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Understanding the Rare Krukenberg Tumor: A Current Review

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Abstract

Krukenberg tumors represent a rare type of secondary ovarian tumors composed of mucinous signet-ring cells. In up to 70% of cases the primary site is a diffuse type gastric carcinoma, which disseminates to the ovary through a retrograde lymphatic pathway.The Krukenberg tumor is a good example of metastatic ovarian organotropism ("seed and soil" hypothesis).The symptoms are nonspecific and usually don't develop until the tumors reach a certain size. The definitive diagnosis can only be made histologically after surgical resection, although imaging findings can indirectly aid in the distinction between benign-malignant and primary-secondary tumors. Immunohistochemistry is the most important diagnostic method in distinguishing primary from secondary ovarian neoplasms, and can usually detect the tissue of origin. The extremely dismal prognosis of Krukenberg tumors is attributed to the fact that they represent an advanced stage metastatic disease. Although the standard treatment is systemic chemotherapydepending on the primary site, there are rough indications that cytoreductive surgery might prolong survival in selected patients.

Key words: krukenberg tumor, ovarian metastasis, secondary ovarian tumor, gastric cancer, signet-ring cells

Introduction

To begin with, the first who stated the idea of the existence of tumors that tend to metastasize to secondary sites that are not related anatomically or vascularly was Paget back in 1889[1]. During the next decade, a German gynecologist and pathologist, named Friedrich Ernst Krukenberg (1871-1946), described a presumably new type of primary ovarian tumor[2]. Krukenberg's experiments showed that this tumor had some significant clinicopathologicalcharacteristics, more specifically ascites and bilateral appearance. Under the microscope, Krukenberg observed the pathognomonic signet-ring cells, which are formed by mucin that pushes the nucleus of the cell on one side. Besides signet-ring cells, these tumors were characterized by solid areas alternating

with myxomatous zones with dominant lymphatic involvement[3]. Krukenberg named these tumors as "brosarcomaovariimucocellularecarcinomatodes"[1]. The first who used the term Krukenberg tumor (KT) seems to be Kraus five years later, who also showed that these tumors were secondary and not primary[4]. However, most articles in the literature report that Schlagenhaufer, and not Kraus, made this discovery six years later[3].

Nowadays, KTs are defined as secondary tumors of the ovaries (STOs) that histopathologically appear as carcinomas that have a significant component (arbitrarily >10%) of mucin-producingsignet-ring cells[5,7]. The most commonly noticed primary site of KTs is gastric cancer (70%), especially the poorly cohesive signet-ring cell type (8), followed by the colorectal tract (10%) and the breast (5%). Other rare sites include: biliary tract and gallbladder, small intestine, appendix, pancreas, uterus, bladder, kidney[7].

Epidemiology

In general, ovarian metastases represent 15-30% of all ovarian tumors and KTs make up about 10% of all ovarian metastases. In more detail, the proportion of non-gynecologic malignancies is estimated to be as high as 60-80% of all STOs (gastrointestinal tract metastases 35-50% and breast metastases 15-30%), whereas the percentagefor gynecologic primary tumors is only 20-40%[9-11]. KTs also own the first place in the category of the most common bilateral metastatic tumor of the ovaries, as they are reported to be bilateral in 70-80% of all cases[7,12,13].

One more important thing that has to be mentioned is the geographic distribution. For example, Asian Countries have a much higher incidence of STOs compared to European countries. This phenomenon can be easily explained if we study the epidemiology of the main cause of KTs, which is gastric cancer. Countries such as Japan and Korea have a much higher incidence of signet-ring cell gastric cancer compared to European countries, resulting in higher prevalence of KTs in these regions[14,15].

A second important factor that is worth mentioning is the age in which KTs are diagnosed. Mean age is about 45 years,and40% of patients are under 40 years old[7]. Studies have shown that patients with primary tumors in the gastrointestinal (GI) tract represent the oldest group, while patients with breast cancer the youngest[10]. Interestingly, KTs commonly appear during pregnancy[7].

Last but not least, two major factors that play a great role in the variability of the incidence of KTs are the laboratory methods used in establishing the diagnosis and the experience of the pathologist[16].

Pathogenesis

Route of metastasis

The exact mechanism of ovarian spread of signet-ring cell tumors is currently unknown[17]. Considering the fact that KTs represent a metastatic disease that is manifested at a relatively young age[8] and that gastric neoplasms can metastasize to the ovaries without involvement of other organs[18], the underlying pathophysiology could be a subject of considerable research interest.

There are three possible mechanisms of spreading: lymphogenous, hematogenous and transcoelomic (across the peritoneal cavity)[19]. The most likely pathway for gastric cancer is the retrograde lymphatic spread[20]. First, cancer cells reach the gastric nodes after having infiltrated the mucosal and submucosal lymphatic vessels of the stomach. This process can happen even during the early stages of gastric cancer[21]. The distance between the receptaculumchyli and the gastric nodes is short. For that reason, cancer cells can easily reach the receptaculumchyli and then the ovaries through the lumbar trunks[20]. Another mechanism that contributes to the lymphogenic pathway is that cancer cells form emboli, causing obstruc-

tion of lymph vessels and inhibition of upward flow. This causes lymph to flow backwards to the ovary[22]. In the case of colorectal and breast cancer, hematogenous spread is the most likely pathway[8.23]. This can partially explain the high incidence of KTs in premenopausal women, who have a greater ovarian vascularity[24]. Although a lot of oncologists and surgeons consider KTs as peritoneal deposits, this is in fact the least possible theory[8].

Ovarianorganotropism

Metastatic organotropism is defined as the tendency of tumors to metastasize preferentially to specific organs[25]. The basic principle of organotropism is that molecular properties of the primary tumor allow the cancer cells to survive better in the microenvironment of the secondary site[26]. This research field is largely unexplored. In the case of KTs, E-cadherin down-regulation has been proposed as a possible mechanism to explain the ovarian organotropism of these tumors[27].

Signs and symptoms

KTs are asymptomatic until they reach a certain size[28]. The most common symptoms are abdominal pain and distention[29]. Interestingly, KTs can cause luteinization of the ovarian stroma and subsequent production of estrogen, progesterone and androgens. These hormonal changes can provoke vaginal bleeding, disturbances of menstrual habits[7] and, rarely, virilism[30]. Ascites is present in about 50% of cases and is associated with a poor prognosis[8]. Occasionally, patients with KTs are presented with nonspecific symptoms, like dyspepsia and weight loss[5.7.10.31]. Finally, extremely rare, but interesting manifestations of KTs are pseudomyxomaperitonei (mucin ascites), especially if the primary site is the appendix[22], and pseudo-Meigs syndrome (triad: KT, ascites, right hydrothorax)[32].

Diagnosis

The final diagnosis of KT is histological and is currently based on the diagnostic criteria of the World Health Organization (WHO). For setting the diagnosis, the following criteria have to be fulfilled: (1) Stromal involvement (2) Mucin-producing neoplastic signet-ring cells (3) Ovarian stromal sarcomatoid proliferation[33].The patient's history, laboratory and imaging tests contribute to the diagnostic procedure. History of gastric cancer can raise suspicion for a metastatic tumor.[34].

KTs are in most cases (about 70%) diagnosed before the primary tumor, but they can be diagnosed during staging (synchronous presentation) or after surgical removal of the primary neoplasm (metachronous presentation)[7].

Ca-125

The Ca-125 marker is usually elevated, as in about 80% of the cases of primary epithelial ovarian tumors[10,35]. Ca-125 levels can mainly be used: (1) As a prognostic factor (2) For post-operative follow-up (3) For early detection of KTs in patients with known GIadenocarcinoma[36,37].

Imaging

Imaging methods including computed tomography(CT), ultrasonography (US), and magnetic resonance imaging (MRI) exhibit large bilateral ovarian masses (in nearly 80% of cases), usually solid but sometimes cystic with solid areas. USshowshyperechoic masses, which sometimes exhibit a characteristic for KTs feature called the "lead vessel sign"(38-40).CT shows bilateralfirm masses with homogeneous enhancement. On MRI with T1 and T2 weighted images, regions of the tumor with desmoplastic reaction are hypointense, whereas mucinous regions are hyperintense[41,42].

Bilateral appearance should always raise suspicion for a metastatic ovarian tumor. It is important

to know that none of the routinely used imaging modalities has proved to be precise enough in differentiating primary ovarian tumors from secondary ones[43,44]. Imaging might, in some cases, reveal the primary origin as well.

Macroscopic features

The characteristic gross morphology of KTs is bilateral asymmetrical ovarian masses. Their color is typically white or yellow, and their surface is solid and smooth. The ovarian surface is usually intact[12,45,47].

Microscopic features

The microscopic features of KTs can be observed with hematoxylin and eosin stain. KTs have an epithelial and a stromal component. The epithelial component consists of mucin-producing signet-ring cells with eccentric nuclei. Different morphological variants of these cells can appear in the same tumor. When there is dominance of the tubular pattern, the tumor is referred to as tubular KT, a subtype that is worth mentioning because of its different differential diagnosis[48]. Edema,sarcomatoid proliferation and desmoplastic reaction are the main characteristics of the stroma. Sometimes the desmoplastic reaction can be so pronounced that the signet-ring cells cannot be seen clearly and there can be a diagnostic confusion with tumors such as fibromas[12,45-47].

Signet-ring cells stain with mucin stains (Mayer mucicarmine, acid-Schiff with diastase digestion and Alcian blue) because of their intracellular mucinous material.Immunohistochemically, the tumor cells are positive for epithelial markers, such as cytokeratins (mainly CK20), but they are vimentin and inhibin negative[36].

Differential diagnosis

The differential diagnosis from other primary and secondary ovarian tumors is based on the characteristic microscopical features of KTs as set by WHO. Sometimes the differential diagnosis can be difficult. The contribution of immunohistochemistry (IHC) is significant.

Histological Differential Diagnosis

The differential diagnosis has to be made between KTs and other ovarian tumors with signet-ring cells,containing mucinous or non-mucinous material. Rarely, it has to be made from tumors without signet-ring cells.Ovarian tumors with signet-ring cells containing mucin include primary mucinous carcinoma and mucinous carcinoid tumors, mainly from the appendix. Ovarian tumors with signet-ring cells without mucin include signet-ring stromal tumor, sclerosing stromal cell tumor, and clear cell adenocarcinoma of the ovary[8].In the case of tubular KTs, the differential diagnosis has to be made from ovarian tumors with lobular pattern, mainly Sertoli-Leydig cell tumors[7,8], especially when KTs occur during pregnancy[49]. Finally, when signet-ring cells present sporadically, KTs can sometimes be confused with fibromas[50].

Immunohistochemistry

IHC plays an important role in the differential diagnosis between primary and secondary ovarian tumors.In the caseof metastatic tumors, it can also be used to identify their primary origin. Cytokeratin 7 and 20 (CK7 and CK20) are the most commonly used antigens in ovarian neoplasms. Generally, a CK7+/CK20- immunophenotype is more typical of a primary ovarian carcinoma, whereas a CK7-/CK20+ or CK7+/CK20+ immunophenotype is an indicator of a metastatic ovarian tumor, usually from the GI tract[51-53].

Prognosis

Prognosis of KT is extremely worse compared to primary ovarian cancer[54]. The majority of patients with KTs die within 2 years and the median survival

is 14 months[55].

Prognostic factors

To date, the factors that influence the prognosis have not been well defined. This is attributed to the absence of prospective studies, contradictory results and the fact that most relevant studies explore the prognosis of STOs in general, without focusing on the strict definition of KTs[19].

Several studies support the hypothesis that an unknown primary site is correlated with a worse prognosis, whereas patients with metachronous presentation have a higher survival rate[28]. Additional favorable prognostic factors include: unilateral KT[56], absence of distant metastases, limited extent of the tumor and R0 resection[57,58]. Furthermore, primary breast cancer is associated with the longest survival, followed by tumors originating in the colon, while patients with primary gastric cancer exhibit the poorest overall survival. The most important clinical finding that foreshadows a dismal prognosis is ascites[59]. Finally, preoperative levels of serum CA 125 greater than 75 U/ml have been related to a worse outcome[28].

Other factors that have been found to influence the survival rate of patients with STOs in general include: age at diagnosis, pre-operative size[28] and presence of peritoneal dissemination[24]. Finally, gene expression profiling (GEP) could be of great importance for the prognostic evaluation of patients with KTs[60].

Treatment

Currently there is no optimal treatment strategy for KTs[8]. KTs represent metastatic disease and thus the routine treatment is chemotherapy depending on the primary tumor[61].

Cytoreductive surgery

The role of cytoreductive surgery in the treatment of STOs is still under debate. Most studies come to the conclusion that optimal debulking prolongs overall survival. Nevertheless, the aforementioned studies are all retrospective, which are often characterized by sampling bias[17] and provide a lower level of evidence compared to prospective studies and randomized trials[62].

According to the current literature, it is reasonable to offer surgical treatment to patients with the following characteristics: young age, good performance status, no distant metastases, feasibility of complete resection and primary colorectal cancer. Cases of gastric origin should be individualized taking into account the fact that patients with metachronous presentation might benefit more from a surgical approach compared to patients with synchronous metastases[17].

In symptomatic patients, palliative surgery should be considered in order to improve quality of life, although chemotherapy could also be applied. Nonetheless, signet-ring cell cancers are characterized by a poor response to chemotherapy. Therefore, surgery is probably the best option for palliative treatment[19].

Adjuvant chemotherapy

The results of studies regarding the impact of adjuvant chemotherapy on survival are contradictory [55,63,64]. However, the majority of the studies support the hypothesis that the administration of systemic chemotherapy after surgery seems to prolong overall survival[15.65,66]. Adjuvant chemotherapy in the case of gastric cancer should be platinum-based, whereas the recommended combination for colorectal cancer is 5-FU/LV with oxaliplatin[67,70].

Prophylactic oophorectomy

At the time of primary GI cancer surgery some surgeons perform prophylactic oophorectomy in order to remove or preventpossible ovarian metastases[71].

However, the majority of women with GI cancer will not develop KTs. Furthermore, oophorectomy can cause long-term harmful consequences, including cardiovascular disease, cognitive impairment, psychiatric disease and osteoporosis. Consequently,prophylactic oophorectomy should not be routinely performed[72].

Oophorectomy should also be considered in case of suspicious visual or palpable ovarian findings while performing surgery for GI cancers. For that reason, it is recommended that general surgeons should perform a thorough examination of the pelvic organs during surgery for gastric, colorectal or appendiceal cancers[73]

KT with unknown primary

In about 10-15% of cases the primary tumor cannot be detected despite a thorough diagnostic workup[13,15]. A basic routine diagnostic evaluation includes: medical history and physical examination, basic blood and biochemistry analysis, CT scans of thorax, abdomen and pelvis and mammography. Endoscopies should be performed only if there are signs, symptoms or laboratory findings that indicate the presence of cancer in a specific location[74].

A possible primary tumor site can be presumed by two laboratory methods: IHC and GEP[75-77] For example, CK20+ CDX2+ and CK7- is the characteristic staining of colorectal cancer[74].

Cancers of unknown primary site (CUPs) have generally a poor prognosis, although there is a subset of patients who have a more favorable overall survival. These subsets are strictly defined, and, among others, includeCUPs with a colorectal IHC or GEP and single metastatic deposits[74].

According to ESMO guidelines regarding CUPs[74], when the origin of a KT remains occult,unilaterality without any other metastatic deposits and/ora colorectal molecular profile or immunophenotyperepresent an indication for site-specific chemotherapy (similarly to patients with known metastatic primary tumors). In any other case, the recommended treatment is low-toxicity empirical chemotherapy.

Conclusion

KTs represent rare secondary ovarian tumors and are characterized by a largely unexplored pathophysiology. The term "Krukenberg tumor" should not be used to describe all metastatic ovarian tumors, because KTs exhibit characteristic histological criteria. There is currently no optimal management strategy, due to the lack of prospective studies. The role of cytoreductive surgery in prolonging survival is still under debate. However, KTs represent an advanced stage of the disease and have in general a dismal prognosis regardless of the treatment strategy.

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