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Characteristics Patients with Borderline Ovarian Tumor at Sanglah General Hospital: From Pre- to Post-operative Approach

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Abstract

BACKGROUND: Specific epidemiology data of borderline ovarian tumor (BOT) might be beneficial for the early diagnosis of BOT. The scarcity of BOT epidemiological data in Indonesia urged the writer to study further.

AIM: The objectives of the study were to obtain the characteristics of BOT patients in Sanglah General Hospital between 2018 and 2019 according to sociodemographic, hormonal, clinical, and patient outcome factors.

METHODOLOGY: This is a descriptive retrospective study. Data were obtained from patient's medical records at medical records installation Sanglah General Hospital between March 2020 and July 2020. Descriptive data collected from medical records were analyzed using Microsoft Excel 2010 and presented in tables and narrative form.

RESULTS: From sociodemographic factors, we found that majority of BOT patients were >40 years old, multiparous women, married, low educated, housewives, and had normal BMI. From hormonal factors, we found that experienced menarche between 11 and 15 years old, most of the patients were already menopause, did not use any contraception. From clinical factors, we found that many were referral cases, with abdominal pain as the main complaint, varied CA 125 and risk of malignancy index levels, unilateral mass, suspected with malignant ovarian cyst when being diagnosed earlier. From patient outcome factors, we found that the majority underwent definitive surgery with no post-operative CA 125 level, no malignant cells on cytology examination, borderline mucinous type in both frozen section and paraffin block examination, and followed up after surgery.

CONCLUSIONS: Clinicians could use these characteristics as a reference in diagnosing a patient who fits the profile.

Introduction

A borderline ovarian tumor (BOT) is a transitional form of benign tumor and malignant tumor. The criteria used to differentiate from malignancy are a stromal invasion. The incidence rate of BOT is 1.8–4.8 of 100,000 women per year [1]. Average age of BOT patients is 10 years younger than an ovarian cancer patient. Premenopausal women from the age of 34–40 years old are frequently diagnosed with BOT [2]. Clinically, 75–85% of BOT cases are often diagnosed at an early stage. Five years expectancy rate of BOT is almost 100% at an early stage of disease and 86–92% at later stage [3].

BOT usually appears as a unilocular cyst with solid papilla projection and positive ovarian crescent sign or cyst with honeycomb nodule on USG [4]. MRI is the most ideal imaging tool to examine BOT with the sensitivity and specificity rate of 45.5% and 96.1%, respectively [5]. To increase the accuracy, positron emission tomography can also be included in the modalities in diagnosing BOT [6], [7]. Many research had tried to study the BOT marker that can differentiate BOT from the malignant and benign ovarian tumors but none had proved the specific marker of BOT [8].

Therapy of BOT had switched from radical to conservative surgery and laparoscopy. At stadium 1, conservative surgery includes unilateral salpingo-oophorectomy or cystectomy. Radical surgery such as abdominal hysterectomy, bilateral salpingo-oophorectomy, and stadium defining procedure (abdominal cavity exploration, abdominal cavity fluid cytology examination, etc.) is performed in the later stage of BOT. In mucinous BOT cases, an appendectomy procedure is also included [9].

Early detection of BOT in high-risk women is crucial because it's affecting the appropriate management for the patient. Clinicians must know in regards to the patient's risk factors and clinical profile for this purpose. Therefore, specific epidemiology data of BOT might be beneficial. The scarcity of BOT epidemiological data in Indonesia urged the writer to study further. The purpose of this study is to generally and specifically present data of BOT cases in Indonesian women that were treated in Sanglah General Hospital, Denpasar.

Objectives

The objectives of the study were to obtain the characteristics of BOT patients in Sanglah General

Hospital between 2018 and 2019 according to sociodemographic (age, parity, marital status, education, occupation, and body mass index), hormonal (menarche age, menstruation status, and history of hormonal contraception), clinical (referral, main complaint, pre-operative CA 125 level, risk of malignancy index [RMI], bilaterality of ovarian mass tumor, and early diagnosis), and the patient outcomes (surgery type, postoperative CA 125 level, cytology result, frozen section result, paraffin block result, and follow-up status) factors.

Methodology

This is a descriptive retrospective study with secondary data from patient's medical records that focused on obstetrics and gynecology policlinic and medical records installation of Sanglah General Hospital between March 2020 and July 2020. All samples fulfilled the inclusion criteria: BOT patient in obstetrics and gynecology policlinic of Sanglah General Hospital between 2018 and 2019 according to pathology anatomy result from paraffin block mass that was taken during operation. Data insufficiency on medical records was set as exclusion criteria.

First, the data of BOT patients were obtained from the gynecology register book in obstetrics and gynecology policlinic of Sanglah General Hospital. From the data, the writer acquired the patient's early diagnosis and medical record number. In the next step, descriptive data collected from gynecologic oncology post-operative reports and medical records were analyzed using Microsoft Excel 2010 and presented in tables and narrative form. The research report was written afterward. This study was approved by the obstetrics and gynecology department of Sanglah Hospital, School of Medicine, Udayana University, Indonesia.

Results

There were 324 (46.69%) cases of both benign and malignant ovarian tumor surgeries in Sanglah General Hospital from 2018 to 2019. According to paraffin block examination, 155 cases (47.84%) were benign, 27 cases (8.33%) were borderline, and 142 cases (43.83%) were malignant. The total samples were 27 cases. The patient's characteristics were presented in the following tables.

Characteristics of BOT patients according to sociodemographic factors

Characteristics of 27 BOT patients in Sanglah General Hospital between 2018 and 2019 according to sociodemographic factors are presented in Table 1.

Table 1: Characteristics of BOT patients according to sociodemographic factors

Profile	n	%
Age (years)		
<20	4	14.82
21–30	3	11.11
31–40	1	3.7
41–50	4	14.82
51–60	9	33.33
>60	6	22.22
Parity		
Nullipara	9	33.33
Primipara	2	7.41
Multipara	12	44.44
Grande multipara	4	14.82
Marital status		
Not married	9	33.33
Married	18	66.67
Education		
Uneducated	0	0
Low	14	51.85
Moderate	11	40.74
High	2	7.41
Occupation		
Not working	1	3.7
Housewife	15	55.56
Student	3	11.11
Entrepreneur	6	22.22
Private employee	0	0
Government employee	0	0
Farmer	2	7.41
BMI		
Underweight	2	7.41
Normal	16	59.26
Overweight	7	25.92
Grade I obesity	2	7.41
Grade II obesity	0	0
Grade III obesity	0	0
Total	27	100

Characteristics of BOT patients according to hormonal factors

Characteristics of 27 BOT patients in Sanglah General Hospital between 2018 and 2019 according to hormonal factors are presented in Table 2.

Table 2: Characteristics of BOT patients according to hormonal factors

Profile	n	%
Menarche (years)		
11	1	3.7
12	8	29.63
13	6	22.22
14	6	22.22
15	6	22.22
Menstrual status		
Not menopause	12	44.44
Menopause	15	55.56
Contraception history		
No contraception	19	70.37
Pill	1	3.7
1 month injection	0	0
3 months injection	6	22.22
Others	1	3.7
Total	27	100

Characteristics of BOT patients according to clinical factors

Characteristics of 27 BOT patients in Sanglah General Hospital between 2018 and 2019 according to clinical factors are presented in Table 3.

Characteristics of BOT patients according to patient outcomes

Characteristics of 27 BOT patients in Sanglah General Hospital between 2018 and 2019 according to patient outcomes are presented in Table 4.

Table 3: Characteristics of BOT patients according to clinical factors

Profile	n	%
Referral		
Yes	22	81.48
No	5	18.52
Main complaint		
Enlarged abdomen	25	92.6
Abdominal pain	1	3.7
Menstrual disturbances	1	3.7
Pre-operative CA 125 levels		
< 35 U/ml	3	11.11
35–<100 U/ml	12	44.44
100–<500 U/ml	11	40.75
> 500 U/ml	1	3.7
RMI		
< 200	5	18.52
> 200	22	81.48
Ovarian tumor mass bilaterality		
Unilateral		
Right	15	55.56
Left	9	33.33
Bilateral	3	11.11
Early diagnosis		
Ovarian cyst	3	11.11
Suspected malignant ovarian cyst	22	81.48
Solid ovarian tumor	2	7.41
Total	27	100

Discrepancy between frozen section and paraffin block result

Our study also found discrepancy between frozen section and paraffin block result that presented in Table 5.

Table 4: Characteristics of BOT patients according to patients outcomes

Profile	n	%
Surgery types		
Conservative		
Cystectomy	0	0
Oophorectomy	0	0
USO	10	37.03
Definitive		
TAH-BSO	2	7.41
TAH-BSO-omentectomy	15	55.56
Post-operative CA 125 level		
No data	22	81.48
< 35 U/ml	5	18.52
> 35 U/ml	0	0
Cytology result		
Not done	2	7.41
Done		
Malignant cells (−)	25	92.59
Malignant cells (+)	0	0
Frozen section result		
Not done	1	3.7
Mucinous cyst adenoma	3	11.11
Serous borderline tumor	4	14.81
Mucinous borderline tumor	15	55.56
Mucinous borderline tumor with microinvasion	1	3.7
Mixed:		
Seromucinous borderline tumor	1	3.7
Borderline Brenner tumor with mucinous cyst adenoma	1	3.7
Serous borderline tumor with clear cell differentiation and microinvasion	1	3.7
Paraffin block result		
Serous borderline tumor	4	14.81
Mucinous borderline tumor	14	51.85
Mucinous borderline tumor with microinvasion	5	18.52
Mucinous borderline tumor with invasive implant	1	3.7
Mixed		
Seromucinous borderline tumor	1	3.7
Borderline Brenner tumor with mucinous cyst adenoma	1	3.7
Serous borderline tumor with clear cell differentiation and microinvasive	1	3.7
Follow-up status		
Uncontrolled	4	14.81
Controlled	23	85.19
Total	27	100

Discussion

In this study, 14.82% of patients were below 20 years old age. This percentage similarity with patients with 41–50 years old age group shown BOT tendency to happen in younger age than ovarian cancer. Research by Gotlieb *et al.* yielded the same result that from 233 BOT patients, 33.9% were <40 years old age and 66.1% were >40 years old age [10]. This might relate to folliculogenesis that occurs in the menstrual cycle. Folliculogenesis causes a change in normal follicle transformation to neoplasm. Thus, the menstrual cycle duration in women's lifetime from menarche to menopause is very important. The faster a woman experience menarche or the longer a woman experience menopause increase the risk of BOT occurrence [11].

Table 5: Discrepancy between frozen section and paraffin block result

Frozen section result (n)	Paraffin block result (n)
Mucinous cyst adenoma (3)	Mucinous borderline tumor (3)
Mucinous borderline tumor (4)	Mucinous borderline tumor with microinvasion (3)
	Mucinous borderline tumor with invasive implant on omentum (1)

Multiparous women accounted for the major population in this study (44.44%) with a parity average which was 2.1 (0–9). Ayhan *et al.* showed that 31% of BOT patients were nulliparous women [12]. Repeated stimulations of ovarian epithelium lead to malignant transformation [11]. Nullipara is associated with repeated ovulations in a prolonged period, thus childless woman has double the risk of ovarian cancer [13].

Of 27 patients, 18 patients (66.67%) were married. Marital status is not directly related to BOT, although it is important as one of the parameters in deciding surgery types. In unmarried patients that are still of reproductive age, conservative surgery is heavily considered. Meanwhile, married women with an adequate number of children might opt for definitive surgery [9].

The majority of BOT patients in this study had low education (51.84%). Education levels related to patient awareness in terms to check early into the medical facility when experiencing BOT symptoms. The clinicians also have an easier time in educating patients thus patients could understand the disease and the procedure afterward.

Housewives took the most part in this study. Similar to Gracella, 43.12% of BOT patients in Dr. M. Salamun Hospital from 2014 to 2016 were housewives. This might be due to housewives generally having more time checking themselves into medical facilities than women with fixed working hours [14].

From research result, there were no patient with grade II or grade III obesity. Higher BMI correlated with BOT occurrences since adipose tissue produces

estrogen that causes folliculogenesis. Domination of normal BMI patients in this study might be due to other risk factors other than BMI; therefore, further study in this regard is still possible.

In this study, the median age of menarche was 13 years old and 44.47% of patients were not yet menopause. Early menarche and late menopause are accountable for the increased risk of BOT. In 2019, Yoshida *et al.* have shown that the average age of menarche women in Brazil was 13 years old [15]. Riman *et al.* found that menopause age of <49 years old correlated with reduced risk of BOT (OR 0.66, CI 95%, 0.39 – 1,11) [16].

Most of the patients (70.37%) were not using contraception. Either hormonal or oral contraception could reduce the risk of BOT due to the prevention of ovulation [17]. However, there was 22.22% of BOT patients injected with hormonal contraception every 3 months in this study.

Sanglah General Hospital is a referral hospital in East Indonesia Region; therefore, almost all patients (81.48%) were referral patients. The average CA 125 level and the median were 362.63 U/ml and 80.12 U/ml, respectively. No specific value of CA 125 in BOT patients was ever established. Massachusetts general hospital reported that 40% of BOT patients had increased CA 125 level, specifically in Stadium II, III, and IV [18].

RMI >200 signifies the potency of tumor malignancy. Twenty-eight patients (84.85%) in this research had RMI >200 while 5 others (15.15%) had RMI <200. This proved that the RMI level is varied among BOT patients thus should not be used as the benchmark in diagnosis.

In this study, initially, 11.11% of patients were diagnosed with an ovarian cyst, 7.41% with solid ovarian tumor, and 81.48% suspected with malignant ovarian cyst. Initial diagnosis acquired through anamnesis, physical examination, USG examination, and CA 125 level. This shown the varieties of BOT patients in terms of the main complaint, physical examination, USG, CA 125 level, and RMI. All of these factors contributed to the early diagnosis of BOT.

Definitive surgery was the most chosen surgery. Half of the BOT patients in Sanglah General Hospital between 2018 and 2019 were >51 years old (55.55%), already menopause (55.56%), and multiparous (59.26%). BOT has a good prognosis and often happens in young age, therefore, the majority of patient choose conservative surgery to preserve fertility [9].

Out of 27 patients, the writer could not get the data of post-operative CA 125 level from 22 people (81.48%). This is because they only controlled their post-operative wound twice to obstetrics and gynecology policlinic Sanglah General Hospital before being referred back to the hospital that referred them. They might have checked their post-operative CA 125 level there. Cadron *et al.* cited that CA 125 level is one of the factors that are being followed up due to relapse years after the primary therapy, especially if the ovary was spared on conservative surgery [19].

From cytology examination, no malignant cells were found in 25 BOT patients (92.59%). Cytology examination is important in BOT management because it enables the detection of the peritoneal implant with moderate accuracy. Similar to this study, Sneige *et al.* found peritoneal implants in 27% of patients. They also obtained the sensitivity, specificity, positive predictive value, and negative predictive value of cytology examination were 69%, 84%, 62%, and 88%, respectively [20].

The majority of patients in this study had mucinous borderline type (74.08%), shown in paraffin block examination. This result was similar to a cohort study in 1978–2006 that found that the majority of BOT patients in Denmark had mucinous type (49.9%) [21].

Twenty-three patients (85.19%) had undergone follow-up after surgery. BOT patient is advised to be evaluated with clinical examination, a transvaginal ultrasound, and CA 125 every 3 months in the first 2 years, every 6 months in 2–5 years, and every year afterward.

Table 5 shows the discrepancy between frozen section and paraffin block result. Seven diagnoses (25.93%) from the frozen section were different from the paraffin block result. All mucinous cystadenoma diagnoses based on frozen section became mucinous borderline tumors when being examined with paraffin block. Three of four patients with mucinous borderline tumor according to frozen section became mucinous borderline tumor with microinvasion in paraffin block while one patient with mucinous borderline tumor turned to mucinous borderline tumor with an invasive implant to the omentum. A study by Arshad *et al.* pointed 15 diagnoses discrepancy between frozen section and paraffin block. The sensitivity of the frozen section was 76.2% while the specificity was 88.7% [22]. Huang *et al.* obtained the frozen section sensitivity rate of 92.7%; however, the underdiagnosis and overdiagnosis prevalences were each 22 cases (14.2%) and 6 cases (3.9%) [23].

Conclusions

From sociodemographic factors, the majority of BOT patients were >40 years old, multiparous women, married, low educated, housewives, and had normal BMI. From hormonal factors, menarche

between 11 and 15 years old, most of the patients were menopause and did not use any contraception. Many BOT patients were referral cases, with abdominal pain as the main complaint, varied CA 125 and RMI levels, unilateral mass, and initially suspected with malignant ovarian cyst when being diagnosed. Based on patient's outcomes, the majority underwent definitive surgery with no post-operative CA 125 level, no malignant cells on cytology examination, borderline mucinous type in both frozen section and paraffin block examination, and followed up after surgery.

This study has several limitations, that is, (1) the small sample number; (2) due to population being Indonesian female, there may be differences in clinical characteristics with other populations. However, because the sample is taken from a homogeneous population, it can be considered the strength of this study.

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