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Krukenberg Tumor- A Review of Literature

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1. Abstract

Krukenberg tumor also known as carcinoma mucocellulare was first described in 1896 by Ernst Krukernberg. It is a metastatic malignancy of the ovary characterized by mucin rich signet ring adenocarcinoma. In this paper, we review the existing literature on Krukenberg tumor throwing light on the critical aspects such as evaluation and management. Recent advances such as evaluation and management and recent advances on the role of metastasectomy in the management of Krunkenberg tumor. Operative removal of KT along with the primary tumor if no other tumor dissemination is present, prolongs survival, however presence of ascites and inoperable primary tumour has very poor prognosis in such cases ovarian metastasectomy has no role in the management. This particular paper will throw light on the understanding this clinical entity in detail so as to understand this clinical entity and its implications.

2. Introduction

Krukenberg Tumor refers to the signet ring subtype of metastatic tumor to the ovary. It is also known as Carcinoma mucocellulare [1,2]. The stomach and colon are the two most common primary tumors to result in ovarian metastasis, pursued by the breast, lung and contralateral ovary [1,2,3]. The tumor represent 5-10% of all ovarian tumours and up to 50% of all metastatic tumours to the ovary. The estimated incidence of the Krukenberg is at approximately 0.16/100000 per year. They tend to develop during the reproductive years. The median patient age at presentation is 45 years [1,3,4]. Abdominal or pelvic pain, abdominal bloating or pain during intercourse may be the presenting symptoms [1,5].

3. Pathology

They contain well defined histological characteristics (mucin secreting "signet ring cells") and usually originate in the gastrointestinal tract. Cytological examination often reveals mucoid degeneration and many large cells shaped like signet rings [1.6]. They can originate from:

- Stomach cancer (signet ring cells); most common
- Colorectal carcinoma; second most common
- Breast cancer
- Lung Cancer
- Contralateral Ovarian Carcinoma
- Pancreatic Carcinoma
- Cholangiocarcinoma/ GB Carcinoma

Radiological features of Krukenberg tumor are non-specific consisting of predominately solid components or a mixture of cystic and solid areas [1,7]. It is often difficult to differentiate from other ovarian neoplasms. There is a variety of metastatic carcinoma to the ovary that can mimic primary ovarian tumors [1,8]. On Ultrasound, these tumors are typically seen sonographically as bilateral, solid and sometimes cystic ovarian masses with clear well defined

margins. An irregular hyperechoic solid pattern and moth eaten like cyst formation are also considered characteristic features [1,8,9]. On CT appearance can be indistinguishable from primary ovarian carcinoma, features will favor towards Krukenberg tumor if concurrent gastric or colic mural lesion is seen. On MRI, Krukenberg tumors may demonstrate some distinctive findings including bilateral complex masses with hypo intense solid components, internal hyperintensity (mucin) on T1 and T2 weighted MR images [1,8].

Strong contrast enhancement is usually seen in the solid component or the wall of the intratumoral cyst. The great majority of Krukenberg tumor is signet ring cell carcinoma arising in the stomach [1]. Signet ring cell scatter in the ovarian stroma with abundant collagen formation or marked edema therefore, Krukenberg tumor can occasionally show low or high signal intensity T2 – weighted images [1,9]. Differentiation between primary and metastatic ovarian carcinoma is of great importance with respect to the treatment and prognosis but may be very difficult based on imaging finding solely [1,10]. It is a stage 4 disease and median overall survival is of the order of 16 months, breakdown by primary tumor location is as follow – gastric: 11 months, colorectal: 21.5 months, breast: 31 months, other (appendix, gall bladder, small intestine, unknown): 19.5 months [1,11].

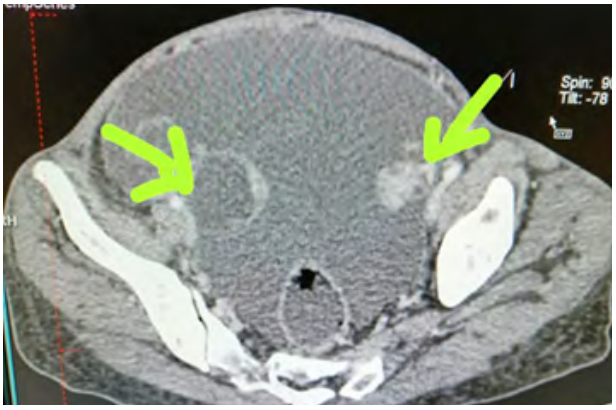

Figure 1: CT abdomen and pelvis depicts an axial section showing bilateral krukenberg tumour

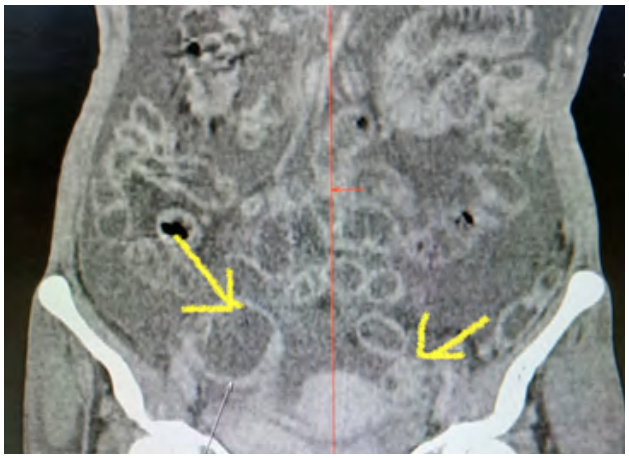

Figure 2: CT abdomen and pelvis depicts a coronal view of bilateral Krukenberg tumor.

3.1. Review of Literature

krukenberg tumor also known as carcinoma mucocellulare was named by Friedrich Ernst Krukenberg who reported a new type of ovarian malignancy in 1896, Six years later this malignancy was discovered to be metastatic- in origin from the primary gastrointestinal site [1]. It is a malignancy of the ovary characterized by mucin rich signet ring adenocarcinoma that primarily arises from a gastrointestinal site in most cases and less common from other sites [1,2]. Over 80% cases are bilateral given their metastatic nature [1,3].

3.2. Etiology

Stomach cancer is the most attributed primary site in 70 % cases. Recent studies note an increasing prevalence of colorectal tumors. Gastric & colorectal cancers collectively account for almost 90% of the primary site [1,12,13]. Less common primary as described in literature are breast, appendix, small intestine, gall bladder, biliary tract, pancreas, ampulla of Vater or uterine cervix [1,13]. Recurrences can occur years after the primary has treated. Krukenberg tumors are also defined as either 'synchronous metastasis 'where metastasis is discovered within 3 months of the primary tumor's diagnosis or 'metachronous metastasis' where the metastasis is found after 3 months or even completion of initial curative therapy [1,14]. The presence of pregnancy with concurrent Krukenberg tumor complicates the diagnosis as the tumor increases in size. It compounds an already increasing abdominal girth from the uterus. Sex hormones can augment gastric cancer dissemination. Placental growth factor levels are elevated in gastric cancer and associated with serosal invasion and lymph node metastasis [1,15].

Epidemiology:

It can be seen in all age groups, however the average age is 35-45 years. Of all the ovarian malignancies diagnosed Krukenberg tumors in Western nations account for less than 4% of these tumors [1,14]. The incidence is higher in Asian countries like Korea, Japan, China where these tumors make up about 20 % of all ovarian cancers [1,14,16].

3.3. Pathophysiology

The exact mechanism of tumor spread is still unknown however is thought to spread via the following mechanism –lymphatic system, haematogenous system, transcoelomic pathway. Haematogenous and lymphatic means spread is via blood & lymphatic system respectively [1,17,18] . The transcoelomic pathway means the actual cancer cells directly spread through the abdominal route to adjacent organs [1,18,19]. It is believed that tumor metastasis occurs via mixed pathway, although the lymphatic pathway is favored over hematogenous spread and lastly peritoneal [1,18]. The lymphatic route is believed to be the most likely route of cancer spread.

3.4. Histopathology

Grossly, the ovaries are symmetrically enlarged with bosselated contour, they are usually solid but can occasionally be cystic. The capsular surface is mostly free of tumor infiltrates, adhesions, implants or deposits which can be deceptive and can appear as a primary ovarian tumor [1,19]. The characteristic finding of this tumor is presence of mucin laden signet ring cells [1]. The diagnostic criteria of WHO based on Serov and

Scully's description are: [1,20]

1. The presence of stromal involvement

2. The ovarian stromal sarcomoid proliferation

3. The presence of mucin producing signet ring cells

Histochemically, the intracytopasmic mucin of the signet ring are neutral and acidic and stained with Mayer mucicarmine, periodic acid Schiff with diastase digestion and Alcian blue stain. The signet ring cells have an eccentric hyperchromatic nuclei often presenting as nests, cords, tubules or acini they diffusely infiltrate the mesenchymal stroma [1,21].

Immunohistochemically these tumor stain positive for cytokeratin (AE1/AE3) and epithelial membrane antigen and they stain negative for inhibin and vimentin. Approximately a third of the patients will have either a positive cytokeratin 7 or cytokeratin 20[1,22]. About a quarter of the patient may have elevated CEA or CA 125 levels.

Even if the individual's values aren't significantly high, they still could be used as gauge therapy [1,20,22].

4. Clinical Presentation

KT-they have variable presentation with non-specific symptoms and obscure signs [1]. One recent meta-analysis revealed that almost half of Krukenberg tumors were synchronous with the primary tumor, about 2/3 rd were bilateral, about 40% had a diameter greater than 10 cm and half had peritoneal involvement with ascites.

Ascites is typically a late feature of peritoneal metastasis which can occur alongside intestinal obstruction, cachexia and heralds a sharp decline in patients qualify of life [1,20].

Krukenberg tumor with benign ascites and right hydrothorax that contain no malignant cells are known as Pseudo-Meig syndrome. These tumors can move about, leading to ovarian torsion and abdominal pain [1,15,20]. Patients can manifest pain during sexual intercourse – the tumor causes a reaction of the ovarian stroma thus provoking hormone production resulting in vaginal bleeding, menstrual changes, hirsutism and virilisation [1,20,26].

4.1. Evaluation

Ultrasound or computed tomography of the abdomen and pelvis often appear as bilateral ovarian masses usually solid however can be cystic as well. Pre-operative level of CA 125 can be elevated and decreases after tumor resection, these levels can be used for follow up of patients after surgery to document complete resection as levels will decline [1,26]. Follow up of patients is also necessary to diagnose metastatic spread to ovaries in patient with history of other cancers example – GI, Breast etc. The presence of a unilateral ovarian mass with elevated CA 125 should alert one of the Krukenberg situation where there is a need to exclude colorectal cancer during the work up. CA 125 also help to predict the prognosis of patients with Krukenberg tumors [1,25,26]

4.2. Management

No optimal treatment strategy for these tumors has been established. Radiation and chemotherapy often a chance of improvement in the overall prognosis [1]. The mainstay of the therapy remains surgical resection with an R0 result. R0 is defined as a microscopically negative margins of resection where no gross or microscopic tumor is found at the surgical site [1,10]. Given the metastatic nature of the disease, all surgery can accomplish is palliation and improvement in quality of life which may be a worthy goal. Data from other sources support the assertion that metastatectomy of one or both the ovaries increases the overall survival [1,15,20]. Prophylactic bilateral oophorectomy is advocated in the setting of unilateral disease as a countermeasure to the risk of eventual contralateral involvement. Metastatectomy is favored over no surgery for its increasing overall survival especially when R0 is felt to be an obtainable result [1,20]. A retrospective analysis showed that patient who underwent palliative surgeries including unilateral or bilateral salphingo-oophorectomy alone or total hysterectomy combined with bilateral salphingo-oophorectomy had a median survival of 17 months [1,13,24].

4.3. Staging

It is classified as stage 4 disease since the Krukenberg tumor is a metastatic disease from the gastrointestinal disease site or other organs [1].

4.4. Prognosis

The prognosis of Krukenberg tumor given the bilateral and metastatic nature, patients usually die in 2 years with a median survival of 14 months reported in literature. The median overall survival of patients with Krukenberg is reportedly 11, 21.5, 31 and 19.5 months for gastric, colorectal, breast and other organs however metastasectomy expressing estrogen receptor beta (ERB), progesterone receptor (PR), peritoneal carcinomatosis and signet ring cells were independent predictors of survival [1,17]. Generally, unilateral Krukenberg tumor fared better as did those with R0 resection. Colorectal cancer were better than gastric cancer particularly when adjuvant HIPEC was added to complete resection. For stomach cancer subtypes, the presence of ERB and PR confers a better prognosis in synchronous patients [1,19,22].

5. Discussion

KT is a metastatic malignancy of the ovary characterized by mucin rich signet ring adenocarcinoma that arises from the gastrointesti-

nal tract in most cases. It was first described by Ernst Krukenberg in 1896, KT constitute 1-2 % of all ovarian neoplasm usually presented in younger females with an average age of 45 years. Majority of the cases are synchronous, but 20-30% occur as metachronous lesion after removal of the primary [1,27]. The prognosis of a patient with KT is extremely poor with an average survival time between 3-10 months; only 10% of the patients survive more than 2 years after the diagnosis. Treatment of the patient with KT is controversial.

In a retrograde analysis of 133 patient with KT, author concluded ovarian metastasectomy might be helpful for prolonging the survival of some patient with KT originated from the stomach. Patients without ascites and with resected primary gastric cancer lesion could get benefit from and be potential candidate for surgical treatment [1,20,27]. They did not recommend patient to undergo ovarian metastectomy if the primary stomach lesion hadn't or could not be resected or if ascites was detected. There is no specific guideline for treating KT, but existing literature favors operative removal of KT along with primary tumor if there is no other dissemination.

In this paper, we reviewed the existing literature on Krukenberg tumor with specific emphasis on etiology, clinical presentation, evaluation and management

6. Conclusion

Krukenberg tumor is a metastatic disease to the ovaries composed of mucin rich signet ring cells. The most common primary site is the stomach. These tumors spread mostly through lymphatic channels. Diagnosis of Krukenberg tumor involves careful radiological evaluation of the gastrointestinal and other potential sites. With a known primary tumors CA-125 levels can help with early detection of ovarian metastasis and assist with the prognosis and monitoring of this disease. Currently no established treatment is available with an extremely poor prognosis for this tumor. The diagnosis and management of KT is complex and should involve an inter professional team that includes hospice staff, palliative care nurses, a pain specialist, oncologist, surgeon, pathologist and radiologist. In all cases it is an metastatic disease and majority of patients are dead within 12-24 months with or without treatment with such a poor outlook, the art of medicine with its focus on comfort and care, becomes just as important as medical or oncological protocol.

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