

# Pancreatic Krukenberg Tumor of the Ovary: A Case Series

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## ABSTRACT

**Introduction:** Metastatic lesions to the ovary, also known as Krukenberg tumors, account for approximately 5–30% of ovarian neoplasms. The location of primary sites and survivability widely varies. Patients with a pancreatic primary site have lower survival rates compared to other primary sites such as colon and breast. Despite this dismal outcome, there is a paucity of data examining the pancreas as the primary site and its associated clinical, radiologic, and pathologic features. **Case Report:** Four women who presented with severe abdominal pain were found to have pancreatic cancer that metastasized to the ovary. Only one woman did not have metastasis to the ovary at time of presentation. Three of the four had bilateral ovarian involvement. One woman's mass was deemed unresectable while the other three women had cytoreductive surgery including bilateral salpingo-oophorectomy. Imaging, pathology, and tumor markers were trended over time. **Discussion:** Characteristics which may support a pancreatic origin of Krukenberg tumors include bilateral, large, multiloculated cystic ovarian masses, surface ovarian involvement, and specific immunohistochemical staining patterns. Comprehensive clinical, radiologic, and pathologic evaluation is essential as identification of pancreatic Krukenberg tumors has a significant impact on patient treatment and prognosis.

**Key words:** Krukenberg, metastasis, ovary, pancreas

## INTRODUCTION

Metastatic lesions to the ovary, also known as Krukenberg tumors, account for approximately 5–30% of ovarian neoplasms.<sup>[1–4]</sup> The most common primary sites include colon, stomach, and breast, which represent about 50–90% of secondary ovarian metastases.<sup>[3–7]</sup> Krukenberg tumors may be difficult to diagnose because they typically present similarly to a primary ovarian malignancy and unfortunately carry a poor prognosis. Overall, survival from all primary sites widely varies but has been shown to be between 5 and 52 months.<sup>[8,9]</sup> Patients with

a pancreatic primary site have lower survival rates compared to other primary sites.<sup>[9]</sup> Despite this dismal outcome, there is a paucity of data examining ovarian metastasis for which the pancreas is the primary site. Here, we report the clinical, radiologic, and pathologic features of four women with pancreatic cancer that metastasized to the ovary.

## PRESENTATION OF CASES

### Case One

The patient is a 45-year-old Hispanic female with no significant medical history who presented with severe left upper quadrant

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and epigastric pain that radiated to her back. On abdominal computed tomography (CT) and magnetic resonance imaging (MRI), she was found to have two small cystic lesions in the pancreatic head and a large mass in the pancreatic neck and proximal body, associated with obstruction of both the common bile duct and pancreatic duct [Figure 1]. Fine-needle aspiration (FNA) was confirmatory of pancreatic adenocarcinoma, and she was initially assigned a Stage IIA (T3N0M0). The mass was deemed unresectable given its encasement of vasculature.

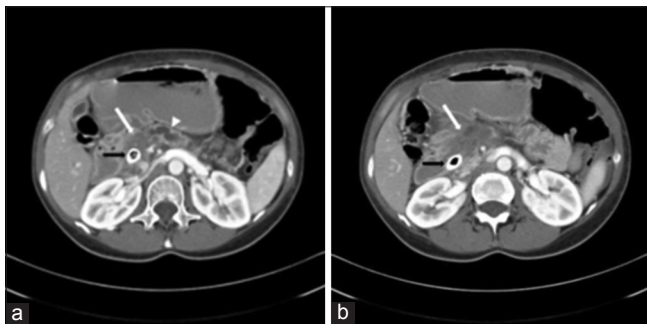
After four cycles of chemotherapy with folinic acid, fluorouracil (5-FU), irinotecan, and oxaliplatin (FOLFIRINOX), repeat imaging showed metastasis to the iliac bone and second-line chemotherapy with Gemcitabine and Abraxane was initiated. On repeat abdominal CT, 6 months after initial presentation, she was found to have further progression of disease with metastasis to the ovaries bilaterally [Figure 2]. CA 19-9 and CA-125 tumor makers were markedly elevated [Table 1]. She sought alternative therapy in the Caribbean and later enrolled in a clinical trial, but experienced progressive disease, passing away 16 months after diagnosis.

## Case Two

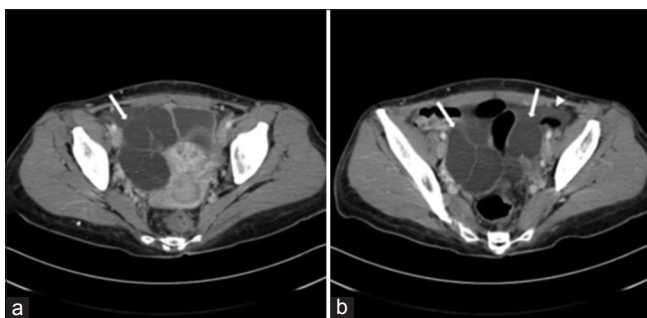
The patient is a 64-year-old female with a strong maternal family history of melanoma, pancreatic, breast, and prostate cancer, who presented with a palpable mass in the right lower

quadrant, jaundice, and abdominal pain. The patient had never undergone genetic testing. Abdominopelvic CT and MRI showed a pancreatic head and neck mass [Figure 3] obstructing the common bile duct and encasing the celiac trunk, superior mesenteric artery, and superior mesenteric vein. There was also a multilocular cystic pelvic mass [Figures 4 and 5]. CA 19-9 was normal, but CA-125 was elevated [Table 1].

She underwent diagnostic laparoscopy with laparoscopic bilateral salpingo-oophorectomy (BSO), excision of abdominal tumors, omentectomy, peritoneal stripping, aspiration of ascites, lysis of adhesions, and ureterolysis. Pathology of bilateral ovaries, omentum, and bladder showed metastatic, well-differentiated mucinous adenocarcinoma. Immunophenotypes were consistent with metastasis from the gastrointestinal tract or pancreas (positive for CK20 and CDX2 and negative for PAX8). She was diagnosed with Stage IV pancreatic adenocarcinoma. After surgery, she started chemotherapy with Abraxane but shortly thereafter, she was admitted to the intensive care unit with septic shock due to bacteremia with vascular complications. She chose to discontinue therapy and transitioned to hospice care.



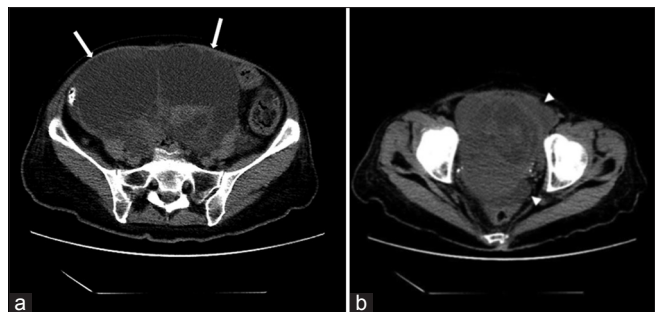
**Figure 1:** (a and b) Computed tomography of the abdomen and pelvis. Mass in the head/neck of the pancreas (white arrow) encasing the portal, superior mesenteric and splenic veins, resulting in pancreatic duct dilatation (arrowhead). Biliary stent in place (black arrow)



**Figure 2:** (a and b) Computed tomography of the abdomen and pelvis. Bilateral complex multiloculated cystic adnexal masses (white arrows) and ascites (arrowhead)



**Figure 3:** Abdominal and pelvic computed tomography. Mass in the head/neck of the pancreas (white arrow) encasing the celiac trunk (arrowhead). Biliary stent in place (black arrow)



**Figure 4:** (a and b) Abdominal and pelvic computed tomography. (a) Bilateral complex multiloculated cystic adnexal masses with solid components (white arrows) and (b) ascites (arrowheads)

**Table 1:** Demographic and clinical characteristics of patients with pancreatic Krukenberg tumors

Age at presentation	Patient 1	Patient 2	Patient 3	Patient 4
	45	64	69	54
Race	Hispanic	Unknown	Hispanic	African-American
Tobacco use	Never	Never	Never	Previous (0.5 pack year history)
Alcohol use	Socially	Socially	Socially	Four drinks per week
CA-19-9 at time of Krukenberg tumor diagnosis (reference range: <35 U/ml)	797	27	369	45,000
CA-125 at time of Krukenberg tumor diagnosis (reference range: <35 U/ml)	65	226	28	323

### Case Three

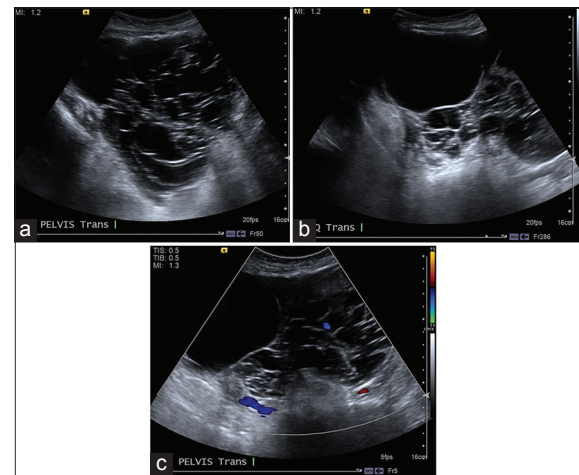
The patient is a 69-year-old Hispanic female with diabetes who presented with severe abdominal and pelvic pain. On abdominopelvic CT, she had a lesion in the pancreatic body and tail [Figure 6] and complex ovarian cysts bilaterally [Figures 7 and 8]. FNA of the pancreatic mass was showed adenocarcinoma. She was diagnosed with Stage IV pancreatic cancer.

Five days later, she underwent exploratory laparotomy, BSO, umbilical hernia repair, appendectomy, and peritoneal biopsies. Pathology of bilateral ovaries and omentum confirmed mucinous neoplasm consistent with metastatic pancreatic adenocarcinoma. Immunohistochemistry was positive for PAX8, CK7, CK20, and CDX2 and negative for ER and SMAD4. CA 19-9 was elevated and CA-125 was normal [Table 1]. She entered surveillance after completing 12 cycles of chemotherapy with FOLFIRINOX, with evidence of pancreatic tumor shrinkage on imaging and decrease of tumor marker, CA 19-9.

### Case Four

The patient is a 54-year-old African-American female who presented with abdominal pain, bloating, constipation, and hematochezia. On abdominopelvic CT, she was found to have a pancreatic mass arising from the tail, which invaded the splenic flexure of the colon, spleen, and left adrenal gland [Figure 9]. She also had omental lesions and a large 24 cm cystic mass in the right ovary with solid components and thick septations [Figure 10]. The left ovary was normal. CT-guided biopsy of the pancreatic and ovarian lesions showed moderately differentiated adenocarcinoma. CA 19-9 and CA-125 tumor markers were markedly elevated [Table 1].

She completed six cycles of FOLFIRINOX followed by one cycle of folinic acid, 5-FU, and oxaliplatin (FOLFOX), with worsening symptomatology due to the large ovarian lesion. She underwent a palliative total abdominal hysterectomy with BSO, omentectomy, and small bowel resection. Surgical pathology report confirmed the presence of metastatic



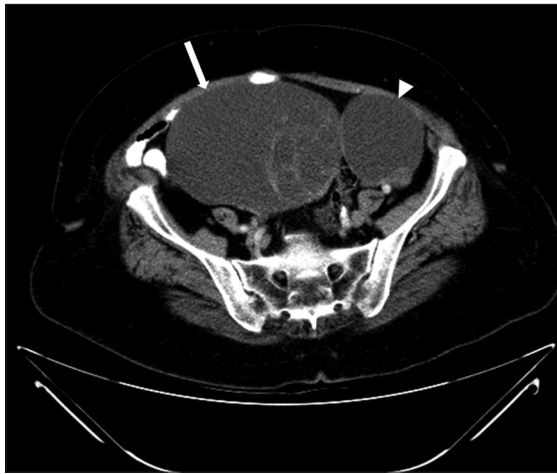
**Figure 5:** Pelvic ultrasound (a-c). (a-c) Complex multiloculated cystic mass in the pelvis, some of the loculations anechoic, others with internal echoes



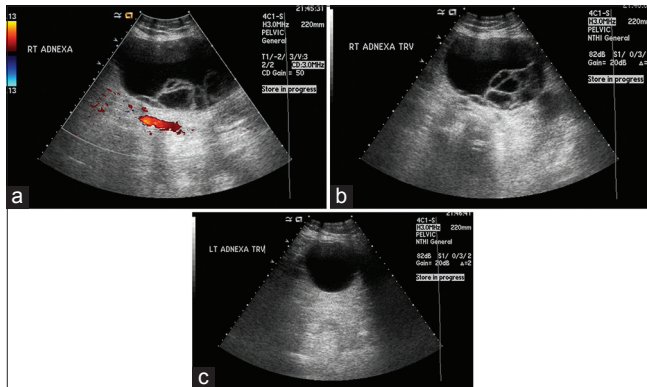
**Figure 6:** Abdominal and pelvic computed tomography. Mass in the body/tail of the pancreas (black arrow), encasing the splenic vessels (arrowheads)

pancreatic mucinous adenocarcinoma to the right ovary, omentum, and small bowel. Immunohistochemistry was positive for PAX8, CK7, and CK20 and negative for CDX2. She resumed systemic chemotherapy postoperatively.





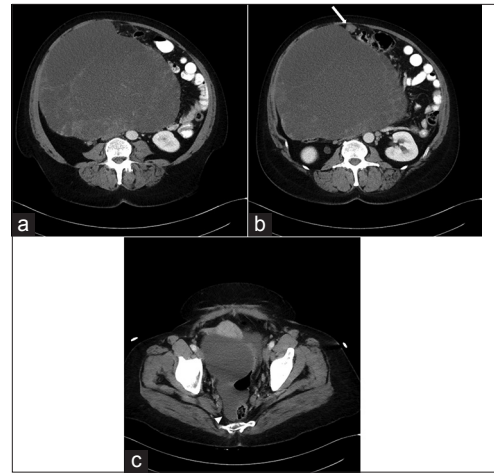
**Figure 7:** Abdominal and pelvic computed tomography. Complex multiloculated right adnexal cystic mass (white arrow) and simple cyst in the left adnexa (arrowhead)



**Figure 8:** Pelvic ultrasound (a-c). (a and b) Multiloculated complex cystic mass in the right adnexa and (c) simple cyst in the left adnexa



**Figure 9:** Abdominal and pelvic computed tomography. Mass in the tail of the pancreas (white arrow), inseparable from the spleen (black arrow), left adrenal gland and splenic flexure of the colon (arrowhead)



**Figure 10:** Abdominal and pelvic computed tomography (a-c). (a) Complex cystic right adnexal mass with thick septations and solid-enhancing components. (b) Peritoneal/omental implants (white arrow). (c) Ascites (arrowhead)

## DISCUSSION

Krukenberg tumors of pancreatic origin are rare, compared to other non-genital primary sites such as colon, stomach, and breast. Clinical diagnosis is challenging and reports have found pancreatic Krukenberg tumors at autopsy in 4–6% of patients.<sup>[4,10]</sup> In fact, most data about pancreatic metastases to the ovary are embedded in larger bodies of work with limited details.<sup>[4,7,9]</sup>

Young and Hart reported on seven patients in a series specific to metastases from pancreatic carcinoma to the ovary nearly three decades ago. All seven patients were found to have mucinous ovarian tumors interpreted as metastasis from the exocrine pancreas. In five patients, the pancreatic and ovarian tumors were found concomitantly, and in two patients, the pancreatic tumors were discovered before the ovarian tumors. In six cases, the ovarian tumors were bilateral, a finding seen in <10% of primary ovarian tumor.<sup>[11]</sup> More recently, Falchook *et al.* explored treatment approaches and survivability of 18 patients with pancreatic cancer metastatic to the ovaries. The majority of patients presented with advanced disease and 11 patients had bilateral ovarian metastasis, with a median size of 14 cm. They found that surgical intervention, versus chemotherapy alone, aided in both palliative and survivability of patients. In addition, they recognized the need for further investigation into molecular profiling of primary pancreatic cancers with ovarian metastasis to guide diagnosis and treatment.<sup>[12]</sup>

In our series, the localization of the primary pancreatic tumor varied, involving the head, neck, and proximal body of the pancreas in one patient, head and neck in one patient, body and tail in one patient, and tail in one patient. The

**Table 2:** Radiologic findings using different imaging modalities in patients with pancreatic Krukenberg tumors

Features	Patient 1	Patient 2	Patient 3	Patient 4
Location of primary pancreatic lesion	Head, neck, proximal body	Head, neck	Body, tail	Tail
Laterality of disease in ovary	Bilateral	Bilateral	Bilateral	Unilateral
Maximum size of ovarian mass (es) (cm)	Inseparable bilateral adnexa: 17×13	Large pelvic cystic mass: 17×13	Right adnexa: 14×10; left adnexa: 8×7	Right adnexa: 24×19
Timing of metastasis to ovary	6 months after presentation	At the time of presentation	At the time of presentation	At the time of presentation
Other sites of pancreatic metastasis	Iliac bone, omentum, peritoneum	Bladder, omentum	Omentum	Omentum, small bowel
Timing of metastasis to other sites	Before ovarian metastasis	At the time of ovarian metastasis	At the time of ovarian metastasis	At the time of ovarian metastasis
Ascites	Yes	Yes	No	Yes
CT features of ovarian metastasis	Bilateral adnexal complex multiloculated cystic masses	Large complex multiloculated cystic pelvic mass	Right adnexa: Complex multiloculated cystic mass; left adnexa: Simple cyst	Right adnexa: Complex multiloculated cystic mass, with solid components and septal enhancement
US features of ovarian metastasis	Not performed	Large complex multiloculated pelvic cystic mass with internal echoes and debris. No significant color Doppler signal	Right adnexa: Complex multiloculated cystic mass; no significant color Doppler signal. Left adnexa: Simple cyst	Complex multiseptated cystic mass in the pelvis; no significant color Doppler signal

ovarian metastases from pancreatic origin were bilateral in three patients and unilateral in one. They presented as either large or rapidly growing adnexal masses. CA-19-9 and CA-125 tumor markers were markedly elevated in two patients, CA-19-9 was normal in one patient, and CA-125 was normal in one patient [Table 1]. Ascites was present in three patients and absent in one. On CT, six of the total seven ovarian lesions presented as complex multiloculated cystic masses and one as a simple cyst. On ultrasound (US), some of the loculations contained internal echoes and some were anechoic, demonstrating no internal signal on color Doppler [Table 2].

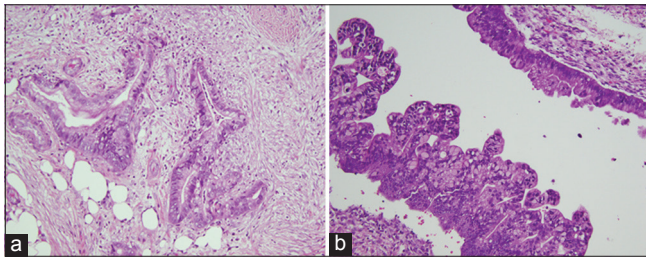
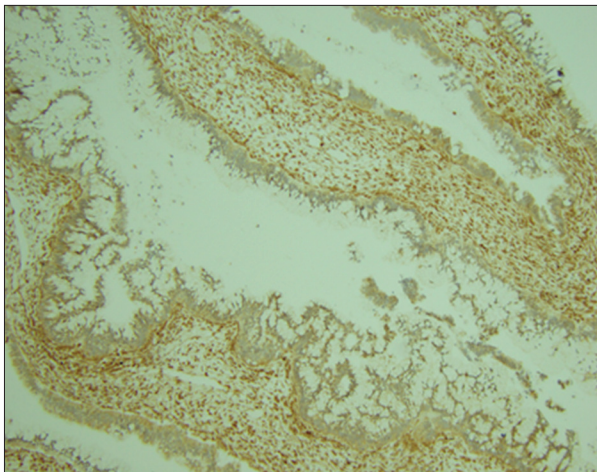
The current literature demonstrates that variability exists in the radiologic features of Krukenberg tumors. On CT and MRI, the tumors may appear complex, with both cystic and solid components and also range in size from 5 to 46 cm.<sup>[13,14]</sup> In some cases, Krukenberg tumors may appear radiologically similar to primary ovarian cancer, with CT findings of large, lobulated masses with cystic and soft tissue components.<sup>[15]</sup> US can also characterize Krukenberg tumors and possibly suggest a primary site. Testa *et al.* found that Krukenberg tumors from the stomach or breast were mostly solid, whereas those from the colon or biliary tract were multilocular.<sup>[16]</sup>

From a pathologic perspective, mucinous tumors of the ovaries are challenging when it comes to determining primary versus metastatic lesions. Many clinical, morphological, and immunohistochemical criteria are traditionally applied to establish a final interpretation, as primary mucinous ovarian tumors most often have an intestinal phenotype and, therefore, can mimic a spread from gastrointestinal or appendiceal malignancy. The main pitfall in diagnosing metastatic pancreatic tumors that involve the ovary is that these can frequently have a deceptively bland histomorphology and, hence, resemble not only a carcinoma but also benign and low malignant potential (borderline) tumors.<sup>[17]</sup> A panel of immunohistochemical stains needs to be applied in this scenario, taking into consideration the focality and intensity of labeling [Table 3 and Figures 11 and 12]. On the morphologic grounds, features that support a metastatic process are bilateral and large ovarian mass(es), lymphovascular invasion, surface ovarian involvement, and, probably the most important factor, prior history of pancreatic malignancy.

Future efforts to create a systematic approach to determining origin of Krukenberg tumors, with suspected pancreatic origin, should be undertaken given the variable clinical, radiologic, and pathologic presentations. In the absence of

**Table 3:** Immunohistochemistry results in the “ideal scenarios” of primary and metastatic mucinous neoplasms involving the ovary

Ovarian neoplasm	PAX8	ER	CK7	CK20	CDX2	SMAD4 (DPC4)
Primary ovarian	+	+	+++	±	±	Retained
Metastasis pancreas	±	-	++	+	+	Lost
Metastasis upper Gi	-	-	+++	±	+	Retained
Metastasis lower Gi	-	-	-	+++	+++	Retained

**Figure 11:** Biopsy of pancreatic mass. Hematoxylin and eosin, x200 magnification**Figure 12:** Biopsy of metastatic pancreatic carcinoma to the ovary (a and b). (a) Hematoxylin and eosin, x200 magnification. (b) SMAD4 immunohistochemistry, x100 magnification. The tumor demonstrates a complex intraglandular architecture and is composed of cells with abundant intracytoplasmic mucin. They are negative (loss of expression) for SMAD4 by immunohistochemistry

known extraovarian primary malignancy, features which support the possibility ovarian metastatic disease, particularly of pancreatic origin, include bilateral, large, and/or rapidly growing multiloculated cystic ovarian masses, especially in the absence of peritoneal implants. Pathologically, focusing on laterality of disease, growth of lesions, histomorphology, and immunohistochemical staining patterns is crucial. While pancreatic Krukenberg tumors portend a poor prognosis, understanding the diagnostic considerations may aid in earlier diagnosis and allow for timely patient intervention where treatments may be benefit.

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