www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i6.153

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Research Paper

Cellular Atypia as a Risk Factor for Persistant Trophoblastic Disease: Prospective Cohort Study

Authors
Dr Uma Thankam[1], Dr Nandini Vamadevan Retnamma[2], Dr Simi Jameela[3], Dr Nirmala Chellamma[4]
[1]Assistant Professor, Department of Obstetrics & Gynecology, SAT Hospital, Government Medical College, Thiruvananthapuram.
[2]Professor, Department of Obstetrics & Gynecology, SAT Hospital, Government Medical College, Thiruvananthapuram
[3]Assistant Professor, Department of Obstetrics & Gynecology, SAT Hospital, Government Medical College, Thiruvananthapuram
[4]Professor & HOD, Department of Obstetrics & Gynecology, SAT Hospital, Government Medical College, Thiruvananthapuram
Corresponding Author
Dr Uma Thankam
Assistant Professor, Department of Obstetrics & Gynecology, SAT Hospital, Government Medical College, Thiruvananthapuram
Mobile: 9446505656 Email: *uma.thankam@gmail.com*

Abstract
Introduction: *Gestational trophoblastic tumours have varying behavior from being locally invasive to metastatic. It would be useful if there is an effective prognosticating method especially in low resource settings. This study was an attempt to identify such a prognosticator.*
Aim: *To look for the presence of atypical cells in the histopathology of vesicular mole, the βhCG level four week after evacuation and look for any association with persistent trophoblastic disease (PTD)*
Material and Methods: *It was hospital based prospective cohort study conducted in a tertiary care hospital. 95 cases of vesicular mole were studied .The patients had a pre evacuation βhCG done and underwent suction curettage. The products were sent for histopathologic examination and apart from identifying the grade of proliferation they were specifically examined for presence of atypical cells. The βhCG levels four weeks after evacuation was checked.*
Results: *On looking at the distribution of atypical cells with βhCG four weeks after evacuation, it is seen that of the 90.6% of the patients with cellular atypia had abnormal levels of status four weeks βhCG levels. With regards to the distribution of atypical cells with the time needed to reach baseline βhCG ,out of the 32 patients with atypical cells 23 (71.9%) had an abnormal βhCG fall.*
Conclusion: *Looking for the presence of atypical cells in the histopathology of vesicular mole can prognosticate the nature of regression of the tumor and help in classifying it as high risk and low risk.*
Keywords: *cellular atypia, persistent trophoblastic disease.*

Introduction

Gestational trophoblastic tumours are all malignant or potentially malignant. Histologically they show various grades of differentiation, from a recognisable chorionic villus structure to highly virulent anaplastic mass of cells[1]. These tumours have a varying behavior, but inspite of it they are almost completely curable. Tradionally it is believed that it is impossible to predict the malignant potential of the tumour from it histology[1]. It is believed that the biological activity and the clinical behavior are better indices of the disease prognosis.

The hydatidiform mole is a tumour of both layers of the trophoblast, syncitiotrophoblast and cytotrophoblast in varying proportions. There is proliferation and pleomorphism of epithelial cells with hyperchromatic and actively mitotic nuclei. The stroma of each villus is odematous destroying the vessels and forming a rounded cyst filled with watery fluid. The chorion is converted into a mass of grape like structures attached by a fine stalk. Suction curettage is the preferred method of evacuation[2].

About 20% of molar pregnancies are at risk of developing persistent tumor.Further all patients are kept on follow up with βhCG weekly till they become normal for three consecutive weeks and then monthly for 6 months. It has always been a dilemma as to who are prone to develop a PTD as the clinical profile post evacuation decided the prognosis.

Aim of the study

To study the presence of atypical cells in the vesicular mole as a predictor for persistent trophoblastic disease and to find its association with βhCG level four week after evacuation. To prove that the presence of atypical cells is a better prognosticator than grading of trophoblastic proliferation.

Material and Methods

It was hospital based prospective cohort study conducted at a tertiary care referral hospital in Kerala under the auspices of the vesicular mole clinic. Ninety five patients who were admitted as molar pregnancy at vesicular mole clinic and evacuated were included in the study. The patients were registered in the clinic, examined, investigated and treated. The evacuated specimen was sent for histopathology examination.

The patients were followed up by βhCG done according to the hospital protocol. All patients had a pre evacuation βhCG estimation done. After appropriate evaluation suction curettage was done. A post evacuation βhCG was estimated. Further the patients were followed up with βhCG estimation every week till it became normal. Once the value touched baseline for three consecutive weeks and then the patients were followed up every month for a period of 6 months. Then βhCG fall pattern was plotted in a graph.

The cases were classified as persistent trophoblastic disease when there was a rise of βhCG, plateau of titers, persistent detectable level after 4 to 5 month of evacuation, myometrial invasion or histological evidence of choriocarinoma. Based on the βhCG fall patients were grouped a normal regression, slow regression and requiring chemotherapy. The βhCG levels 4week after evacuation was also checked. The presence of atypical cells was studied with regards to βhCG fall and also βhCG at 4 weeks.

Ethical committee clearance was obtained from institutional ethiacl committee. The data was entered in the proforma. Appropriate statistical test (Chi-square test) was applied to analyze the results.

Results

Ninety five cases of vesicular mole were included in the study. Majority of the patients were in the 20 to 25 year age group(45.1%). Among the patients, 45.3% belonged to O+ve blood group. The number of primi parous patients was almost equal to the number of multiparous patients.54% of the patients were diagnosed at 8 to 12 weeks period of amenorrhea. 78.9% cases were complete moles and the rest were partial moles.

About 41.1% (39) patients had βhCG values between 40,000 and 100000 and 21% (20) patient had values more than 100000 before evacuation. The value of βhCG was elevated in 40 (42.1%) of the patients at the end of four weeks of evacuation and level reached the normal leval by 12 weeks in 62 patients (70.5%). When we assess the regression pattern of βHCG, 61 patients (64.2%) showed a normal regression, 22 (23.2%) had a slow regression and 12 (12.6%) required chemotherapy. (Table 1)

Chemotherapy was given for 12(12.6%) patients based on hospital protocol. When the relation of trophoblastic proliferation with cellular atypia and need for chemotherapy was studied, it was noted that 5/ 5 of the patients with mild trophoblastic proliferation who required chemotherapy, 4/6 of the moderate proliferation group and 2/2 of the severe proliferation group had atypical cells.

Thirty two cases (33.7%) showed atypical cells on histopathological examination. On looking at the distribution of atypical cells with βhCG four weeks after evacuation, it is seen that of the 32 patients with cellular atypia 29 (90.6%) had abnormal levels of status four weeks βhCG levels. This was found to be statistically significant. (Chi square 16.68, p value 0.001.) (Table 2)

With regards to the distribution of atypical cells with the time needed to reach baseline βhCG, out of the 32 patients with atypical cells 23 (71.9%) had an abnormal βhCG fall. (Chi square -29.36, p value 0.001) This is suggestive of a strong association between the presence of cellular atypia and the time needed for βhCG to reach baseline levels. (table 3)

When the distribution of atypical cells with the type of regression was studied, 9 patients (28.1%) with atypical cells had normal regression, 12 (37.5%) had slow regression and 11 (34.4%) patients required chemotherapy. (Chi square 32.13, p value 0.001). (Table 4)

Table 1. Relation of trophoblastic proliferation with cellular atypia and need for chemotherapy

Proliferation	Chemotherapy			Atypical Cells		
Mild	Yes	5	14.2%	Yes	5	100
				No	-	0
	No	30	85.7%	Yes	4	13.3
				No	26	86.7
Moderate	Yes	6	12%	Yes	4	66.7
				No	2	33.3
	No	44	88%	Yes	12	27.3
				No	32	72.7
Severe	Yes	2	20%	Yes	2	100
				No	-	0
	No	8	80%	Yes	5	62.5
				No	3	37.5

Table 2. Distribution of atypical cells with βHCG 4 weeks after evacuation

			Atypical cells		Total
βHCG 4 weeks After evacuation			Yes	No	
	Normal	Number	3	33	36
		%	8.3	91.6	100
	Abnormal	Number	29	30	59
		%	49.15	15.84	100
	Total		32	63	95
Chisquare = 16.68; p value- 0.001					

Table 3. Distribution of atypical cells with the time needed to reach baseline βHCG

			Atypical cells		Total
Time needed to reach baseline βHCG			Yes	No	
	Normal	Number	9	53	62
		%	14.5	85.5	100
	Abnormal	Number	23	10	33
		%	69.7	30.3	100
	Total		32	63	95
Chisquare = 29.36; p value- 0.001					

Table 4. Distribution of atypical cells with the type of regression

			Atypical cells		Total
Type			Yes	No	
	Normal	No	9	52	61
		%	14.7	85.2	100
	Slow	No	12	10	22
		%	54.5	45.5	100
	Chemotherapy group	No	11	1	12
		%	91.6	8.4	100
Total			32	63	95
Chisquare=32.13 with 2df ; p value – 0.001					

Discussion

Gestational Trophoblastic Disease (GTD) shows an interestingly marked geographic variation in its distribution. These variations have been attributed to environmental factors, extrinsic factors, high fertility rates with an increased incidence of abortions[3]. Several authors have pointed out that the high prevalence of GTD in this area is related to the poor socioeconomic conditions, malnutrition and frequent pregnancies[4]. Moreover there is an increased incidence of awareness among the health care providers in this region of the need to follow up GTD, hence there is a high incidence of GTD in our centre.

Most authors point out a rising risk of molar pregnancy over the age of 40 years[5]. In young women under the age of 20 years the risk is relatively increased and this early peak may be due to over reporting of cases or under reporting of pregnancies[6]. In the present study the mean age of the patient was 24.34 years. Several studies have reported an excess of type A blood group and deficit of type O in women with choriocarinoma[7]. Prognosis was seen worst with B or AB. Previous studies in the hospital (Thankam S 1992-95) shows no relationship of blood group with development of GTD.The present study is in conformity with it.

According to Bagshawe[8] (1976) the first pregnancy is at most risk. Park (1971)[9] reported no significant association with gravidity. In the previous studies conducted by this hospital no association with gravidity was identified. The present study again fails to find an association between the two.

The incidence of partial mole in previous study from our centre was 9.1%. (P.C.Ansamma 1989-90),14.68% (Thankam.S 1992-95) and in the present study 21.1%. Looking for cellular atypia was proposed by a study conducted at RCC[10] In the present study there was a 33.7% incidence of nuclear atypia. High βhCG values were used as bad prognostic markers in various studies and also by the WHO scoring system[11]. The present study however fails to show a positive relationship in the initial βhCG values and development of PTD.

While 86% of the normal regression group showed absence of cellular atypia, 92% of the chemotherapy group showed the presence of cellular atypia. In the slow regression group the results were equivocal. In the present study 90% of the patients with cellular atypia had abnormal levels of status 4 weeks βhCG. Both these parameters put together could identify 92% of the spontaneously regressing tumours. A multivariate analysis[10] of prognostic indicators in complete

hydatidiform mole showed a 100% identification of low risk lesions (spontaneously regressing lesions) and 80% identification of high risk lesion by using a serum βhCG four weeks after evacuation combined with cytological abnormalities.

Of the 32 patients with cellular atypia 23 (72%) had abnormal βhCG fall and 84% patients without atypical cells had a normal βhCG fall. This shows a strong association between the presence of cellular atypia and fall of βhCG to baseline. While the proportion of patients who required chemotherapy was in the range of 12-20% irrespective of the degree of trophoblastic hyperplasia, the presence as well as absence of atypical cells marked well with the occurrence of PTD. In order to predict the behavior of the vesicular mole , various investigations had tried to grade them on the basis of degree of hyperplasia and differentiation of the trophoblast. (Drisoll, 1977).

The value of such a grading was a controversy since the time of Hertig and Sheldon[12]. Tow and Yung et al (1967)[13], Elston and Bagshawe et al 1972[14], have showed that histological grading has little value in predicting the course of the disease and response to chemotherapy. David et al 1991[11] had also put forth that the histologic grade of complete mole does not correlate with the frequency of metastases, incidence of high risk metastatic disease, the presence of residual trophoblast on curettage or the development of resistance to single agent chemotherapy.

Conclusions

Using cellular atypia could predict the outcome of nearly 90 % of the PTD. Prognosticating vesicular mole could be done in a effective, cheaper and easier method using the above method.

Acknowledgements

We thank Dr Jayalekshmi, Professor, Department of Pathology, Government Medical College, Thiruvananthapuram and Dr Prabha Balaram, Professor, Regional Cancer centre, Thiruvananthapuram for their contribution in histopathological examination.

References

1. Jeffcoate's principles of Gynaecology 8th International edition 2014
2. Ross S Berkowitz, Donald P Goldstein, Jonathan S Berck "Gestational Trophoblastic Diseases" Novak's Gynaelogy Fourteenth edition 2008
3. Buckley, Jonathan D "The Epidemiology of molar pregnancy and choriocarcinoma" Clinical Obstetrics and Gynaecology, Vol:27,No.1 1984 153-158
4. Yen S , ;Mac Mahon.B "Epidemiology features of trophoblastic diease" AJOG 1968,101:126
5. Keith Edmunds D "Gestational Trophoblastic Diseases" Dewhurst's Text book of Obstetrics and Gynaecology for postgraduates 6th edition(2000) 61-75
6. Robin P Farias ,Eisner, Jonathan .S.Berek ,Manual of clinical oncology 4th edition (2000) 264-68
7. Gary Cunningham F ,Paul C Mcdonald, Norman F. Grant "Trophoblastic Diseases" Williams Obstetrics 20th edition (1998) 669-693
8. Richard H .J .Begent, Kenneth D. Bagshawe :Treatment of Advanced Trophoblastic Disease: Gynaecologic Oncology :Vol10 cancer treatment and research pp155-186
9. Park WW. :Choriocarcinoma A study of its pathology London Heinemann 1971
10. P.Balaram, M.John,T.N.Rajalekshmy, A. Mathew, S.Enose, V.P.Gangadharan."A Multivariate analysis of prognostic indicators in complete hydatidiform moles" European Journal of Obstetrics and Gynecology and Reproductive Biology: 87: 1999;69-75
11. John R. Lurain MD, Lisa A Casanova MD, David Sott Miller MD, Alfred W.Rademaker PhD Prognostic factors in

gestational trophoblastic tumors: A proposed new scoring system based on mulivariate analysis AJOG Vol 164, Issue 2,Feb 1991, Pages 611-616

12. Hertig AT, Sheldon WH "Hydatidiform Mole: A pathologic-clinical correlation of 200 cases " AJOG (1947)53:1
13. Tow, W. S. H., and Yung, R.H.(1967), The value of histological grading in prognosticating of hydatidiform mole.J. Obtet.Gynae.Brit.Cwlth 74,292 191
14. Elston CW "The Histopathology of Trophoblastic Tumours" J Clin Pathology(1976):10(suppl):111