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An Up-to-Date Understanding of the "Krukenberg Tumor" Mechanism

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Abstract

Krukenbergtumor is a metastatic ovarian tumor with its primary site being the gastrointestinal tract. The pathogenesis of Krukenberg tumor formation is still in its hypothetical stage though the current understanding suggests lymphatic, hematogenous and transcoelomic route as the 3 major route of metastasis. There is a lack of description in the literature related to the pathway of metastasis. Here, we intend to search the available literature and provide a thorough review, which may be helpful to the readers to understand the issue of mechanism of Krukenberg tumor metastasis more clearly.

Keywords

Krukenberg Tumor, Ovary Cancer, Metastasis, Gastrointestinal Cancer

1. Introduction

Krukenberg tumor is a metastatic tumor of the ovary that originates from the gastrointestinal tract. The characteristic this kind of tumor shows is the presence of mucin-filled signet-ring cells, which account for at least 10% of the tumor [1]. The diagnostic criteria of the WHO are based on the pathological description by Serov and Scully for making the diagnosis of Krukenberg tumor [2]. The description states that the following features should be present: 1) the presence of stromal involvement, 2) the presence of mucin producing neoplastic signet ring cells and 3) ovarian stromal sarcomatoid proliferation. In ovarian metastasis, signet-ring cell carcinomas are associated more often than other carcinoma type by a ratio of about 4:1 [3]. Krukenberg tumor was first described by a German pathologist Friedrich Ernst Krukenberg in 1896 but it was only 6 years later in 1902 Schlagenhaufer pointed out the true metastatic nature of the Krukenberg tumors [4]. It is difficult to know the

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precise incidence of ovarian metastasis. In general, Krukenberg tumor is a rare disease. Only about 1% to 2% of all ovarian tumors are Krukenberg tumor but in some countries like Korea, Japan and China where the incidence of stomach cancer is very high this rare disease is not so un-common [5] [6]. In most Krukenberg tumor cases, stomach is the main primary site. Some studies have shown stomach cancer to be primary site in about 70% of Krukenberg tumor cases [5]. Gastric and colorectal cancers together account for almost entire (90%) of the primary site for the origin of this tumor [5] [7]. The prognosis of a Krukenberg tumor is poor. The median survival period is only 14 months, since such metastasis involves rapid cell growth and proliferation [8]. Pathologically distinguishing Krukenberg tumor from a primary ovarian cancer is not always easy. But it is very important to clinically distinguish Krukenberg tumor from the primary ovarian cancers because the treatment protocols, chemotherapy response, and prognosis are significantly different between the two [7] [9]. Complete metastasectomy provides survival benefit in selected cases. The route of metastasis of tumors originating from the gastrointestinal tract is still in the hypothetical stage. Although the mechanism of Krukenberg tumor formation remains inconclusive [10], the current understanding suggests three major possible pathways of metastasis: lymphatic, hematogenous, and transcoelomic metastasis. Lymphatic and hematogenous metastasis meaning the cancer cells metastasis via the lymphatic channels and blood vessels respectively, where as transcoelomic metastasis is when the free-floating cancer cells spread intra abdominally. However, due to the detection of original tumor at advanced stage majority of the cases may involve mixed metastatic pathways. Lymphatic and hematogenous spread, especially lymphatic spread is widely believed to play the possible role in cancer metastasis from primary gastrointestinal site to the ovaries [10].

2. Discussion

In 1902, Schlagenhaufer described the establishment of metastatic nature in most Krukenberg tumor [4]. Since then, it has been witnessed that many carcinomas, including stomach, colon, rectum, breast, thyroid, gallbladder, pancreas and malignancies originating from the female genital tract may metastasize to the ovaries [11]. Gastrointestinal tract is the major nongenital source from which most of the cancers metastasize to the ovary. Despite a century long establishment of metastatic nature of ovarian tumor, the metastatic pathway of tumor arising from gastrointestinal tract is still in its hypothetical stage [12]. Still there is very few literature description related to this issue. The reason for so may be the rare incidence of this disease “Krukenberg tumor” which renders the chance for the clinician from making a comprehensive observation. Other reason may be the fact that different doctors frequently handle patients with metastatic ovarian tumors at different periods of the disease process thus interrupting the continuity of observation. In addition ovarian metastasis is often termed as a late presentation of cancer [13], thus the treatment is palliative which frequently do not include a comprehensive assessment of disease extension. As a result, the pathway of metastasis to the ovaries from cancers of the gastrointestinal tract has not been convincingly described [14]. It is crucial and essential to elucidate the mechanisms of Krukenberg tumor metastasis in order to improve the prognosis of such patients.

Krukenberg tumor demonstrates the selective spread of cancers, often in the stomach-ovarian axis. Because of the fact that gastric neoplasms selectively metastasize to the ovary presenting ovarian-specific metastasis without other tissues involvement, it has since long drawn the attention of many pathologists [15]. Though the primary site for metastatic ovarian cancer are various including breast, appendix, gall bladder, pancreas, uterine cervix, urinary bladder, renal pelvis etc. but the majority, more than 90% of the of the metastasis is from either stomach or colorectum [16]-[18]. Many study showed stomach to be the main primary site, some showed it being as high as 76% [16] [17] [19]. But some recent article also showed a higher incidence of KT of colorectal origin compared with those of gastric origin [17] [18]. There are various routes by which many tumors arising from primary organs spread to the ovaries. But the mechanism of Krukenberg tumor formation remains illusive. Direct spread is one of the pathways for cancer invasion into adjacent organ. Some researchers believe spread from more distant sites is mainly via other routes, for example, blood vessels, lymphatic, and surface implantation from intra-abdominal cancers. The current understanding of the mechanism of Krukenberg tumor suggests three possible pathways of metastasis: lymphatic, hematogenous, and transcoelomic metastasis. Because the original cancers are detected at advanced stagethere are many cases with mixed metastatic pathways [5] [20] [21]. Yukio Yamanishi *et al.* [22] investigated the metastatic pathways from the primary organs to the ovaries examining the microscopic findings from 18 original and 18 metastatic ovarian tumors. They also examined the immunohistochemical findings of metastatic ovarian tumors using victoria blue stain for vascular invasion and

D2-40 expression for lymphangio invasion. Their result showed out of 7 gastric cancers, 4 cases *i.e*. 57% had ovarian lymphangio invasion, but none out of 6 colorectal cancers had ovarian lymphangio invasion ($P < 0.05$). Also among the 7 gastric cancers none had ovarian vascular invasion. On the other hand, out of 6 colorectal cancers 4 (67%) showed to have ovarian vascular invasion. There were significant differences between them ($P < 0.05$). Thus their hypothesis suggesting relatively higher rate of vascular metastasis from the colorectal cancers than from the gastric cancers, and relatively higher rate of lymphatic metastasis from the gastric cancers than from the colorectal cancers seems justifiable. Al-Agha and Nicastri also support the concept where they suggest the most likely route of metastasis of gastric cancer to the ovaries is lymphatic spread [5].

Of the 3 three possible: lymphatic, hematogenous, and transcoelomic pathways of metastasis, the retrograde lymphatic spread has been evidenced by many researchers to be by far the most likely route of metastasis. As we know stomach is the main primary site for the origin of Krukenberg tumor. Several explanations have been provided in the literature to prove retrograde lymphatic spread to be the most acceptable mechanism for the metastasis of cancer from stomach to the ovary. In many cases of Krukenberg tumor lymphatic permeation is microscopically noted at the hilum and cortex of the ovary. Review of literature for early gastric carcinoma by Kakushima N, Kamoshida T, Hirai S, *et al.* reported 8 cases of KT where at primary gastric carcinoma cancer cells was only confined to mucosa and submucosa [23]. As we know there is a rich lymphatic plexus at the gastric mucosa and submucosa, the lymphatic spread in the above mentioned 8 cases of early gastric cancers couldthus be explained. Also some studies have shown, when the number of metastatic lymph node in the case of gastric carcinoma is increased there is a higher risk of ovarian metastasis [24]. Atrophic gastritis has also been viewed as a risk factor of metastases because in the atrophic gastritis patients, lymphatic capillaries get closer to the mucosal surfacethus facilitating more easy infiltration of the intramucosal cancer cells into the lymphatic capillaries [23]. Yamanishi, Yukio, *et al*. in their study stated the reason for lymphatic metastasis from stomach to the ovary as the lymphatic vessel anatomy. Via the lumbar trunk urogenital lymph vessel tracts give rise to the receptaculum chili, which connect to the intestinal trunks. Via celiac nodes the intestinal trunks connect to the gastric, hepatic, pancreaticolineal, and mesenteric nodes (superior mesenteric and mesocolic nodes). The distance from the receptaculum chili to the gastric nodes is short, so the gastric cancer cells easily metastasize via the receptaculum chili to the urogenital lymph vessel trunks, which supply the ovaries [22]. Chang *et al*. [25] in their study evaluated the relation of the lymph node status and ovarian metastasis in colon cancer patients. They also concluded retrograde lymphatic spread to be the route of metastasis and the ovaries were among the first organs involved with such metastasis. Kakushima N *et al*. [23] states in favor of lymphatic spread of KT. In ovarian hilum, ovarian cortex, mesoovarium and mesosalpinx there are large amount of lymphatic tissue where carcinomatous emboli are frequently observed in KT [23]. Tazaki T *et al.* had done a study to observe lymph vessel permeation in the ovarian hilum where they found all oftheir 10 cases had lymph vessel permeation by cancer cells at the ovarian hilum [26]. Further in favor of retrograde lymphatic spread, Asbun HJ *et al*. suggest that the cancer cells from GI carcinoma could invade the retroperitoneal lymph nodes, which could obstruct the lymphatic vessels and thus countercurrent the lymphatic fluid to the ovaries [27].

Among other mechanisms, direct deep invasion have also been suggested by few authors to explain the progression of KT [7]. Yamanishi, Yukio, *et al*. in their study observed a high frequency of direct pathological invasion into the ovary in the primary cancers with location near the ovaries. Many authors have considered peritoneal spread not to be a predominant mode of ovarian metastasis of cancer cells because in most cases of KT there is absence of peritoneal involvement such as adhesions, seeding, implantations or tumor infiltration on the external surface of the ovary [3] [5]. And even on gross pathological examination these tumors present as an enlarged ovaries with bosselated surface and the capsular surface is usually smooth and lack any implants [3]. In contrast Jeung, Y.J *et al*. had the opinion that the most important predictor of KT is the T stage of primary carcinoma. There is a major chance of cancer cells invading the ovaries when the serosal layer or tissue beyond is invaded by GI cancer in female patients. Based on the cases of advanced T stage of primary GI cancer, the tumor cells could easily be scattered into the peritoneal cavity forming a metastasis to ovaries [7] [10]. So attention should always be paid regarding transcoelomic metastasis to ovaries from advanced GI carcinomas. The study result of Li Qiu *et al*. showed the 1-year and 2-year metastasis-free survival rates were 48.5% and 18.2% in T3 group, compared with 14.3% and 0 in T4 group ($P = 0.031$) [10].

In contrast Kuwabara, Y *et al*. [28] performed an *in vivo* model of ovarian metastasis. In their experiments, eight different human carcinoma cell lines were transvenously and intraperitoneally implanted in immune-deficient mice to study the mechanisms underlying ovarian-specific metastasis. They examined the capacity of

these cell lines for ovarian metastasis, and succeeded in establishing an *in vivo* ovarian-metastasis model with stromal reaction in the ovarian tumor. All cell lines demonstrating some capacity for metastasis to the ovary showed loss or reduction of E-cadherin expression thus they further investigated whether E-cadherin down-regulation could be involved in ovarian-specific metastasis. And their result showed loss or reduction of E-cadherin expression on immunoblotting and/or immunohistochemistry thus they hypothesized that E-cadherin down-regulation might have some in ovarian-specific metastasis.

As we know majority of the KT patients are young females. The greater vascularity of the ovaries in young female facilitating hematogenous spread is well accepted by many authors [3] [29]. Tamura PY *et al*. did study of gastric carcinoma in young people. The patients they studied were all less than 36 years. They in their study found the ovaries were involved in 55% of the cases [29]. Few authors favor the theory of hematogenous spread through thoracic duct [30]. Yamanishi, Yukio, *et al*. [22] in their study using immunohistochemical methods found that the rate of vascular metastasis from the colorectum to the ovary was significantly higher than from the stomach to the ovary. They suggest the reason for higher rate of hematogenous metastasis from colorectum than from stomach to the ovaries is because the area, number and volume of vessels are all larger in the colon than those of the stomach. Also Moore *et al*. have suggested hematogenous pathways for metastasis from colon to the ovary, because in their study they found that the laterality of metastasis from colon cancer to the ovary did not correspond to the side of the primary lesion [31].

3. Conclusion

Krukenberg tumor is a metastatic ovarian tumor mostly arising from stomach and colon as primary site. Mucin-laden signet ring cells histologically characterize it. It is crucial and essential to elucidate the mechanisms of Krukenberg tumor metastasis in order to improve the prognosis of such patients. Despite a century long establishment of metastatic nature of ovarian tumor, the metastatic pathway of tumor arising from gastrointestinal tract is still in its hypothetical stage. The current understanding of the mechanism of Krukenberg tumor suggests three possible pathways of metastasis: lymphatic, hematogenous, and transcoelomic metastasis. Of these, retrograde lymphatic spread seems to be more acceptable pathway of metastasis. E-cadherin down-regulation as the possible mechanism of ovarian specific metastasis has been proposed. And such *in vivo* model of ovarian metastasis is needed in search for and to outline more definitive pathway for Krukenberg tumor metastasis.

References

[1] Nakamura, Y., Hamamatsu, A., Koyama, T., Oyama, Y., Tanaka, A. and Honma, K. (2014) A Krukenberg Tumor from an Occult Intramucosal Gastric Carcinoma Identified during An Autopsy. *Case reports in Oncological Medicine*, **2014**, Article ID 797429. http://dx.doi.org/10.1155/2014/797429

[2] Serov, S.F., Scully, R.E. and Sobin, L.H. (1973) International Histological Classification of Tumors. No. 9. Histological Typing of Ovarian Tumours. WHO, Geneva, 1-56.

[3] Young, R.H. (2006) From Krukenberg to Today: The Ever Present Problems Posed by Metastatic Tumors in the Ovary: Part I. Historical Perspective, General Principles, Mucinous Tumors Including the Krukenberg Tumor. *Advances in Anatomic Pathology*, **13**, 205-227. http://dx.doi.org/10.1097/01.pap.0000213038.85704.e4

[4] Schlagenhaufer, F. (1902) XXX. Ueber das metastatische Ovarialcarcinom nach Krebs des Magens, Darmes und anderer Bauchorgane (Part 1 of 2). *Gynecologic and Obstetric Investigation*, **15**, 485-506. http://dx.doi.org/10.1159/000283419

[5] Al-Agha, O.M. and Nicastri, A.D. (2006) An In-Depth Look at Krukenberg Tumor: An Overview. *Archives of Pathology & Laboratory Medicine*, **130**, 1725-1730.

[6] Jiang, R., Tang, J., Cheng, X. and Zang, R.Y. (2009) Surgical Treatment for Patients with Different Origins of Krukenberg Tumors: Outcomes and Prognostic Factors. *European Journal of Surgical Oncology* (*EJSO*), **35**, 92-97. http://dx.doi.org/10.1016/j.ejso.2008.05.006

[7] Jeung, Y.J., Ok, H.J., Kim, W.G., Kim, S.H. and Lee, T.H. (2015) Krukenberg Tumors of Gastric Origin versus Colorectal Origin. *Obstetrics & Gynecology Science*, **58**, 32-39. http://dx.doi.org/10.5468/ogs.2015.58.1.32

[8] Moghazy, D., Al-Hendy, O. and Al-Hendy, A. (2014) Krukenberg Tumor Presenting as Back Pain and a Positive Urine Pregnancy Test: A Case Report and Literature Review. *Journal of Ovarian Research*, **7**, 1. http://dx.doi.org/10.1186/1757-2215-7-36

[9] Khan, M., Bhatti, R.P., Mukherjee, S., Ali, A.M., Gilman, A.D., Mirrakhimov, A.E. and Iroegbu, N. (2015) A

26-Year-Old Female With Metastatic Primary Gastrointestinal Malignancy Presenting as Menorrhagia. *Journal of Gastrointestinal Oncology*, **6**, E21.

[10] Qiu, L., Yang, T., Shan, X.H., Hu, M.B. and Li, Y. (2011) Metastatic Factors for Krukenberg Tumor: A Clinical Study on 102 Cases. *Medical Oncology*, **28**, 1514-1519. http://dx.doi.org/10.1007/s12032-010-9610-4

[11] Petru, E., Pickel, H., Heydarfadai, M., Lahousen, M., Haas, J., Schaider, H. and Tamussino, K. (1992) Nongenital Cancers Metastatic to the Ovary. *Gynecologic Oncology*, **44**, 83-86. http://dx.doi.org/10.1016/0090-8258(92)90017-D

[12] Young, R.H. and Scully, R.E. (1991) November. Metastatic Tumors in the Ovary: A Problem-Oriented Approach and Review of the Recent Literature. *Seminars in Diagnostic Pathology*, **8**, 250-276.

[13] Mazur, M.T., Hsueh, S. and Gersell, D.J. (1984) Metastases to the female Genital Tract: Analysis of 325 Cases. *Cancer*, **53**, 1978-1984. http://dx.doi.org/10.1002/1097-0142(19840501)53:9<1978::AID-CNCR2820530929>3.0.CO;2-1

[14] Bidus, M.A., Elkas, J.C. and Rose, G.S. (2012) Germ Cell, Stromal, and Other Ovarian Tumors. *Clinical Gynecologic Oncology*, 329-365. http://dx.doi.org/10.1016/b978-0-323-07419-3.00012-6

[15] Willis, R.A. (1973) The Spread of Tumors in the Human Body. 3rd Edition, Butterworth, London, 319-363.

[16] Yada-Hashimoto, N., Yamamoto, T., Kamiura, S., Seino, H., Ohira, H., Sawai, K., Kimura, T. and Saji, F. (2003) Metastatic Ovarian Tumors: A Review of 64 Cases. *Gynecologic Oncology*, **89**, 314-317. http://dx.doi.org/10.1016/S0090-8258(03)00075-1

[17] Man, M., Cazacu, M. and Oniu, T. (2006) [Krukenberg Tumors of Gastric Origin versus Krukenberg Tumors of Colorectal Origin]. *Chirurgia* (*Bucharest, Romania*: 1990), **102**, 407-410.

[18] McGill, F., Ritter, D.B., Rickard, C., Kaleya, R.N., Wadler, S. and Greston, W.M. (1998) Management of Krukenberg Tumors: An 11-Year Experience and Review of the Literature. *Primary Care Update for OB/GYNS*, **5**, 157-158. http://dx.doi.org/10.1016/S1068-607X(98)00047-X

[19] Kiyokawa, T., Young, R.H. and Scully, R.E. (2006) Krukenberg Tumors of the Ovary: A Clinicopathologic Analysis of 120 Cases with Emphasis on Their Variable Pathologic Manifestations. *The American Journal of surgical Pathology*, **30**, 277-299.

[20] Young, R.H. (2007) From Krukenberg to Today: The Ever Present Problems Posed by Metastatic Tumors in the Ovary. Part II. Advances in Anatomic Pathology, **14**, 149-177. http://dx.doi.org/10.1097/PAP.0b013e3180504abf

[21] Parker, R.T. and Currie, J.L. (1992) Metastatic Tumors of Ovary. *Gynecologic Oncology*, **2**, 987-999.

[22] Yamanishi, Y., Koshiyama, M., Ohnaka, M., Ueda, M., Ukita, S., Hishikawa, K., Nagura, M., Kim, T., Hirose, M., Ozasa, H. and Shirase, T. (2011) Pathways of Metastases from Primary Organs to the Ovaries. *Obstetrics and Gynecology International*, **2011**, Article ID 612817. http://dx.doi.org/10.1155/2011/612817

[23] Kakushima, N., Kamoshida, T., Hirai, S., Hotta, S., Hirayama, T., Yamada, J., Ueda, K., Sato, M., Okumura, M., Shimokama, T. and Oka, Y. (2003) Early Gastric Cancer with Krukenberg Tumor and Review of Cases of Intramucosal Gastric Cancers with Krukenberg Tumor. *Journal of Gastroenterology*, **38**, 1176-1180. http://dx.doi.org/10.1007/s00535-003-1227-3

[24] Kim, N.K., Kim, H.K., Park, B.J., Kim, M.S., Kim, Y.I., Heo, D.S. and Bang, Y.J. (1999) Risk Factors for Ovarian Metastasis Following Curative Resection of Gastric Adenocarcinoma. *Cancer*, **85**, 1490-1499. http://dx.doi.org/10.1002/(SICI)1097-0142(19990401)85:7<1490::AID-CNCR9>3.0.CO;2-G

[25] Chang, T.C., Changchien, C.C., Tseng, C.W., Lai, C.H., Tseng, C.J., Lin, S.E., Wang, C.S., Huang, K.J., Chou, H.H., Ma, Y.Y. and Hsueh, S. (1997) Retrograde Lymphatic Spread: A Likely Route for Metastatic Ovarian Cancers of Gastrointestinal Origin. *Gynecologic Oncology*, **66**, 372-377. http://dx.doi.org/10.1006/gyno.1997.4793

[26] Tazaki, T., Nishimura, H., Yakushiji, M., Matsumura, T., Higashijima, H. and Morisaki, H. (1990) Histomorphological Studies of Krukenberg Tumor on Early Ovarian Metastatic Lesion. *Nihon Sanka Fujinka Gakkai Zasshi*, **42**, 353-359.

[27] Asbun, H.J. and Hughes, K.S. (1993) Management of Recurrent and Metastatic Colorectal Carcinoma. *The Surgical clinics of North America*, **73**, 145-166.

[28] Kuwabara, Y., Yamada, T., Yamazaki, K., Du, W.L., Banno, K., Aoki, D. and Sakamoto, M. (2008) Establishment of an Ovarian Metastasis Model and Possible Involvement of E-Cadherin Down-Regulation in the Metastasis. *Cancer Science*, **99**, 1933-1939. http://dx.doi.org/10.1111/j.1349-7006.2008.00946.x

[29] Tamura, P.Y. and Curtiss, C. (1960) Carcinoma of the Stomach in the Young Adult. *Cancer*, **13**, 379-385. http://dx.doi.org/10.1002/1097-0142(196003/04)13:2<379::AID-CNCR2820130223>3.0.CO;2-F

[30] Taylor, A.E., Nicolson, V.M. and Cunningham, D. (1995) Ovarian Metastases from Primary Gastrointestinal Malignancies: The Royal Marsden Hospital Experience and Implications for Adjuvant Treatment. *British Journal of Cancer*, **71**, 92. http://dx.doi.org/10.1038/bjc.1995.18

[31] Moore, R.G., Chung, M., Granai, C.O., Gajewski, W. and Steinhoff, M.M. (2004) Incidence of Metastasis to the Ovaries from Nongenital Tract Primary Tumors. *Gynecologic Oncology*, **93**, 87-91. http://dx.doi.org/10.1016/j.ygyno.2003.12.039

Abbreviation

KT—Krukenberg Tumor