KRUKENBERG TUMOR. (Literature review)

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Summary
Krukenberg tumor represents an uncommon metastatic tumor of the ovary. This paper provides a review of the major pathologic manifestations of Krukenberg tumor, patient characteristics, clinical and laboratory features, prognostic factors, and its pathogenesis. Knowledge of the diagnostic manifestations of the tumor leads to the correct diagnosis and prevents tumor misclassification, thus avoiding improper clinical management. Prognosis of Krukenberg tumor is still very poor but there seem to exist several factors that appear to have an impact on survival. There is no established treatment for Krukenberg tumors.
Key words: Krukenberg tumor, metastasis, ovary

Rezumat. Tumoarea Krukenberg. (Revista literaturii)
Tumoarea Krukenberg este o tumoare metastatică rară a ovarelor. Acest articol prezintă o revistă a manifestărilor majore morfologice, caracteristicilor pacienţilor, manifestărilor clinice şi de laborator, factorilor de pronostic şi a patogenezei tumorii Krukenberg. Cunoaşterea manifestărilor diagnostice ale tumorii rezultă într-un diagnostic corect şi preîntâmpină clasificarea incorectă a tumorii, astfel, evitând conduita incorectă. Pronosticul în caz de tumoare Krukenberg este foarte rezervat, însă pare să existe câţiva factori care ar avea un impact asupra supravieţuirii. Nu există un tratament standardizat al tumorilor Krukenberg.
Cuvinte-cheie: tumoare Krukenberg, metastaze, ovar

Резюме. Опухоль Крукенберга. (Обзор литературы)
Опухоль Крукенберга является редкой метастатической опухолью яичников. В данной статье представлен обзор морфологических особенностей, характеристик больных, клинических и лабораторных проявлений, прогностических факторов и патогенеза опухолей Крукенберга. Знание проявлений опухоли ведет к правильному диагнозу и исключает её неверную классификацию, избегая, таким образом, ошибочной тактики. Прогноз в случае опухоли Крукенберга все ещё неблагоприятный, хотя существует ряд факторов которые могут влиять на выживаемость. На данный момент не существует установленной методики лечения опухолей Крукенберга.
Ключевые слова: опухоль Крукенберга, метастаз, яичник

Overview

The term "Krukenberg tumor" should be reserved for tumors with an appreciable component (arbitrarily defined as >10% of the tumor) [1] of signet-ring cells and no evidence of another specific diagnosis such as clear cell carcinoma or mucinous carcinoid, or any other primary neoplasm that rarely has signet-ring cells. Krukenberg tumor (KT) represents a metastatic signet ring cell adenocarcinoma of the ovary. KT is infrequent, accounting for 1% to 2% of all ovarian tumors. Friedrich Krukenberg, a German gynecologist and pathologist, described in 1896 what he presumed was a new type of primary ovarian neoplasm. The true metastatic nature of this lesion was recognized 6 years later. About 76% of KTs originate in the stomach, 11% in the intestines (usually colon or rectum), 4% in the breast, 3% in the biliary system, 3% in the appendix, and the remaining 3% in miscellaneous sites such as pancreas, uterine cervix, urinary bladder (including urachus), and renal pelvis [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. In many cases, the primary tumor is very small and can escape detection. A history of a prior carcinoma of the stomach or another organ can be obtained in only 20%-30% of the cases [3].

It is well known that adenocarcinomas composed of signet ring cells of various organs have a tendency to metastasize to the ovaries much more commonly

than adenocarcinomas of other histologic types from the same sites. The most common finding of these is gastric adenocarcinoma of signet ring cell type, mainly from the pylorus [4,5]. The frequency of KT varies depending on that of gastric carcinoma in the analyzed population. For example, in countries such as Japan, which has a high prevalence of gastric carcinoma, KT accounts for a large proportion (17.8%) of all ovarian cancers [6].

KT is an example of the selective spread of cancers, most commonly in the stomach-ovarian axis. The route of metastasis of gastric carcinoma to the ovaries is thought to be the retrograde lymphatic spread as there are several evidences supporting this concept. First, lymphatic permeation at the hilum and cortex is microscopically noted in many cases of KT. Second, review of the literature reveals several reported cases of KTs with primary gastric carcinomas that were confined to the mucosa and submucosa [7]. It should be remembered that gastric mucosa and submucosa have a rich lymphatic plexus and their invasion usually accounts for the spread of early gastric cancers. Third, some studies showed that the risk of ovarian metastasis in gastric carcinoma increases when there is an increased number of metastatic lymph nodes [8]. Last, peritoneal involvement is usually absent and the external surface of the ovaries in KTs often lacks any seedings, adhesions, implantations, or tumor infiltrations–an observation that may oppose the peritoneal spread theory and further supports the theory of retrograde lymphatic spread [9].

The primary carcinoma in KTs can be clinically occult. Thorough examination of the gastrointestinal tract and other sites may fail to find the primary carcinoma. The primary tumor may remain undetected for several years after oophorectomy. Therefore, a diagnosis of ‘‘primary KT’’ has been proposed for some cases in which either there is long-term survival after KT resection without detection of the primary tumor, or a complete autopsy examination fails to find an extraovarian primary tumor [10]. However, many authors do not accept the term primary KT for the following reasons. (1) Primary carcinomas, particularly those arising in the breast and stomach, may be very small, requiring thorough sectioning to detect them, and it is possible that small primary tumors could be missed; (2) it is known that mammary and gastric carcinomas may remain silent for many years; (3) some primary ovarian tumors may have signet ring cells, and this may be responsible for some reported cases of primary KT in the earlier literature. These tumors include the primary ovarian, mucinous carcinoid, and the signet ring stromal tumor of the ovary. Overall, although primary KT may exist, one should exercise considerable caution before making such a diagnosis [9].

Clinical features

Women with KTs tend to be unusually young for patients with metastatic carcinoma as they are typically in the fifth decade of their lives, with an average age of 45 years. This young age of distribution can be related in part to the increased frequency of gastric signet ring cell carcinomas in young women [11]. The symptoms that patients with a KT have are extremely variable. Common presenting symptoms are usually related to ovarian involvement, the most common of which are abdominal pain and distension (mainly because of the usually bilateral and often large ovarian masses). This neoplasm is one of the ovarian tumors most often associated with stromal luteinization and endocrine manifestations as a result.

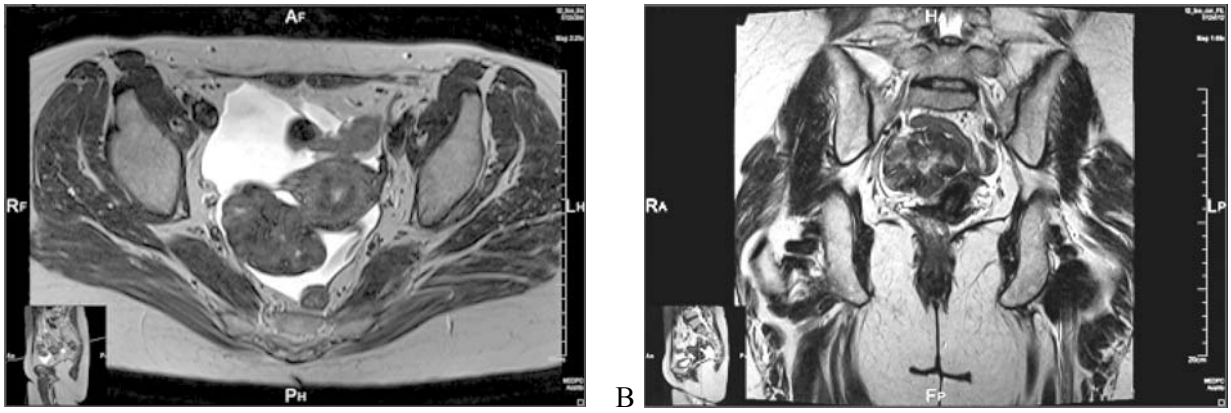
Although symptoms related to the ovarian tumors usually dominate, (only 25% to 30% of patients are initially known to have a primary tumor) in some cases they are overshadowed by symptoms related to the primary tumor at its original site or at other sites of metastatic spread. Examples of the latter are: pulmonary symptoms due to pleural effusion or massive embolization of tumor in the lungs; gastric symptoms not related to primary gastric cancer; ureteral obstruction and pain due to bone metastases [12]. Diffuse infiltration of the marrow may result in thrombocytopenia purpura, anemia, and leukoerythroblastosis [13].

In these various cases the ovarian tumors may be ‘‘incidental’’ findings found during evaluation of the varied symptoms.

At operation ascites is common and liver metastases are rare. If not already known, the carcinoma that has resulted in the KT is usually either found intraoperatively or becomes evident within the next 6 months. The primary neoplasm, however, is hard to find because of its small size in some cases and is not detected until 5 or more years after the metastatic tumor in the ovary in rare instances [12].

Radiologically, KTs on abdominopelvic sonography, computed tomographic or MRI scans usually appear as bilateral ovarian masses. The masses are usually solid but can also be cystic [14] (**Figure 1**).

Preoperative serum CA 125 levels in patients with KTs can be elevated, though they subsequently decrease after tumor resection. 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 primaryadenocarcinomas (gastrointestinal, in particular) for early detection of ovarian metastasis [15].



A B

Fig.1 A,B. *MRI scan showing bilateral ovarian solid masses*

Management

No optimal treatment strategy for KTs has been clearly established in the literature. Whether a surgical resection should be performed has not been adequately addressed. Lower rate of resectability when the primary tumor metastasizes to other sites (in addition to the ovaries) and the overall poor prognosis are the 2 major factors that usually dissuade resection of KTs. On the contrary, if metastasis is limited to the ovaries, surgery may render the patient free of residual disease and the survival time may increase [16]. Hence, the significance of early detection of ovarian metastasis and the importance of serum CA 125 level monitoring (as discussed previously) are vital. Chemotherapy or radiotherapy has no significant effect on prognosis of patients with KTs.

Patients with KTs have an overall mortality rate that is significantly high. Authors in almost all the reported cases underline the poor outcome of this tumor. Most patients die within 2 years (median survival, 14 months) [17]. The prognostic factors for KTs have not been well established, but several studies show that the prognosis is poor when the primary tumor is identified after the metastasis to the ovary is discovered, and the prognosis becomes worse if the primary tumor remains covert. This has been supported by a study that showed that the survival rate was low in the patients who underwent surgery on the ovarian tumor simultaneously or before the surgery on the primary carcinoma, compared with the survival rate of patients who underwentsurgery on the ovarian tumor after the surgery on the primary carcinoma [18].

Pathologic features

KTs are bilateral in more than 80% of the reported cases. The ovaries are usually asymmetrically enlarged, with a bosselated contour. The sectioned surfaces are yellow or white; they are usually solid, although they are occasionally cystic (**Figure 2**). Importantly, the capsular surface of the ovaries with KTs is typically smooth and free of adhesions or peritoneal deposits. Other metastatic tumors to the ovary tend to be associated with surface implants. This may explain why the gross morphology of KT can deceptively appear as a primary ovarian tumor. However, bilateralism in KT is consistent with its metastatic nature. The size is variable; most are over 5 cm, with an average size of about 10 cm, but they are typically not huge neoplasms, uncommonly exceeding 20 cm [12].

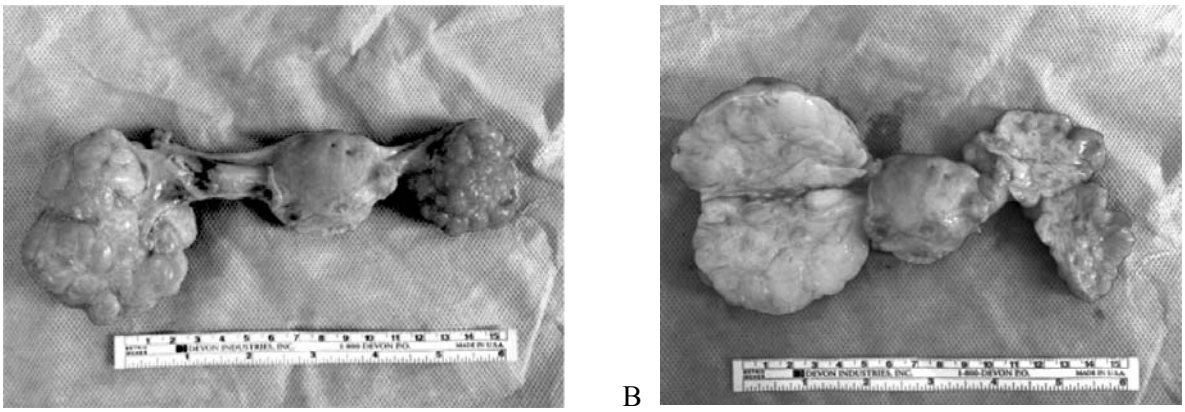


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Fig. 2 A,B. *Gross specimen: bilateral asymmetrically enlarged ovaries with a bosselated contour*

Microscopically, KT has 2 components: epithelial and stromal. The epithelial component is composed chiefly of mucin-laden signet ring cells with eccentric hyperchromatic nuclei. The cytoplasm of the signet ring cells can be eosinophilic and granular, pale and vacuolated, or it can contain a large vacuole with a central to paracentral eosinophilic body composed of mucin. Some tumor cells may lack a mucin vacuole. Mitotic activity is sparse. The signet ring cells can be single, clustered, nested, or they can be arranged in tubules, acini, trabeculae, or cords. Several different patterns can appear in one tumor.

The histochemical identification of intracytoplasmic mucin in the signet ring cells is essential for KT diagnosis. Immunohistochemically, the tumor cells are immunoreactive to epithelial markers, such as cytokeratins (AE1/AE3), and epithelial membrane antigen, and they do not show immunoreactivity to vimentin and inhibin [19]. Immunohistochemical evaluation may aid in distinguishing primary ovarian carcinomas from metastatic carcinomas. Cytokeratins 7 and 20 (CK7 and CK20) immunophenotype is the most commonly used analysis. Primary ovarian carcinomas are almost always immunoreactive to CK7 (90%–100%) but generally are not immunoreactive to CK20. By contrast, metastatic gastric carcinoma tends to be less frequently positive for CK7 (55%) but is positive for CK20 in approximately 70% of cases. Colorectal adenocarcinomas are usually negative for CK7 but positive for CK20 in most cases. Tumors metastasizing from the appendix are commonly positive for CK20 but positive also for CK7 in 50% of cases [20-22]. Use of source-specific antibodies can increase the diagnostic confidence. For example, immunoreactivity for carcinoembryonic antigen and CDX2 together with the immunoexpression pattern of CK7-/CK20+ increases the confidence inpointing toward the colorectal origin of the primary [23]. The mesenchymal component of KT is of ovarian stromal origin and is composed of plump and spindle-shaped cells with minimal cytologic atypia or mitotic activity.

Differentiation from other types of metastatic ovarian tumors is important, particularly mucinous metastases of appendiceal origin. The relation between the ovarian mucinous tumors and low and high grade mucinous adenocarcinomas of the appendix in these cases, in which pseudomyxoma peritonei [24] is typically present, has been controversial until relatively recently but there is now a broad consensus that the ovarian tumors are metastatic from the appendix [25-29]. The ovarian tumors in these cases are often bilateral, and usually are large and multilocular. Mucin may be notable on the external surface. The locules typically contain abundant thick mucin sometimes being likened to ‘‘bags of jelly’’. In many cases mucin dissects into the ovarian stroma (pseudomyxoma ovarii). As is typical of many cases of metastasis, particularly from abdominal viscera, there is usually surface ovarian involvement. This may be in the form of mucin apparently simply ‘‘sitting’’ on the ovarian surface whereas in other cases there is an associated hyaline stromal reaction [12].

Conclusions

KT is a metastatic ovarian tumor that is histologically characterized by mucin-laden signet ring cells. Stomach is the most common primary site, but other organs can serve as a primary site. The lymphatic system is the most likely route for metastasis. Diagnosis of KT with unknown primary warrants careful investigation of mainly the digestive tract and other potential sites. CA 125 levels can be used for screening for early detection of ovarian metastasis as well as for monitoring the course of disease. The prognosis of KT is poor and no curative treatment is currently available.

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ORIGINAL DIAGNOSTIC METHOD OF THE EARLY POSTOPERATIVE COMPLICATIONS IN THE ABDOMINAL SURGERY

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Summary. Original diagnostic method of the early postoperative complications in the abdominal surgery

Results of the monitoring of optical density of the venous blood plasma of 120 patients with acute surgical pathology, carried out at the pre-operational and post-operational periods, were presented. It was revealed that the development of the intra-abdominal post-operational complications is accompanied by the rise of the optical density of the venous blood plasma at the wave length $\lambda = 280$ nm over 0,58 UA. It is important that such rise goes before the clinical and laboratory manifestations of the complications, which allows to conduct their early diagnostics.

Key words: optical density of the venous blood plasma, diagnostics, post-operational complications