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Case Report:
Tubular Krukenberg Tumor with an Occult Primary

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Abstract:
Tubular Krukenberg tumor with an occult primary can cause problems in histopathologic diagnosis, by mimicking primary ovarian tumors. We present one such occurrence in a 32year old female who underwent surgery for bilateral malignant ovarian tumor. Gross examination of both ovarian tumors revealed bosselated, smooth outer surface with a few cysts on the surface. Cut surface was grey-white to yellowish in colour with cysts filled with serous fluid at the periphery. Microscopic examination revealed mucin laden signet ring cells, predominantly showing tubular architecture within a cellular ovarian stroma. The cytoplasm of these cells varied from granular eosinophilic to pale vacuolated appearance and showed PAS and mucicarmine positive mucin. Differential diagnosis with other primary ovarian tumors is discussed.

Key Words: Krukenberg tumors; Tubular variant; Ovary

Introduction:
Krukenberg tumors (KT) are rare among ovarian metastases, but responsible for the most frequent diagnostic confusions with primary ovarian cancers. Especially those with an occult primary can cause diagnostic confusion with the primary ovarian tumors. Distinction from the latter is of great importance as misclassification of Krukenberg tumor as a primary ovarian tumor may lead to suboptimal treatment of the patient. We report a case of tubular Krukenberg tumor in a 32 years old female with an occult primary tumor and discuss the diagnostic difficulties that arise with such an occurrence.

Case Report:
A 32 year old female presented with fullness of lower abdomen, polymenorrhagia and decreased appetite since 2months. CT scan revealed a large well defined soft tissue density mass lesion with heterogenous solid and cystic components in both uterine adenexa measuring 16x11.5cm (right side) and 12x6cms (left side) respectively. In addition there were gross ascitis and significant retroperitoneal lymphadenopathy. Possibility of bilateral malignant sex cord stromal tumor was suggested. Serum levels of CA-125 was also raised (1410u/ml). Patient underwent total abdominal hysterectomy with bilateral salphingo-ophorectomy.

On gross examination, ovarian tumors were measuring 17x11x9cms and 12x8x5cms respectively. Both ovarian tumors showed bosselated, smooth outer surface with a few cysts on the surface. Cut surface showed lobulated, grey white to yellowish colour with cysts filled with serous fluid at the periphery.

Microscopic examination of the sections from both ovaries showed mucin laden signet ring cells, predominantly showing tubular architecture within a cellular ovarian stroma (Figure2). The cytoplasm of these cells varied from granular eosinophilic to pale vacuolated appearance and showed PAS and mucicarmine positive mucin. The diagnosis of bilateral Tubular Krukenberg was given. Detailed radiographic and endoscopic exploration of the digestive system of the patient did not reveal any primary tumor.

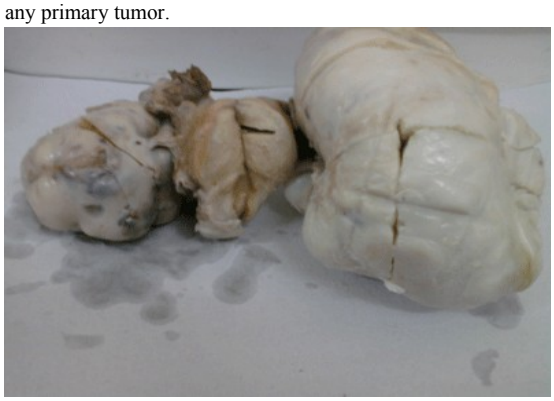

Figure 1: Photograph of hysterectomy specimen with bilateral ovarian tumors with bosselated outer surface

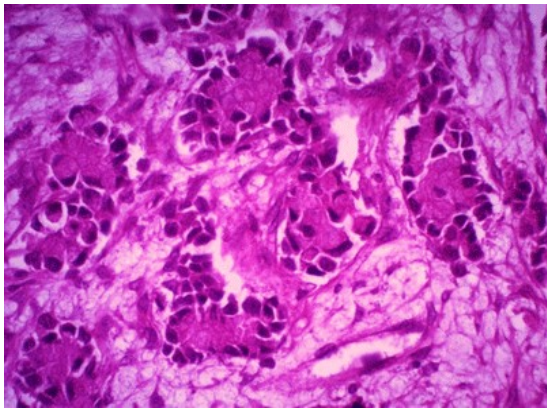

Figure 2: Photomicrograph revealing signet ring cells arranged in tubular pattern. (H&E,40x)

Discussion:

Krukenberg-type tumors (KT) are rare among ovarian metastases. They are responsible for the most frequent diagnostic confusions with primary ovarian cancer. They are peculiar tumors with uncertain pathogenesis, challenging etiological diagnosis and poorer prognosis for the primary.[1] Krukenberg tumor is a metastatic signet ring cell adenocarcinoma of the ovary, accounting for 1% to 2% of all ovarian tumors.[1] Stomach is the primary site in most Krukenberg tumors (70%). Carcinomas of colon, appendix, and breast (mainly invasive lobular carcinoma) are the next most common primary sites. Rare cases of Krukenberg tumor originating from carcinomas of the gallbladder, biliary tract, pancreas, small intestine, ampulla of Vater, cervix, and urinary bladder/urachus have been reported.[2] The interval between the diagnosis of a primary carcinoma and the subsequent discovery of ovarian involvement is usually 6 months or less, but longer periods have been reported. A history of a prior carcinoma of the stomach or any other organ can be obtained in only 20% to 30% of the cases.[3] In many cases, the primary tumor is very small and can escape detection. In such a situation, diagnosis of Krukenberg tumor warrants careful radiographic and endoscopic exploration of the digestive system in an attempt to detect the primary carcinoma.In the present case,meticulous radiographic and endoscopic investigation failed to detect any primary carcinoma.

Novak and Woodruff[4] have defined the criteria to qualify a Krukenberg tumor as primary tumor of the ovary (Primary krukenberg tumor). This includes

1. Complete postmortem examination - if the patient was dead at the time of the case report, absence of primary tumor in any organ except the ovary should be proved by a detailed autopsy study.
2. If the patient was living at the time of the case report, and a surgical resection of the tumor was done, then the patient should have survived for *5* years or longer. An analysis of 19 acceptable cases reported in the literature favor the existence of primary Krukenberg tumor of the ovary.[5]

While the entity of primary Krukenberg tumor cannot be unequivocally denied, all women with typical Krukenberg tumors should be considered as having metastatic carcinoma, usually from the stomach, until proven otherwise.[3] Our patient is fine six months following surgery. However longer follow up is needed to call it a primary Krukenberg tumor.

The diagnosis of Krukenberg tumors largely depends on the recognition of its characteristic light microscopic features . However, Krukenberg tumors may mimic other metastatic or primary ovarian tumors. Distinction from the latter is of great importance as misclassification of Krukenberg tumor as a primary ovarian tumor may lead to suboptimal treatment of the patient. Tubular Krukenberg tumors (i.e., tumors in which the cells are predominantly arranged in tubules) must be distinguished from other ovarian tumors displaying annular or tubular pattern. The major tumor in this group is Sertoli-Leydig cell tumor, particularly if intracellular mucin is not evident on routine staining. Tubular Krukenberg tumors are frequently bilateral, and compulsive sampling of the tumor usually demonstrates the typical signet-ring cells filled with mucin. The nuclei of tubular Krukenberg tumors are more atypical than those within the tubules of Sertoli-Leydig cell tumors. Presence of signet ring cells within the tubules is inconsistent with Sertoli-Leydig cell tumor. In contrast to Krukenberg tumor, Sertoli-Leydig cell tumor stains positive to inhibin but negative to cytokeratins or epithelial membrane antigen.[6] Other ovarian tumors with a tubular pattern that can enter the differential diagnosis in this group include well-differentiated endometrioid carcinoma (metastatic or primary), clear cell carcinoma and tumors of wolffian origin. Differentiation can be made on the basis of their characteristic histologic features.[6] Bullon A et al[7] reviewed a series of 70 Krukenberg tumors and found 13 cases with a predominant tubular pattern. Eleven of them had been diagnosed by the referring pathologist as a tumor in the sex cord-stromal category, usually a Sertoli-Leydig cell tumor and no diagnosis was given in the other two cases. Three factors contributed to the erroneous diagnoses in their cases which included: a prominent tubular pattern, luteinization of the stroma of the tumor in five cases, and associated virilization in two cases. Each tumor, however, contained typical signet-ring cells that were readily demonstrable with mucicarmine stains. With their experience ,they concluded that the diagnosis of Krukenberg tumor must always be considered in the differential diagnosis of an ovarian tumor with a tubular pattern even though endocrine manifestations are present. Rarely, primary mucinous carcinomas of the ovary may contain signet ring cells, but not in great number. However, careful consideration of the clinical background, distribution of disease, gross characteristics and spectrum of routine microscopic findings, will lead to the correct diagnosis in the majority of cases and at the very least lead to formulation of a considered differential diagnosis such that use of special techniques may be judicious and those results placed in context of the time-honored clinical and pathologic features.

Preoperative serum CA 125 levels in patients with Krukenberg tumors can be elevated, though they subsequently decrease after tumor resection.[8] On the basis of this observation, serum CA 125 level can be used for (1) postoperative follow-up of patients for evaluation of complete resection of the tumor, and (2) follow-up of patients with a history of primary adenocarcinomas (gastrointestinal, in particular) for early detection of ovarian metastasis. Serum CA 125 level also can help predict the prognosis.

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