Metastatic Tumours in Ovaries

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INTRODUCTION

The ovaries provide a fertile area for metastases and are the most commonly involved organs in the female genital tract, regardless of the location of the primary tumour.[1] Around 5-10% of all adnexal masses detected on physical examination are metastatic tumours of the ovary (MTO), though incidence rates for secondary tumours in this organ rise as high as 40%, depending on the geographical location.[2]

Metastatic tumours can be confused with primary tumours of the ovary.[3,4] The reason for that is in the fact that the metastatic tumours have the histopathology similar to the primary ovarian tumours.[5,6]

Although it is difficult to estimate the percentage of metastatic ovarian tumours from extra-genital primary sites, the incidence has been reported to range between 7% and 12.5%.[2,4] The gastrointestinal tract is the first site to be scanned. The breast is the second most important primary site.[5] Because ovarian metastasis develops in advanced stages of extra-genital organ tumours, it generally carries a poor prognosis.

By the incidence of secondary deposits, we may point out cancers of the colon, stomach, breast and endometrium, as well as lymphomas and leukemias.[9-11, 24] Ovarian metastases have been detected in 32-38% of breast cancer patients; 28-35% of women with colorectal cancer; and 16% of women with genital tract tumours (endometrium, uterine cervix, vagina, vulva.[25] Lately, special attention has been paid to mucinous tumours of the appendix, pancreas and biliary tract, which commonly spread to the ovary, resembling thus mucinous borderline tumour or mucinous ovarian carcinoma.[26] Other malignant epithelial tumours, but also sarcomas and blastomas, can too metastasize to the ovary, though such metastases are fairly rare.[27] In a compilation by Olivier M et al (2007), incidences of metastatic ovarian tumours have been represented in the following table:

Table: Incidences of ovarian metastasis in different series [12-23]:

Primary Site (Ref)	Greene et al (12)	Webb al (13)	Mazar r et al (14)	Demopoulos et al (15)	Gagnon and Tetu (16)	Fujiwara a et al (18)	Yada-Hashimoto et al (19)	Moore et al (20)	Ayhan et al (21)	Skimi sda et al (22)
Breast	42%	31%	46%	32%	64%	13%	9%	5%	27%	75%
Stomach	2%	8%	6%	6%	58%	18%	15%	4%	17%	41%
Colorectal	15%	38%	40%	12%		4%	7%	19%	18%	75%
Uterine	18%	12%	16%	14%	26%		15%		64%	
Uterin	1%	3%	14%	0%			9%		4%	
Others	1%	8%	21%	12%	18%	25%	9%	31%	21%	64%

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MTO are bilateral in 70% of the cases and present as multiple superficial or parenchymatous, mostly solid nodules of various sizes. Ovaries themselves can be normal in size, slightly enlarged, or sized more than 10 cm in diameter. The presence of implants on the surface of ovaries, multi-nodularity and intravascular tumour emboli are of use in the diagnosis of MTO which reaches ovaries via abdominal cavity or Fallopian tubes.[24]

Histopathologic appearance of most MTO is similar to the one in ovarian cancers. Differential diagnosis of primary and secondary malignant tumours of the ovary is difficult if it is based only on clinical and histopathologic characteristics of the tumour. Immunohistochemistry has an important role in differential diagnosis of primary and metastatic ovarian tumours, and thus in appropriate treatment administration and assessment of prognosis.[24]

For convenience we can divide the metastatic tumours of the ovaries into 2 broad groups:

A.   Metastasis from the gonadal organs.

B.   Metastasis from the extra-genital organs.

Krukenberg's tumour: (KT) :

Defined by an ovarian carcinoma that contains a significant component (at-least 10% of the tumour area) of mucin-filled signet-ring cells typically lying within a cellular stroma derived from the ovarian stroma. Recently this term has been used inappropriately by some authors to include: all glandular carcinomas metastatized to the ovary or all metastatic ovarian carcinomas arising in gastrointestinal tract. Almost all the KTs are metastatic.[25]

This entity was first recognized by Paget, J. (1854) in *Lectures on Surgical Pathology,* as a distinctive form of ovarian tumour associated with mammary or gastric cancer of "fibrous hard" nature. However they did not opine whether the tumour was primary or secondary. Latter Krukenberg, F. et al (1896) identified 6 cases of Krukenberg's tumours containing signet ring cells. However he then erroneously identified these lesions as primary fibrosarcoma containing mucinous cells.[26]

This tumour can be seen in a wide age range varying from 13 to 84 years and 40% of the tumours are seen in < 40 years of age [5].Clinically the patient may be asymptomatic or may present with abdominal swelling or pain in abdomen (90%) or hormonal manifestations like post menopausal bleeding, hirsutism, virilization etc.

Krukenberg's tumours are bilateral tumour in 3/4 of the cases and often the involvement of the smaller ovary may be identifiable only on microscopical examination. And in 20-30% of cases the primary gastric carcinoma and the Krukenberg's tumour are diagnosed concurrently.

The modes of metastasis are: blood flow, lymphatic spread, trans-peritoneal spread [25].

Gross findings: > 80% of the krukenberg's tumour are bilateral, in comparison to 15% bilateral primary endometrial or mucinous tumours. The ovaries may be of normal size or sometimes may be > 10 cm in size. The cut surfaces are solid, firm fleshy, rubbery or vague nodular and grey-white to yellow in colour. Few smaller cystic cavities filled with mucinous material can be identified. Necrotic or haemorrhagic areas may be seen.

Microscopical findings: Microscopically these tumours are comprised mainly of epithelial and stromal components. Different histological patterns can be identified like- classical pattern tubular pattern, varied spectrum of glandular differentiation and miscellaneous or combined histological types [25]. Microscopically a pseudo-lobular pattern is identified with cellular periphery and edematous central part. Classically single mucin filled signet ring cells or groups, trabecular arrangement of cells are noted. The stromal component may resemble a ovarian fibroma and show storiform patterns. Cells with a clear vacuole and an eosinophilic center or bull's eye appearance can be seen. Where the eosinophilic material are usually positive for mucicarmine and negative for periodic acid Schiff stain [5].In tubular type of Krukenberg's tumour round or oblong tubules comprised of signet ring cells are seen. In tubule-glandular pattern glands lined by lat cells

are usually appreciated. However in the latter type the stroma is pauci-cellular. Feathery degeneration of the collagenous stroma can be identified.

Determination of unknown primary from ovarian metastatic lesions

One of the most important clinical concerns is to identify the site of primary tumour from an ovarian metastatic lesion. And histopathological examination can be a great help in this matter apart from the radiological and endoscopic examinations. There have been wide arrays of antibodies which can be used by immunohistochemical examination to get an idea of an unknown primary lesion.[30]

Here the different combinations of immunohistochemical markers have been discussed:

Usefulness of CK7/ Colon ovarian tumour antigen [COTA]:

CK7 has been identified in various epithelial tumours including ovarian tumours. However it has not been detected in colon carcinomas. COTA have been detected both in ovarian and colonic primary carcinomas.[31] In a study by Lee E S et al (1998) incorporating a cohort of primary ovarian, colonic and metastatic ovarian carcinomas from various primary sites of gastro-intestinal tract, CK7 and COTA was identified in 95% and 50% of primary ovarian tumours respectively, CK7 was negative in 95% and in COTA was positive in 68% in primary colonic neoplasms. From this study the authors concluded that combined use of CK7 and COTA can differentiate primary ovarian from primary colonic carcinomas. However it should be kept in mind that, while using these combinations of IHC markers, it cannot detect metastatic lesions from a gastric primary, as many of the gastric carcinomas are negative for both CK7 and COTA.[31]

Usefulness of IHC markers in differentiating primary endometrial versus primary ovarian tumours:

Approximately 15-30% of women with endometrioid ovarian carcinoma also have cancer of uterine corpus [5]. Distinguishing a primary ovarian from primary endometrial tumour is always a challenge to the histopathologist, especially when the histologies are similar but not exact (e.g., pure endometrioid versus endometrioid with well-differentiated squamous differentiation, such as in adenoacanthoma) or if the tumour in the second organ is metachronous (i.e., occurring at a subsequent time).[5] The problem is further exaggerated by the varying criteria used by different pathologists to distinguish metastatic from synchronous primary tumours. This distinction, however, is of great clinical importance because of the significantly better prognosis of patients with synchronous primary tumours. Though there are few morphological pointers to speculate the primary site from the following criterias, but study of the IHC markers can only be objective in this issue. The differentiating points are:

A. The presence of a pre-cancerous lesion is a strong morphological indicator of in-situ genesis. In the endometrium, these processes include endometrial hyperplasia, especially if atypical, or the recent and more narrowly defined lesion, endometrial intraepithelial neoplasia.[3,5] Similarly presence of a potentially precancerous processes in the ovary such as endometriosis or a preexisting benign or borderline tumour of similar histological type suggests de novo development of the cancer in the ovary[5]

B. Different histological types of synchronous endometrial and ovarian tumours are also good evidence of independent primaries. However there are exceptions to this concept and difference of histology cannot be taken as sole criteria to differentiate between these lesions. About 15% to 25% of ovarian tumours with endometrioid histology are associated with a histologically similar lesion in the endometrium.[5]

C. Bilateralism and multifocal lesions over the ovarian serosa is also a pointer towards metastatic lesion to ovaries.[5]

D. Identification of tumour emboli in the lumen of the fallopian tubes also suggests metastasis. This is most often associated with serous tumours arising in the endometrium that implant on the ovary by retrograde

Metastatic tumours from the gonodal organs in ovaries [5]:

Primary site	Incidence	Route of extension
Endometrium	35-40%	☐ Lymphatic/vascular ☐ Fallopian tube emboli ☐ Invasion through myometrium
Fallopian tube	13%	☐ Direct extension ☐ Surface implantation
Cervix	3-10%	☐ Direct ☐ Lymphatic/vascular
Other Uterine Tumour	Rare	☐ Any of the above
Vulva/vagina	Rare	☐ Any of the above

Metastasis from the extra-genital organs:

Primary site	Incidence	Sub-types/ specific site of origin
Breast	10%	Lobular-3.6%, ductal-2.6%, signet ring-1.8%
Stomach	70% of Krukenberg's	Signet ring cells-41%, intestinal type carcinoma stomach 17%
Intestine	4-10%	Sites: Rectum/sigmoid colon-77%, descending colon- 5%, ascending colon- 9%, caecum-9% sub-types: Intestinal type-most common, signet ring 5.4%, small cell-rare
Appendix	Rare	Intestinal adenocarcinoma Mucinous type Low grade mucinous epithelial neoplasm
Carcinoid Tumour	2%	Sites: appendix(most common), colon, stomach, pancreas, lung
Adrenal	25-30%(autopsy series)	Neuroblastoma
Malignant melanoma	18% (autopsy series)	95% bilateral
Pulmonary & mediastinum	5% (autopsy series)	Small cell carcinoma (most common) Large cell undifferentiated Poorly differentiated adenocarcinoma
Pancreas	rare	Mucinous tumour
Gall bladder/bile duct	rare	
Liver	Rare	Hepatocellular carcinomas
Kidney/urinary bladder	Rare	
Extragenital sarcomas	Rare	Rhabdomyosarcoma (most common), leiomyosarcoma

transmission.

E. In a metastatic intestinal carcinoma, there is evidence of necrosis, the glands are poorly differentiated and squamous differentiation is not seen in these glands. Whereas in ovarian endometrioid carcinoma necrosis is not seen, the glands are well

differentiated and squamous differentiation is not uncommon.[5]

However in many instances these criterias fail. Surprisingly, there is little literature exploring the utility of the well established ovarian cancer marker CA125 in diagnosing synchronous primary tumours [5]. And in our experience many a times CA125 remains < 35IU/L and does not help in these situations.

In such a situation use of IHC markers are necessary to differentiate between these lesions.

Endometrioid carcinoma of ovary: Approximately 40% of primary ovarian carcinomas are estrogen receptor (ER) and/or progesterone receptor (PR) positive. They are also positive for CK7 (97%), CK20 (13%), EMA, vimentin (31%), B72.3 (86%), CEA (30%) and OC-125 (76%).

Endometrioid carcinoma of endometrium: The endometrial carcinomas are also positive for ER and PR (30-35%). In addition it can be positive for Bcl2 (65%), Her2Neu, vascular endothelial growth factor (VEGF) protein and can show accumulation of p53 protein.

Molecular studies: Many molecular studies were performed to see the difference of molecular profile between

The most common primary sites of metastasis are as follows:

Primary sites	Incidences
Stomach	76%
Colon and rectum	11%
Gall bladder/biliary tract	3%
Breast	4%
Others (small intestine, appendix, pancreas, rarely uterus, urinary bladder, renal pelvis	6%

Table: Presumption of possible primary tumour based on CK7/CK20 status

IHC status	Possible primary sites
CK7+/CK20+	Pancreas, bile duct, urothelium, gastric carcinoma (30%)
CK7+/CK20-	Lungs, breast, endothelium, ovary, thyroid, salivary gland, mesothelium
CK7-/Ck20+	Large bowel (95%), Merkle cell carcinoma, gastric adeno CA
CK7-/CK20-	Adrenal cortex, liver, kidney, adrenal gland

Primary Tumours	CK7	CK20
Colonic adenocarcinoma	16%	94%
Ovarian adeno-carcinoma	97%	13%
Lung adeno-carcinoma	100%	4%
Breast adeno-carcinoma	97%	6%
Merkel cell carcinoma	0%	95%
Lung small cell carcinoma	20%	1%

these two tumour types and it can be used when IHC cannot determine. the primary site. Expression of *WT1* has been sited as a marker of ovarian primary [5]. In a study by Irvin et al (2005) it has been shown that presence of *â-catenin* mutation is a marker of primary tumours of both ovarian and endometrial tumours [32]. Copy number analysis (CNA) and gene expression profiling was performed showed LOH of chromosome 17p and 10q along with 30 separately identifiable genes in endometrial carcinomas including *PTEN* mutation.[32]

Usefulness of CK7 and CK20 IHC profile to determine possible primary site of tumours:

The diverse and unique expression of CK 7 and CK 20 in different epithelial carcinomas has been found to be useful in determining the primary sites of metastatic tumours in ovaries [33]. Usually expression of either of these markers in >5% tumour cells taken as positive and the distribution and intensity of staining is determining factor. Combined use of these two markers help in narrowing down the differential diagnoses of a possible primary site.

However the patterns of this IHC expression are not so simple and considerable over-expression can be identified. Numerous studies shave been performed and shows a pattern of CK7/CK20 expression in the following common epithelial tumours:

CK7 expression has been identified in majority of the adenocarcinoma to some extent. The finding of CK 7 negativity has greater diagnostic value. When a carcinoma is CK7-negative, the differential diagnosis should include prostate, renal cell, neuroendocrine, hepatocellular, and adrenal carcinomas, carcinoid tumours, germ cell tumours, and squamous cell carcinomas of various origins with exception of cervical squamous cell carcinoma. Metastatic tumours from the uterine cervix are usually CK7 positive [33]. It should also be remembered that CK20 negativity not always rules out a colorectal primary. As shown in the table CK 20 positivity is seen in the majority of cases of colorectal adenocarcinoma and over 30% of cases of gastric adenocarcinoma. However, rectal adenocarcinoma *de novo* can be CK 7+/CK 20+ or CK7+/CK 20- [33]. Poorly differentiated

carcinomas or right sided colon carcinomas can be CK20 negative. Pattern of staining can often be helpful, as in merkel cell tumour CK20 positivity is seen as a specific dot like positivity.

Usefulness of other IHC markers those can supplement CK7/CK20 panel [34-35]:

Actually many markers are there which can be used to specify the source of primary tumour precisely. Some examples can be given:

Breast carcinomas- ER+, PR+, Her2neu/ERBB2+, GCDFP-15+, vimentin-

Colon carcinoma- K-ras+, CDX2+, â-catenin+, CEA+, CA125-,

Renal Clear Cell CA- CK7+, CD10-

Pancreatic & bile duct CA- CA 19-9+, DPC4-, ER-, PR-

AdenoCarcinoma uterine cervix- ER-, PR-, p16+ (*Exception*-serous adeno-carcinoma ovary can be p16 positive).

Ovarian AdenoCarcinoma Vs Epithelioid Mesothelioma- calretinin-, keratin 5/6-, B72.3+, CA 19.9+, Leu-M1+.

Metastatic Endocervical ademcarcinoma1 (ECA) *Vs* Uterine CA (UEC)-

CEA- strong cytoplasmic and luminal + in ECAs (100%) weak and luminal in UECs (up to 50%),Vimentin+ in UEC, ER/PR +in UEC, p16+ in ECA (serous CA can be +), p53 protein + in 80% of uterine serous CA; only seen in 10-20% UEC

Appendicular adenocarcinoma- CK18+, CK20+, CEA+, CK7-, HAM-56-

Intestinal carcinoid tumours-

Chromogranin, synaptophysin, PGP 9.5, CK (dot +)

Primary Mucinous Carcinoma *versus* Metastatic Colon Carcinoma

Primary mucinous carcinomas are frequently positive for CK20 [5]; hence, CK20 cannot be used to distinguish these tumours from metastatic colon carcinoma. Cytokeratin 7 is more useful in this situation, as it is diffusely positive in ovarian carcinoma and negative or focally positive in colon carcinoma. Ovarian mucinous carcinoma is negative for â-catenin and positive for MUC5AC, whereas colon carcinoma shows a

reverse pattern. CDX2 is a sensitive but nonspecific marker for colon carcinoma. HAM 56 is typical of a primary than the metastatic ovarian carcinoma. Metastatic tumours in addition are usually bilateral, small (<10cm) and show frequent signet-ring cells.[5]

The presence of ovarian metastases is a sign of poor prognosis of the non-genital primary tumour. Surgical management is necessary both for diagnostic and for palliative purposes. Cytoreductive surgery is applied in a number of patients, aiming to prolong survival and to improve quality of life.

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