CASE REPORTS

HEREDITARY MUCINOUS OVARIAN CANCER COMPLICATED WITH OMENTAL METASTASIS: A CASE REPORT

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Abstract

Approximately 80% ovarian tumorsare benign, and these arise mostly in young adult females. Malignant tumors are more prevalent in ageing women, between the ages of 45-65 years. Mucinous ovarian cancer represents about 5% of epithelial ovarian cancers (EOC).We have reported a case of mucinous cystadenocarcinoma in 35-year-old lady with metastasis to omentum.Imaging (radiograph & CT scan) studies showed a large right sided pelvic mass with probable origin in the right ovary. Cancer antigen-125 was elevated, while carcinoembrionic antigen and alpha-fetoprotein were normal. Mutational profiles shown distinct finding, as KRAS mutations positive nevertheless p53 and BRCA mutations are absent. She had undergone total abdominal hysterectomy with bilateral salphingo-oopher-ectomy along with pelvic dissection for removal of lymph nodes at the age of 35. She was given advice for radiotherapy with 3 cycles of che-motherapy with cisplatin and paclitaxel. To the best of our knowledge, this is the one of the littlecase of ovarian mucinous cystadenocarcinoma being reported at a relatively young age, and the first case being reported from Bangladesh.

Key words: *Mucinous, Cystadenocarcinoma, Salphingo-oopher-ectomy, Ovarian neoplasm.*

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Introduction

There are three major histologic types based on the distinction of the neoplastic epithelium: serous, mucinous, and endometrial tumors. The degree of epithelial proliferation is allied with the biologic behaviour of the tumor and is classified as benign (minimal epithelial proliferation), borderline (moderate epithelial proliferation), and malignant (marked epithelial proliferation with stromal invasion)[1].About 80% are benign, and these come mostly in young adult females between the ages of 20 and 45 years. Borderline tumors occur at slightly older ages. Malignant neoplasms are more usual in senior women, between the ages of 45 and 65 years.Ovarian cancer accounts for 3% of all cancers in females and is the fifth most common cause of death due to cancer in women in the United States[2]. Epithelial ovarian cancer (EOC) remains the most lethal gynaecological malignancy around the globe. Among the various histotypes, mucinous epithelial ovarian cancers represent approximately 3-5% of total EOC presentations[3]. World Health Organization histological classification, categorized ovarian neoplasms interpreting to the most probable tissue of origin. It is nowadays supposed that tumors of the ovary arise eventually from one of three ovarian components: (1) surface epithelium derived from the coelomic epithelium; (2) the germ cells, which migrate to the ovary from the yolk sack and are pluripotent; and the stroma of the ovary, counting the sex cords[4].Malignant tumors have usually typical clinical presentation as like dull abdominal pain and distention, urinary and gastrointestinal tract symptoms due to compression by the tumor or cancer invasion. They may remain entirely asymptomatic and occasionally are found unexpectedly on abdominal or pelvic examination or during surgery. Irrespective of the types, mainstream of the malignant tumorshas usually spread outside the ovary by the time a conclusive diagnosis is made[5-7]. The mostcommon primary sites for mucinous carcinomas metastatic tothe ovary are gastrointestinal, pancreas, cervix, breast, and uterus[8].

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Case report

According to the patient, she was completely alright 3 months back. Since at that time, she complains of a mass on the right side of the pelvis and which is gradually increasing in size. It is accompanied with dull, constant pain for last two months and isrelated with nausea and vomiting. She also complains about a slight sense of fullness subsequent to small meal and increased urination frequency every day and usually remained constipated for last two months. The patient noticed that, recently she has lost body weight (old dresses became loose) without dieting or exercise and has been complaining of fatigue for last three months. She denied for any swelling or pain on the left side of the pelvis. She had not experienced any breathlessness, dysmenorrhea, dyspareunia or postcoital bleeding or any recent injury.She did mention, of irregular menstrual cycle with oligomenorrhoea for past 2 months. She is non-hypertensive, or non-diabetic. No history of recent surgery or hospitalization.Not under significant medications, no history of contraceptive pill uses or hormone replacement therapy. Her mother died at age of 66 from an ovarian malignancy. No history of breast cancer among the close family members. Menarche at age 11 years. The cycle is average 28±2 days.Duration of menstrual flow is usually 3-5 days, flow is moderate, menstrual cycle is irregular for last 2 months. She is gravida 3, para 2, and working as administrative staff in private clinic.

On general physical examination, the patient is ill looking, cachexic and pale,pulse: 86/min,

BP: 140/90 mm Hg, Respiratory rate: 16 breaths /min, afebrile, pitting oedema—absent, no clubbing, jaundice, cyanosis or koilonychia, lymphadenopathy or neck swelling noticed,body weight 45 kg,BMI: 17.4.

During Systemic examination, Lip, teeth, oral cavity showing normal finding. Generalized mild abdominal distension from epigastric to hypogastric region. The massis firm to hard in consistency, mobility restricted; margins are ill defined, tendered andis arising from the right lower pelvis. The kidneys are not palatable. There is no tenderness over the renal angle. Shifting dullness present. No renal bruit. Bowel sound is intact.Findings on external genital organ is normal. Speculum examination of vagina, shows healthy external OS, no discharge, cysts, polyps, ulceration or fungating growth are absent. Per-vaginal examination (PV),shows the fornixes are clear. The uterus is of normal size, contour, and mobile. Bimanual examination,uterus in anteverted position. Rectovaginal examination, shows normal rectum and parametrium.

Laboratory investigation showing,RBC: 3.5 x 10^{12} /L, WBC: 5.8 X 10^{9}/ L (4.0-10.0), Platelet: 261 X 10^{9}/ L (150-400), Hb: 10 gm/dl (12.0-17.0). Random blood sugar- 11.9 mmol/L (4.0-7.8), Quantitative Serum âHCG: < 2 U/L, Liver function test and renal profiles:shows normal findings. Tumor marker analysis, CA 125 level of 243 U/L (normal, 0 to 35 U/L), Carcino Embryonic Antigen (CEA), alphafeto protein, and lactate dehydrogenase, oestrogen, and testosterone is within normal limits.Plain radiographof abdomen revealssolid cystic mass occupying whole of right iliac fossa. Ultra-sonographic findings are suggestive of solid cystic mass of size 21 cm × 13.2 cm × 13 cm cystic lesion, arising from right adnexa with internal septations and calcifications within.Contrast enhanced computed tomography scan (CT scan) of abdomen exposes well de-fined multi-loculated predominantly cystic abdominopelvic intraperitoneal mass lesion with enhancing septas and liquid mucinous components within and extending from sub-hepatic location to pubic symphysis inferiorly.

Gross histological appearance shows an enlarged right ovary mea-suring 21×10×5 cm with intact capsule. Cut section was multi-lobulated with presence of solid cystic areas. Cysts ranged in size from 0.5 to 4.5 cm and were filled with thick, viscous mu-cinous fluid. **Microscopic sections**, on histological examination, revealed solid and cystic areas displaying multiple layers of mucin producing atypical mucinous epithelium, loss of gland architecture with large areas of necrosis, focally infiltrating the stroma. Suggesting in favour of mucinous cyst adeno carcinoma. Sections from the omentum revealed metastatic tumordepositsSegments from the omentum reveal metastatic tumor deposits. Ascitic fluid cytology was positive for malignant cells.

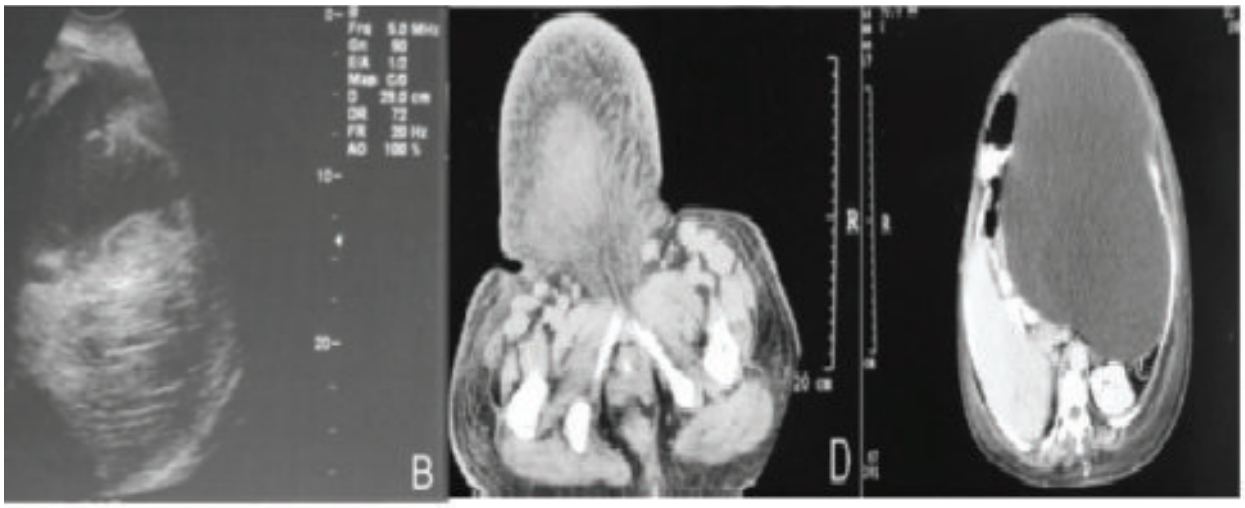

Fig.-1: *A. Ultrasound images of the heterogeneous mass, which occupies the entire right iliac fossa, B-C: Contrasted computed tomography (CT) scan revealing an extra-large mass with well-defined limits, and heterogeneous coefficient of attenuation, which was predominantly liquid in peritoneum.*

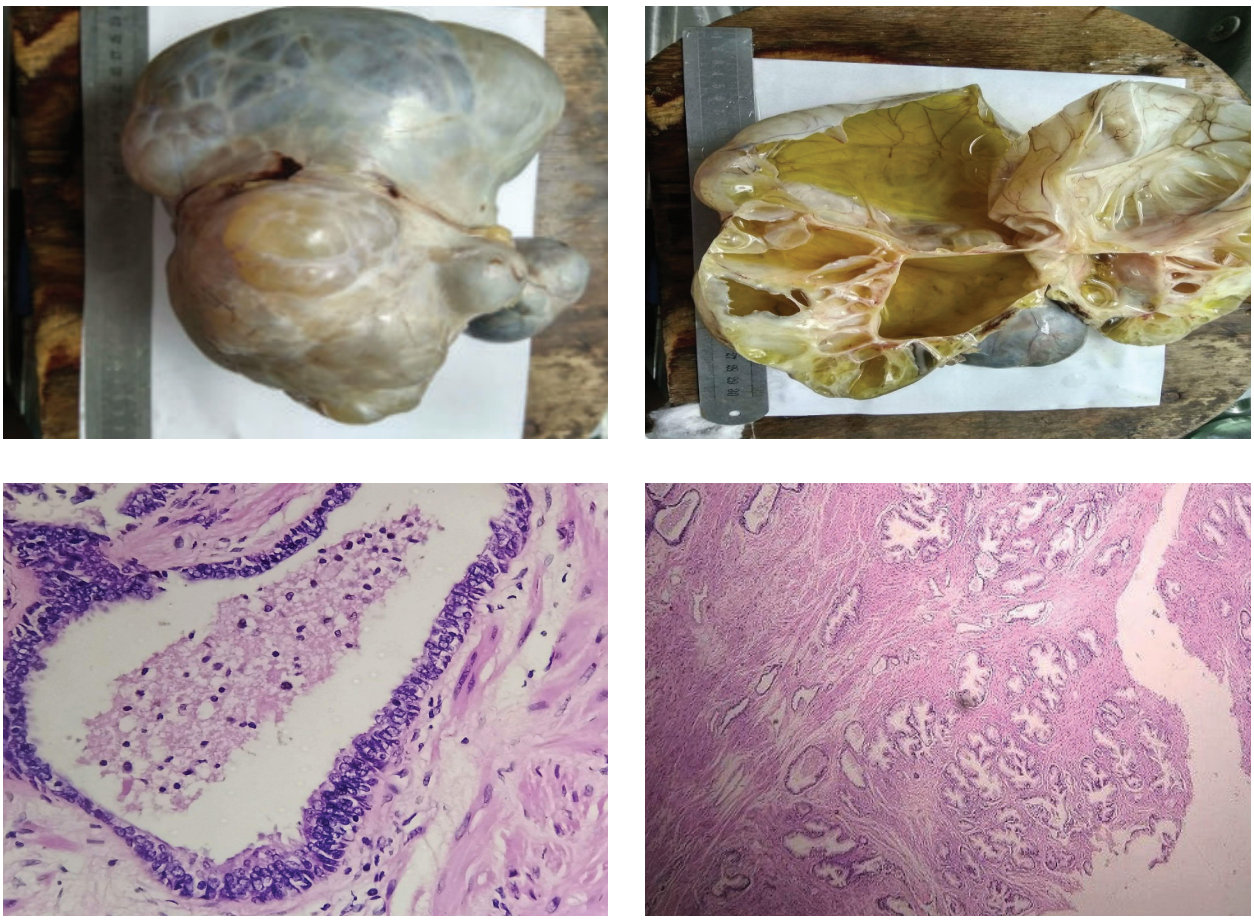

Fig:2 *A-B: Gross: ovarian cyst. Cut section is solid cystic with multi-loculated cysts filled with mucinous material. (C-D) Microscopy: back to back arrangement of glands lined by mucin secreting epithelium infiltrating the stroma (H&E, ×40).*

Discussion:

Mucinous tumors are less common than other epithelialtumors, accounting for nearly 30% of all ovarian tumors. They happen principally in inner adult life and are infrequent before puberty and after menopause. Primary ovarian mucinous carcinomas are relatively uncommon and account for fewer than 5% of all ovarian cancers. Although several molecular studies have been done over the years, very few molecular genetic alterations have been identified in mucinous tumors. The one consistent alteration that has been identified is mutation of the *KRAS* proto-oncogene[9].

Mutations of Ras pathway centrals to the expression of constitutively active Ras proteins as observed in nearly 30% of human cancers. Extra cellular-signal-regulated kinases (ERK) promote cell proliferation, cell survival and metastasis particularly upstream activation by the epidermal growth factor receptor (EGFR) and Ras small guanosine triphosphatases (GTPases). ERK1/2 are Serine/Threonine kinases and their activities are positively regulated by phosphorylation and mediated by MEK1 and MEK2. It is well recognized that phosphorylated ERK (pERK) is animportant downstream constituent of the Ras/Raf/MEK/ERK signaling pathway[10]. After phosphorylation, it translocates to the nucleus, where it leads to changes in gene expression and regulates various transcription factors such as Ets family transcription factors (Elk-1). The Ras/Raf/MEK/ERK signaling cascades also play a perilous role in the transmission of signals from growth factor receptors to regulate gene expression and thereby avert apoptosis[11].

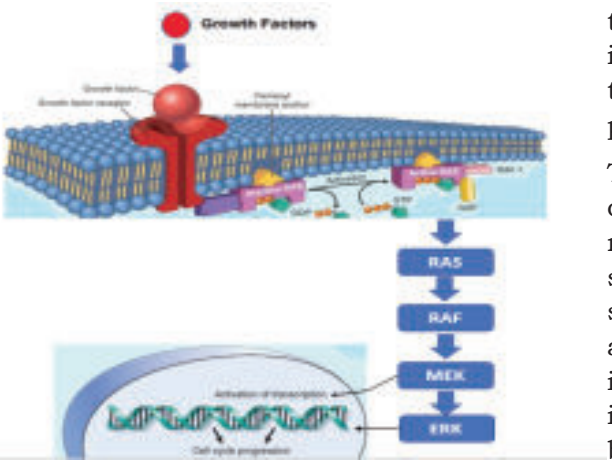

Fig.-3: *Ras/Raf/ERK mediated signal transduction pathways for cell growth & proliferation.*

Ovarian tumors are remarkably silent and rarely give *riseto symptoms* other than those induced mechanically by the size of the mass. It is this feature which makes them so dangerous; malignant ones are often inoperable by the time they are diagnosed, commonly in Stages III and IV. In our case patient presented with alarge right pelvic tumor associated with dull aching pain localized to the tumor[12]. The explanation of this is unknown; it can occur even before the growth erodes its capsule and is exposed to the peritoneum. In the case of malignant metastatic cancers there may be complain of vomiting, frequency of micturition and difficulty in evacuating the bowel. When an ovarian tumour emerges from the pelvis it comes to lie behind the abdominal wall, displacing the intestines above and to the side, the uterus usually lying below and behind its lower pole manifest all these clinical features. Cachexia, anemia &edema of the legs is common[13].Cancer cachexiais a reformist loss of body fat & lean body massaccompanied by profound weakness, anorexia. It is due to action of soluble factors eg. cytokines produced by the tumour or host in response to tumour like TNF-á and interlukin-1 produced from macrophages, hypothalamus, some other factors produced by tumour (proteolysis induce factor) which increase catabolism of muscle and adipose tissue by acting directly on fat and muscle proteins[14].

There are evidences from various studies, cancer induced pallor occurs bytumor activates monocytes and macrophages, which, in turn, stimulate other inflammatory cells, such as stroma cells, natural killer cells, dendritic cells and cytotoxic lymphoid cells. The result is an increased production and secretion of inflammatory cytokines, such as interleukin-1 beta (IL-1âb), IL-6, tumor necrosis factor alfa (TNF-á), and interferons (IFNs), which are able to induce the development of anemia. TNF-á inhibits hemoglobin production in a

proportional fashion to the down-regulation of GATA-1 and also affects erythropoiesis induced by erythropoietin. Other cytokines, such as interleukin-6 (IL-6), IL-1 and interferon-ã, have also been shown to inhibit erythroid precursors[15].

In our case, laboratory data shown Carcinoembryonic antigen (CEA)CA 125 level of 243 U/L which is well above the normal limit. CEA is the most useful serum tumor marker to identify mOC preoperatively and to follow the progress of a patient with mOC post-operatively. CEA is elevated in almost one third ovarian carcinomas. It is much more likely to be elevated in mOCs than in nonmucinous ovarian carcinomas (88 % vs. 19 %)[16]. Other biomarkers have been investigated as potentially useful in the differentiation of mucinous from other types of epithelial ovarian cancers. Immunoassay evaluation of 58 serum biomarkers in patients with serous, mucinous, clear cell, and endometrioid ovarian carcinomas revealed significant differences in levels between serous and mucinous ovarian carcinomas.Contrast enhanced computed tomography scan (CT scan) of abdomen exposes well de-fined, size 21 cm × 13.2 cm × 13 cm cystic lesion, arising from right adnexa multi-loculated predominantly cystic, abdominopelvic intraperitoneal mass lesion with enhancing septal and mucinousliquid components within and extending from sub-hepatic location to pubic symphysis inferiorly[17].

The gold standard for the treatment of any suspected ovarian mass includes intact removal of the involved adnexa with intraoperative pathology evaluation. When the surgeon entered the abdomen, he was careful to remove the involved ovary intact, without spillage of the mucinous contents, as rupture of a stage III mOC may increase its potential for recurrence[18]. This implied laparotomy, total hysterectomy, bilateral salpingooophorectomy, and up on staging procedure including lymphadenectomy. In this case, tumors of the ovary is large, the surgeons had performed an exploratory laparotomy with removal of the both adnexa, total hysterectomy, bilateralsalpingo-oophorectomy. The abdomen and pelvis was meticulously explored by the surgeon for to check any abnormality[19]. In the present case, tumor appears to be widespread as per the staging recommended by FIGO, stage-III. Secondary deposits are in the omentum, and on the visceral and parietal peritoneum (including the undersurface of the diaphragm) which becomes studded with small nodules which guided surgeon for the maximal debulking surgery[20].

Mucinous ovarian tumors signify a distinct histologic entity. They differ significantly from other types of epithelial ovarian cancers in their pathogenesis, pathologic characteristics, molecular signature, and clinical behavior and prognostic outcome.Management of this cases differ from their adult or postmenopausal counterparts, asdebulking radical surgery performed, fertility sparing conservative couldn't be adopted,proper hormonal replacement and psychological therapy need to ensure.

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