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Review Article

Krukenberg tumor: a systematic overview of its origin

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Abstract:

The incidence of krukenburg tumor is increasing among other secondary ovarian cancers, yet many aspects are still not well understood. In this review, we present a group of secondary ovarian malignant cell sources after we have labeled each subset under the system to which they belong. Also, we talked about the statistics that have been documented for different origins, and how invasive cells reach the ovaries. However, knowledge of these concepts may be involved in developing innovative treatments or even dedicating existing methods to obtain best possible results.

Keywords: krukenberg tumor; ovarian tumor; spread; secondary tumor

Introduction

Cancer is a defective emergence from the genetic system responsible for regulating cellular growth. The world carries huge burdens from cancer, as the annual incidence in 2020 among adolescents and adults was estimated at 89,500 new cases and claimed 9270 lives last year. Moreover, there has been an increase in the number of new cases across all age groups by 3% per year. [1,2]

Cancerous tumors have clinical and health importance, so many researchers have enlisted their researches to understand these overgrowths well and to discover their types, behavior, and consequences.

Krukenburg tumor is a secondary ovarian cancer as a result of spread from the primary one. It is usually characterized by the appearance of signet ring cells filled with mucinous material when studied at the histopathological level. [3]

Statistics about this tumor can't be overlooked, where it represents about 1 to 2% of all ovarian tumors, which can be doubled from 10 to 20 times in some East Asian countries. [4] It is also an unwelcome surprising scenario for obstetricians and gynecologists as many cases in which the tumor was detected by an acute massive bleeding during childbirth or operations.

Now we have a background on what the tumor is and its complications according to what has been mentioned and elaborated in previous literature, but when we talk about what initial cancer tumors lead to this tragic finding, we find that previous studies have mostly taken them in form of sporadic case reports, and the knowledge stock lacks review articles that combine most of these basic cancers into a single space. In this review, we aim to collect as many of the most common and rare cancers that lead to krukenburg tumor as provided in the case reports. In addition to collecting them, we will classify them based on their subordinate to the body systems, so that they can be easily known to the reader.

With this article, we seek to add to the research database a new manuscript that would enhance the general understanding of krukenberg tumor. Also, it helps to predict the course of many types of malignant tumor and raise the clinical sense about the differential diagnosis of krukenberg tumor origins.

Digestive & Hepatobiliary Tract

The difference still exists as to which most cancer causes the secondary spread of ovaries. However, in some East Asian countries such as Korea and Japan, gastric cancer ranges from 23.4% to 30.4%, taking the lead. On the other hand, colorectal cancer and breast cancer are at the top in both Europe and USA. [5,6]

Although the mechanism of malignant cell infiltration has not yet been well understood, the digestive tract includes a variety of pathological mechanisms where it has been found that gastric cancer spreads through the lymphatic vessels in a retrograde manner in many cases has been estimated at 57%. Colorectal cancer spreads by the blood circulation in 67% of cases, and these results have been confirmed by D2-40 and Victoria blue stain, respectively. [7]

Other original cancers that rarely stand behind krukenburg tumor and have been charged through case reports, such as hepatocellular carcinoma (HCC)

which has emerged in a form considered to be one of the rarest variants of HCC. Fibrolamellar hepatocellular carcinoma has been confirmed by immunohistochemical studies. Also, esophageal adenocarcinoma, small intestine adenocarcinoma, gallbladder cancer, cholangiocarcinoma of the hilum, and adenocarcinoid of the appendix were involved and were challenging cases. They were not properly diagnosed until laparotomy has been done. In the same context, gastroesophageal junction adenocarcinoma sends secondary metastatic cells to ovaries and the emerged mass was initially diagnosed as inguinal hernia. [8-14]

Even common cancers can exhibit variants of a unique and uncommon incidence, they also play a role in the events of krukenburg tumor, as in the case of neuroendocrine carcinoma of the rectum, which has a prevalence rate of only 1% among other colorectal cancer variants. [15]

Glandular System

When talking about glands, it worth mentioning breast cancer which ranks first in common sources of secondary malignant cells in ovaries in America by 33.3%, and second place in Netherland and Greece by 14.3% and 15.5%, respectively. [5]

Breast cancer has a strong relationship with krukenburg tumor as a study found that 87% of cases showed clinical and histopathological features indicating that both ovaries were affected, ranging from nest cells, cords, sheets, and single cells. [16]

As for the types of breast cancer that have been involved in a secondary spread to ovaries, they have varied between invasive ductal carcinoma, invasive lobular carcinoma, both ductal and lobular carcinoma, and adenocarcinoma of not otherwise specified. [16]

Also, pancreatic cancer can lead to krukenberg tumor. As in this condition the diagnosis was confusing and raises the question of what the tumors are? are both of them primary, or one is primary and another one is secondary. [17]

Respiratory System

The involvement of pulmonary adenocarcinoma in the pathogenesis of krukenburg tumor can be considered extremely rare. Anyway, this case was confusing as it was initially treated as dysphagia and weight loss. Later, it was discovered that she was also suffering from right ureter stenosis. After a biopsy was taken from peritoneal nodes and histological tests were performed, it confirmed that all these manifestations were due to infiltration from lung cancer. [18]

Urinary Tract

Although urinary bladder cancer has a very little chance of being one of the original malignancies of krukenberg tumor, a case has been recorded which the authors consider being the first of its kind. Unfortunately, she was correctly diagnosed 8 months after the initial diagnosis of granulosa cell tumor by autopsy. [19]

Circulatory System

Surprisingly, hematological malignancies play a role in the incidence of secondary ovarian involvement, specifically krukenburg tumor. But this surprise will come to an end after looking at this report of a teenager who was a known case of Burkitt lymphoma presented with diffuse infiltration of both ovaries, the stomach, the bowels, and the peritoneal membrane. [20]

Discussion

Krukenberg tumor is characterized by mucin-secreting signet ring cell, and this a rare type of adenocarcinoma. Adenocarcinoma means a malignancy of epithelial tissue with secretory properties. When looking at the meaning, most of the krukenburg tumor origins which cases have been recorded apply to it, since the majority of gastric cancers and malignancy of the lower third of the esophagus are adenocarcinomas, since the latter has histological characteristics similar to those of the stomach epithelium. [21]

Colorectal cancer is often adenocarcinoma because the lining of the colon and the upper part of the rectum contain goblet cells that secrete mucus facilitates the excretion process. [22] However, the rest of the digestive tract and its assistant organs, breast, lungs, and urinary bladder exhibit adenocarcinoma as one of their malignant forms, though extremely rare in some organs.

Since signet ring cell carcinoma originates from organs that can do adenocarcinoma, it is expected that these organs will be sources of secondary signet ring cancer cells in the ovaries. Contrary to what has been said, Burkitt lymphoma does not undergo the concept of adenocarcinoma, as B-cells are not an epithelial tissue, even though they secrete antibodies. So, they cannot form primary signet ring cells to be secondary ones in the ovaries, yet a case has been reported. [20] This case raises several questions, which are where those cells came from? Also, could there be a link between signet ring cell carcinoma and connective tissue? and can these malignant cells belong to blood and lymph, which in turn belong to the connective tissue?

The incidence of krukenberg tumor ranges from 1% to 2% among ovarian tumors and this percentage rises to 20% in China, Korea and Japan.[3]

Out of five women who have undergone laparoscopic surgery as a management for adnexal mass associated with cancers from non-reproductive malignancies, one woman suffers from adenexal cancer. 60% of these cancers is krukenburg tumor.[23]

Demographic characteristics may vary as the average age of incidence in an analytical study of one hundred twenty cases is forty-five years. In another study, ninety-seven cases were found to have a mean age of fifty-five years. Despite this slight disparity, we can say that women in the middle age are the most affected group. [24,25]

At the genetic level, it has been shown that the involvement of genetic amplification of the receptor tyrosine kinase (RTK) in krukenberg tumor is low. Also, the loss of FHIT gene is directly related to the occurrence of krukenberg tumor, where this fact was reached by the Immunohistochemical study using anti-FHIT antibodies that demonstrated that FHIT is absent in all krukenberg tumor samples. [23,24]

The expression of programmed death ligand 1 (PD-L1) has an important predictive role since the presence of PD-L1in krukenberg tumor from gastric cancer refers to bad outcomes and the the opposite is true for krukenberg tumor from colorectal cancer.[25]

Usually, the gross pathological features are that both ovaries are metastasized with asymmetrical enlargement and white yellowish or grayish color. The surface is solid and knobby, and their capsule have no indications that the tumor is secondary. [26,27]

Although mucin-secreting signet ring cells is a pathognomic feature of krukenburg tumor, there are other important histological features for tumor identification. They described first by Scully and Serov, then World Health Organization depended upon them to design the diagnostic criteria. These microscopic manifestations are affected ovarian stroma, and sarcomatoid growth of the ovarian stroma that can be seen with hematoxylin and eosin stain. Since the epithelial part of krukenberg tumor consists of mucin-secreting signet ring cells, it can be stained by periodic acid-Schiff with diastase digestion, Alcian blue, and Mayer mucicarmine stain. [28,29]

At the level of immunohistochemical study, krukenberg tumor stains positive for cytokeratins and epithelial membrane antigens, and it stains negative for vimentin and inhibin. [30,31]

The source of the secondary ovarian cancer cells comes from many organs that follow different systems in the human body as mentioned earlier. These organs are involved in causing krukenburg tumor to spread their cancer cells in several ways that have not yet been adequately identified. What we can say at the moment is that there are three proven pathways through which the original tumor can infiltrate, which are by hematologic spread, via the lymphatic vessels, or directly through the coelomic membrane, and in some times the infiltration can occur by more than one pathway that the blood and lymphatic pathways are often with each other. [4,5,23]

Also, no clear regulator is governing the spread, but there are some hypotheses that the method of infiltration from any primary tumor is likely determined by the anatomical nature of the organ from which it originated. For example, gastric cancer makes its way to ovaries mainly through lymphatics, and if we consider dissecting the stomach, the mucosal and submucosal layers contain dense lymphatics that facilitate infiltration even at early stages. In contrast, the ovaries are connected to the urogenital lymphatic network, which in turn connects to the intestinal trunk via cisterna chyli. The intestinal trunk connects to the stomach lymph nodes contract through the celiac nodes. Besides, the blockage of the lymph nodes behind the peritoneum with cancerous cells of the stomach forces the lymph current to reverse to the ovaries. In the late stages of gastric carcinoma, the lymphatic and blood methods can co-spread, and by applying the concept of anatomical background, the stomach is supplied by five arteries and veins, that is, it is rich with blood supply. This may contribute to clear the picture of the spreading mechanism. [7,24]

Colorectal cancer is one of the differential diagnoses of the sources of krukenburg tumor, and so far it has shown a tendency to spread through blood vessels. This tendency can be supported by the abundance of the direct blood vessels from both superior and inferior mesenteric systems. [7]

Transcoelomic infiltration plays an essential role in the spreading process if the tumor in the ovaries is primary, but secondary ones have very little chance to guide the infiltration. Although the hypothesis of malignant cells falling after separation from the stomach into the bottom dragged by gravity seems to make some sense. [25]

On the other hand, why are all these malignancies exactly choosing the ovaries to send their cancer cells? That question leads us to identify organotropism. Many studies have targeted that concept to find out the factors that favor only a particular organ. It concluded that the target structure could contain factors essential to the life and activity of malignant cells, invasive cells may be attracted by certain molecules from that organ, forming new blood vessels at the destination, and the ability of the cells to invade only suited that organ. Despite all these explanations, the concept of organotropism is still not clear enough. [26]

For initial investigations, they are ultrasound or CT scans of the abdomen and pelvis. confirmation tests include histopathological study intended to establish at least 10% mucin-filled signet ring cells. However, World Health Organization (WHO) has issued diagnostic criteria built on the Serov and Scully description, namely the presence of sarcomatoid growth in the ovarian stroma, affected ovarian stroma, as well as the signet ring cells. Furthermore, the positivity of cytokeratin AE1/AE3 and epithelial membrane antigen, and negativity of vimentin and inhibin in the immunohistochemical study. [4,27]

Different krukenberg tumor origins are likely to vary the treatment method. This difference is not about the main lines of any malignant tumor treatment, but about the subtypes of each line and the feasibility of monotherapy or dual therapy. Some studies have demonstrated the high effectiveness of cytoreductive surgery, while hyperthermic intraperitoneal chemotherapy has shown its usefulness, whether alone or combined with surgery, in addition to having fewer side effects than chemotherapy. If the invasion is limited to ovaries, the role of surgery is maximized, and if beyond that, palliative surgery may begin with salpingo-oophorectomy and may reach the level of salpingo-oophorectomy with hysterectomy, in addition to primary tumor treatment. [4,28,29]

Conclusion

Origins of krukenburg tumor are not exclusive to gastric, colorectal, and breast cancers. So doctors need to update their knowledge so they can detect it early, and that reflects positively on treatment options and outcomes.

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Conflict Of Interest

No conflicts exist.

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