Full length article

The predictive role of CA-125 in the management of tubo-ovarian abscess. A retrospective study

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ABSTRACT

Objective: Tubo-ovarian abscess (TOA) is a well-established sequel of acute pelvic inflammatory disease (PID). While as up to 25% of women will experience conservative treatment failure, the factors associated with treatment failure are not clearly-established, and the role of Cancer antigen 125 (CA-125) is under-studied. We aim to evaluate the role of CA-125 in the conservative management of TOA.

Study design: A retrospective cohort study conducted at tertiary university-affiliated hospital during 2007-2018. Ninety one patients were diagnosed with a TOA and underwent a trial of conservative management with intravenous antibiotics. Patients who eventually underwent surgical intervention were compared with patients managed conservatively.

Results: Overall, 39/91 (42.8%) underwent an invasive intervention subsequent to failed antibiotic treatment. Patients who experienced conservative treatment failure had higher medians of inflammatory markers as CRP (15.7 vs. 10.8 mg/L, p = 0.02), WBC count (14.2 vs. 12.4 1,000/mm^3, p = 0.04) and platelet count (374 vs. 295 10^9/L, p = 0.04) at admission. Higher levels of CA-125 at admission were found in those who required an invasive intervention (57 vs. 30 U\ml, p = 0.02) as well. The largest diameter of TOA at admission was higher in those who required an invasive intervention as compared to those who were successfully treated conservatively (75 mm vs. 57 mm, p = 0.01). CA-125 level was found to be the only independent factor associated with conservative treatment failure (OR; 95% confidence interval [CI], 1.27, 1.08–1.48, p = 0.03).

Conclusion: Elevated CA-125 serum levels were found to be associated with failure of conservative parenteral antibiotic therapy for TOA. This finding should be better evaluated in a prospective manner.

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Introduction

Tubo-ovarian abscess (TOA) is one of the substantial well recognized sequels of acute pelvic inflammatory disease (PID) and affects up to 15% of women diagnosed with a PID and up to one third of those who require hospitalization [1–3]. TOA is a complication of a polymicrobial infection. In addition to known sexual transmitted disease (STD) pathogens such as Neisseria gonorrhoeae and Chlamydia trachomatis, various gram negative and gram positive aerobic an anaerobic pathogens are known to account for PID infections [4,5]. The mechanism of TOA formation involves upper genital tract invasion of pathogens coupled with a substantial inflammatory response resulting in tissue necrosis, and followed by proliferation of pathogens and abscess formation [6].

Conservative management of TOA includes broad-spectrum intravenous (IV) antibiotics as the first line treatment [4], with treatment success rates of up to 75%–85% [7,8]. In those who fail to respond to initial antibiotic treatment, an invasive intervention is often required. In recent decades the utilization of minimally invasive drainage techniques in this setting has gained popularity including transvaginal ultrasound-guided drainage and computed tomography (CT) -guided or ultrasound-guided percutaneous drainage [9–11].

While up to one fourth of women will experience conservative treatment failure [4,7,8], the factors associated with treatment failure are not clearly-established.

The CA 125 is a glycoprotein, initially identified on the surface of the ovarian carcinoma cell line, which is widely distributed on the surface of both healthy and malignant cells of mesothelial origin

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Abbreviations: PID, pelvic inflammatory disease; TOA, tubo-ovarian abscess.
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[28]. Occasionally, raised serum CA 125 levels are found in the setting of various benign and inflammatory conditions due to increased local expression in the area of inflammation.

CA-125, while studied vastly as a marker of pelvic inflammation and pelvic pathological processes [12–14], remains under reported in its relation to TOA management. Given the paucity of literature, we aimed to evaluate the role of CA-125, as well as other clinical predictors, in the management and treatment of TOA.

Materials and methods

Patients

This is a retrospective cohort study. The study cohort comprised all women diagnosed with a TOA and admitted for an inpatient care in a tertiary medical center during 2007- 2018. TOA diagnosis was made in accordance with diagnostic criteria published in recent guidelines by the United States Centers for Disease Control and Prevention criteria for PID and TOA [4]. In short, a TOA diagnosis was established in sexually active women experiencing pelvic or lower abdominal pain, excluding other etiologies for their complaints and including adnexal mass (per vaginal ultrasound or contrast-enhanced CT) and associated tenderness. Women were identified using hospital medical records. We excluded those with incomplete data, and cases in which a pelvic abscess was from a gastrointestinal origin.

Data collection

For the purpose of this study, we abstracted patients' hospital admission records, gynecological ward follow-up charts, laboratory and imaging scans reports, operation reports and discharge letters from the electronic medical record database of the gynecological unit in our medical center. Records were reviewed by a single reviewer (G.L). Women's records were reviewed for demographic, medical, and surgical history, and for treatment undertaken for TOA. The following data were extracted: women's characteristics [(age, body mass index (BMI), gravidity, parity, history of documented pelvic inflammatory disease, ethnical origin, previous pelvic surgery, recent medical or surgical procedures, marital status and current usage of an IUD (type of IUD and time elapsed since IUD insertion)], current admission characteristics: [body temperature, C reactive protein (CRP) serum level, white blood cells (WBC) count, erythrocyte sedimentation rate (ESR), TOA size, antibiotics given, duration of time between admission and invasive procedure, indication for invasive procedure, length of stay, readmissions and microbiological data.

Recent IUD insertion was regarded as IUD inserted in the previous 4 weeks [15]. Body temperature was regarded as body oral temperature at admission measured in Celsius centigrade. Readmission was defined as re-hospitalization during a 30-day period after discharge [16].

Treatment protocol

In general, all women with an evidence of TOA were hospitalized for a trial of antibiotic treatment initiated at admission. Antibiotic treatment regimens chosen was in accordance with the Center of Disease Control and Prevention (CDC) guidelines (Table S1) [4]. In our center, all women are treated with parenteral antibiotics for 48 h after clinical improvement. Followed by oral therapy which is home prescribed to complete the 14 days of treatment on an outpatient basis.

Treatment failure was defined as persistent pain and/or fever following initial parenteral antibiotics for 48–72 h [17].

IUD removal was performed at the discretion of the attending gynecologists at the emergency department. Bacterial culture isolates identification was performed using the Vitek2 or Vitek MS systems (BioMerieux, St. Louis, Mo, USA). As in all patient with a complicated adnexal mass, CA-125 serum level were drawn at hospitalization. PCT drain placement was performed under US guidance following clinical and sonographic evaluation suggesting proper access for via vaginal or abdominal approaches. When access for US-guided PCT drain placement was deemed difficult, CT guided PCT was performed following radiologic consultation, mainly from the gluteal or flank regions.

Statistical analysis

Descriptive statistics were used to summarize the entire cohort and to compare women in the study groups. Women's characteristics are described as proportions for categorical variables and medians, interquartile ranges and means for continuous variables without a normal distribution. Significance between groups was assessed by the Chi square test and -Fisher's exact test for categorical variables. The Student t-test was used for analysis of continuous variables with normal distribution and the Mann–Whitney U test for analysis of continuous variables with skewed distribution. A 2-sided P-value < 0.05 indicated statistical significance. A multivariate logistic regression model was established to evaluate the independent relationships between failed antibiotic therapy and variables found to be statistically significant in univariable analysis. The data were analyzed using Software Package for Statistics and Simulation (IBM SPSS version 22, IBM Corp, Armonk, NY).

Results

During study period, 474 women were diagnosed with PID that met the hospitalization criteria [4]. Of these, 91 women (19.1%) had evidence of TOA and constituted the final study cohort. Overall, thirty nine (42.8%) underwent an invasive intervention subsequent to failed antibiotic treatment (invasive intervention group). The remaining 52 women were treated with intravenous antibiotics only (conservative treatment group).

Table 1 summarizes the demographic and clinical characteristics of women in relation to treatment outcome. Of note, higher proportion of unmarried women was found in those who required an invasive intervention.

Physical examination findings at admission did not differ between study groups. Women who experienced conservative treatment failure had higher medians of inflammatory markers as CRP (15.7 vs. 10.8 mg/L, p = 0.02), WBC count (14.2 vs. 12.4 1,000/mm^3, p = 0.04) and platelet count (374 vs. 295 10^9/L, p = 0.04) at admission. Moreover, higher levels of CA-125 at admission were found in those who required an invasive intervention (57 vs. 30 U \ml, p = 0.02). Rate of bilateral disease involvement and the presence of free pelvic fluid did not differ between the groups. The largest diameter of TOA at admission was higher in those who required an invasive intervention as compared to those who were successfully treated conservatively (75 mm. vs. 57 mm, p = 0.01). No cases of primary or post-treatment peritonitis were encountered during the study period.

Predictors

A binary logistic regression analysis was performed using the variables found to be significant in the univariate analysis (Table 2). Table 2 presents the results of the analysis. CA-125 level was found to be the only independent factor associated with conservative

Table 1
Patient and disease characteristics and outcomes according to antibiotic treatment outcome.

Women	Total n=91	Invasive treatment n=39	Invasive treatment n=39	Conservative success n=52	p value
Age, years	39 [30-47] (38)	38 [30-47] (37)	38 [30-47] (37)	40 [30-49] (39)	0.64
BMI	26.2 [23.0-27.2] (26.1)	26.0 [22.8-27.5] (26.0)	26.0 [22.8-27.5] (26.0)	25.9 [23.0-27.9] (25.7)	0.78
Martial status					0.04
Married	66 (72.5%)	24 (61.5%)	24 (61.5%)	42 (80.7%)	
Unmarried	25 (27.5%)	15 (38.5%)	15 (38.5%)	10 (19.3%)	
Obstetrical history					
Parity	3 [2-3] (2)	2 [0-2] (2)	2 [0-2] (2)	2 [0-3] (2)	0.15
Gravidity	2 [0-4] (3)	2 [0-4] (2)	2 [0-4] (2)	3 [0-5] (3)	0.24
History of ectopic pregnancy	5 (5.4%)	3 (7.6%)	3 (7.6%)	2 (3.8%)	0.42
Previous cesarean delivery	22 (24.1%)	8 (20.5%)	8 (20.5%)	14 (26.9%)	0.48
Medical history					
History of PID	17 (18.6%)	7 (17.9%)	7 (17.9%)	10 (19.2%)	0.78
Recent gynecological evaluation[*]	12 (13.1%)	5 (12.8%)	5 (12.8%)	7 (13.4%)	0.92
Recent gynecological surgery	4 (4.4%)	1 (2.5%)	1 (2.5%)	3 (5.7%)	0.46
Previous pelvic surgery	12 (13.1%)	7 (17.9%)	7 (17.9%)	5 (9.6%)	0.24
Comorbidity[+]	10 (10.9%)	3 (7.6)	3 (7.6)	7 (13.4)	0.38
Intrauterine device type	17				
Copper	13 (76.4%)				
Hormonal	4 (13.6%)				
Time elapsed from IUD insertion to PID diagnosis, weeks	350 [150-600] (58)				
Insertion of IUD < 4 weeks before PID diagnosis	0 (0%)				
IUD affixed		4 (10.2%)	4 (10.2%)	13 (25.0%)	0.07
IUD removed		4 (100%)	4 (100%)	12 (92.3%)	0.57
Clinical characteristics					
Fever >38°C at presentation	16 (17.5%)	8 (25.8%)	8 (25.8%)	8 (21.0%)	0.64
CRP at admission, mg/L	13.2[6.4-16.2] (13.3)	15.0[11.3-17.2] (15.7)	15.0[11.3-17.2] (15.7)	7.4 [3.7-13.8] (10.8)	0.02
WBC at admission, ×1,000/mm³	13.9 [11.1-16.1] (13.3)	14.3 [12.1-16.2] (14.2)	14.3 [12.1-16.2] (14.2)	13.0 [8.9-15.1] (12.4)	0.04
Peripheral Neutrophils, %	79.6 [72.6-86.6] (77.5)	80 [71-86] (78)	80 [71-86] (78)	79 [72-87] (77)	0.81
ESR at admission, millimeters per hour	53.0 (34.2-81.0) (58.5)	52 (35-92) (60)	52 (35-92) (60)	54 (25-80) (56)	0.71
Platelets, 10^9/L	309 (281-400) (334)	350 (290-404) (374)	350 (290-404) (374)	294 (271-344) (295)	0.04
Cancer antigen 125, U\mL	35 (32.5-46) (45)	42 (35-71) (57)	42 (35-71) (57)	30 (25-36) (30)	0.02
Imaging Characteristics of TOA					
Largest TOA diameter, mm	67 [52-71] (64)	70 [64-95] (75)	70 [64-95] (75)	56 [44-70] (57)	0.01
Bilateral disease involvement	7 (7.6%)	3 (7.6%)	3 (7.6%)	4 (7.6%)	1.0
Outcome					
Length of hospitalization, days	9 [5-12] (10)	11 [9-15] (14)	11 [9-15] (14)	6 [4-10] (7)	<0.001
Readmission	11 (12.1%)	6 (15.3%)	6 (15.3%)	5 (9.6%)	0.40

All continuous variables are expressed as median [interquartile range] (mean).
BMI – body mass index, CRP – C reactive protein, ESR – estimated sedimentation rate, IUD – intrauterine device, PID – pelvic inflammatory disease, WBC – white blood cell.
[+] Comorbidities –hypertension, diabetes, dyslipidemia, hypothyroidism, ischemic heart disease.
[*] Recent gynecological evaluation – evaluation by a gynecologist in the last 2 weeks without prescription of an antibiotics or removal of an intrauterine device.

treatment failure (OR; 95% confidence interval [CI], 1.27, 1.08–1.48, p = 0.03).

Microbiologic characteristics

Overall, 32 cultures were sampled from a TOA during invasive procedures, of which 13 (40.6%) were positive. The most common pathogen cultured was *Escherichia coli* (61.5%). Empiric treatment administered at time of admission was adequate in 12/13 (92.3%) of cases. Out of 61 urine cultures taken, 20 (32.7%) were positive. Eight out of 42 (19.0%) cervico-vaginal isolates cultures taken were positive. Of note, 2/14 (14.2%) of blood cultures taken at admission were culture positive. Five women with positive TOA cultures had identical isolates to those cultured from additional sites (urine, n = 4; blood, n = 1).

Interventional treatment

Of the 39 women who required an invasive intervention, 20 (51.2%) underwent percutaneous drain placement under imaging guidance (computed tomography or ultrasound). Of these, one patient was opted for laparotomy due to drainage failure. Eight women (20.5%) underwent laparoscopy, of which one transformed to laparotomy. Of the remaining 11 women, transvaginal drainage under ultrasound guidance was performed in 6 women (15.5%) and laparotomy was performed in 5 (12.8%) women. The median time elapsed from patient admission to invasive treatment was 4 (3–7 interquartile range) days.

Women at the invasive intervention group had higher mean length of stay (14 vs. 7 days, p < 0.001). Readmission rate was comparable between study groups. There were one event of readmission after US-guided vaginal drainage and 3 readmissions after CT-guided PCT drain placement. Our cohort included 23 nulligravid women. Of them, 5 were under 20 years of age. Among them, we performed 3 laparoscopic surgeries and one vaginal drainage placement

Table 2
Binary logistic regression analysis of factors associated with conservative treatment failure ∞.

Characteristic	Adjusted OR	95% CI	P-value
Largest TOA diameter, millimeters	1.11	0.97-1.29	0.13
CRP at admission, mg/L	0.92	0.79-1.07	0.25
WBC at admission, ×1,000/mm³	1.42	0.94-2.15	0.10
Platelets, 10^9/L	0.99	0.97-1.01	0.40
Cancer antigen 125, U\mL	1.27	1.08-1.48	0.03

CRP – C reactive protein, TOA – tubo-ovarian abscess, WBC – white blood cell.
OR odds ratio, CI confidence interval.
∞ Analysis was performed for all significant variables in the initial univariate analysis, except for marital status and length of stay.

Discussion

In our retrospective cohort study performed among 91 women with TOA, we found several factors associated with treatment outcome, of which CA-125 level was the only factor independently associated with conservative treatment failure. Using this knowledge, treating physicians may more adequately predict an eventual conservative treatment failure which will potentially aid in patients' counseling and treatment approach determination.

Several studies have previously aimed to identify clinical and imaging parameters among women with TOA, with conflicting results reported [5,9,18–27]. Moreover, the predictive role of CA-125 in the management of TOA has been understudied.

Previous reports have shown that increased CA 125 levels are detected among PID patients and correlate with the severity of PID [13,14]. To the best of our knowledge, only one report has addressed the association between TOA treatment outcome and serum CA-125 levels [28]. In this study, involving 36 women who underwent serial evaluations of CA 125 serum levels during antibiotic treatment, CA-125 level had the strongest association with conservative treatment failure among other laboratory markers evaluated (e.g. ESR, CRP). Our findings concur with the aforementioned report, and further highlight the important value of CA-125 determination in this setting.

In univariate analysis, the size of TOA correlated with treatment outcome. This is in line with previous studies that demonstrated a positive correlation between TOA size and conservative treatment failure [22,23,29,30], although this association did not remain significant in the multivariate model, this may relate to the relatively small sample size of the current cohort.

The association of inflammatory markers with treatment outcome among women with TOA remains unestablished. Several studies have shown that WBC count and ESR and CRP levels at admission were higher in women that eventually failed conservative treatment [21,23,29,31]. Nevertheless, a recent report among 144 women negates this notion [32]. The role of platelets, which are involved in regulating inflammatory response, has also been evaluated in this setting. It was previously shown that mean platelets volume, a negative surrogate of platelet count, is elevated among PID patients [33] and that elevated platelets count has a prognostic role among admitted medical patients [34]. In light of the aforementioned findings, we investigated the role of platelets count as a predictor amongst other inflammatory markers. In the present study, WBC and platelet counts and CRP levels at admission were significantly higher among women in the treatment failure group; however, these associations did not remain significant in the multivariate model. Of note, ESR and peripheral neutrophils percentage were not found to be associated with treatment outcome in the current study.

Interestingly, our conservative treatment failure rate of 42.8%, coupled with recent reports demonstrating similar high rates of failure [23,29], might question the previously reported high rates (up to 85%) of antibiotics treatment success among TOA patients [1,35]. It is possible that major changes in resistance patterns of pathogens involved in this condition which have developed in the two decades following the publications of the latter studies, account for the large difference found in medical treatment success rates.

In our study, we found that marital status was associated with treatment outcome, as the proportion of unmarried women was 2-fold higher in those who required an invasive intervention. This is in contrast to the findings of a recent study that demonstrated higher proportion of unmarried in the conservative treatment group [23]. We believe that this finding is confounded by other determinants as in both studies; this factor did not remain independently associated with treatment outcome.

Nevertheless, our study has several limitations. The retrospective design and the relatively small sample size of this study raise the possibility of biases inherent to such investigations. In addition, we could not exclude the possibility that other unknown factors (e.g. non evaluated confounders) could explain the differences found between the study groups. Nevertheless, the strengths of our study include the novelty of determinants examined, including CA 125 and platelet count at admission. Moreover, the standardized antibiotic empiric protocol administered further contributes to the generalizability of our findings.

Mean length of stay of 14 days for patients with interventional treatment should be underlined. Patients who underwent an interventional treatment represent cases of treatment failure. Thus, these subset of patients underwent a trial of antibiotics therapy with failed treatment response, thus correlating with prolonged length of stay. Moreover, as in our institution, PCT drainage procedure is performed only following formal radiologic consultation and the lack of urgency of this procedure, further contribute to the longer length of stay observed in this group

Conclusion

In summary, our study provides additional novel insight into the characteristics associated with failure of conservative parenteral antibiotic therapy. It remains to be determined whether patients' risk stratification at admission would identify those who might benefit from early invasive intervention. Further prospective studies are warranted to confirm our findings and better delineate the optimal treatment approach for women with TOA.

Funding

Acknowledgments

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2019.05.004.

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