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Case Report

Surgery Section

An Unusual Evolution of Krukenberg Tumour: A Case Report

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ABSTRACT

Krukenberg tumours are rare metastatic tumours of the ovaries characterized by the presence of mucin-producing neoplastic Signet Ring Cell Carcinoma (SRCC). At first glance, this tumour may be confused with a primary ovarian tumour. Surgery and chemotherapy combination have led to improvement in prognosis, but it still remains severe. We report the case of a 60-year-old woman with a Krukenberg tumour rising from a low differentiated gastric adenocarcinoma. The patient was clinically stable for 26 months after surgery until she experienced a prompt decline and died of cerebral haemorrhage within two weeks. The aim of this article was to give an overview of the Krukenberg tumour starting from our case report and comparing it with clinicopathological characteristics of this pathology derived from a review of recent literature.

Keywords: Gastric cancer, Mucinous tumours, Ovarian cancer, Signet ring cell carcinoma

CASE REPORT

A 60-year-old woman, in menopause for about ten years, came to our clinic complaining of pelvic discomfort and about 12 kg of progressive weight loss but no specific symptoms of gastrointestinal disease. She did not have a family history of malignancy and no significant past history. An abdominal examination showed no palpable masses and the breast examination was normal. The gynaecological examination of the vagina, uterus and adnexal left field was normal, while the adnexal right field was larger in size. An abdomen ultrasound confirmed an ill-defined heterogeneous ovarian mass and her chest radiograph was normal.

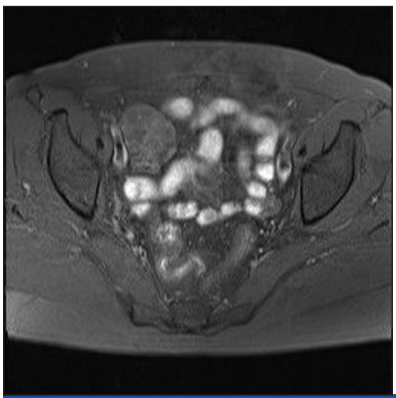
The following haematological tumour markers were normal: Carcinoembryonic Antigen (CEA): 2.9ng/ml (Normative values: <5ng/ml), Cancer Antigen 125 (CA125): 16.3U/ml (Normative values: <30.2U/ml), Carbohydrate Antigen (CA19.9): 12,90U/ml (Normative values: <35.00 U/ml), HE4 (Human epididymis protein 4): 60pmol/l (Normative values: ≤140pmol/l). In addition, the ROMA index (Risk of Ovarian Malignancy Algorithm) [1] indicated that the patient had a low risk of developing ovarian cancer.

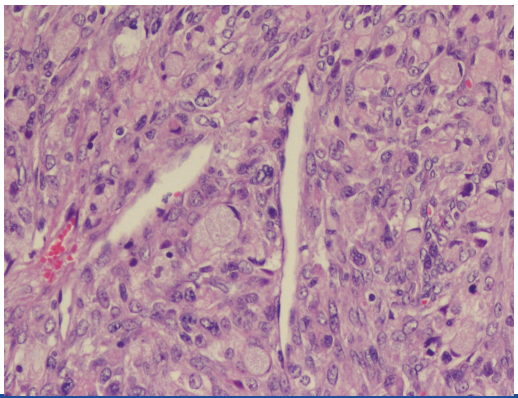
An MRI scan with contrast of the lower abdomen and pelvic region revealed a complex solid mass in the right adnexal with an irregular structure and pronounced enhancement. The uterus (with cervix) and the left tube appeared normal. No lymph nodes were palpable [Table/Fig-1].

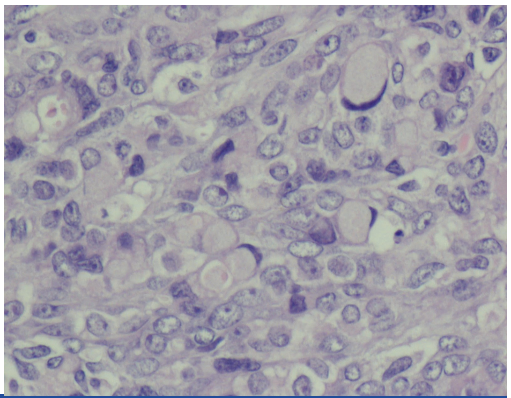
After recurrent episodes of metrorrhagia, transvaginal ultrasonography (TVS) confirmed the presence of a solid mass (9.2X7.2cm) in the right ovary while the left ovary was regular (2.7X1.2cm) with a compact echo structure. The patient underwent a diagnostic uterine hysteroscopy with an endometrial biopsy which showed no neoplastic elements and only endometrium hypotrophic fragments. The cytology pap-test did not reveal any alterations.

The patient underwent an exploratory surgery and the extemporaneous examination of the right ovary showed a smooth surface completely replaced by an encapsulated neoplasm mass measuring 10X7X3cm in size, compatible with a poorly differentiated adenocarcinoma. She underwent a total extra fascial abdominal hysterectomy, a bilateral salpingo-oophorectomy, an upper third colpectomy and omentectomy, with a bilateral pelvic lymphadenectomy. Para-aortic-caval nodes explorations, peritoneal fluid sampling and a bilateral pelvic and a sub-diaphragmatic biopsy were performed.

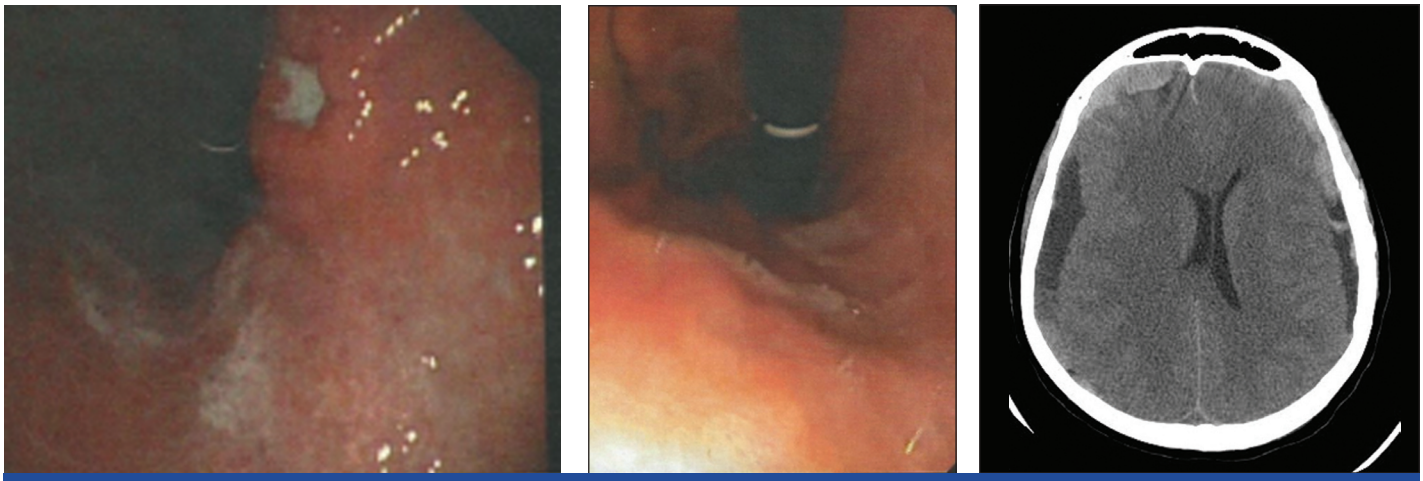
The surgical specimen from the right ovary, after paraffin embedding, showed poorly differentiated adenocarcinoma with mucin-containing signet-ring cells (AFN-SRs). Peritoneal washing cytology was negative for neoplastic cells. Uterus, peritoneum and omentum and lymph nodes did not show any neoplastic infiltrations, but the biopsy revealed the presence of an adenocarcinoma in the left ovary and tube which contained variable numbers of Signet Ring Cells (SRCC) [Table/Fig-2a&b]. The histologic examination has led to Stage pT2aNxMx (FIGO IIA). Immunostaining showed positive CK7, CK20, CKPan markers but ER, Ca125, inhibin alpha, actin and desmin were negative.







[Table/Fig-1]: Magnetic resonance imaging showed large pelvic mass arising from the right adnexa.
[Table/Fig-2a,b]: Krukenberg tumor showing signet-ring cells. A: magnification 10X; B: magnification 40X.



[Table/Fig-3]: Esophagogastoduodenoscopy releaved ulcerated lesion with a fibrinous substratum in the body of the stomach before treatment.
[Table/Fig-4]: Esophagogastoduodenoscopy showed the absence of the lesion after treatment.
[Table/Fig-5]: Cranial CT scan showed a transfalcial ernation with axial deviation due to cerebral hemorrhage.

Due to the histological results, we suspected a Krukenberg tumour thus a contrast-enhanced computed tomography scan of the neck, chest and abdomen was performed. Multiple and scattered lymphadenomegaly were found at the thoracic level (prevascular, paratracheal, precarinal, sub carinal and right paraesophageal regions). The CT showed wall thickening in the pre-antral region of the abdomen (3cm wide and with a maximum thickness of 13mm), multiple nodules at the gastrohepatic and gastrocolic ligaments and the presence of intercaval-aortic and para-aortic left lymphadenomegaly. The CT did not reveal any parenchymal metastasis. The patient underwent a colonoscopy which was negative. In order to detect a primary GI malignancy, an E.G.D.S. (esophagogastroduodenoscopy) was performed: it revealed the presence of a small whitish ulcerated lesion with a fibrinous substratum, and recognized profits in the gastric body and chronic gastritis supported by *Helicobacter pylori* [Table/Fig-3].

The histopathology of the biopsy specimen revealed a poorly differentiated gastric adenocarcinoma with signet ring cells and finally, a metastatic gastric adenocarcinoma with a Krukenberg tumour was diagnosed.

A bone scintigraphy of whole-body scan with (99m) technetium-hydroxymethylene diphosphonate identified multiple skeletal lesions with osteo-thickener characteristics diffused in various skeletal segments: the skull, clavicles, shoulder blades, shoulders, the whole spine, numerous ribs, the pelvis and the proximal femur. In view of the stadium and immunohistochemical characteristics of the disease, the patient was treated with chemotherapy oxaliplatinum (148mg) and 5-fluorouracil (4872mg) with 14-day cycles. A total body CT, performed nine months after surgery, was stationary; also the EGDS showed no presence of lesions [Table/Fig-4]. No suspicious lesions were documented and a mediastinal lymphadenopathy of reduced dimensions as well as an abdomen CT and skeletal lesions showed no significant changes or aggravations, contrarily the multiple lesions showed a shading aspect.

Till the next 26 months post-surgery the patient was clinically stable. Unfortunately, the patient experienced a rapid deterioration of her condition within a span of 10 days and she visited us. On investigation it was found that there was a massive metastatic spread to the bone marrow. The patient died of cerebral haemorrhage due to Disseminated Intravascular Coagulation (DIC) within the next two weeks [Table/Fig-5].

DISCUSSION

Krukenberg tumours are unusual metastatic tumours of the ovaries first described by Friedrich Krukenberg in 1896. In 1902, Schlagenhaufer emphasized that these ovarian tumours do not originate in the ovary, but are metastases from a primary malignancy somewhere else. Moreover, Schlagenhaufer stated that the most common primary site is the gastrointestinal tract [2].

Nowadays, the term “Krukenberg tumour” indicates any ovarian metastatic carcinoma deriving from a primary malignancy. However, the World Health Organization’s diagnostic criteria states that a diagnosis of a Krukenberg tumour is based on the presence of stromal involvement, mucin-producing neoplastic Signet Ring Cells (SRCC) and ovarian stromal sarcomatoid proliferation [3].

The finding of a malignant ovarian tumour poses an immediate clinical question: is it primary or metastatic? The management and the prognosis of the disease varies depending on the primary tumour; therefore, therefore, it is essential to identifying it promptly. Krukenberg tumours are not common and they only represent 1-2% of all ovarian tumours [4]; estimated incidence of these tumours is approximately 0.16 per 100000 per year [5]. The majority of the patients are between the ages of 20 years and 60 years and it is more common in premenopausal women than in postmenopausals. There are some several reports of Krukenberg cancer during pregnancy with bad prognosis [6,7].

Regarding the average age, affected patients were relatively young: on 23 patients (including the indexed case), 10 patients were younger than 40 years, 7 patients are aged between 41-50 years and 6 patients were older than 50 years; moreover, 3 patients out of 23 (13,04%) were pregnant.

Krukenberg tumours are rare during pregnancy, but generally predict a serious prognosis [8]. Diagnosis is difficult because presenting symptoms are often attributed to pregnancy like worsening abdominal pain, ascites and virilization. The tumour may be confused with other adnexal masses such as teratomas and corpus luteum cysts, which are common during pregnancy [8,9].

The major signs of metastasis are: bilaterality (of 74% has bilateral ovarian cancer and 26% has unilateral tumour); size of the injury (less than 10 cm); surface involvement; extensive intra-abdominal spread and a widespread infiltrative pattern. On the contrary, only two morphological patterns exclude a primitive origin: the presence of colloid and signet ring cells. The features favouring primary origin are unilaterality, size greater than 12 cm, a smooth external surface and often association with other ovarian pathologies [10].

Many patients initially report symptoms of metastases instead of a primary tumour. Symptoms are abdominal swelling and discomfort, weight loss, respiratory distress, chest pain, followed by nausea, vomiting or epigastric pain [11]. In addition, physical examinations often reveal the presence of abdominal or pelvic masses.

The literature analysis revealed that 16 patients out of 23 (69,56%) had abdominal discomfort or pain; 35% of the total patients showed abdominal or pelvic mass and in the remaining cases, the patients had other symptoms such as pelvic pain, hypermenorrhea, nausea and vomiting, 52% patients had ascites at the time of diagnosis and it appeared like Pseudo-Meigs' Syndrome in two patients [12,13].

In many instances, ovarian cancer may be the first sign of a tumour process originated elsewhere several years before [4,8,12-30]. Specifically, signet ring cell mucinous carcinomas of the ovary are mostly metastases of the stomach, the pancreas, the biliary tract and the appendix. They can be colorectal tumours and primary tumours of the urinary bladder, of renal pelvis and of uterine cervix. Corpus or mammary tumours with signet ring cells and bone metastases are very rare [15]. Occasionally, the primary tumour is never discovered [14].

Three possible metastasis pathways have been identified: lymphatic, haematogenous, and transcoelomic metastasis, but the retrograde lymphatic spread has been demonstrated to be the most likely pathway [2,6,31,32].

When a Krukenberg tumour is suspected, accurate examinations of the gastrointestinal organs should be conducted and it is important to look for the presence of primary tumours. For this purpose, the main imaging techniques employed to make a diagnosis of a Krukenberg tumour are: a pelvic ultrasound, a CT and a pelvic MRI, but they are not specific enough because the tumour reveals mostly solid components, or a mixture of cystic and solid areas [16].

Transabdominal sonography of abdomen and pelvis is primary imaging and screening modality for females with gynaecological illness [4]. With a pelvic ultrasound, Krukenberg tumours are typically seen as solid ovarian masses, with clear well-defined margins. A characteristic feature is an irregular hyperechoic solid pattern and a moth eaten like cyst formation. Another suggestive sign is the presence of a large lead vessel penetrating the mass from the periphery and nourishing the tumour by branching in tree pattern, known as lead vessel sign, with high speed and low resistance on spectral Doppler. This colour Doppler sign is more frequently detected in ovarian metastases compared with primary invasive ovarian carcinomas. Sonography and colour Doppler imaging are decisive in rising the suspicion of a metastatic tumour [4].

Krukenberg tumours may show some typical features on an MRI, such as bilateral, lobulated and solid masses. On T2-weighted MR images, the solid tumour components typically show heterogeneously low to high signal intensity. Areas of decreased intensity are either randomly or peripherally located, histologically corresponding to increased cellularity seen with fibrous stroma, while areas of increased intensity represent edema within the connective tissue. Signal voids can frequently be observed within the tumours, representing increased tumour vascularity. At both contrast-enhanced CT and T1-weighted MR imaging, the solid components usually demonstrate homogeneous enhancement [31]. Moreover, tumours originating from the stomach may be denser on a contrast-enhanced CT than those originating from the colon [33,34].

Microscopically, metastatic tumours show a variety of patterns according to the site of the primary tumour. Pathological reports describe metastatic tumours as about 60% of cases being lesions that appear as diffusely solid tumours, multiple solid nodules, partially cystic masses or, rather infrequently, completely cystic lesions. Even when the primary tumour is solid, metastases in the ovaries may be cystic or semi cystic. Extensive areas of haemorrhage and/or necrosis are common [26,35]. The lesion often reveals surface implants marked by numerous bosses and vascular invasion.

A pathognomonic diagnostic feature of a Krukenberg tumour is the presence of mucin-filled signet-ring cells associated with a conspicuous proliferation of cellular non-neoplastic ovarian stroma. Epithelial elements other than the signet-ring cells are mostly microcystic tubules and glands which are often small and their cell lining is compressed [11,26].

Immunohistochemistry can be very valuable in distinguishing primary ovarian tumours from metastatic tumours [26]. Tumours are stained with Periodic Acid-Schiff with Diastase (PAS-D). Immunohistochemical staining is performed on formalin-fixed, paraffin-embedded tissue sections using the antibodies specific for the antigens, Cytokeratin 7 (CK7) and Cytokeratin 20 (CK20) [36]. A CK7+/CK20– immunophenotype favours a primary ovarian carcinoma, while, on the contrary, a CK7–/CK20+ or CK7+/CK20+ immunophenotype (CK20 positivity, in particular) favours a metastatic gastrointestinal carcinoma [37].

The presence of a tumour can be detected by markers. None of these substances can be used as prevention or screening, but they can be used to strengthen or confirm a diagnosis (in our case, the markers were within the limits). The tumour markers, CA125 and HE4, are currently included in the "Risk of Ovarian Malignancy Algorithm" (ROMA) for discerning benign from malignant pelvic masses. ROMA is an innovative calculation based on the values obtained from the HE4 and CA125 markers, and it provides a numeric value that classifies a patient based on her risk of developing ovarian cancer [38].

A Krukenberg tumour should be treated with excision of the primary tumour and ovarian metastasectomy if other dissemination or ascites are absents, to lengthen the survival time especially in patients with primitive tumour arising from the stomach [39]. Numerous studies have examined the issue of metastasectomy and cytoreductive surgery for Krukenberg tumours (including palliate symptoms). The concerns regarding surgical complications are relatively modest because metastasectomy for Krukenberg tumours is a sufficiently safe surgical procedure with a short postoperative hospital stay [40].

Majority of patients undergo chemotherapy with a platinum agent such as cisplatin or oxaliplatin and plus 5-fluorouracil. Platinum-based therapy continues to be the principal regimen used for disease that recurs ≥6 months after prior therapy. In non-randomized studies, the response rate to platinum analogues is greater than non-platinum therapies [40,41]. The median survival time after the diagnosis of a Krukenberg tumour is reported to be from 7 to 14 months [40,42].

A Pubmed research using the keywords "krukenberg tumour", "ovarian metastasis" and "gastric cancer" led us to evaluate both cases report and research studies, from 2005 to 2015. Only cases which reported patient's age, clinical presentation, therapy and follow-up were considered and these consisted of 22 cases [Table/Fig-6] [4,8,9,12-14,17-30,43].

CONCLUSION

Krukenberg tumour is a rare disease with a rapid progression. It is characterized by the presence of mucin-producing signet ring cells that are mostly metastases of gastrointestinal tract. The diagnosis of the primary site of the lesion is crucial in this tumour but, despite the recognition of the primary lesion and targeted therapy, the prognosis remains very poor. In our case the patient remained clinically stable for 26 months until she experienced a rapid deterioration of her clinical conditions over the course of 10 days. She suddenly died due to a several cerebral haemorrhage.

Reference	Age	Clinical presentation	Others factors	Side	Extend of disease	Treatment	Follow-up
Yamagishi [17] 2005	40 yrs	Abdominal pain	Pleural effusion	Bilateral	Gastric cancer	HSO CT	Died 28 months after
Cetin [12] 2005	47 yrs	Abdominal pain	Pseudomeigs' syndrome	Bilateral	Gastric cancer Liver and Peritoneal metastases	G HSO MTS[1] CT	Died 36 months after
Chicos [18] 2007	62 yrs	Abdominal discomfort	ascites	Bilateral	Gallbladder cancer	MTS[2] HSO	Died 5 months after
Ozdegirmenci [19] 2007	22 yrs	Pelvic pain	Virilization, ascites,	Bilateral	Gastric cancer	HSO CT	Died 5 months after
Reichert [43] 2007	43 yrs	Pelvic mass	Periaortic lymph node mass,anemia, leukemia	Left	Confined to ovary	HSO	Died 3 months after
Baba [20] 2007	53 yrs	Lower abdominal mass	Helicobacter pylori infection, pericardial effusion	Bilateral	Gastric cancer and lymph node	G MTS[3] CT	Died15 months after
Uharcek [21] 2007	52 yrs	Abdominal mass	Peritonitis carcinomatosa	Bilateral	Appendix, omentum	HSO MTS[4] CT	Died 18 months after
Hornung [22] 2008	41 yrs	Hypermenorrea, abdominal discomfort, nausea, emesis	Virilization	Bilateral	Gastric cancer, intestine cancer	CT HSO	Died 6 months after
Bilbao [23] 2008	45 yrs	Lower abdominal pain	Hepatomegaly, ascites	Bilateral	Hepatocarcinoma	left hepatectomy HSO MTS[5] CT	Died
Stojnic [24] 2011	31 yrs		Pregnancy, ascites	Bilateral	Gastric cancer	CES HSO MTS[6] CT	Neonate died; patient died 6 months after
Habib [25] 2012	35 yrs	Abdominal pain		Right	Gastric cancer	HSO CT	Died
Habib [25] 2012	55 yrs	Epigastric pain	ascites	Bilateral	Pancreas cancer Peritoneal dissemination	HSO CT	Died
Nakamura [14] 2014	45 yrs	Lower Abdominal mass	Hepatitis B, pleural effusion, ascites, chronic gastitis	Left	Bones, Gastric cancer after biopsy	HSO CT	Died
Shiono [26] 2014	44 yrs	Epigastric pain, abdominal mass	ascites	Bilateral	Colon cancer, multiple liver metastases	HSO MTS[7] CT	Died 34 months after
Co PV [9] 2014	38 yrs	Abdominal pain, nausea, bilious vomiting	Pregnancy, ascites	Left	Omentum and gastric cancer	CT	Died
Hatwal [27] 2014	25 yrs	Abdominal distension and pain, amenorrhea abdominal lump		Bilateral	Gastric cancer	HSO	Died after few months of surgery
Sun [8] 2015	35 yrs	Abdominal pain	Pregnancy, colon cancer history	right		CES HSO CT	Died after 19 months
Sahin [28] 2015	36 yrs	metrorrhagia, pelvic pain and discomfort during urination, abdominal mass	ascites	Bilateral	Colon cancer	HSO CT MTS[8]	Lives after 6 months
Fujimoto [29] 2015	58 yrs	Gastric cancer	anaemia	left	Colon cancer	G OOP MTS[9] CT	Lives after 60 months
Hiremath [4] 2015	39 yrs	Amenorrhea, abdominal Pain, nausea, night sweats, loss of weight and appetite, abdominal mass	bilateral pleural effusion, anaemia	bilateral	Hepatic nodules, Gastric cancer, lymph nodes	OOP CT	Lived after 4 months
Berthè [30] 2015	32 yrs	Ascites, fever, Epigastric pain, pelvic pain	Constipation, cardial incontinence Pyloric Stenosis	bilateral	Gastric cancer, peritoneal carcinomatosis, omentum, hepatic nodules	CT	Died after 1 month
Horimatsu [13] 2015	50 yrs	abdominal fullness, dyspnea	Pseudomeigs' syndrome	bilateral	Gastric cancer, Lymph nodes	OOP CT	Died after 27 months
Spinelli 2016	60 yrs	Pelvic discomfort, weight loss, metrorrhagia		bilateral	Gastric cancer, bones, lymph node	HSOMTS[10] CT	Lives after 15 months

[Table/Fig-6]: Clinical features of patients with Krukenberg tumours from review of literature from 2005 to 2015 [4,8,9,12,14,17-30,43].

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