiation and nodal metastases and recurrence. Lastly, in the previously mentioned case series, those with moderate atypia and higher mitotic rates comprised a larger proportion of those also with lymph node metastases and recurrence.

While clinical features are neither specific nor reliable in differentiating between high- and low-grade PCAs, certain clinical findings may suggest a malignant entity, such as the presence of a painless mass, lack of tenderness and a degree of fixation to surrounding tissues on palpation, and cranial VII neuropathy. The radiological differential diagnosis of a solitary mixed cystic-solid parotid lesion is broad. Considerations include focal presentation of Sjogren syndrome, lymphoepithelial cysts, first branchial cleft cyst, Warthin's tumor, acinic cell carcinoma, mucoepidermoid carcinoma, salivary duct carcinoma, and metastatic thyroid papillary carcinoma. In most cases, imaging findings of parotid tumors are nonspecific. Low-grade malignant parotid tumors may appear deceivingly nonaggressive and well-defined. Instead, the mainstay of imaging is delineating the extent of the disease preoperatively, which includes evaluating deep or superficial lobe involvement, extraglandular invasion of adjacent structures, perineural invasion, and cervical lymph node metastases. The magnetic resonance imaging findings of an intermediate-grade PCA revealed a well-marginated, heterogeneous mass and with predominantly T1 and T2 prolongation, consistent with mixed cystic-solid components. From a histological standpoint, the extent of papillary morphology in PCA is variable. Hence, the pathological differential diagnosis can be broad, and includes salivary duct carcinoma, metastatic thyroid papillary carcinoma, mucoepidermoid carcinoma,

| Study         | Year | Country | Gland | Age | Gender | Grade | Histology | Recur | LN | Ex |
|---------------|------|---------|-------|-----|--------|-------|-----------|-------|----|----|
| Chen et al.¹³ | 1990 | China   | 16 P, 1 SM, 5 minor | 37.¹ | M:F | “Poorly-differentiated” 12/22 | High mitotic rate, pleomorphism, disorderly arranged | 8/12 | 3/12 | N/A |
| Pollett et al.¹⁰ | 1997 | Canada | Minor | 80 | M | High | High mitotic rate, pleomorphism, abnormal mitotic figures | Y | Y | Y |
| Yamada et al.¹⁴ | 2007 | Japan | SL | 67 | M | High | High mitotic rate, abnormal mitotic figures | Y | Y | N |
| Koc et al.¹¹ | 2010 | Turkey | SM | 74 | M | Intermediate | Pleomorphism, nuclear atypia | N/A | N | N |
| Khatib et al.¹² | 2016 | India | P | 55 | M | Intermediate | Perineural and lymphovascular invasion | N/A | Y | N |

Gland: salivary gland involvement; Minor: minor salivary glands; SL: sublingual gland; SM: submandibular gland; P: parotid gland; M: male; F: female; Y: yes, N: no, N/A: not available; LN: lymph node metastases; Ex: extranodal extension.

*Case series of 22 papillary cystadenocarcinomas without individual case-by-case clinical, demographic, and histopathologic findings; average age of the 22 cases within series.

| Low-grade features | High-grade features |
|--------------------|---------------------|
| Mild pleomorphism  | Marked pleomorphism |
| Low mitotic rate   | High mitotic rate   |
| Necrosis absent    | Necrosis present    |
| Lymphovascular invasion absent | Lymphovascular invasion present |
| Perineural invasion absent | Perineural invasion present |
CONCLUSION

Although PCA is considered a low-grade carcinoma, both clinically and histologically high-grade features may be seen. No universally advocated grading system exists, but high-grade PCA tends to demonstrate locally aggressive features, cytologic atypia, high mitotic rate, necrosis, and absence of papillary features. An association between histologically high-grade features and lymph node metastases and recurrence may exist, but meaningful conclusions are limited by the low number of studies in the existing literature and the low level of evidence.

References

1. Alldredge MB. Papillary cystadenocarcinoma of the salivary glands: an unusual entity. Curr Opin Otolaryngol Head Neck Surg 2005;13(6):532-535.
2. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
3. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: review of the literature and clinicopathologic features. Cancer 1998 Oct 15;83(8):1661-1666.
4. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
5. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
6. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
7. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
8. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
9. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
10. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
11. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
12. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
13. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
14. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
15. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
16. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
17. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
18. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
19. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
20. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
21. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
22. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
23. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
24. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
25. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
26. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
27. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
28. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
29. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
30. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
31. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.
32. Black LC, Hsu DT, Gnepp DR. High-grade papillary cystadenocarcinoma of the parotid gland: a clinicopathologic analysis of 22 cases. J Clin Pathol 2000 Sep;53(9):671-675.