ARID1A protein expression in endometriosis-associated ovarian carcinomas

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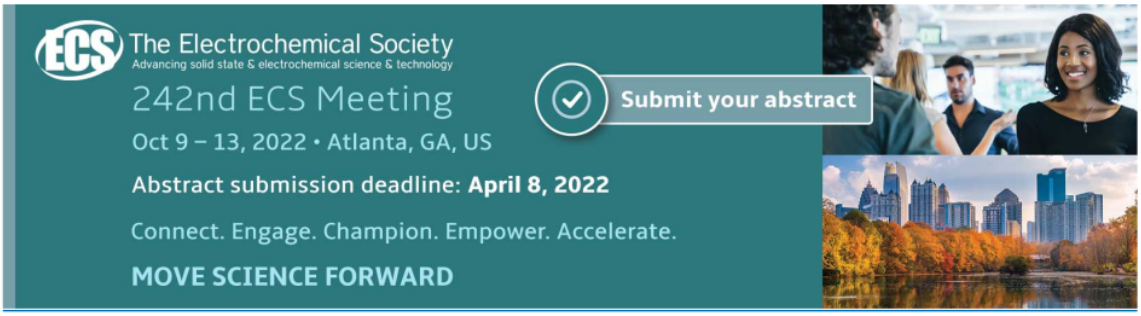

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ARID1A protein expression in endometriosis-associated ovarian carcinomas

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Abstract. Epithelial ovarian carcinoma is leading cause of death among gynaecologic malignancies. Somatic mutation of ARID1A gene often observed in endometriosis-associated ovarian carcinoma cases. This mutation causes loss of ARID1A protein expression on tumor-bearing tissues. This study aims to investigate ARID1A protein expression in endometriosis-associated ovarian carcinoma cases in Indonesia. The archive of Formalin-fixed paraffin embedded (FFPE) tissue of 11 endometrial carcinomas (EC), 16 clear cell carcinoma (CCC), and 23 serous carcinomas (SC) from January 1, 2016, to December 31, 2017. The ARID1A expression were analyzed by using Kolmogorov Smirnov and Fisher's Exact Tests. Majority of patients were older than 50 years (90%). Loss of ARID1A expression in tumor tissue was significantly low in the SC group (8.7%) compared to the EC group (27.3%) and the CCC group (62.5%) (p = 0.021). This study showed that ARID1A expression, was not associated with FIGO stage (p = 0,423), and with histological grade of the cases in EC group (p = 0,544) and SC group (p = 0,395). Loss of ARID1A expression was more frequently found in EC and CCC cases. Loss of ARID1A expression was not associated with FIGO stage and histological grade.

1. Introduction

Epithelial ovarian carcinoma is the leading cause of death among gynaecologic malignancies. By 2014, in the United States was estimated that there were 21.980 cases of ovarian carcinoma [1]. Generally, epithelial ovarian carcinoma are classified into two types: type I and II. Type I ovarian carcinoma consists of clear cell carcinoma (CCC), endometrioid carcinoma (EC), mucinous carcinoma and low-grade serous carcinoma (LGSC), while type II ovarian carcinoma consists mainly of high-grade serous carcinoma (HGSC) [2–6]. The incidence of endometriosis-associated ovarian carcinoma according to a study by Somigliana is clear cell carcinoma (35%), endometrioid carcinoma (27%), serous carcinoma (5%) and mucinous carcinoma (4%) [7]. According to a study by Winarto at Cipto Mangunkusumo Hospital Jakarta (2014), the incidence of endometriosis-associated ovarian carcinoma is around 14% in clear cell carcinoma and 28% in endometrioid carcinoma of all cases of ovarian malignancy [8].

AT-rich interactive domain 1A (ARID1A) gene mutations highest is found in clear cell carcinoma and endometrioid carcinoma [9]. These mutations lead to the loss of ARID1A protein expression. The ARID1A or BAF250a protein is one of the subunits of the SWI-SNF complex that contributes to the regulation of gene expression as well as tumor suppressor genes. The loss of ARID1A expression is more common in endometriosis-associated ovarian carcinoma than endometriosis-unassociated

ovarian carcinoma [9–13]. The patients without ARID1A mutations have a better therapeutic response than patients with ARID1A mutations [14]. The loss of ARID1A protein expression (due to ARID1A mutation) could be used as an early screening for endometriotic lesions to develop into clear cell carcinoma and endometrioid carcinoma. One study says an unexpressed or a low expression of ARID1A indicates a resistance to anti-cancer drugs [14–16]. As of now, only one study has been reported about the ARID1A protein expression in Indonesia by Winarto et al (2014) in Cipto Mangunkusumo Hospital Jakarta which found a decrease in ARID1A expression associated to oxidative stress in endometriosis, serous carcinoma, mucinous carcinoma, clear cell carcinoma, and endometrioid carcinoma) [8].

The aim of this study was to compare the level of ARID1A protein expression in ovarian clear cell carcinoma, endometrioid carcinoma, and serous carcinoma in Department of Anatomical Pathology of RSMH Palembang, from January 1st, 2016 - December 31st, 2017.

2. Methods

This is a retrospective, observational, analytic study with a cross-sectional design which was conducted from January 1st, 2018 until June 30th, 2018 in Department/Division of Anatomical Pathology of Dr. Moh. Hoesin General Hospital Palembang. The sample of this study was the archives of haematoxylin-eosin and formaldehyde fixed paraffin embedded (FFPE) preparation from patients who have been diagnosed histopathologically as endometrioid carcinoma, clear cell carcinoma, and serous carcinoma of ovarian carcinoma which was stored in Department/Division of Anatomical Pathology, Faculty of Medicine, University of Sriwijaya/Dr. dr. Mohammad Hoesin General Hospital from January 1st, 2016 to December 31st, 2017. The samples were taken by purposive sampling of 50 samples, consisting of clear cell carcinoma (16 samples), endometrioid carcinoma (11 samples), and serous carcinoma (23 samples). From the observed samples, there was an endometriotic focal in the form of foci of haemosiderophages on the clear cell carcinoma and endometrioid carcinoma. An Immunohistochemical assay using ARID1A antibody was performed on the study samples.

An immunohistochemical assessment was performed semiquantitatively by the authors and two Anatomical Pathologist using the monoclonal ARID1A primary antibody and observed using a binocular light microscope Olympus type CX 22. The assessment of ARID1A expression in this study was to evaluate the wide and intensity of the stain. The wide of the staining was classified into five groups: 0 (0%), + (≤10), ++ (11-50%), +++ (51-80%), ++++ (> 80%). The intensity of the staining was classified into four groups: 0 (negative), 1 (weak), 2 (moderate), 3 (strong). After then, the ARID1A immunoreactivity was scored by multiplicating the wide and the intensity with a result of a score from 0 to 12. ARID1A expression was negative if the scores were 0 and positive if the scores were ≥1. After all data were collected, a univariate analysis was performed to explore the distribution of the patients' characteristic. Kolmogorov Smirnov and Fisher's Exact Test were used to evaluate the difference of ARID1A protein expression.

3. Results

The clinical characteristics of ovarian endometriosis-associated ovarian carcinoma are shown in table 1. Most of the ovarian endometriosis-associated ovarian carcinomas were found in the age group> 50 years with 45 cases (90%). All EC patients were found in the age group > 50 years with 11 cases (100 %), CCC patients in the age group> 50 years at 12 cases (75%), and SC patient in the age group > 50 years at 22 cases (95.7%). Patients with endometriotic lesions in the form of foci of haemosiderophages were found in 8 cases with the most common histopathologic subtypes were CCC with 6 cases (37.5%), followed by EC with 2 cases (18.2%), whereas in the SC group, no endometriotic lesions were found. FIGO staging system of EC mostly at stage III with 6 cases, CCC with 9 cases (56,3%), and SC with 17 cases (73,9%).

Regarding the EC, they were found to be at an early stage (I) with 2 cases (18.2%) and advanced stage (II, III, IV) with 9 cases (81.8%). In CCC, there were 5 cases (31.3%) at an early stage (I) and 11 cases (68.8%) at an advanced stage (II, III, IV). In the SC group, 2 cases (8.7%) were found to be at an early stage and 21 cases (91.3%) at advanced stage (II, III, IV).

The most common histopathologic subtypes of ovarian endometriosis-associated ovarian carcinoma were SC (23 cases, 23%), CCC (16 cases, 32%) and EC (11 cases, 22%). The histopathologic grade of EC was found mostly in grade III with 6 cases (54.5%), grade II with 2 cases

(18.2%), and grade I with 3 cases (27.3%). The most common histopathologic grade of SC was high-grade with 18 cases (78.3%) and low-grade with 5 cases (21.7%). The EC sample showed that the most common staining intensity was weak-positive from 4 out of 11 cases (36.4%), CCC samples showed that the most common intensity was 0 (negative) from 10 out of 16 cases (62.5%), while the SC samples showed the intensity of staining were more common in moderate from 12 out of 23 cases (52.2%).

Immunoreactivity of ARID1A was assessed based on the wide of the stained area (figure 1), where in the case of EC, the most common staining wide was 0%, ≤10%, and 51-80% each with 3 cases (27.3%). In the CCC cases, the staining wide was mostly at 0% with 10 cases (62.5%). In the case of SC, the most common staining wide were> 80% with 8 cases (34.8%). The results of ARID1A expression in EC cases were 3 cases (27,3%) showing a negative result, 8 cases (72,7%) showing a positive result. In the CCC group, 10 cases (62.5%) showed a negative result, 6 cases (37.5%) showed a positive result, while 2 cases (8.7%) of SC showed a negative result and 21 cases (91.3%) showed positive results. The result of statistical analysis using the Fisher Exact Test showed no significant association between FIGO clinical stage and ARID1A expression (p = 0,423). The results of statistical analysis using Kolmogorov Smirnov test showed that there was a significant association between histopathologic subtype of endometrioid carcinoma (EC), clear cell carcinoma (CCC), and serous carcinoma (SC) with the expression of ARID1A (p = 0,021). Furthermore, the results of statistical analysis using Kolmogorov Smirnov Test showed no significant association between the histopathologic degree of endometrioid carcinoma (EC) grade I, II and III with ARID1A expression (p = 0,544). The result of the statistical analysis showed no significant association between low-grade endometrioid carcinoma (grade I) and high-grade endometrioid carcinoma (grade II, III) on ARID1A expression by using Fisher Exact Test (p = 0,152). The statistical analysis showed no significant association between low-grade and high-grade serous carcinoma on the expression of ARID1A using Fisher Exact Test (p = 0,395).

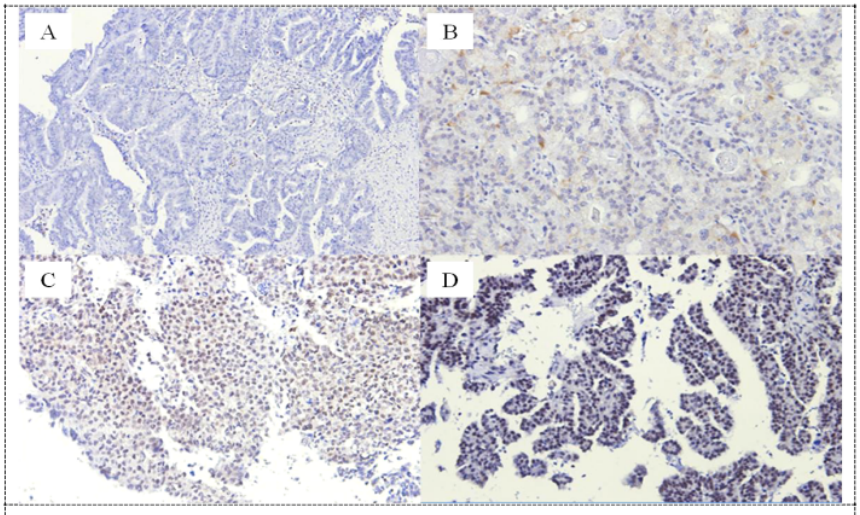

Figure 1. Immunoreactivity of ARID1A A. Negative expression of ARID1A in EC, B. Weak immunoreactivity of ARID1A in CCC C. Moderately immunoreactivity of ARID1A in EC D. Strong immunoreactivity of ARID1A in SC.

4. Discussions

According to WHO 2014, the incidence of EC occurs in the fifth and sixth decade, with an average of 58 years old and average incidence of CCC is at 55 years old [17]. This is consistent with this study in which the majority of ovarian endometriosis-associated ovarian carcinoma were above 50 years of age (90%) and all EC cases were over 50 years of age. In CCC, 12 (75%) cases were over 50 years old, 3 (18.8%) cases were 40-49 years old, and only 1 (6.3%) cases at 30-39 years age group. In this study, 1

(6.3%) case of EC was found to be at the 30-39 years' age group and 3 (18.8%) cases at 40-49 years' age group; this could be caused by several possible factors such as hereditary, hormonal, chronic inflammation, and infertility [18,19]. However, no further exploration was conducted in this study due to incomplete data of the patients.

Table 1. The characteristics of clinicopathologic aspect of ovarian endometriosis-associated ovarian carcinoma.

Clinical Aspect	Histopathologic Subtype			Total (n = 50)
	EC (n = 11)	CCC (n = 16)	SC (n = 23)	
	n (%)	n (%)	n (%)	n (%)
Age				
- < 20 y.o.	0 (0)	0 (0)	0 (0)	0 (0)
- 20 – 29 y.o.	0 (0)	0 (0)	0 (0)	0 (0)
- 30 – 39 y.o.	0 (0)	1 (6.3)	0 (0)	1 (2.0)
- 40 – 49 y.o.	0 (0)	3 (18.8)	1 (4.3)	4 (8.0)
- > 50 y.o.	11 (100)	12 (75.0)	22 (95.7)	45 (90.0)
Total	11 (100)	16 (100)	23 (100)	50 (100)
Endometriotic lesion				
- Presence	2 (18.2)	6 (37.5)	0 (0)	8 (16.0)
- Absence	9 (81.8)	10 (62.5)	23 (100)	42 (84.0)
Total	11 (100)	16 (100)	23 (100)	50 (100)
FIGO staging				
- Stage I	2 (18.2)	5 (31.3)	2 (8.7)	9 (18.0)
- Stage II	2 (18.2)	1 (6.3)	2 (8.7)	5 (10.0)
- Stage III	6 (54.5)	9 (56.3)	17 (73.9)	32 (64.0)
- Stage IV	1 (9.1)	1 (6.3)	2 (8.7)	4 (8.0)
Total	11 (100)	16 (100)	23 (100)	50 (100)
FIGO staging				
- Early stage (I)	2 (18.2)	5 (31.3)	2 (8.7)	9 (18.0)
- Advanced stage (II, III, I)	9 (81.8)	11 (68.8)	21 (91.3)	41 (82.0)
Total	11 (100)	16 (100)	23 (100)	50 (100)
Histopathologic subtype	11 (22,0)	16 (32,0)	23 (46,0)	50 (100)

Table 2. The association of ARID1A expression with histopathologic subtypes of endometrioid carcinoma (EC), clear cell carcinoma (CCC) and serous carcinoma (SC).

ARID1A Expression	Histopathologic Subtype				p value
	EC n (%)	CCC n (%)	SC n (%)	Total n (%)	
Negative	3 (27.3)	10 (62.5)	2 (8.7)	15 (30.0)	0.021
Positive	8 (72.7)	6 (37.5)	21 (91.3)	15 (70.0)	
Total	11 (100)	16 (100)	23 (46.0)	50 100)	

Based on WHO 2014 data, the average incidence of HGSC is at 63 years of age while LGSC is said to be at one-decade earlier [17]. In this study, 22 (95.7%) cases of SC were aged over 50 years, 1 (4.3%) case was 40-49 years old. This study demonstrated a different results where LGSC and HGSC had an average of 56 years of age. The menopause age has a higher risk of ovarian carcinoma. Furthermore, there are many other risk factors including reproductive factors, ovulatory and hormonal factors, inflammation, and other risk factors [20].

This study showed that endometriotic lesions were found in EC and CCC. No endometriotic lesions were found in SC cases. Endometriotic lesions in EC were found in 2 (18.2%) out of 11 cases. Endometriotic lesions in CCC were found in 6 (37.5%) out of 16 cases. Endometriotic lesions were

more common in CCC than EC. The results of this study are consistent with several other studies which that women with ovarian endometriosis have a higher risk of developing epithelial ovarian carcinoma, particularly the clear cell and endometrioid carcinoma subtypes [8,9], [21–23] . Katagiri et al (2012) found that the FIGO stage I-II were 75% of all cases and FIGO stage III-IV were 25% of all cases. A study conducted by Choi et al (2017) found that the most common ovarian carcinoma patients were at FIGO stage I (36%) [24,25].

Ovarian endometriosis-associated ovarian carcinoma is a carcinoma which derived from endometriosis, especially type I ovarian carcinoma including EC, CCC, LGSC, mucinous carcinoma, and HGSC [26,27]. The incidence of ovarian carcinoma associated with ovarian endometriosis is varied. In developing countries, the incidence of CCC is approximately 12%, 11% in EC, whereas SC is most common with 68%. In Asian countries such as Japan, the percentage of CCC is higher> 20% with a higher prevalence of endometriosis [28]. The results of this study showed a similar finding which found 11 cases of EC (22%), 16 cases of CCC (32%) and 23 cases of SC (46%). This is probably due to different hereditary, hormonal, chronic inflammatory factors in each region.

The histopathologic degree (grade) of ovarian EC is approximately equal to uterine EC. EC grading is based on tumor microscopic appearance; architectural patterns, cell nucleus features, or both. Architectural grading is based on the extent to which tumors are composed of solid masses or glandular. Based on the architecture, a 5% or less growth of solid mass was regarded as grade 1, between 6 and 50% solid growth regarded as grade 2, and if more than 50% were considered as grade 3[18,20]. In this study, the most common histopathologic grade of EC were grade III with 6 cases (54.5%), grade II with 2 cases (18.2%), and grade I with 3 cases (27.3%). In contrast to the study by Lowery et al (2013), 35% of the histopathologic grade of EC were grade I, 33% with grade III and also 33% with grade II [14]. This is due to hormonal factors (the influence of long-term estrogen hormone). No studies have related the hormonal factors to the histopathologic degree of ovarian carcinoma. The results of a study by Guan et al (2011) showed that the HGSC were higher with 32 cases (34.4%) compared with LGSC cases with 19 cases (20.4%) [22]. The results of this study were similar where HGSCs were higher with 18 cases (78.3 %) than the LGSC with 5 cases (21.7%). The high number of HGSC cases showed the association with TP53 and BRCA1/2 mutations [18,20].

This study showed a negative ARID1A expression in 3 cases of EC (27.3%) and positive in 8 cases of EC (72.7%). ARID1A expression was negative in 10 cases (62.5%) and positive in 6 cases (37.5%) of CCC. The expression of ARID1A on SC was negative in 2 cases (8.7%) and positive in 21 cases (91.3%). The results of this study were in accordance with the study by Takeda et al (2016) that suggested ARID1A mutation occurred 46-57% in ovarian clear cell carcinoma and 30% in endometrioid carcinoma and the study by Lowery et al (2012) that demonstrated ARID1A mutation occurred in 41% of CCC and 48% of EC [9,14]. The highest rate of ARID1A mutation in gynaecologic cases are in clear cell carcinoma and endometrioid carcinoma [9]. Jones et al (2010) first described ARID1A as a tumor suppressor gene with the highest mutation in clear cell carcinoma and endometrioid carcinoma, but not in the serous tumor [29]. The results of this study differed from that of Katagiri et al (2012) which imply ARID1A mutation occurred 15% in CCC and 0% in HGSC and of Wiegand et al (2017) that indicate ARID1A mutations occurred 46% in CCC, 30% in EC, and no mutation in HGSC [25,26]. This may be due to different populations and sampling techniques. In this study, 2 SC cases with negative ARID1A protein expression possibly due to ARID1A mutations because of the pathogenesis of LGSC and HGSC were considered as type-1 ovarian carcinoma although its incidence is very rare [6]. Genetic molecular studies suggest gene mutations in LGSC and HGSC were differ. The HGSC is associated with TP53 mutations, while the LGSC is associated with KRAS or BRAF mutations.

ARID1A expression on FIGO clinical stage was negative in 5 cases and positive in 35 cases. Using the Fisher Exact Test, the statistical analysis showed no significant association between FIGO clinical stage and ARID1A expression (p = 0,423). These results are consistent with the research of Choi et al (2017) and Lowery et al (2012) that there is no significant association of ARID1A expression with FIGO clinical stage (p = 0,593) [24,29]. The results are different from those of Katagiri et al (2012) which implies a significant relationship between ARID1A expression with FIGO clinical stage (p = 0.003) [25].

A significant association between the histopathologic subtype of endometrioid carcinoma (EC), clear cell carcinoma (CCC), and serous carcinoma (SC) on ARID1A expression (p = 0.021, Table 2).

The results of this study are consistent with the research of Katagiri et al (2012). Samartzis et al (2013), and Wiegand et al (2017) which states that ARID1A mutations occur in EC and CCC [25,26,28] . The results are similar to those of Takeda et al (2012) that the ARID1A mutation in CCC is about 58-62%, in this study, it was 62.5%; ARID1A mutation in EC about 30%, while it was 27.5% in this study [9]. Negative ARID1A expression signifies a mutation of the ARID1A gene. Patients without ARID1A mutations had a better therapeutic response than with one. A study demonstrated thatan unexpressed or low expression of ARID1A indicates a resistance to anti-cancer drugs [15,29].

The results of this study showed no significant association between the histopathologic degree of endometrioid carcinoma (EC) grade I, II, and III on ARID1A expression (p = 0,544), no significant association between the histopathologic grade of low-grade EC (grade I) and high-grade EC (grade II, III) on ARID1A expression by using Fisher Exact Test (p = 0,152). This is in accordance with a study by Lowery et al (2012) that there is no relationship between ARID1A expression with EC grading [14].

This study result, using Fisher Exact Test, showed that there was no significant association between the histopathologic grade of low-grade SC and high-grade SC on ARID1A expression (p = 0,395). These results are inconsistent with the results of Wiegand et al (2017), Guan et al (2011), and Pearce et al (2012) which did not demonstrate any ARID1A mutation in SC [22,26,29].

5. Conclusions

The loss of ARID1A expression is a common finding in EC and CCC. The loss of ARID1A expression is not associated with the FIGO staging system and histopathologic degree of EC and SC.

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