***Persistant gestational trophoblastic tumor***

**Highly malignant chemo sensitive tumor occur in two categories:**

**A-non metastatic lesion : usually confined to uterus in form of invasive mole and is follow [ 15%] of primary HM.**

**B- metastatic lesion : usually lead to distant metastasis and is follow [5%] of primary HM.**

***Incidence and epidemiology :***

1. **Geographical distribution: similar to that of HM. west [1 :10.000- 1 :70.000 ] pregnancy, middle east [ intermediate position ], Asia [1- 250 - 1-6000].**
2. **Age > in old, parity > in high parity, socioeconomic > in poor.**
3. **Antecedent pregnancy: HM in [50% -75%], normal term pregnancy [ 25%], abortion [ 25%].**
4. **Maternal blood group: > in group A, < in group O.**

***Pathology of persistent GTT:***

**Macroscopic appearance:**

**Dark hemorrhage tumor mass on uterine wall, cervix and vagina could perforate uterine wall or invade blood vessels leading to metastases.**

**Microscopic appearance:**

**Invasive mole: trophoblastic extensive deep myometrial penetration, may reach peritoneal covering of uterus or vagina with necrosis of muscles and preservation of villous pattern usually lacking tendancy of widespread metastasis.**

**Choriocarcinoma: completely disorganized growth with bizarre forms of cytotrophoblasts and syncytiotrophoblast, with variable cellular anaplasia and absence villi.**

***Clinical feature of persistent GTT:***

**a-uterine cramps and bleeding which is the commonest complaint and is either internal bleeding due to myometrial infiltration by tumor and lead to perforation and hemoperitoneum, or external bleeding.**

**b-offensive vaginal discharge.**

**c-cachexia, weakness and pyrexia as disease advances.**

**d-not uncommon, patient has no specific complaint and she diagnosed during surveillance after molar pregnancy when one of the indication of chemotherapy is encountered.**

**d-signs and symptoms of metastatic lesion: metastasis may be local to broad ligament and paracervical tissues or through blood stream to the lungs most commonest site of metastasis [75%] leading to dyspnea and hemoptysis, vagina next common site of metastasis [50%] leading to bleeding nodules, CNS lead to seizure and CVA, liver metastasis.**

***Investigations of persistent GTT:***

**a-HCG: important in the diagnosis and clinical staging of persistent GTT HCG should normalize [48 hours after term delivery], [2 weeks after abortion] and [6-8 weeks after HM]. So persistent increase levels of HCG mean persistent GTT.**

**b-CXR to detect lung metastasis.**

**c-imaging techniques U/S,CT scan, MRI. [ MRI is superior to U/S and CT scan in evaluating abdominal and pelvic organs and CNS metastasis.**

***Staging of persistent GTT:***

**Numbers of factors identified which influence prognosis of persistent GTT in a positive way they are as follows:**

**1-increasing HCG before starting treatment because it reflect larger mass.**

**2- metastasis and this include :**

**a-Site of metastasis worst prognosis with CNS metastasis because chemotherapy agents usually do not cross blood brain barrier, liver metastasis associated with poor prognosis because chemotherapy rapidly detoxified in liver.**

**b-Numbers of metastatic lesions the more the numbers the poor the prognosis.**

**3-size of largest mass: the larger the mass the poorer the prognosis.**

**4-antecedent pregnancy: worst prognosis when antecedent pregnancy is term normal pregnancy, better prognosis with abortion, best prognosis when antecedent pregnancy is H, mole.**

**5-pregnancy – treatment interval: longer the interval between pregnancy and chemotherapy the worse the prognosis.**

**6-previous unsuccessful chemotherapy: associated with poor prognosis due to drug resistance may be due to impermeability of chemotherapy to tumor mass because of scarring and fibrosis or accumulating drugs toxicity.**

**7-ABO group : worst prognosis in blood groups B,AB.**

**8-age poor prognosis if[ > 39 ]and parity >[ 3 or 4].**

**Each of the above mentioned prognostic variables is given a score ranging from [ zero to 30 ] zero if absent and 30 if present.**

**By calculating the score of the patient : final score**

**+ [< 50 ]allocated as low risk G.T.T.**

**+ [ 55-95 ] allocated as medium risk G.T.T.**

**+ [ >95 ] allocated as high risk G.T.T.**

**So staging affect survival rate and choice of chemotherapy , this based mainly on HCG levels and metastasis and is not a pathological classification.**

***Treatment of persistent GTT:***

**Optimum result encountered in highly specialized centers, same policy of treatment in invasive mole and metastatic choriocarcinoma .**

***Treatment modalities:***

**Chemotherapy= main stay of treatment.**

 **Surgery=certain limited indication.**

**Radiotherapy= limited indication.**

**Further management and follow up.**

***Chemotherapy of persistent GTT:***

**Chemotherapy is indicated in all cases of persistent GTT. metastatic or non metastatic forms of tumors are highly chemosensitive.**

**Protocol for chemotherapy agents are selected according to degree of risk of patient [ low, medium, high ] which indicated by her pre treatment prognostic score. Low risk category responds to single drug and medium, high risk category require combination of drugs.**

**Low risk category:**

**Survival rate [100 %] carries best prognosis responds to single agent chemotherapy either methotrexate or actinomycin D**

**Methotrexate : it is the drugs of choice in single chemotherapeutic courses because its simplicity and low toxicity [ its low toxicity attributed to the availability of antidote folinic acid which reduce toxicity and allow use of higher dose.**

**How to give methotrexate ?**

**Before starting chemotherapy send for CBP, LFT, RFT and is given parentrally [iv – im] excreted in urine so its contraindicated in renal failure, the coarse constitutes [8 days] , methotrexate given every other day alternating with folinic acid.**

**D1=D3=D5=D7= methotrexate D2=D4=D6=D8= folinic acid.**

**HCG should be assessed twice weekly to ensure that it is regressing satisfactorily, if HCG is increase or plateau which mean drugs resistance and you need to change agent.**

**WBC count and platelet count sent for daily so stop chemotherapy if [WBC count < 1000], [platelet count <50.000].**

**Toxicity of methotrexate may be encountered**

**a-myelosuppression: thrombocytopenia, granulocytopenia.**

**b-mucus membrane: stomatitis, oesophagitis, vaginitis, conjunctivitis.**

**c-skin rush, nephrotoxicity, hepatotoxicity.**

**When 8day course completed give [7- 14]days rest then start second course of methotrexate in similar manner and you need [ 2-4] courses**

**To reach undetected level of HCG. When HCG level undetected give[ 2-3]extra courses of methotrexate because approximately[ 100.000] trophoblast cells may escape detected by RIA of HCG.**

 **actinomycin D: given parenterally in courses consisting of 5 days , spaced by [7- 14]days rest repeat courses until you reach undetectable level of HCG followed by[ 2-3]extra courses, monitor patient condition by CBP, LFT, RFT and is given and monitor patient response by HCG twice weekly.**

**Medium risk category:**

**Overall survival rate [ 95 %], they resist methotrexate when used as single agent combination chemotherapy improves prognosis significantly. The following agents are added to methotrexate.**

**^Actinomycin, 6 mercaptopurine, vincristine and cyclophosphamide.**

**High risk category:**

 **biggest therapeutic challenge, survival rate [40 – 65% ] they require seven drugs combination courses include: alklating agent as chlorambucil + methotrexate + Actinomycin D + vincristine and others, they also require prophylactic intra thecal methotrexate on each alternating course to prevent CNS metastasis, also these drugs combined in courses spaced by [7- 14]days rest.**

 ***Surgical treatment of persistent GTT.***

**In pre chemotherapy era hysterectomy was the treatment of choice in persistent GTT and at that time it may resulted in favorable outcome with HM or invasive mole but was totally inadequate for metastatic choriocarcinoma. Now we are in the era of chemotherapy,**

 **success of chemotherapy replaced hysterectomy favorable pregnancy outcome is possible after successful chemotherapy so is best to avoid hysterectomy and preserve reproductive function.**

 **Surgical treatment is indicated in the following :**

 **a-drugs resistance focus: diagnosed when find focus with persistent increase in HCG despite drugs combination so hysterectomy if the focus confined to uterus or salvage surgery e.g lobectomy if the focus confined to lung or vaginal nodules excision.**

**b-uterine perforation: by invasive mole lead to hemopeirtonium.**

**c-heavy uncontrollable uterine bleeding.**

**Hysterectomy with preservation of ovaries because ovarian metastasis is very rare.**

***Radio therapy of persistent GTT.***

**persistent GTT not sensitive to radio therapy, it is of no benefit in chemotherapy resistance tumor may be indicated in cases of brain or liver metastasis who develop hemorrhage into these metastatic lesions after chemotherapy.**

***Further management of persistent GTT:***

**By quantitative assessment of HCG the aim of follow up is to diagnose remission which define as 4 consecutive weekly -ve HCG assay. And to detect relapse and majority of relapses occur in the first 12 months of remission, contraception essential during treatment and during the first year of remission by barrior methods then OCCP after normalization of HCG levels.**

***Follow up scheme***

**a-monthly HCG assay in the first year.**

**b-twice per a year for 5 years.**

**c-once per a year for 5 years.**

**Plus follow up previous metastatic lesion by appropriate tests**

**CXR for lung metastasis and MRI for pelvic, abdominal viscera and CNS.**

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