

Correlation of Mature Cystic Teratomas With CA19-9

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ABSTRACT

Background: Mature cystic teratomas are the most common germ cell tumor account 10-20% of all ovarian tumors. Several tumor markers have been linked to their presence & development of complications. **Objective:** To evaluate the relation between mature cystic teratomas with tumor marker CA19.9. **Patients and Methods:** A case-control study conducted in Babylon Teaching Hospital for gynecology & Pediatrics & private clinic during the period February-December 2018 included, 50 women with ovarian dermoid cyst and 50 healthy women as controls, full history & thorough clinical examination were done and further investigation performed accordingly. CA19.9 level was investigated in blood samples. Surgery in form of laparoscopy or laparotomy was done for dermoid cyst patients & specimens sent for histopathology to confirm diagnosis. **Results:** CA19.9 was significantly higher in patients with dermoid cyst compared to that in control, 46.5 ± 23.84 vs. 11.22 ± 3.8 respectively. ($p < 0.001$). The receiver operating characteristic (ROC) curve analysis revealed that CA19.9 produced a sensitivity of .2%, specificity of 96%, accuracy of 84%, positive predictive value of 95% and negative predictive value of ..%. According to these values of validity, CA19-9 was good enough to predict ovarian dermoid cyst. There was positive correlation with diameter of the dermoid cyst.

Conclusion: CA19.9 was significantly correlated with and good predictor of dermoid cyst. A strong correlation exists between CA19.9 level and the diameter of the tumor.

Keywords: mature cystic teratomas , Dermoid cyst, Epidemiology , risk factors, Complications ,CA19.9,

1. INTRODUCTION

The word Teratomas is derived from the Greek “teras”, which is translated into “monster”(1). Mature cystic teratomas or ovarian dermoid cysts is considered to be the commonest germ cell tumor that found in the adolescent .. It is a benign tumor that is derived from ovarian germ cells, and it develops from fully differentiated ectodermal, mesodermal & endodermal tissue (3) Mature cystic teratomas account for 10-20% of all ovarian tumors (4). Peak incidence occurs in women aged between (20-40 years) during their reproductive period of life (5). It constitutes 20-50% of all the benign tumors of the ovaries, whether in adults or younger age group (6). Some study show that mature cystic teratomas accounts for up to two-thirds of benign masses found in ovaries, and the incidence of malignant transformation is 1-3% of cases, although it may occur in any age (.). Increasing age is associated with increase in the frequency of malignant chances, this increase is prominent after menopause, reaching up to 19% (8). However, in about 15% of patients with dermoid cysts, they are found in a bilateral configuration (9). Mature cystic teratomas may be complicated with rupture, infection, torsion, hemolytic anaemia, chemical peritonitis and malignant changes(10). The most common of them is torsion, constituting approximately 8% of cases, the risk of occurrence of torsion during pregnancy is mainly at the end of the 1st trimester and during the 2nd trimester(11). The ovarian torsion can cause acute abdominal pain that present at emergency department(12). Cystic teratomas rupture rarely occur, and can be spontaneous or associated with torsion. The rupture may occur suddenly leading to shock or hemorrhage with acute chemical peritonitis(13). Cysts rupture lead to peritonitis and bowel obstruction due to leakage of sebaceous contents from the cyst(14).

Mature cystic teratomas are diagnosed using certain imaging methods including plain x-ray, ultrasound, computed tomography and magnetic resonance imaging (15). Pelvic ultrasound is considered to be the first line investigation for the diagnosis of dermoid cyst, and is the preferred imaging procedure. It is observed as hyperechoic extension arising from the inner surface of a cyst, often with hair within, or calcifications and fat. Mature cystic teratomas have a wide range of appearances on ultrasound due to their variable internal composition. Colored Doppler ultrasound helps to identify the vascular component within the mass when color Doppler see a twisted pedicle this is called (whirl pool sign) this strong diagnosis of torsion(16). But normal color Doppler is not exclude the diagnosis of torsion (1.).

Computed tomography (CT) images show fat-fluid level, calcification, rokitansky protuberance and tufts of hair. The presence of these tissues confirm the diagnosis of ovarian teratomas in approximately 98% of cases(18). CT has high sensitivity in the diagnosis of ovarian cyst. Certain study had shown that the sensitivity of CT scan in detection of mature cystic teratomas is 96%. CT scan commonly performed in preoperative evaluation of the mass when ultrasound non diagnostic or equivocal(19). CT scan finding suggest rupture ovarian dermoid cyst include hypo attenuating fatty fluid below right hemidiaphragm(20). The malignant transformation is suspected when tumor size greater than local, soft tissue plugs and cauliflower appearance with irregular border (21).

Cancer antigen 19-9 (CA 19-9): There are certain tumor marker related to dermoid cyst include CA19-9, CA125, carcino embryonic antigen, CA15-3 and α -feto protein (AFP) (22). Cancer antigen 19-9 (CA 19-9) is the most important tumor marker that is widely used in the diagnosis of dermoid cyst, it is a protein presents on the surface of certain malignant cells and it can be detected by blood test in laboratory and sometimes in other body fluids. It is shed by the tumor cells(23). CA19-9 is a monosialoganglioside produced by mucinous tumors of the gastrointestinal tract include the pancreas and biliary tree and it is elevated in primary ovarian tumor. This antigen was first identified by a monoclonal antibody (NS-1116-19-9) obtained during immunization with a membrane extract prepared from the colon carcinoma cell line SW-1116. It was specified as heterogeneous group of glycoconjugates, including N- and O- linked glycoproteins, and glycosphingolipids. They share the terminal sequence, as in figure (4), named sialyl-lewis x tetrasaccharide(24). Normal level of CA19-9 in serum up to 3. unit/ml. The antigen is detectable in blood serum and other bodily fluids or extracts through enzyme-linked fluorescent assay procedure. CA19-9 has important role in the management of gastrointestinal cancers in order to monitor the response to treatment and predict recurrence of carcinoma during follow up (25).

The relationship of CA 19-9 with dermoid cyst:

The relationship between CA 19-9 and clinical specifications of MCT are not well documented but there is one study that conclude that increase in CA 19-9 is related to larger tumor diameter and higher rate of ovarian torsion (26). CA 19-9 is used as a method for the diagnosis of MCT (2). The study show that CA 19-9 levels were correlated with larger tumor size although they failed to show positive relationship between bilateral ovarian cyst

and CA19-9 elevation(28). Serum level of CA19-9 begins to be high when tumor size more than 4 cm(29). There is certain study shows significant correlation between CA 19-9 elevation with presence of fat component in MCT(30). CA 19-9 have been raised depend on tumor diameter, rate of torsion and rate of malignant transformation and the extent of necrosis (31). Elevated CA19-9 level may be as result of rupture of the dermoid cyst leading to spillage of fat or bonny tissue from cyst wall into blood stream. A weakened cyst wall due to large diameter of the cyst may be another cause of the elevated CA19-9 level. Increase level of this marker related to malignant changes. There are significant changes in serum level of CA 19-9 in post-menopausal patient with ovarian torsion (32).

2. PATIENTS and METHODS

This was a case control study was conducted in the Department of obstetrics and gynecology in Babylon Maternity and pediatric Teaching Hospital, Babylon, Iraq. From the period of February 2018 to December 2018 after approval by Iraqi board of medical specialization.

This Study involves 100 women, fifty of them with ultrasound features suggestive dermoid cyst and fifty women without ovarian pathology as control. Detailed history was taken from patients including age, marital status, parity, occupation and residence, patients either asymptomatic or present with acute symptom. Gynecological history, past medical history, family history and drug history. Five ml of venous blood was aspirated for measuring level of CA19.9. Control group were women who mostly presented for family planning unit & some volunteers after doing ultrasound of pelvis to be sure that no accidental finding of adnexial mass is present. Sample of blood (5 ml) for measuring CA19.9 was also taken. Surgery in form of laparoscopy or laparotomy was done for patients & specimens sent for histopathology for conformation of the diagnosis.

Data analysis performed using SPSS ® software for windows version 24 and statistical tests applied accordingly at a significance level of 0.05.

3. RESULTS

There were 50 cases with ovarian dermoid cyst and 50 apparently healthy women enrolled in this case control study, both groups were almost matched for demographic characteristics and body mass index (BMI), in all comparisons , P. value > 0.05, not significant, (**Tables 1**). The obstetrical history of the studied groups is shown in (**Tables 2**), where no statistically significant differences had been found between both studied groups regarding the obstetrical history or menopausal status, in all comparisons, (P. value > 0.05). The distribution of CA19-9 levels of women in both studied groups revealed that the mean CA19-9 level was significantly higher in ovarian dermoid cyst cases compared to that of controls; 46.5 ± 23.84 (range: 6.91 – 161.1) U/ml vs. 11.22 ± 3.8 (range: 2.4 – 4.64) U/ml, respectively, (P< 0.001, highly significant). Additionally, the median CA19-9 level was also significantly higher in ovarian dermoid cyst cases than controls; 33.5. vs. 8.9., (P. value < 0.001, highly significant), regarding the range and interquartile range (IQR) both were higher in cases than controls, (**Table 3**).

Further distribution of CA19-9 levels was performed using the upper limit of normal reference range of 3. U/ml and the studied cases and controls were categorized into subgroups according to this cutoff point; Elevated CA19-9 (> 3. U/ml) was found in 36 cases (.2%) compared to only 2 (4%) controls while 14 cases and 48 controls had normal (\leq 3. U/ml) CA19-9, with highly significant difference (P<0.001). From other point of view according to risk ratio of having elevated CA19-9, ovarian dermoid cyst cases were about 2.5 folds more likely to have elevated CA19-9 levels compared to controls (Risk ratio = 2.45, P<0.001), additionally, the elevation rate was higher in cases than controls, (.2%) vs. (4%), respectively, (**Table 4**). Regarding biopsy results, 48 cases proved as benign mature cystic teratomas, two cases had malignant transformation with the dermoid which was squamous cell carcinoma.

Table (1): Demographic characteristics of the studied groups

Variable		Cases (N=50)		Control (N = 50)		P. value
		No.	%	No.	%	
Age (year)	< 30	15	30.0	12	24.0	0..8
	30 - 39	18	36.0	16	32.0	
	40 - 49	10	20.0	13	26.0	
	50 or more	.	14.0	9	18.0	
Residence	Urban	46	92.0	45	90.0	0..1
	Rural	4	8.0	5	10.0	
Occupation	Housewife	44	88.0	42	84.0	0.54
	Employee	6	12.0	8	16.0	
BMI	Normal	13	26.0	15	30.0	0..3
	Overweight	25	50.0	21	42.0	
	Obese	12	24.0	14	28.0	
Menopause	Premenopausal	43	86.0	41	82.0	0.59
	Postmenopausal	.	14.0	9	18.0	

Table .: Obstetrical history of the studied groups

Variable		Cases (N=50)		Control (N = 50)		P. value*
		No.	%	No.	%	
Gravidity	1 – 2	2.	54.0	29	58.0	0.92
	3 – 4	10	20.0	9	18.0	
	> 4	13	26.0	12	24.0	
Parity	Primi	8	16.0	6	12.0	0..6
	1 – 2	20	40.0	24	48.0	
	3 – 4	12	24.0	9	18.0	
	> 4	10	20.0	11	22.0	
Miscarriage	Yes	9	18.0	6	12.0	0.41
	No	41	82.0	44	88.0	

Table (3): Distribution of CA 19-9 levels of Dermoid cyst cases and controls

Statistic	Cases (N=50)	Control (N = 50)	P. value
Mean \pm SD	46.5. \pm 23.84	11.22 \pm 3..8	< 0.001
95% CI of mean	39.90 – 53.24	10.16 – 12.2.	
Range	6.91 – 161.2	2.40 – 4..64	
Median	33.5.	8.9.	< 0.001
IQR	21.26 – .031	6.95 – 11.64	

Table (4): Distribution of CA 19-9 levels of Dermoid cyst cases and controls

CA19-9 level*	Cases (N=50)		Control (N = 50)		Total
	No.	%	No.	%	
Elevated (> 3. U/ml)	36	.2.0	2	4.0	38
Normal (\leq 3. U/ml)	14	28.0	48	96.0	62
Total	50	50.0	50	50.0	100
Risk ratio = 2.45 (95% CI of risk ratio: 1.82 – 3.29), P. value < 0.001					

4. DISCUSSION

This study has compared two groups of women regarding relationship between mature cystic teratomas and the tumor marker CA 19-9. Each of the two groups is composed of 50 females. The first group (cases group) included women with ovarian dermoid cyst, while the second group (control group) included women who are without ovarian pathology. Comparison between the two study groups regarding age have shown no statistically significant difference. Similar comparisons between the two study groups were also performed regarding residence, occupation, body mass index (BMI), and menopausal status, all those characteristics were found to be similar between the two study groups with no significant differences between them. Obstetrical history was also compared between the two study groups using the gravida/para/abortion (GPA) system. No statistical difference was observed between the two study groups regarding obstetrical history, which further ensures that the two study groups are closely similar. The level of tumor marker CA19-9 was compared between the two study groups and shown a highly significant difference in the level of the tumor marker between the two groups. Patients with ovarian dermoid cyst were found to have a mean CA19-9 level four times higher than that found in controls. This elevated level that equals (46.5 ± 23.84) U/ml is closely similar to the level described by Ahmadzadeh et al. of (46.13 ± 11.65) U/ml in their study conducted in Iran on 2016, which included a total of 33 patients with ovarian dermoid cysts (33). Kyung et al. have also demonstrated a similar relationship in their study conducted on 163 women in Korea (34). In a closely related manner, Var et al. had conducted a retrospective study from 2006 through 2010. in order to identify the relationship between tumor markers of the serum (including CA19-9 among other tumor markers) and tumor size of ovarian dermoid cyst. Their study included the clinical notes of 20 patients that underwent surgery for ovarian dermoid cyst. They demonstrated that CA19-9 is the most valuable tumor marker for dermoid cyst, and it was superior to CA125, CA15-3, CEA, and AFP. They also suggested that tumor size is the most important factor that influences the elevation in CA19-9(35). A cut-off point of 3.2 U/ml has been calculated through the utilization of receiver operating characteristic (ROC) curve, and choosing the cut-off point with the highest sensitivity and specificity, which were 92% and 96%, respectively, for this particular cut-off point. Based on this cut-off value, it was found that 92% of the patients in cases group had elevated CA19-9 levels while only 4%

of the members of control group had elevated level of that tumor marker. Patients with ovarian dermoid cyst were found to be 2.5 times more likely to have elevation of the tumor marker CA19-9 as compared to the controls. Mean diameter of the ovarian dermoid cysts among the study participants was (11.33 ± 4.13) cm with a range of (3.20 – 22.0) cm. This is relatively similar to the findings by Dede et al. in their study conducted on 80 participants, who observed that tumor size range was (3.0-20.0) cm, with a mean of $(.2 \pm 4.5)$ (36). Patients with bilateral cysts were found to have significantly higher levels of CA19-9 tumor marker as compared to patients with unilateral cysts. However, only 12% of the patients had bilateral cysts. This is similar to the results reported by Al-Fozan et al in their observational study conducted on 336 females, who concluded that only 13.4% of dermoid cysts occurs bilaterally, This is consistent with the finding by Kyung et al. in their study, who have have shown that there is a direct relationship between CA19-9 level and the size of the tumor(3.) Atabekoglu et al. have suggested in their case report published in 2005 that a complete pre-operative workup for the patients is necessary in order to detect any signs of the presence of malignancy. They justified this suggestion by explaining that despite the fact that elevation in serum tumor markers levels do not necessarily confirm the existence of a malignant tissue, but high levels of these markers are considered a challenge to the clinician in differentiating between benign and malignant tumors (38).In our study we have two cases that their histopathological show malignant transformation with mature cystic teratomas which is squamous cell carcinoma.

5. CONCLUSIONS

Ovarian dermoid cyst is the most common germ cell tumor in reproductive age group. It accounts 10-15% of all ovarian tumors. The majority of dermoid cysts are unilateral but bilateral dermoid is found in 10-15% of cases. The present study demonstrates correlation of ovarian dermoid cyst with CA19-9. The sensitivity and specificity of CA19-9 in prediction of dermoid cyst where .2%, 96% respectively and positive predictive value 95%, negative predictive value ..%. Correlation between CA19-9 level and the diameter of the tumor was found to be highly significant.

Ethical Clearance

Ethical clearance and approval of the study are ascertained by the authors. All ethical issues and data collection were in accordance with the World Medical Association Declaration of Helsinki 2013 for ethical issues of researches involving humans, verbal and signed informed consent obtained from all patients. Data and privacy of patients were kept confidentially. .

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