INTRODUCTION

Gestational trophoblastic diseases (GTD) include hydatidiform mole without spontaneous reversal of human chorionic gonadotropin (HCG) levels after 8 weeks after aspiration or cell retention, invasive mole, and choriocarcinoma. Choriocarcinoma can also occur outside of molar pregnancy in 55% of cases: Primary choriocarcinoma. Several studies have shown prognostic factors to adapt the treatment to the severity of each case. We present the results of a retrospective study that involved 20 cases of MTGP treated, between January 2008 and December 2015, at the Department of Obstetrics and Gynecology of the Maternity and Neonatology Center of Tunis. We discuss the clinical and therapeutic aspects.

PATIENTS AND METHODS

We collected epidemioclinical data for each patient.

The pre-therapeutic assessment included:

- A biological assessment (a complete blood count, a liver test with alkaline phosphatase, and a renal assessment and a serum HCG level),
- Chest X-ray;
- A chest CT scan for abnormal chest X-rays;

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• An abdominal ultrasound;
• A thoracoabdominal and cerebral CT scan for choriocarcinoma.

The treatment included uterine aspiration or curettage followed by chemotherapy according to the different protocols indicated according to the three prognostic groups that were established by referring to the classification of the Gustave-Roussy Institute (GRI):

• The first group was that of the hydatidiform moles (molecular retention). Chemotherapy included Monodrug methotrexate (MTX) at 15 mg/m² twice weekly, administered by intramuscular injection until serum HCG normalization was achieved and continued for 6 weeks post-conversion. In case of secondary elevation (during treatment or after obtaining a normalization of HCG serum level), catch-up chemotherapy according to the Actinomycin and Etoposid (AE) protocol (Actinomycin: 0.75 mg/m² on day 1 and Etoposide: 150 mg/m² on day 1) weekly treatment continued 6 weeks after conversion of HCG or APE (Actinomycin: 0.3 mg/m² at day 1, day 2, day 3, day 14, day 15, and day 16, cisplatin: 100 mg/m² at day 1 and Etoposid: 100 mg/m² at day 1, day 2, day 3, day 14, day 15, and day 16 or in the lightened version, etoposid: 150 mg/m² at day 1 and day 14, actinomycin: 0.75 mg/m² at day 1 and day 14, and cisplaty 100 mg/m²; the 28 days to be continued for two cycles after normalization of serum HCG levels) was administered;

• The second group was trophoblastic tumors with a good prognosis: Patients with a mole hydatiform and in whom, after uterine curettage, markers were elevated primary or secondary in the absence of any chemotherapy (these patients were receiving chemotherapy with either MTX or AE) or patients with gestational trophoblastic tumor (GTT) without any histology of choriocarcinoma with a single metastatic site, regardless of the number of metastases in this site (these patients were receiving chemotherapy by protocol AE). If the persistence of elevated serum HCG, the tumor was considered chemoresistant, and the treatment was similar to that of GTTs with poor prognosis;

• The third group was trophoblastic tumors with poor prognosis: It included all cases in which a histological diagnosis of placental choriocarcinoma was obtained, regardless of obstetric history and clinical presentation, and all other cases of GTT that were not histologically proven choriocarcinomas with more than one metastatic site or resistance to mono or multidrug therapy. These patients received chemotherapy using the APE protocol.

RESULTS

Epidemioclinical data
The average age was 32 (range: 20–49). Choriocarcinomas occurred in three cases after a molar pregnancy and in one case after an abortion. Metrorrhagia was the most frequent reason for consultation (80%), it was associated with uncontrollable vomiting in four patients (20%), and abdominopelvic pain in six patients (30%). Lung metastases were revealing in one case. Gynecological examination showed one vaginal mass in one patient and one breast nodule in another. 19 patients had aspiration or curettage, which was unique in nine patients. Weekly monitoring of HCG showed no normalization after 8 weeks in three cases, the primary or secondary rise in fifteen cases, and a decrease in HCG followed by stagnation at three successive dosages in a single case. 10 patients had a second or even a third aspiration for suspicion of molar retention in view of the persistence of metrorrhagia, the lack of standardization or the resurgence of HCG. Monitoring the evolution of HCG plasmatic levels after rebreathing had always shown a resurgence of tumor markers.

The pathological examination concluded that there was one partial mole in one patient, one complete mole in two patients, one invasive mole in 13 patients, and one choriocarcinoma in four patients. At the end of the extension assessment, five of our patients were metastatic: Pulmonary sites isolated in two patients, associated with bladder involvement in one patient and vaginal involvement in another patient. Only one patient had three metastatic sites: Pulmonary, hepatic, and breast. It was ultimately 20 cases of PMTG (three cases of molar retention, 13 cases of invasive moles including two metastatic cases and four cases of choriocarcinoma including one non-metastatic case).

Surgery
Three patients had a hysterectomy. It was performed in the presence of choriocarcinoma in two multiparous women and a woman in complete remission (CR) after the end of chemotherapy and in the persistence on ultrasound of a large uterine residual mass whose histological examination concluded that a totally necrotic uterine tumor.

Response to chemotherapy
• The hydatiform moles: The three patients in this group were in CR after MTX chemotherapy;
• Tumors with good prognosis: This group included 13 patients. Eight patients were treated initially with MTX including four CR (50%) and four resistance cases (50%) who were caught by chemotherapy with AE (two cases) or APE (two cases). The remaining five were treated with AE chemotherapy with CR in 100% of cases;
• Tumors with poor prognosis: Two of the four patients in this group were not evaluable (one patient was lost to follow-up after a single APE treatment, and the other died after febrile aplasia after chemotherapy after the second APE course). The other two evaluable patients were on CR.
Toxicity of chemotherapy
Grade II–III digestive toxicity was noted in 12 patients (46%) treated according to the AE or APE protocol. MTX chemotherapy was well tolerated, apart from Grade II and III mucositis observed in four patients (15%). Three patients treated with the AE or APE protocol presented Grade II and III leukopenia with a toxic death (observed with the old APE protocol). In addition, we did not note any late toxicity, including no cases of secondary leukemia.

Evolution and subsequent fertility
All the patients put in CR were healed. Three patients had a pregnancy >1 year after the end of chemotherapy, with the delivery of three newborns in good condition.

DISCUSSION
GTT incidence rates vary widely by geographic distribution. In fact, this rate goes from one mole per 2000–3000 pregnancies in Europe and North America[11] to one mole per 100–200 new pregnancies in Africa, South-East Asia, and Latin America.[2] The percentage of persistent trophoblastic disease after molar evacuation and therefore requiring chemotherapy treatment varies according to the different published series from 8% to 36%.[3,4,5] These PGTDs are mainly represented by invasive moles in our series (65%) as well as in other series of the literature (75–80%).[8,5] Furthermore, choriocarcinoma accounted for only 20% of the PGTD in our series, whereas it is observed in 60% of cases in other series of the literature.[2] The geographical distribution of choriocarcinomas is similar to that of hydatiform moles, with a frequency of 1/2000–1/4000 pregnancies in western countries,[1] compared to 1 in 250–1/1600 pregnancies in Asia.[6] Several risk factors in the genesis of GTT have been reported in the literature. Age appears to play a role in the development of PGTD with a rate of 37% in patients over 40 years of age and 56% in those over 50 years of age.[10] The low socioeconomic level appears to be a very important risk factor, since the highest incidence rates are found in underdeveloped countries, where malnutrition and deficiency of animal fats and vitamins are frequently associated.[8,9] According to a Senegalese study by Cisse et al.,[9] the risk factors for developing choriocarcinoma after the evacuation of a mole were: Age >40 years, multiparity and preservation of the uterus. They, therefore, recommend expanding hysterecmy indications for women at risk. The average age of our patients was 32 years; this average is comparable to that of other series that are in the third decade.[10] The diagnosis can be evoked during the follow-up of a molar pregnancy with an unfavorable evolution at the weekly follow-up by the assay of the serum HCG,[10] which was the case in 95% of our patients, in front of metrorrhagia[11] (observed in 80% of our patients), in predominantly pulmonary metastatic sites,[12] which was observed in one of our patients or the presence of a complication.[13] The clinical symptomatology is very polymorphous, and it is dominated by metrorrhagia, which can be observed in 90–96% of cases, the latter is often associated with abdominopelvic pain and an accentuation of the sympathetic signs of pregnancy.[14,15] In our series, 80% of patients had metrorrhagia, 30% had abdominopelvic pain, and 20% exaggerated sympathetic signs. Lung metastases are the most frequent (80% of cases)[14,15] they have been observed in all our metastatic patients. Several prognostic factors have been reported in the literature; they were then grouped into several classifications to define prognostic and therapeutic groups. In 1988, the GRI team published the results of a multifactorial analysis of 162 patients with GTT and defined a high-risk group by the presence of one of the following factors: Histological diagnosis of choriocarcinoma, antecedent of normal pregnancy, initial presentation with more than one metastatic organ, and initial resistance to chemotherapy; the patients are, thus, divided into three prognostic groups: The simple hydatiform moles which are treated by a monochemotherapy by MTX, GTTs of good prognosis with the absence of the four aforementioned factors which are treated by the association AE, and the GTTs poor prognosis defined by the presence of at least one of the aforementioned factors that are treated by a polychemotherapy type APE.[16] In contrast, the clinical classification and the WHO classification, recently modified by FIGO, classify GTTs into two groups: Low-risk and high-risk taking into account different prognostic factors, with a much lighter treatment[17] [Table 1]. In our series, we have adopted the GRI classification. Therapeutically, it is recommended to perform only one aspiration, even in case of tumors of good prognosis, the second curettage being ineffective,[10] this was clearly confirmed in our study. Hysterectomy has limited indications: For hemostatic purposes in case of cataclysmic hemorrhage, in elderly women who no longer want other pregnancies and for residual choriocarcinoma lesions resistant to chemotherapy. In addition, surgery may also have a place in the treatment of chemosensitive accessible metastases.[18]

Our work confirms the extremely chemosensitive character of PMTGs. Indeed, CR was obtained in 100% of evaluable patients. While MTX monochemotherapy has been successfully used in all hydatiform mole cases, MTX resistance has been observed in GTTs of good prognosis once in two. Nevertheless, a CR could always be obtained after combination chemotherapy of type AE or APE. The failure rate of MTX observed in our patients (50%) is comparable to data in the literature, with 40% primary resistance to this substance. This has prompted the GRI team to immediately use effective chemotherapy with the AE protocol to avoid chemoresistance, which is considered a factor of poor prognosis.[19] Finally, our results confirm the remarkable efficacy (100% CR) of the APE protocol in GTTs with poor prognosis. The rate of CR with this protocol was 93% in the series of Lhomme et al.[19] However, the significant toxicity observed in patients treated with multidrug therapy deserves
to be analyzed. In particular, the 25% toxic death rate with the APE protocol seems unacceptable in the context of a curable disease in >80% of cases. The AE protocol, less toxic than the APE protocol, was nevertheless responsible for frequent digestive toxicity (87%) as well as dermatological side effects in 25% of cases. It then seems necessary to ask the following question: Have we over-treated our patients? In our series, the prognostic classification adopted was that of the GRI. The four patients treated according to the APE protocol were classified in the group with poor prognosis due to the histological diagnosis of choriocarcinoma (four) and/or the presence of more than one metastatic site (three patients). Indeed, according to the GRI classification, the existence of histological evidence of choriocarcinoma is enough to consider the disease as high risk, even in the total absence of metastases. In contrast, the clinical classification as well as the WHO classification, recently modified by FIGO, are by definition based on metastatic GTT and do not include histology as a prognostic criterion. Non-metastatic GTTs are not included in these classifications and are uniformly treated with monochemotherapy regardless of other prognostic factors. Thus, it can be assumed that a certain number of patients considered to have a poor prognosis according to the GRI would be rather of good prognosis, or even for non-metastatic cases, purely excluded from the prognostic evaluation if a different classification was used. Be that as it may, and regardless of these classification problems, the significant toxicity of the APE protocol makes it necessary to modify it to improve the therapeutic ratio. Indeed, to reduce the bone marrow toxicity of APE, without modifying its efficacy, a new APE protocol with reduced doses and a different rate of administration is currently used.

In our series, 16 patients were considered to be of good prognosis according to the GRI classification. Being non-metastatic, these patients do not respond, therefore, to the WHO classification modified by FIGO. Be that as it may, the cure was achieved in 100% of the cases, regardless of the chemotherapy initially given. In addition, if one was to refer to the FIGO classification, these patients would then be treated with MTX monochemotherapy as first-line treatment with MTX resistance treatment, which could consist of Actinomycin D monochemotherapy instead of AE protocol. Only the rare patients (5%) presenting an escape with two successive monochemotherapies (MTX then Actinomycin D) would then be candidates for multidrug therapy, for example, of the BEP type. Nevertheless, it should be remembered that such therapeutic de-escalation should be considered only in patients who can be closely followed. However, patients referred to our center often come from socioeconomically disadvantaged backgrounds, which can compromise the regularity of care and supervision. Patients with such a risk should continue to receive first-line multidrug therapy, while others may benefit from a less aggressive therapeutic approach, taking into account the acute toxicity of the AE protocol, as well as the significant risk of leukemias secondary to etoposide that can appear after several years.

**CONCLUSION**

The epidemioclinical criteria of our patients did not present any particularity. Repeated aspirations are useless. Our study confirmed the extremely chemosensitive character of PGTDs. In view of data from the WHO classification modified by FIGO and taking into account the efficacy/toxicity ratio, therapeutic de-escalation would be justified, at least in patients who are likely to be lost to follow-up.

**REFERENCES**
