LETTER

To,
The Editor
International Journal of Medical Sciences and Clinical invention

Subject: To submit paper for Publication

Respected Sir/Madam,

I Dr. Parul Gupta (Associate Professor, Department of Pathology, ELMCH, Lucknow) wants to submit **Case Report** for publication titled as "**Breast Carcinoma With Choriocarcinomatous Features"** in the upcoming issue of your journal: International Journal of Medical Sciences and Clinical invention.

Kindly accept the above manuscript.

Yours' sincerely,
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Dated: 07/09/2018

TITLE PAGE

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BREAST CARCINOMA WITH CHORIOCARCINOMATOUS FEATURES

ABSTRACT:

Breast cancer with choriocarcinomatous features is a rare variant of breast malignancy with poor prognosis and poor response to treatment. The tumour cells express high expression of human chorionic gonadotropin in cancer cells such as multinucleated syncytioblast like giant cells. The histogenetic origin of these cells is unknown but the most reliable theory involves a metaplastic process. The frequently found metaplastic changes are squamous, spindle cells, or osseous, chondroid, or matrix production. Non-gestational choriocarcinomatous differentiation is extremely rare in breast neoplasms. Choriocarcinomatous differentiation has also been described in tumour arising from many organs including lung, rectum, colon, stoamach and urinary bladder. Most of the patient with choriocarcinomatous features presents with high grade disease, that is exhibiting an aggressive clinical course with an overall survival of less than a year. In this case report, the history, physical examination, laboratory findings and pathological findings of breast carcinoma in a 40year old woman are described. The patient underwent lumpectomy of left breast. Microscopically the tumour was reported as Invasive ductal carcinoma with choriocarcinomatous features. Nottingham grade III, ER- Negative, PR-Negative, HER2-neu Negative . Histology of choriocarcinoma in breast is distinctly unusual. Before making a confirmatory diagnosis of breast cancer with choriocarcinomatous features a

possibility of metastatic choriocarcinoma to the breast should always be ruled out because of its poor prognosis.

Key words: Choriocarcinoma, Breast, cancer, β hCG

INTRODUCTION:

Choriocarcinomatous differentiation in a carcinoma, earlier has been described in tumors of the bladder, oesophagus and colon, [1-3] but it is quite rare in breast carcinomas. Most of them are presented with high-grade disease, i.e exhibiting an aggressive clinical course with an overall survival of less than a year. [4,5] Elevated serum Human chorionic gonadotropin (hCG) found in 12% to 33% of patients with breast carcinoma. However, the majority of these tumors are not associated with choriocarcinomatous differentiation. [6,7] Breast carcinoma with choriocarcinomatous features (BCCF) is a distinct variant of breast carcinoma. It was described for the first time in the literature in 1981 by Saigo and Rosen. [8] Immunohistochemistry (IHC) shows that BCCF tumor cells express serum hCG and hCG antibodies.[9] Histopathologically, BCCF have highly atypical cancer cells morphologically similar to choriocarcinoma cells admixed with a malignant epithelial and/or mesenchymal component. [10] Most cases of BCCF have shown areas of breast-infiltrating ductal carcinoma or ductal carcinoma in situ with choriocarcinomatous features.[10,6] Although breast carcinomas may produce various ectopic substances, including human chorionic gonadotropin, it is difficult to identify morphologic differentiation compatible with the hormone produced by a tumor.[6] We report a case of 40 year old woman of breast cancer with choriocarcinomatous features.

CASE REPORT :

A 40-year-old perimenopausal woman presented with a rapidly growing palpable mass in the upper outer quadrant of the left breast since 2 months. She had no previous history of hydatidiform moles or choriocarcinoma. On Fine Needle Aspiration Cytology a diagnosis og Fibroadenoma was made. On imaging High Resolution Ultrasonography showed a ill defined

hypoechoeic mass in left breast with a suspicion of Fibroadenoma breast. The patient underwent a lumpectomy. Specimen revealed fragmented greyish white friable tissue pieces altogether measuring 4x4cm . ares of hemorrhage and necrosis were seen(Figure 1). Histology of the lesion shows sheets of highly pleomorphic tumor cells with an increased nucleo-cytoplasmic ratio, prominent nucleoli, moderate amount of amphophilic cytoplasm, with frequent mitotic figures. No tubule formation seen. Admixed areas show syncytiotrophoblast-like multinucleated giant cells with abundant eosinophilic cytoplasm, occasional cytoplasmic vacuoles.(Figure 2,3). Some bizzare , large , multinucleated cells with smudge nuclei extending their irregular, elongated cytoplasmic processes around clusters of monocytic tumor cells mimicking the biphasic growth pattern.(Figure 4). The area of choriocarcinomatous differentiation comprised approximaterly 25% of the entire invasive carcinoma. A diagnosis of invasive ductal carcinoma breast with foci of choiocarcinomatous differentiation (NOTTINGHAM GRADING: 3+3+2=8) Grade III was made. Following confirmation of malignant breast tumor left mastectomy with ipsilateral axillary lymph node dissection was performed. The product from the left mastectomy showed no residual neoplasia. There was also lymphovascular, perineural invasion,skin or nipple infiltration.Ten lymph nodes were identified of which only 1 lymph node showed metastatic deposits (Figure 5).IHC staining was performed on paraffin-embedded tissue sections, using a standard avidin-biotin-peroxidase complex method. Immunohistochemically only the multinucleate choriocarcinoma resembling tumor cells were reactive for hCG antibody, but negative for Estrogen Receptor, Progestrone Receptor, HER2/*neu* was observed. A diagnosis of BCCF was confirmed based on IHC and histological phenotype results. Measurements of serum human chorionic gonadotrophin and female sex hormones were not performed in the preoperative period.The postoperative serum β-hCG level was not increased significantly.

DISCUSSION

Choriocarcinoma histology in the breast is a rare entity.[11,12] and there are 2 distinct terms for choriocarcinoma in the breast: Metastatic choriocarcinoma to the breast and Breast cancer with choriocarcinomatous features(BCCF).[6] The first report of BCCF was published by Saigo and Rosen in the year 1981 [8]. It was an unusual case report of a breast carcinoma in a 55-year-old woman. Grossly it was 2.5-cm tumor consisting areas of invasive ductal carcinoma admixed with areas very similar to choriocarcinoma and was partially hemorrhagic.[13]
Carcinoma metastatic to the breast, it is a rare event mostly with a history of hydatiform mole or choriocarcinoma. Metastatic choriocarcinoma to the breast Patients presenting with BCCF are mostly pregnant, have been previously pregnant, or have a known history of hydatiform mole or choriocarcinoma. [14,15] Breast is an infrequent site for metastasis from extra- mammary neoplasms. Frequency of these metastasis ranged from 0.5- 6.6 of all breast malignancies. According to frequency, primary tumor source for breast metastasis are lymphomas, melanomas, rhabdyomayosarcomas, lung and ovarian tumors. [16]
However, Presence of invasive or in situ ductal carcinoma as well as a negative gynecologic history in patients with BCCF are key for correct diagnosis.[6,4] BCCF is characterized by increased level of β hCG in cancer cells. [10,4] Source of β hCG is presumed to be the tumor itself. In about 12% to 60% of patients with breast carcinoma shows weak tumor immunostaining for subunits of β hCG too which may have a role in synthesis and secretion of estrogen and progesterone.[4] But high levels of serum β hCG and also strongly positivity for β hCG antibody in IHC study are extremely rare in usual breast carcinoma and are in favour of metastatic choriocarcinoma to the breast or breast carcinoma with choriocarcinomatous features.[4]

Syncytiotrophoblast like multinucleated giant cells are present in BCCF. The histogenetic origin of these cells is unknown but the most reliable theory involves a metaplastic process. The frequently found metaplastic changes are squamous, spindle cells, or osseous, chondroid, or matrix production.[6,8]

In World Health Organization classification of breast tumors, BCCF is considered as a distinct variant of invasive carcinoma of no special type, and it is not classified as a common metaplastic carcinoma.[6,17] BCCF is an aggressive tumor with many patients presenting with lymph node ,distant metastasis and have poor prognosis. [6,17] Erhan et al. reported 2 of 4 patients were disease-free for 2 and 4 years after diagnosis, respectively. [6]

BCCF patients having disease-free interval of 1 year after surgery have also been reported.[18,15].

The etiology for the poor prognosis of BCCF still remains unexplained, although a possible mechanism is elucidated is as follows: pregnancy-associated proteins such as β hCG acts as immunosuppressive agent causing tumor cells invade host immune system and ultimately leading to highly invasive cancer. [19-21] In a study by Y Zhu et al patient had surgical resection of both BCCF and BCCF metastatic to the kidney, but serum β hCG levels were normal. Thus, it can be said that β hCG might not play an immunosuppressing role in their case.[22]

IHC study for β hCG antibody is necessary to confirm the choriocarcinomatous diagnosis in the breast. Metaplasia of gastrointestinal adenocarcinoma to choriocarcinoma is very common, hence it is recommended to evaluate CEA for distinct metastasis from gastrointestinal tract or other origins to breast. Imaging studies such as ultrasonography and CT scan are very useful for investigating origin of metastasis to the breast and concurrent metastasis in other organs.[18]

The differential diagnosis of BCCF includes poorly differentiated anaplastic infiltrating ductal carcinomas (mainly depends on the positive staining of HCG in BCCF).[10] Another D/Dx is the primary renal tumor expressing HCG (usually high stage renal transitional-cell carcinoma), a very rare form of renal tumor. [23] Presently, treatment for BCCF involves surgical resection similarly as for other breast carcinomas. It is a rare tumor, the best chemotherapeutic regime is yet to be established, with previously reported cases showing a poor response to chemotherapy.[6,17]

In comparison to BCCF, metastatic choriocarcinoma to breast is an aggressive and widely metastasizing tumor, but it responds well to chemotherapy and sometimes surgery can be avoided. However, breast carcinoma with choriocarcinomatous feature are highly malignant, usually have aggressive clinical course but evaluation of their nature, histogenetic behaviour and effective treatment modality is yet to be established. Therefore it is essential to make an early diagnosis of BCCF and to initiate appropriate treatment protocols.[9]

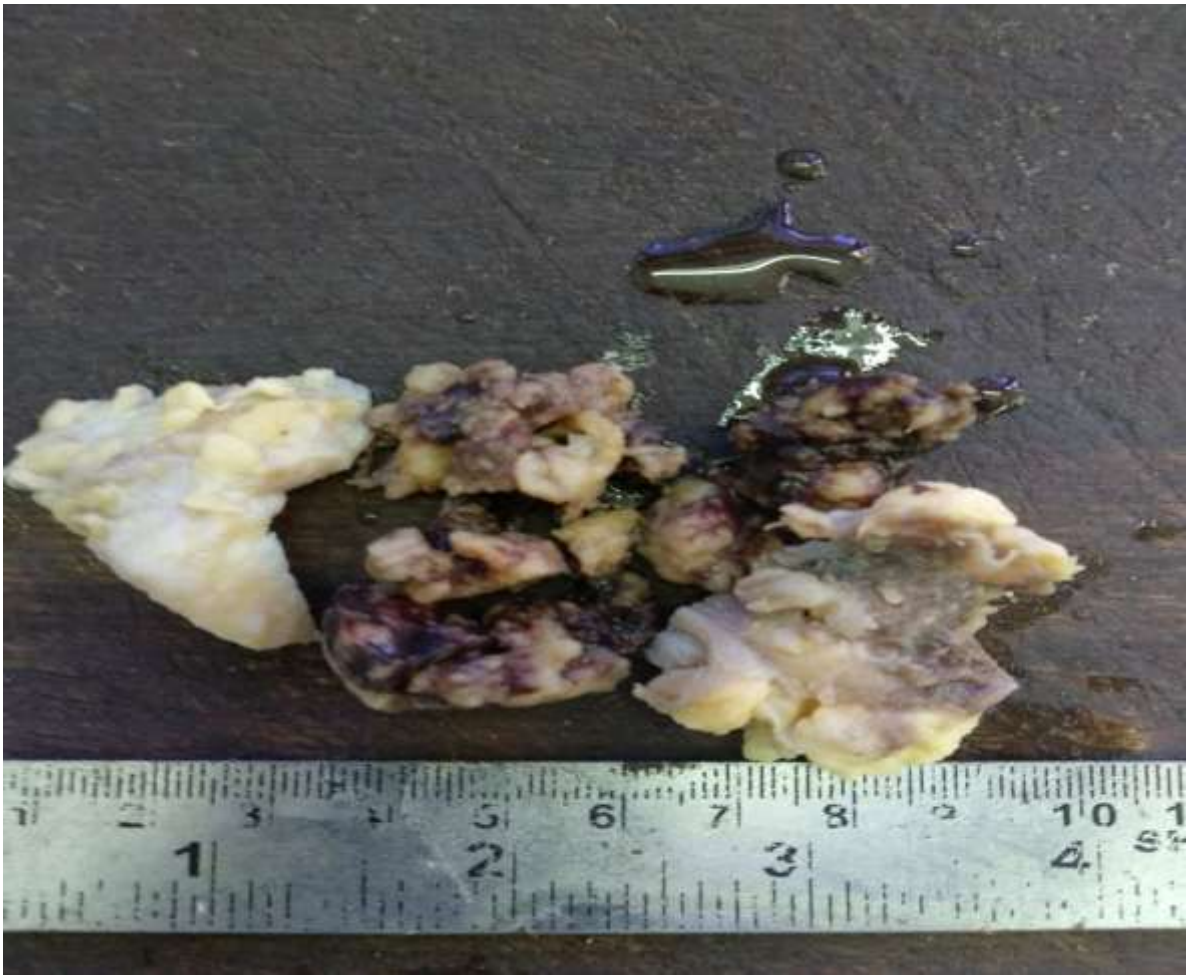

Figure 1: Gross, Lumpectomy specimen showing multiple fragmented grey white to grey brown soft tissue piece altogether measuring 4x4cm

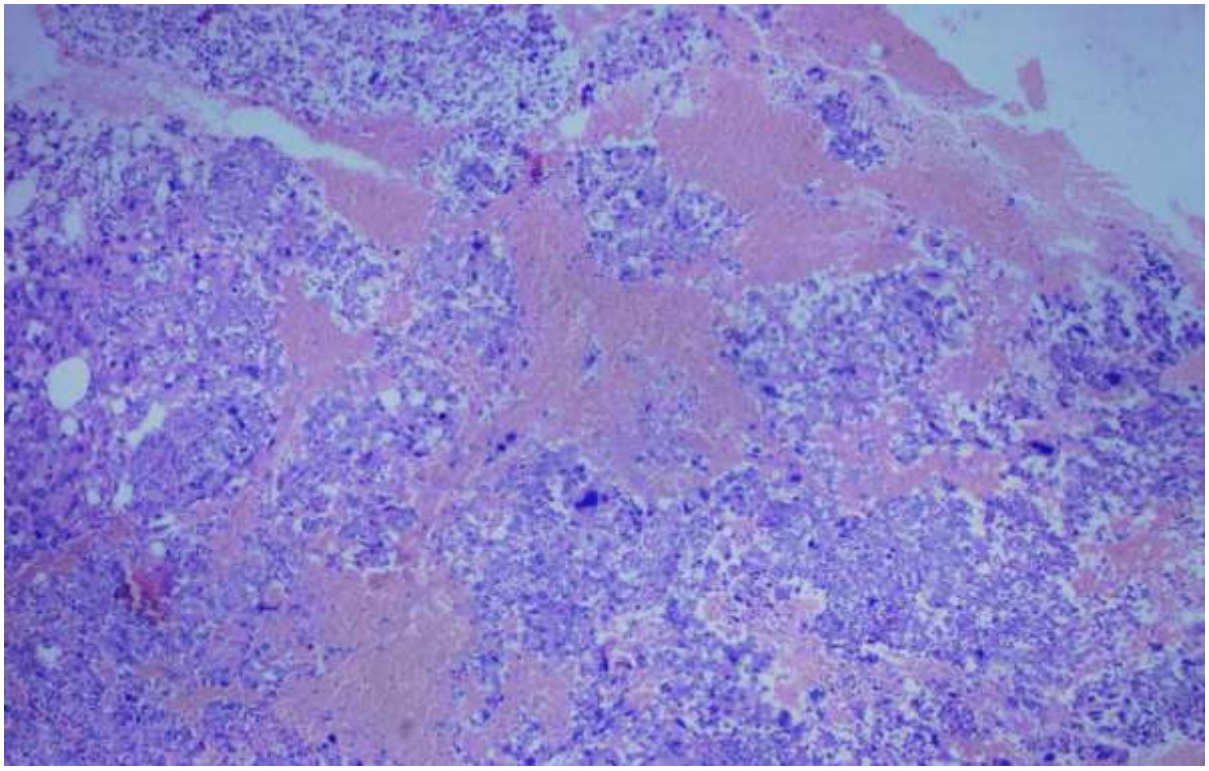

Figure 2: Microscopy (40X) Solid sheets of malignant cells admixed with multinucleate bizarre cells with necrosis and heamorrhage.

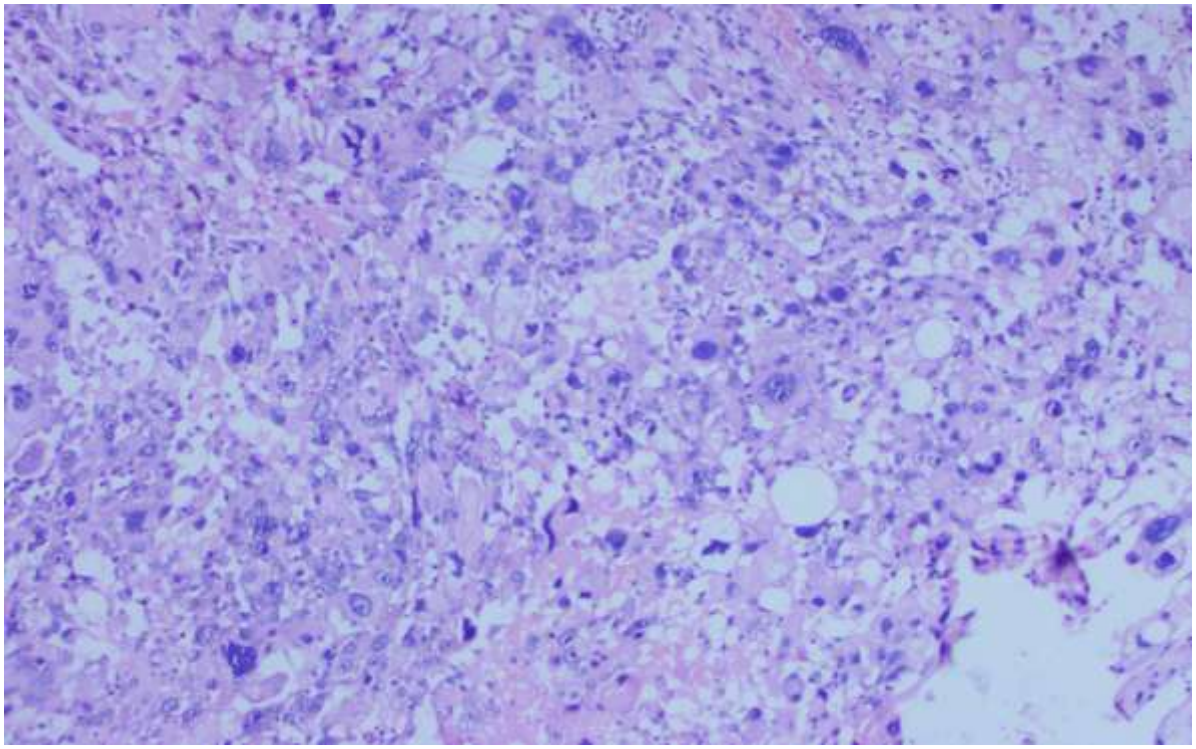

Figure 3: Microscopy(100X) Multinucleate & bizarre atypical cells have markedly pleomorphic hyperchromatic nucleus, abundant eosinophilic cytoplasm and few cells show cytoplasmic vacuoles.

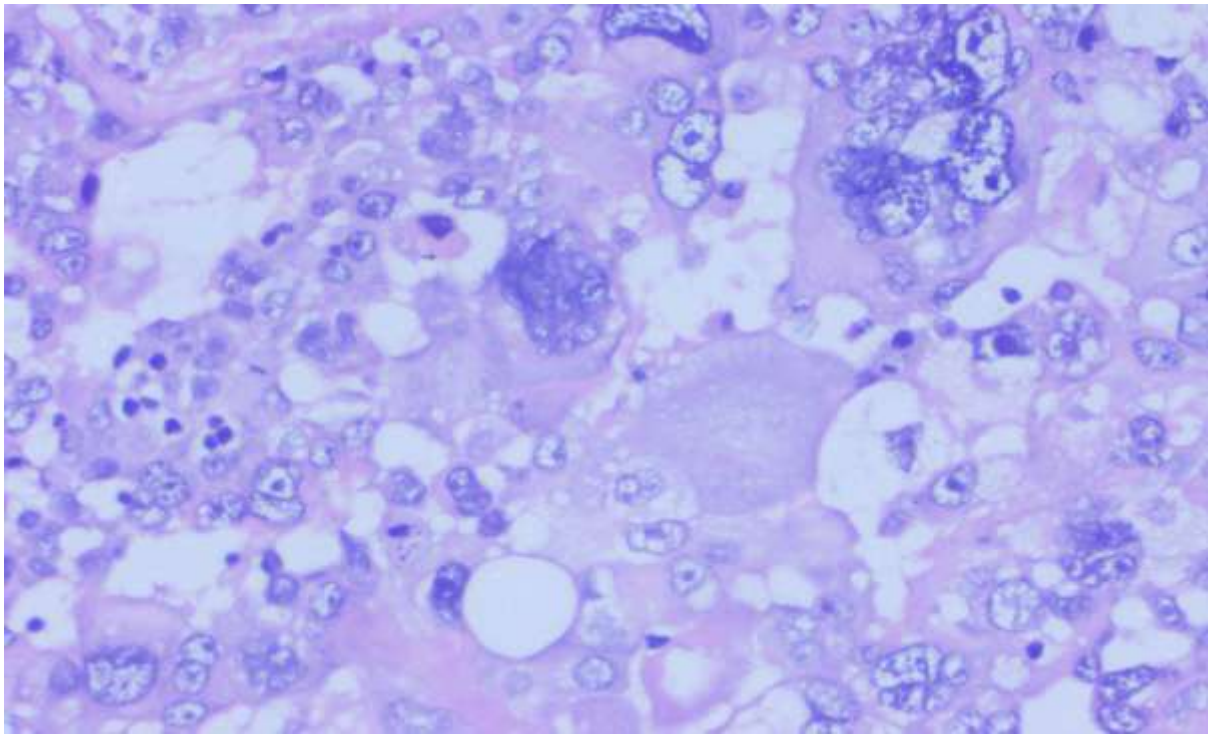

Figure 4. Microscopy(400X): Bizzare , large , multinucleated cells with smudge nuclei extending their irregular, elongated cytoplasmic processes around clusters of monocytic tumor cells mimicking the biphasic growth pattern of choriocarcinoma.

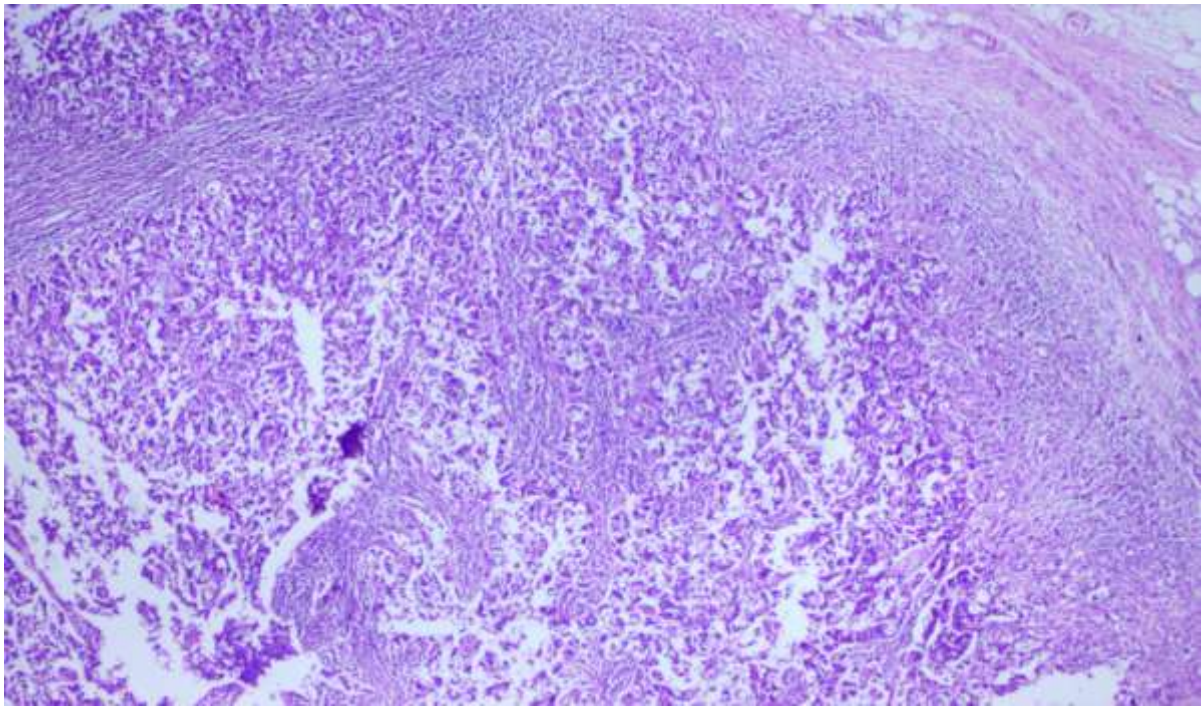

Figure 5.Microscopy(40X): Lymph node Metastasis, Malignant cells are seen obliterating the normal lymph node architecture.

CONCLUSION:

Finally, the significance of diagnosing the choriocarcinomatous features in an invasive ductal carcinoma is that these tumors are highly malignant and have an aggressive clinical course and most patients die within a few months due to multiple metastases.[4,17]

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