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CASE REPORT

Ampullary adenocarcinoma with testicular metastasis: A case report with clinicopathological insights

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Abstract

Ampullary adenocarcinoma (AD) with testicular metastasis is exceptionally rare. This case report presents the clinicopathological features of a rare case of ampullary AD with testicular metastasis, confirmed by clinical history, histomorphology, and immunohistochemistry. A 63-year-old male underwent pancreaticoduodenectomy in April 2023 for obstructive jaundice and imaging findings of a bile duct space-occupying lesion. Postoperative pathology revealed moderately to poorly differentiated ampullary AD (pancreatobiliary type) with observed intravascular tumor thrombi, perineural invasion and lymph node metastasis. Fifteen months after surgery, the patient was readmitted upon presenting with a progressively enlarging right testicular mass, accompanied by discomfort and a dragging sensation. Imaging suggested metastatic potential, and radical resection of the right testis was performed. Histopathological examination of the postoperative specimen revealed multifocal AD nests infiltrating the testicular tissue. The AD components were positive for CK, CK7, CK19, CK20, and villin and negative for PLAP, inhibin-α, vimentin, MelanA, alpha-fetoprotein, glypican-3, and SALL4. In conclusion, patients with ampullary AD with testicular metastasis often present with scrotal swelling and pain. Diagnostic clues may be derived from patient age, clinical course, and imaging findings, while definitive diagnosis relies on histopathology and immunohistochemistry.

Keywords: Ampullary adenocarcinoma; Testicular metastasis; Clinicopathological features; Imaging; Immunohistochemistry

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1. Introduction

Testicular metastasis is rare due to the low temperature of the scrotum and/or the presence of the blood-testis barrier. In adults, common tumors metastasizing to the testis include leukemia, lymphoma, renal cell carcinoma, malignant melanoma, prostate cancer, lung cancer, and colorectal cancer. In children, neuroblastoma, Wilms tumor, and rhabdomyosarcoma may metastasize to the testis.[1-4] Ampullary adenocarcinoma (AD) with testicular metastasis is extremely rare,[1-4] and patients often present with scrotal swelling and pain. We herein report a case of ampullary AD with testicular metastasis and review the relevant literature to discuss its clinicopathological features.

2. Case presentation

A 63-year-old male presented with obstructive jaundice in April 2023. Imaging revealed a tumor located in the ampullary region, showing an irregular soft tissue mass in the duodenal papilla area with poorly defined borders. On arterial phase imaging, the tumor demonstrated mild to moderate heterogeneous enhancement with persistent enhancement in the delayed phase. Associated findings included intra- and extrahepatic bile duct dilation, main pancreatic duct dilation, and obstruction at the ampullary region. The tumor exhibited ill-defined margins with the pancreatic head and abnormal enhancement within the pancreatic parenchyma. The patient underwent a pancreaticoduodenectomy, and the resected specimen was submitted for histopathological examination, with final tumor classification reported as "pancreaticoduodenectomy specimen." Starting in July 2024, the patient noticed a right testicular mass without obvious cause, approximately 1.0 cm in size, hard in texture, and poorly demarcated from the testis. The patient did not experience chills, fever, testicular pain, or abnormal urethral discharge and did not pay much attention to it at the time. Later, the mass progressively enlarged with a sensation of heaviness and discomfort.

In December 2024, the patient revisited the outpatient clinic. Specialist examination revealed normal penile development, a hard mass of about 4.0 cm × 3.0 cm palpable in the right scrotum, poorly demarcated from the testis, non-tender, with no significant abnormalities in the right scrotum. Ultrasound contrast of the bilateral scrotum, testis, and spermatic vein indicated a hypoechoic area in the right testis, enlargement of the right epididymis, and a cystic mass in the right testicular tunica vaginalis. Pelvic magnetic resonance imaging revealed a nodular lesion in the right testis showing T1 low signal and T2 high signal, approximately 1.9 mm in diameter, with solid components appearing as high signal on diffusion-weighted imaging (DWI) and low signal on apparent diffusion coefficient (ADC). Post-contrast imaging showed heterogeneous marked enhancement with non-enhancing necrotic areas (Figure 1A), suggestive of metastasis. A round-like T1 and T2 high-signal focus was observed in the right epididymal region, about 17 mm in length, with marginal enhancement post-contrast, suggestive of a hemorrhagic cystic lesion. Biochemical tests for four reproductive tumor markers, which were alpha-fetoprotein (AFP), human epididymis protein 4, cancer antigen 125, and beta-human chorionic gonadotropin (β-HCG), were all within normal ranges. The patient was admitted to the hospital with a preliminary diagnosis of right testicular tumor and underwent a radical

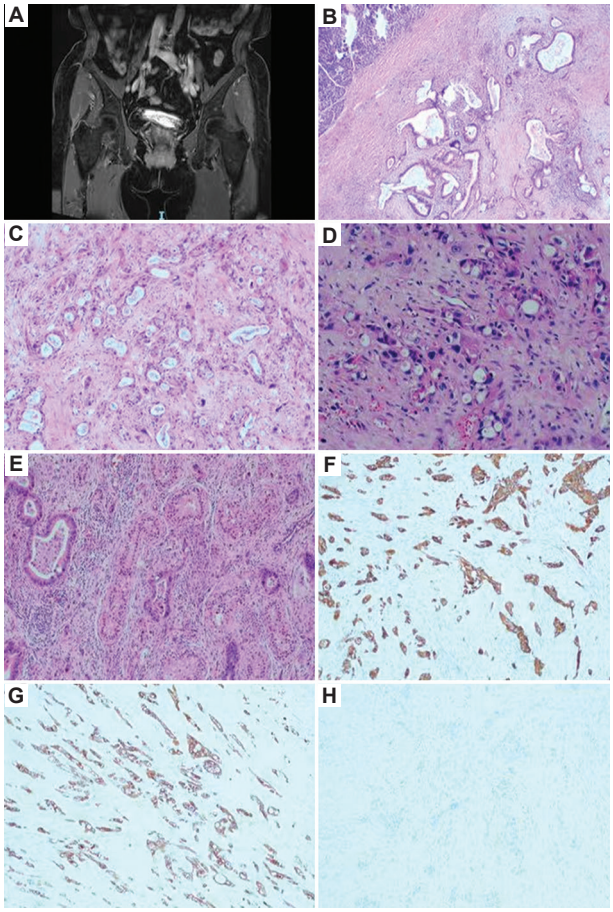

Figure 1. Pathological images of the patient. (A) Pelvic magnetic resonance imaging indicating a mass observed in the right testicle, showing low T1 signal and high T2 signal. The solid component exhibits high signal on DWI with low ADC values. Heterogeneous significant enhancement is seen after contrast administration, with necrotic non-enhancing areas visible. (B) Histopathological image of primary tumor in the ampulla showing moderately to poorly differentiated adenocarcinoma. The tumor is arranged in relatively small glandular structures, with or without branching, and shows a prominent stromal reaction. The upper left corner of the image shows pancreatic tissue (HE, medium magnification). (C) Histopathological image showing testicular tumor arranged in relatively small glandular structures, with or without branching, accompanied by a prominent stromal reaction (HE, high magnification). (D) Histopathological image showing testicular tumor cells arranged in single or stratified layers of cuboidal to low columnar epithelium, with some cells exhibiting marked atypia (HE, high magnification). (E) Histopathological image showing testicular tumor cells replacing seminiferous tubules, presenting a "destructive pattern" (HE, high magnification). (F) Immunohistochemistry image showing testicular tumor cells positive for CK7 (EnVision method, high magnification). (G) Immunohistochemistry image showing testicular tumor cells positive for CK19 (EnVision method, high magnification). (H) Immunohistochemistry image showing testicular tumor cells negative for SALL4 (EnVision method, high magnification).
Abbreviations: DWI: Diffusion-weighted imaging; ADC: Apparent diffusion coefficient; HE: Hematoxylin and eosin; CK7: cytokeratin 7; CK19: cytokeratin 19; SALL4: Sal-like protein 4.

right orchiectomy. Postoperatively, the "radical right orchiectomy specimen" was sent for examination.

In April 2023, the patient's "pancreaticoduodenectomy specimen" consisted of partial gastric tissue (5.5 cm × 4.0 cm × 3.0 cm), duodenum (10.0 cm in length, maximum diameter 2.0 cm), pancreas (6.0 cm × 2.5 cm × 2.0 cm; cut surface gray-yellow, medium consistency), and common bile duct (4.0 cm in length, circumference 3.5 cm). The main pancreatic duct was dilated, with a maximal diameter of 4.0 cm. A gray-white tumor measuring 3.0 cm × 2.0 cm × 1.0 cm was observed in the duodenal papilla region, displaying a gray-white, firm cut surface with ill-defined borders, invading the full thickness of the duodenal wall and pancreatic parenchyma. One lymph node was detected near the duodenum (maximum diameter 1.2 cm) and one near the pancreas (maximum diameter 1.0 cm). Additional lymph nodes submitted included five from the celiac trunk, one from the first hepatic hilum, and one from the hepatic artery. Microscopically, the ampulla harbored a moderately to poorly differentiated AD of pancreatobiliary type (Figure 1B). The carcinoma infiltrated the full thickness of the duodenal wall and pancreatic parenchyma, with observed perineural invasion and intravascular tumor thrombi. The two lymph nodes detected near the duodenum and pancreas showed no metastatic carcinoma (0/2). As for the submitted lymph nodes, all five celiac trunk lymph nodes showed no metastatic carcinoma, one of two first hepatic hilum lymph nodes contained metastatic carcinoma, and the hepatic artery lymph node showed carcinoma involvement within fibroconnective adipose tissue. The pathological tumor staging at that time was pT3bN1Mx.

In December 2024, a specimen of the patient's radically resected right testis was obtained, measuring 6.0 cm × 3.0 cm × 3.0 cm, with a smooth surface and intact capsule. The cut surface revealed a gray-white tumor (2.5 cm × 2.0 cm × 2.0 cm) adjacent to a cystic cavity (2.0 cm × 2.0 cm × 2.0 cm) containing gray-brown gelatinous material, with no clear epididymal structure observed. The spermatic cord measured 1.8 cm in length, with a stump diameter of 0.2 cm. Microscopic examination demonstrated tumor arranged in relatively small glandular lumens, with or without branching, accompanied by a prominent stromal reaction (Figure 1C). Tumor cells were single-layered or stratified, cuboidal to low columnar, with some cells exhibiting significant atypia (Figure 1D). Cytoplasm was relatively eosinophilic and nuclei were round. Tumor cells replaced the seminiferous tubules, presenting a "destructive pattern" of infiltration (Figure 1E).

In the AD component of the patient's pancreaticoduodenectomy specimen, immunohistochemical analysis revealed positive expressions of cytokeratin 7 (CK7), cytokeratin 20 (CK20), mucin 1, and mucin 5AC, while CDX2 and mucin 2 were negative. In the right testicular radical resection specimen, the AD component showed positive expressions for creatine kinase (CK), CK7 (Figure 1F), CK19 (Figure 1G), CK20, and villin, while placental-like alkaline phosphatase (PLAP), inhibin-α, vimentin, MelanA, AFP, glypican-3, and Sal-like protein 4 (SALL4) (Figure 1H) were negative.

3. Discussion

Ampullary AD is a relatively rare malignant tumor of the digestive tract, accounting for approximately 0.2% of gastrointestinal malignancies. The majority of ampullary carcinomas are classified as ADs.[5] The ampulla of Vater is the junction of the main pancreatic duct and the distal common bile duct, surrounded by the pancreatic head and duodenal tissues. Ampullary AD can arise from either the intestinal epithelium or the epithelium covering the pancreatobiliary ducts, thus comprising two histological subtypes: intestinal type and pancreatobiliary type.[6] According to literature, the prognosis of these two subtypes differs significantly—the median survival for intestinal-type ampullary AD is 115.5 months, whereas that for pancreatobiliary-type ampullary AD is only 16 months (p<0.001). Therefore, accurate pathological subtyping is crucial for predicting prognosis and guiding clinical treatment.[7] In this case, the histological morphology of the ampullary tumor was consistent with pancreatobiliary-type ampullary AD, and synchronous lymph node metastasis was observed, suggesting a potentially poor prognosis for this patient.

Metastasis of advanced ampullary AD is common, but testicular metastasis of ampullary AD is considered extremely rare, with only two cases reported globally to date.[8,9] In total, fewer than 30 cases of ampullary AD or pancreatic ductal AD with testicular metastasis have been documented in the literature.[10-13] The most recent case of ampullary AD with testicular metastasis was reported by Lane *et al.*[9] in 2014. The patient was a 70-year-old man who initially presented with abdominal pain and chills. He underwent endoscopic retrograde cholangiopancreatography with biliary stent placement and brush cytology, which revealed AD. Laboratory tests also showed elevated cancer antigen 19-9. The patient subsequently underwent pancreaticoduodenectomy, with postoperative pathology confirming ampullary AD and lymph node metastasis. He received adjuvant chemotherapy and radiotherapy. Twenty-one months postoperatively, he returned with a right inguinal mass. Computed tomography imaging revealed free fluid in the right inguinal canal, prompting right hydrocele repair and excision of a non-communicating encapsulated cyst of the

spermatic cord. Although no gross evidence of metastatic tumor was found in the cyst, microscopic examination identified a moderately differentiated AD histologically identical to the primary ampullary AD, leading to a final diagnosis of ampullary AD with testicular metastasis. The ampullary AD case with testicular metastasis reported here shares similarities with Lane *et al.*'s case[9] but also exhibits differences—our case not only showed that the microscopic AD resembles the primary ampullary AD but also has a grossly visible mass, consistently characteristic of the typical ampullary AD.

In 2021, Zhang *et al.*[13] reviewed ampullary AD and pancreatic ductal AD cases with testicular metastasis reported over the past 40 years. Their study revealed that the typical presentation was a slowly enlarging, painless or painful palpable mass, with no specific gastrointestinal symptoms. Metastasis occurred with equal frequency in the left and right testes. In their cohort, the average diameter of metastatic tumors was 3.6 cm (range: 1.6–6.5 cm), and pancreatic ductal AD originating from the pancreatic tail was most likely to metastasize to the testes. Table 1 summarizes the clinical data of pancreatic ductal AD patients with testicular metastasis reported in the past decade. Although our case involved ampullary AD with testicular metastasis, it shared similarities with pancreatic ductal AD cases in terms of patient age and clinical presentation.

In terms of diagnosis and differential diagnosis, clinically, there are no specific distinguishing features between primary and secondary testicular tumors. Both can present with local pain, tenderness, and swelling. Additionally, serum markers such as AFP and β-HCG have some significance in differentiating primary from secondary testicular tumors.[13] Taylor *et al.*[14] reported a case of pancreatic ductal AD with testicular metastasis accompanied by a significant increase in β-HCG levels (serum β-HCG levels were 10 times higher). The patient was 77 years old, so in this case, the elevated β-HCG levels supported the diagnosis of a secondary rather than a primary testicular tumor. In fact, patient age is more meaningful than serum markers in distinguishing primary from secondary testicular tumors. Zhang *et al.*[13] found that primary testicular tumors typically occur in patients aged 30–40, while the incidence of secondary testicular tumors peaks between 50 and 60, with an average age of onset at 59. For elderly patients presenting with testicular enlargement, the possibility of a secondary testicular tumor should be considered.

Pathological examination is the gold standard for distinguishing primary from secondary testicular tumors. The presence of tumor thrombi in the vasculature of the testicular parenchyma supports the diagnosis of a secondary tumor. According to García-González *et al.*,[15] secondary testicular tumors microscopically exhibit destructive and/or interstitial patterns. The destructive pattern is characterized by sheets of malignant cells replacing the seminiferous tubules, while the interstitial pattern shows tumor cells located in the stroma without involving the seminiferous tubules. The histological pattern in this case was consistent with the destructive pattern.

Today, immunohistochemistry is considered the most sensitive and specific method for determining the origin of a tumor. Testicular metastases from AD must be differentiated from primary testicular tumors such as germ cell tumors and malignant mesothelioma. Seminoma, the most common germ cell tumor of the testis, expresses PLAP, OCT3/4, SALL4, and SOX7. Embryonal carcinoma is positive for CK, CD30, PLAP, SALL4, and AE1/AE3.

Table 1. Reported cases of pancreatic ductal adenocarcinoma metastasizing to testis in literature over the past 10 years

References	Patient age	Symptoms	Duration of symptoms	Metastatic sites	Primary tumor location	Treatment	Prognosis
Kim *et al.*[10]	69 years old	Scrotal swelling, pain	-	Tunica vaginalis, liver, peritoneum, omentum	Pancreatic tail	Hydrocelectomy+gemcitabine chemotherapy	-
Hou *et al.*[11]	65 years old	Scrotal swelling, pain	9 months	Left testis, right lung	Pancreatic body	Radical orchiectomy+pancreatic mass resection+right lung tumor biopsy	Alive at 9-month follow-up
Yu *et al.*[12]	50 years old	Scrotal swelling, pain	-	Testis, epididymis, spermatic cord	Pancreatic tail	Ultrasound-guided fine needle aspiration (FNA) of pancreatic tumor+radical orchiectomy+chemotherapy	Alive at 4-month follow-up
Cormio *et al.*[3]	36 years old	Scrotal swelling, pain	21 months	Right testis, liver	Pancreatic tail	Radical orchiectomy+chemotherapy	Died 3 months later
Zhang *et al.*[13]	65 years old	Scrotal swelling, pain	1 month	Tunica vaginalis, testis, liver, omentum, retroperitoneum	Pancreatic tail	Radical orchiectomy	Died 3 months later

Note: "-" indicates no available data.

Yolk sac tumor expresses AFP and glypican-3, while testicular choriocarcinoma expresses β-HCG, CK, PLAP, and inhibin-α. Testicular malignant mesothelioma is a rare tumor arising from the tunica vaginalis or albuginea. Although it also predominantly affects elderly men (55–75 years) and presents with scrotal swelling and pain, it expresses D2-40, Wilms tumor 1, calretinin, CK5/6, epithelial membrane antigen, and vimentin. According to literature reports, testicular metastases from ampullary AD express CK7 and CK20 but are negative for PLAP, AFP, β-HCG, calretinin, and inhibin.[5] The immunohistochemical profile of the AD cells in this case was consistent with these reports.

In this case, determining whether the testicular tumor was primary or metastatic involved several considerations. First, the testicular tumor and ampullary AD had similar histomorphological features, both exhibiting tubular or glandular patterns with abundant intravascular tumor thrombi and perineural invasion. Second, their immunophenotypes were identical: the testicular tumor expressed CK7 and CK19 but not PLAP, inhibin-α, vimentin, MelanA, AFP, glypican-3, or SALL4. Therefore, based on the patient's age, disease sequence, imaging findings, and pathological results, we concluded that the testicular tumor was not a concurrent primary tumor but rather a metastasis from the ampullary AD.

Regarding pathogenesis, the routes by which primary tumors metastasize to the testis may include retrograde arterial or venous embolism, retrograde lymphatic spread, direct extension along the vas deferens to the epididymis, and peritoneal seeding via the tunica vaginalis.[16-18] Most scholars support retrograde lymphatic spread as the primary mechanism, though some suggest that multiple pathways may overlap,[10] collectively contributing to the development of metastatic testicular tumors. For example, in the case reported by Kim *et al.*,[10] the patient also had para-aortic lymph node metastases and multiple liver metastases. Additionally, the patient presented with a hydrocele and pain as initial symptoms and exhibited extensive peritoneal metastases. Thus, the authors speculated that lymphatic spread, hematogenous spread, and peritoneal seeding via the tunica vaginalis all contributed to tumor development in that case. In our patient, tumor thrombi were observed in the vasculature of the ampullary tumor, and concurrent metastases were found in the lymph nodes near the hepatic portal. Therefore, we speculate that retrograde arterial/venous embolism and retrograde lymphatic spread may have jointly contributed to the metastasis.

Ampullary AD with testicular metastasis, like pancreatic ductal AD, is often diagnosed at an advanced stage, with implications for both treatment and prognosis. Due to the scarcity of reported cases of ampullary AD with testicular metastasis and the lack of follow-up data after metastasis, the prognosis of such patients remains unclear. A review of pancreatic ductal AD cases with testicular metastasis revealed that most patients underwent radical orchiectomy, while some received chemotherapy with agents such as gemcitabine or capecitabine. Overall, pancreatic ductal AD patients with testicular metastasis have a poor prognosis and high mortality. Literature review shows that about two-thirds of patients died during follow-up, with fewer than 1% surviving for 5 years after diagnosis. The shortest survival period was only 2 months.[10,12] It should be noted that Lane *et al.*[9] reported a case of ampullary AD with testicular metastasis. Although no follow-up was conducted after metastasis, they provided pretreatment follow-up and treatment details: the patient received 5 weeks of adjuvant chemotherapy with capecitabine and a total of 4500cGy of radiation therapy, followed by 4 months of adjuvant gemcitabine therapy alone. However, testicular metastasis still occurred, suggesting that advanced ampullary AD has a poor prognosis and that chemotherapy may not fully alter its progression.

4. Conclusion

In summary, we report a rare case of ampullary AD (pancreatobiliary type) with testicular metastasis. In the diagnosis of ampullary carcinoma, distinguishing between intestinal and pancreatobiliary types has prognostic and therapeutic implications. For elderly patients presenting with scrotal swelling, pain, and imaging findings suggestive of a testicular mass, the possibility of metastatic ampullary AD to the testis should be considered, and pathological examination should be performed for confirmation.

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Conflict of interest

The author declares no conflict of interest.

Author contributions

This is a single-authored article.

Ethics approval and consent to participate

This study constitutes a retrospective case report and meets the criteria for ethics exemption. The institutional ethics committee does not issue corresponding ethics approval numbers.

Consent for publication

Not applicable

Availability of data

Not applicable.

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