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Original contribution

Ovarian mucinous neoplasms, intestinal type, in premenopausal patients, develop in abnormal ovaries☆,☆☆

Elvio Silva MD [a,*], Anais Malpica MD [a], Andres Roma MD [e], Preetha Ramalingam MD [a], Grace Kim MD [d], Rania Bakkar MD [f], Sanam Loghavi MD [a], Stacey Kim MD [f], Alexandra Shaye-Brown MD [g], Mario L. Marques-Piubelli MD [b], Gary Chisholm MD [c], David M. Gershenson MD [c], Isabel Alvarado-Cabrero MD, PhD [h]

[a] *Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, 77030, USA*
[b] *Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, 77030, USA*
[c] *Gynecologic Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, 77030, USA*
[d] *Department of Pathology, University Southern California, Los Angeles, CA, 90033, USA*
[e] *Department of Pathology, University of California, San Diego, CA, 92161, USA*
[f] *Department of Pathology, Cedars Sinai Medical Center, Los Angeles, CA, 90048, USA*
[g] *Department of Otolaryngology and Communicative Sciences, University of Mississippi, Jackson, MS, 39216, USA*
[h] *Department of Pathology, Mexican Oncology Hospital, Mexico City, 06720, Mexico*

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Summary Although several studies have addressed different aspects of mucinous neoplasms arising in the ovary, such as their clinicopathologic features, immunohistochemical profile, and molecular characteristics, no study has presented an analysis of the ovarian tissue where these neoplasms arise. In this study, we included 196 cases of intestinal-type ovarian mucinous neoplasms in premenopausal patients. Our main goal was to perform a rigorous examination of the ovarian tissue surrounding these neoplasms. We also reviewed the clinicopathologic features of these cases. For comparison, the background ovarian tissue in 85 cases of ovarian serous neoplasm and in 29 cases of metastatic neoplasms to the ovary, as well as 57 normal ovaries, was examined. All the patients in this study, which included those with mucinous and with serous neoplasms primary in the ovary, those with

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* Corresponding author. The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd. Houston, TX, 77030, United States
E-mail address: elviogsilva@yahoo.com (E. Silva).

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metastatic tumors to the ovaries, and those with normal ovaries, were also premenopausal. Patients affected by ovarian mucinous neoplasms ranged in age from 13 to 52 years (median = 36 years). Nulligravidity was seen in 50%, 32%, and 22% of patients with mucinous carcinomas, mucinous borderline neoplasms, and mucinous cystadenomas, respectively. Ovarian mucinous intestinal neoplasms arise in abnormal ovaries characterized by two important features: (1) an abnormal ovarian cortex, seen in 95% of the cases, which is hypocellular or with no distinction between the cellular cortex and medulla, and (2) a remarkable paucity of primordial follicles. The abnormalities detected in the background ovarian tissue might provide insights into the tumorigenesis of these neoplasms and might facilitate their distinction from metastasis to the ovary, in premenopausal patients.

1. Introduction

Primary ovarian mucinous neoplasms still represent an enigma from the pathogenetic standpoint and remain a diagnostic challenge in certain cases wherein it is virtually impossible to distinguish them from metastatic adenocarcinoma to the ovary [1,2]. Approximately 85−90% of mucinous tumor primaries in the ovary are of intestinal type, and 10−15% of them are of endocervical, seromucinous, or mixed type. Both types are very different, with the mixed type frequently associated with endometriosis or other epithelial ovarian neoplasms and the intestinal type rarely associated with teratomas or with Brenner tumor [3].

Most mucinous carcinomas of the ovary, in contrast to more common serous ovarian carcinomas, are found at a very early stage; however, when found at an advanced stage, mucinous carcinomas are more aggressive than serous ovarian neoplasms [3−8]. Lymph node metastases, which are seen in 10% of ovarian serous carcinomas of the ovary, are very rare in mucinous carcinomas [9−11].

Although several studies have addressed important clinicopathologic and molecular features of mucinous neoplasms in the ovary, no study has addressed the characteristics of the background ovarian tissue in these neoplasms [1,2]. In this study, we reviewed a cohort of ovarian mucinous tumors in premenopausal patients with a specific focus on the features of the residual ovarian tissue.

2. Materials and methods

This retrospective review of 310 cases included 196 ovarian mucinous intestinal neoplasms, 85 serous neoplasms, and 29 metastases to the ovaries. Among the 196 mucinous intestinal neoplasms, 83 were cystadenomas, 49 were borderline neoplasms, and 64 were carcinomas. None of the mucinous neoplasms had received previous adjuvant therapies. The cases were diagnosed based on the definitions used by the World Health Organization [12]. In the cases of carcinomas, the diagnosis of a possible metastasis was ruled out based on numerous imaging and endoscopic studies. Six cases of mucinous carcinomas in the ovary were not included because we could not determine if these cases were primary or metastatic. Cases associated with a Brenner tumor or with teratomas were not included. In mucinous tumors, the following parameters were obtained from the medical records: the patient's age, gravidity, body mass index (BMI), stage of disease, and follow-up. However, our main goal was to review the residual ovary, including the presence of primordial follicles; therefore, all patients included in this study were premenopausal. Because it has been proven that a very important part of the ovary is the cellular cortex, where the enzymatically active stromal cells are located [13,14], we required at least 3 mm of the residual cortical ovary to be present in some sections from each neoplasm in the histologic sections of all cases reviewed. This measurement was based on our previous study of normal ovaries, wherein we found that the cellular cortex was within 3 mm of the surface of the ovary [15]. In addition, based on our previous study, the average number of primordial follicles was calculated by counting the number of primordial follicles per low-power field (10 × 5 mm area) [15].

Two to 12 (mean = 4) slides were available for review with more than 3 mm of residual cortical tissue. Slides from 40 mucinous neoplasms including 20 carcinomas, 18 borderline neoplasms, and 2 cystadenomas were stained with estrogen and progesterone receptors, and 20 of these cases were also stained with inhibin.

The residual ovary in the cases of mucinous neoplasms was compared with the residual ovarian tissue of 114 lesions including 85 serous neoplasms, composed of 17 cystadenomas, 33 borderline neoplasms, and 35 carcinomas, and 29 metastases to the ovaries, 24 were from the gastrointestinal tract, 3 were from breast cancer, and 2 were from the endocervix; 20 of these 29 metastatic neoplasms included extensive mucinous areas. All the patients in this study, which included those with mucinous and serous neoplasms primary in the ovary, those with metastases to ovaries, and those with normal ovaries, were premenopausal. Findings from all of these cases were compared with those from 57 normal ovaries previously reported in the [15].

The *P* values were obtained using the chi-square test and one-way analysis of variance/Kruskal-Wallis test (nonparametric test). The *P* values were adjusted using a step-up Bonferroni correction. To determine the relationship between different variables, we used a logistic regression model.

2.1. Definitions used in this study

2.1.1. Normal ovarian cortex

The normal ovarian cortex, the most superficial part of the ovary, is composed of a thin, fibrotic, superficial area—the albuginea—and a hypercellular area composed of spindle cells with the axis parallel to the surface. Primordial follicles containing oocytes are usually seen at the interface between the albuginea and the hypercellular area. Very few vessels are found in the cortex. The usual thickness of the ovarian cortex is between 0.5 mm and 1 mm. The ovarian cortex is easily recognized because it is over the medulla, which is significantly less cellular and contains numerous vessels.

2.1.2. Hypocellular cortex

The hypocellular cortex in contrast to the normal cortex has the cellularity of the medulla but lacks the numerous vessels found in the medulla. In these cases, it is still possible to separate the cortex from the medulla because of the presence of more spindle cells in the cortex.

2.1.3. Ovarian tissue with no distinction between the cellular cortex and medulla

In these cases, the cortex and medulla are replaced by a uniform tissue composed of small- to medium-sized cells separated by equidistant spaces and very few vessels resembling nonspecific mesenchyma. This is ovarian tissue because (1) in some cases, it continues with a regular ovarian cortex. (2) These cells are not regular fibroblasts because the nuclei are positive for estrogen and progesterone receptors, similar to the stromal cells of the ovary. (3) The monotonous, uniform distribution of these cells is different from the haphazard distribution of larger fibroblasts seen in desmoplastic reaction around tumors. (4) In some cases, primordial follicles are seen, but not in the upper third, as is seen in normal ovaries; usually, these follicles are displaced toward the middle part of this tissue.

Institutional review board approval was obtained prior initiation of the study.

3. Results

3.1. Mucinous neoplasms

The 196 ovarian mucinous neoplasms included 83 cystadenomas, 49 borderline neoplasms, and 64 carcinomas. The diagnosis of carcinoma was based on intraepithelial atypia (11 cases), confluent pattern (33 cases), and stromal invasion (20 cases). Most of the carcinomas were obtained from the files of MD Anderson Cancer Center and from the Mexican Oncology Hospital.

The ages of patients in this study ranged from 13 to 52 years, with a median of 36 years. The median age of the patients with mucinous carcinomas (33 years) was lower than that of patients with cystadenomas (36 years) or borderline neoplasms (38 years). The differences in the age of the patients are not significant (*P* value: 0.551).

Information regarding gravidity was available for 175 patients. Fifty-eight (33%) were nulligravidas, with the percentage being higher in patients with carcinoma (25/50 [50%]) than in patients with borderline neoplasms (17/53 [32%]) or in patients with cystadenomas (16/72 [22%]). Nulligravidity was significant among the three types of tumors (*P* value: 0.0065). In patients for whom additional information about gravidity was available, impaired fecundity was found in 3 of 24 (12%) patients with carcinomas, in 5 of 31 (16%) patients with borderline neoplasms, and in 8 of 62 (13%) patients with benign neoplasms. Difference in impaired fecundity was not significant among the three types of tumors (*P* value: 0.8970).

In a logistic regression model, when comparing gravidity status and the type of tumor (cystadenoma, borderline neoplasm, and carcinoma) with age as the control, these variables have an independent behavior. Nulliparous patients had 5.49 more chances to have a carcinoma than a cystadenoma ($P < 0.001$).

BMI was available for 127 patients. Most of the patients were grouped into one of only two groups: normal or obese. In patients with cystadenomas, the distribution was similar between those in the normal and in the obese BMI groups (22/59 [37%] in both). In patients with borderline neoplasms, more patients were in the normal group (14/29 [48%]) than in the obese group (8/29 [27%}). In patients with carcinoma, the distribution was similar between the normal group (15/39 [38%]) and the obese group (17/39 [43%]). The differences between the three types of mucinous tumors are not significant (*P* value: 0.4492).

Follow-up was obtained in 39 of the carcinoma cases (range = 1−15 years [median = 6 years]). Seven patients with intraepithelial carcinomas (all stage IA) had no evidence of disease at 2−10 years. All 21 patients with carcinomas by expansile pattern had stage I disease, with 19 having no evidence of disease at 1−15 years after treatment. One patient is alive with disease at 1 year, and 1 died of disease at 3 years; in these two cases, the neoplasms had been disrupted during surgery. Of the 11 patients with invasive carcinomas, 9 had stage I disease and 2 had stage III disease. Eight patients died of disease in 1−4 years, 1 is alive with disease at 6 years, and 2 (both with stage IA disease) were alive with no evidence of disease at 8 and 9 years.

Table 1 Unilocular vs multilocular cysts in mucinous cystadenomas, borderline neoplasms, and carcinomas.

Type of mucinous tumor	Unilocular vs multilocular	*P* value
Cystadenoma, n = 83	29 vs 54	0.24270
Borderline neoplasm, n = 49	5 vs 44	0.00037
Carcinoma, n = 64	14 vs 50	0.0000

3.2. Pathology

The size of the mucinous neoplasms ranged from 1 to 45 cm, with a median of 14 cm. The median sizes for borderline neoplasms and for carcinomas (18 cm for both) were larger than the median size for cystadenomas (11 cm) (*P* value < 0.0001).

Thirty-five (18%) of the 196 mucinous neoplasms were unilocular, and 161 (82%) were multilocular. Table 1 shows the differences in unilocular vs multilocular tumors, with significance being significant in borderline tumors (*P* value = 0.00037) and in carcinomas (*P* value = 0.0000).

Microscopically, an important feature of the intestinal-type ovarian mucinous neoplasms was the presence of a capsule, usually measuring 0.5–1.5 mm (Fig. 1).

This capsule was usually composed of fibrous/hypocellular tissue or in some cases hypercellular tissue. A fibrous capsule was also seen in serous cystadenomas and serous borderline tumors; however, in serous carcinomas and metastases, the neoplasms were in direct contact with the ovarian parenchyma, without a fibrous capsule.

In 72 of the 161 (45%) multilocular neoplasms, the stroma between the glands and cysts was hypercellular. In the remaining 89 neoplasms (55%), the stroma was hypocellular/fibrotic.

The following two important histologic features showed that mucinous intestinal neoplasms develop in abnormal ovaries: changes in the ovarian cortex and the paucity of primordial follicles.

The ovarian cortex was abnormal in 187 of 196 (95%) patients. Either the cortex was hypocellular and fibrotic or there was no distinction between the cellular cortex and the medulla. The entire cortex and medulla have the appearance of nonspecific mesenchyma. Primordial follicles were seen in these areas. Table 2 and 3 show the composition of the ovarian cortex in the three types of mucinous neoplasms compared with serous neoplasms, metastases and normal ovaries. Only in rare cystadenomas, 9 of 85 tumors (11%) had the normal cortex. Review of 85 serous tumors showed no distinction between the cortex and medulla around the tumor in only 1 of 85 cases (1%). In mucinous tumors, there was no correlation between the areas of ovarian tissue without distinction between the cortex and medulla and the size of tumors.

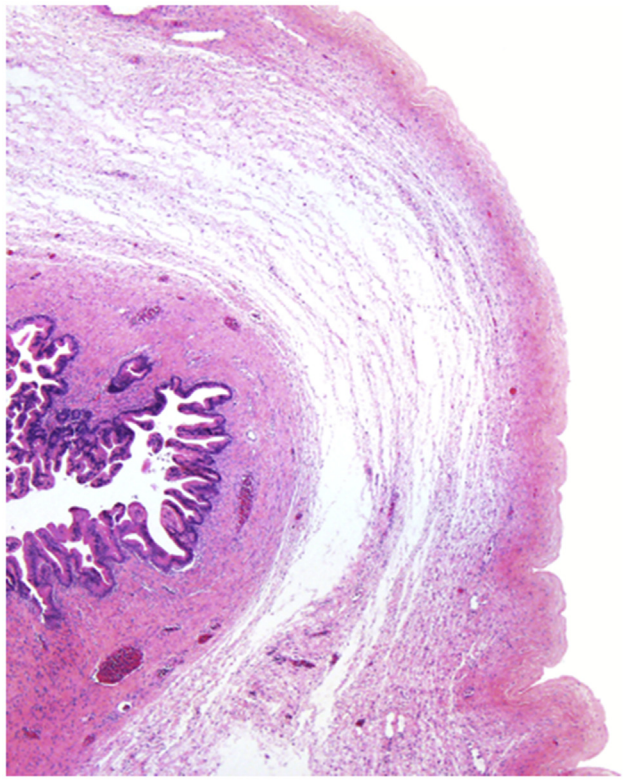

Fig. 1 Mucinous tumor with a thick fibrous capsule. The residual ovary has a hypocellular cortex, and there is edema in the medulla.

The paucity of primordial follicles was obvious in all types of mucinous intestinal neoplasms. A <0.5 average was noted in 61 of 83 (73%) cystadenomas, in 41 of 49 (84%) borderline cases, and in 56 of 64 (87%) carcinomas. Tables 4 and 5 show the average number of primordial follicles in the various types of mucinous neoplasms compared with serous neoplasms, metastases to ovaries, and normal ovaries. Table 6 shows a lack of relationship between a low number of primordial follicles and the size

Table 2A Ovarian cortex in various types of ovarian mucinous intestinal neoplasms.

Ovarian cortex	No. (%) of cystadenomas	No. (%) of borderline neoplasms	No. (%) of carcinomas	*P* value
Normal	9 (11%)	0	0	0.0011
Hypocellular	60 (72%)	27 (55%)	17 (27%)	<0.0001
Ovary without distinction between the cortex and medulla	14 (17%)	22 (45%)	47 (73%)	<0.0001
Total no. of cases	83	49	64	

Table 2B Ovarian cortex of mucinous intestinal neoplasms compared with serous neoplasms, metastases, and normal ovaries.

Ovarian cortex	All mucinous tumors	No (%) of serous neoplasms	No. (%) of metastases to ovaries	No. (%) of normal ovaries	*P* value
Normal	9 (5%)	35 (41%)	11 (78%)	54 (100%)	<0.0001
Hypocellular	104 (53%)	49 (58%)	3 (21%)	0	0.0004
Ovary without distinction between the cortex and medulla	83 (42%)	1 (0.5%)	0	0	<0.0001
Total no. of cases	198	85	29	54	

Table 3A Average number of primordial follicles by type of mucinous tumor.

Average no. of primordial follicles[a]	No. (%) of cystadenomas	No. (%) of borderline neoplasms	No. (%) of carcinomas	*P* value
<0.5	61 (73%)	41 (87%)	56 (87%)	0.0931
0.5 to 1	9 (11%)	8 (13%)	4 (6%)	0.2323
>1	13 (16%)	0	4 (6%)	0.0038
Total no. of cases	83	49	64	

[a] Average number of primordial follicles per low-power field (5 mm).

Table 3B Average number of primordial follicles of mucinous neoplasms compared with serous neoplasms, metastases to the ovaries, and normal ovaries.

Average no. of primordial follicles[a]	All mucinous tumors	No (%) of serous neoplasms	No. (%) of metastases to ovaries	No. (%) of normal ovaries	*P* value
<0.5	158 (80%)	38 (45%)	5 (17%)	8 (14%)	<0.0001
0.5 to 1	21 (11%)	17 (20%)	5 (17%)	9 (17%)	0.0354
>1	17 (9%)	30 (35%)	19 (66%)	37 (68%)	<0.0001
Total no. of cases	196	85	29	54	

[a] Average number of primordial follicles per low-power field (5 mm).

Table 4 Ovarian mucinous tumors, intestinal type: a comparison of the number of cases with <0.5 primordial follicles for low-power fields (5 mm) and the size of the tumors.

Diagnosis	Tumor size		*P* value
	<10 cm	≥10 cm	
Cystadenoma	21/30 (70%)	40/53 (75%)	0.5874
Borderline	6/7 (86%)	35/42 (83%)	0.8746
Carcinomas	9/11 (81%)	47/53 (89%)	0.5312

of the tumors. The two most important histologic features of mucinous tumors can be seen in Fig. 2. In the ovarian tissue, it is not possible to separate the cortex from the medulla, replaced by nonspecific connective tissue. Very few primordial follicles are seen in this ovary of a 23-year-old patient. Fig. 3 shows a sharp contrast in cases of similar-sized tumors: Fig. 3A and B show results of patients with serous borderline neoplasms, Fig. 3C shows results of a patient with a metastatic mucinous carcinoma, and Fig. 3D shows results of a patient with a primitive neuroectodermal tumor of the ovary. All these four patients are aged between 20 and 30 years. A hypercellular cortex with numerous primordial follicles is seen.

Fig. 4 shows three additional cases of metastatic tumors to the ovary, where the hypercellular cortex with primordial follicles is seen. Fig. 5 is a typical residual ovarian tissue with no distinction between the cortex and medulla in a 13-year-old patient with very few primordial follicles. In Table 7, we compared 20 mucinous carcinomas with 20 serous carcinomas and with 10 polycystic ovaries. All these 50 patients were aged between 20 and 30 years, and the ovaries measured between 9 and 14 cm. There is no difference in nulligravidity; however, the two most important histologic features of mucinous ovarian intestinal tumors show a significant difference.

Another important feature supporting the hypothesis that intestinal-type ovarian mucinous neoplasms develop in abnormal ovaries is the low frequency of cystic follicles (Table 8). In the residual abnormal ovary, cystic follicles were found in 16 of 83 (19%) cystadenomas, in 7 of 49 (14%) borderline cases, and in 6 of 64 (9%) carcinomas. By way of contrast, cystic follicles were found in 40 of 85 (47%) serous neoplasms, 14 of 29 metastases, and 28 of 39 normal ovaries.

Between the capsule and the abnormal ovarian cortex is a hypocellular, edematous area, with numerous small vessels representing the ovarian medulla. In 10 of 83 cystadenomas, 3 of 49 borderline neoplasms, and 5 of 64 carcinomas, there was no medulla area around the capsule. In these cases, the tissue in the abnormal ovarian cortex continued with the capsule.

In 13 of the 196 (7%) mucinous neoplasms cases, at the periphery of the neoplasms, the abnormal ovarian cortex of the mucinous tumor continued with an area with histologic features of the normal cortex.

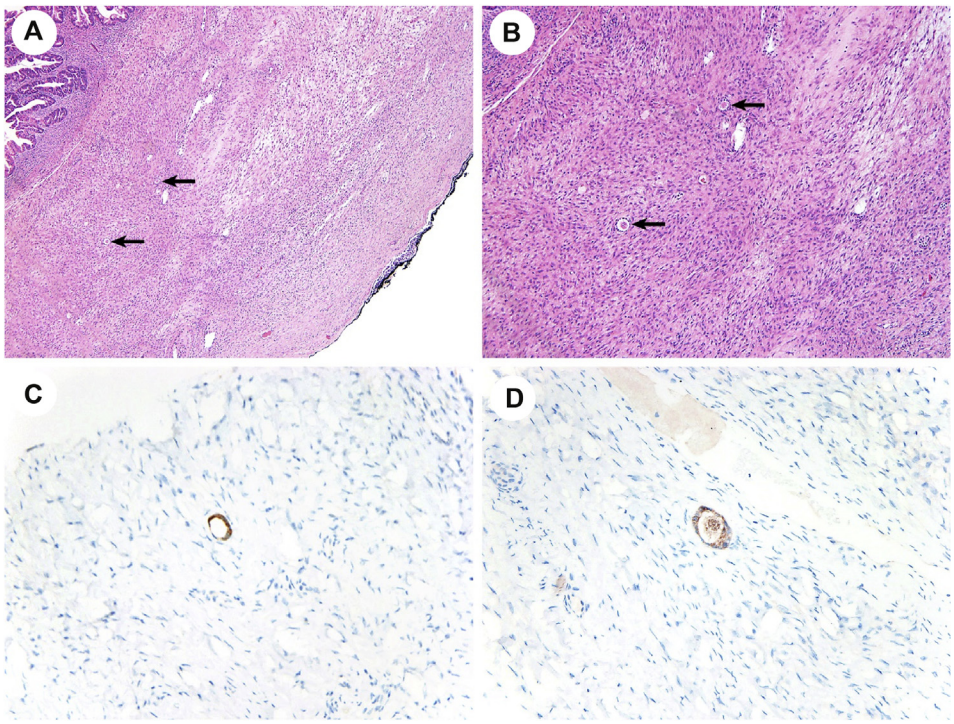

Fig. 2 A—B, Residual ovarian tissue in a case of mucinous carcinoma in a 23-year-old patient. There is no distinction between the cortex and the medulla. The tissue resembles nonspecific mesenchyma. Rare primordial follicles are seen (Arrows). C—D, Inhibin stains the granulosa cells of the primordial follicles.

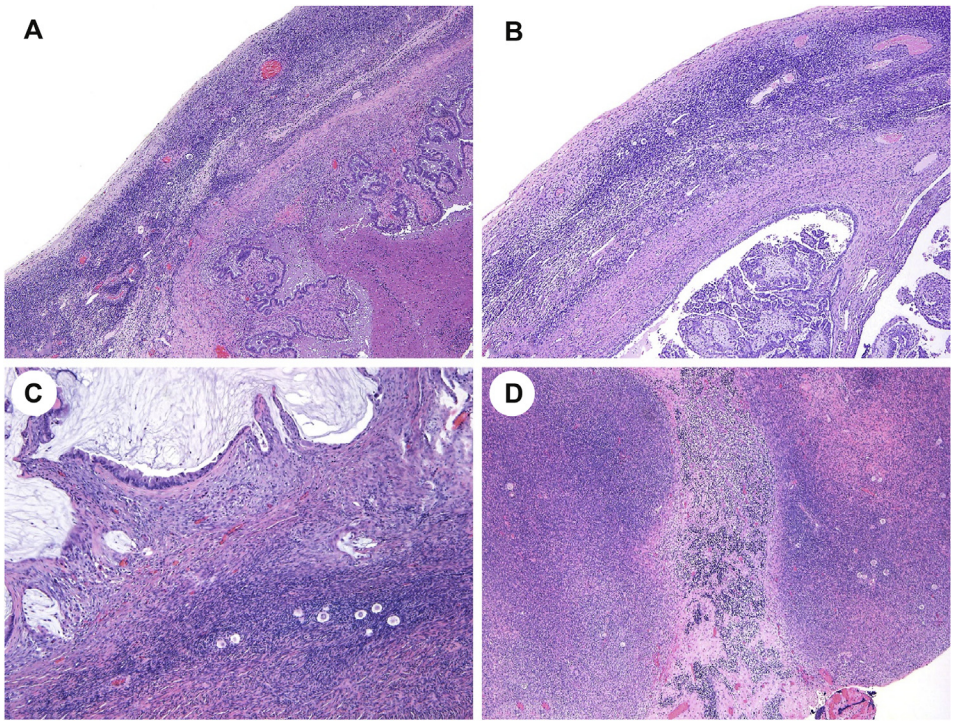

Fig. 3 A—B, Borderline serous neoplasms in a 22-year-old (panel A) and 25-year-old (panel B) patient. C, Metastatic mucinous carcinoma in the ovary from appendix in a 26-year-old patient. D, Primitive neuroectodermal in the ovary in a 30-year-old patient. All cases show a hypercellular cortex with numerous primordial follicles.

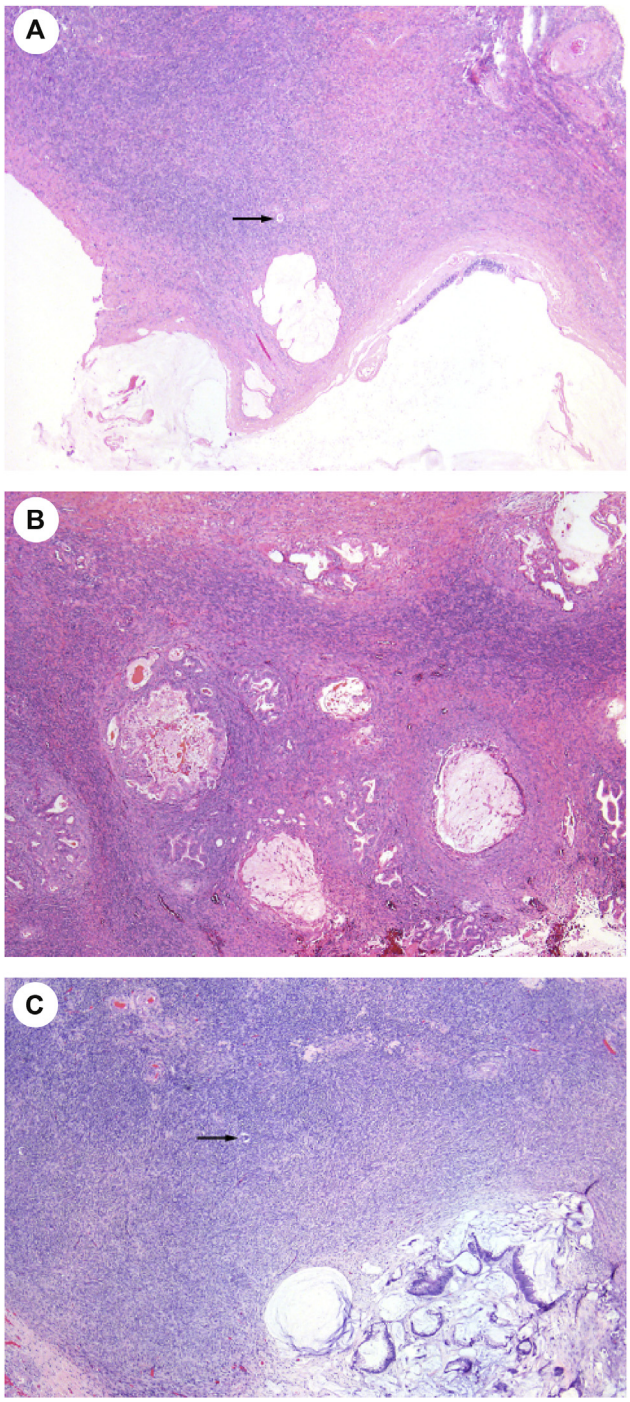

Fig. 4 Cases of mucinous carcinomas metastatic to the ovaries in premenopausal patients from the small bowel (A), pancreas (B), and colon (C). The residual ovary showing the normal cellular cortex with primordial follicles (arrow). Note the absence of the capsule around the tumors.

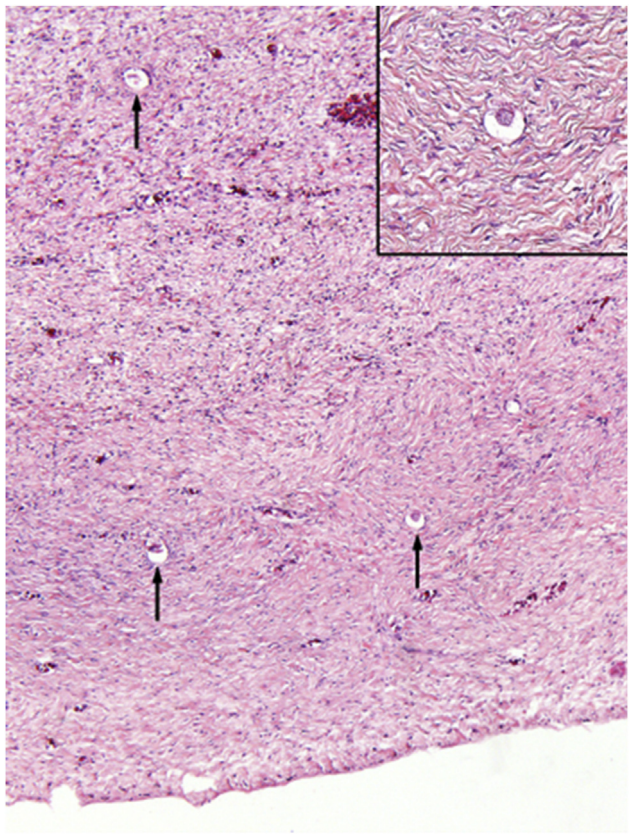

Fig. 5 Residual ovary composed of immature ovarian tissue with primordial follicles, some displaced far from the ovarian peritoneal surface, in a 13-year-old patient with mucinous carcinoma. There is significant reduction in primordial follicles for a 13-year-old patient.

Table 5 A comparison of the most important features of mucinous carcinomas with serous carcinomas and patients with polycystic ovaries.

Important Features	Mucinous carcinoma	Serous carcinoma	PCO	*P* value
No. of cases	20	20	10	
Nulligravidity	9 (45%)	4 (20%)	3 30%)	0.286
Primordial follicles <0.5	16 (80%)	8 (40%)	2 (20%)	0.0027
Ovary without distinction between the cellular cortex and medulla	14 (70%)	1 (5%)	0	<0.001

NOTE. All patients are aged between 20 and 30 years and the ovaries measure between 9 and 14 cm.
Abbreviation: PCO, polycystic ovary.

A very important feature of ovarian mucinous intestinal neoplasms is the presence of unusual calcifications. They were more frequent in cystadenomas (37/83 [45%]) than in borderline neoplasms (15/49 [31%]) or in carcinomas (14/64 [22%]; *P* value = 0.0138). The calcifications were elongated and rectangular, and they could be small, but frequently were large and ending in sharp shapes. They were usually found immediately under the epithelium.

In 39 cases, the contralateral ovary was resected, and it showed an ovarian cortex and the number of primordial

Table 6 Cystic follicles in the residual ovaries of mucinous tumors compared with normal ovaries, serous neoplasms, and metastases to ovaries.

Mucinous Tumors vs.

No. of Cystic Follicles = 29
Total No. of Cases = 196
(15%)

	No. of Cystic Follicles / Total No. of Cases (%)	p Value
Normal Ovaries	28/39 (72%)	0.000
Serous Neoplasms	40/85 (47%)	0.000
Metastasis	14/29 (48%)	0.005

follicles and follicular cysts similar to the normal ovaries. In addition, in 5 of the 39 cases with contralateral ovaries, a mucinous cystadenoma was found in 2 cases, a mucinous cystadenoma with Brenner tumor was found in 2 cases, and a mature teratoma was found in 1 case.

In all 40 cases of mucinous neoplasms that were stained for immunohistochemical analysis, the stromal cells were positive for estrogen receptors. Progesterone receptors were positive in 36 cases. The mucinous epithelial cells were negative for both markers.

Inhibin was positive in the granulosa cells of the primordial follicles in the 15 cases, wherein these follicles were still present in the sections used for immunohistochemistry analysis (Fig. 2C and D).

In four cases with areas of necrosis, and one case with spillage of mucin in the stroma, inflammatory cells were seen in the ovarian stroma.

4. Discussion

In this study, we included only premenopausal patients. The median age of patients with carcinoma (33 years) was lower than that of patients with cystadenomas (36 years) or borderline neoplasms (38 years). These differences were not significant.

The data from the Surveillance, Epidemiology, and End Results [16] cancer registry showed that 26% of mucinous ovarian cancer cases are diagnosed in patients younger than 44 years [8].

Information about gravidity for mucinous neoplasms is not clear in the literature [17].

We found that 58 of 175 (33%) patients were nulligravidas. This was significantly higher than the percentage in the normal population, which is approximately 10% [18]. Comparing gravidity status and type of mucinous tumor with age or control, nulliparous patients had 5.49 more chances to have a carcinoma than a cystadenoma ($P < 0.001$).

Based on this study, we are proposing that the paucity of primordial follicles containing oocytes could be a reasonable explanation for the high percentage of nulligravidity in these patients. It is interesting that when these patients get pregnant, the incidence of impaired fecundity (difficulty in carrying a pregnancy to live birth) is not different from that of the normal population (11%). Impaired fecundity in patients with intestinal mucinous ovarian neoplasms ranged from 10% in carcinomas to 15% in borderline neoplasms.

Regarding the distribution of the BMI in patients with mucinous tumor, it is interesting that in each group of mucinous neoplasms, a significant number of patients had a normal BMI: 22 (37%) of 59 cases of cystadenomas, 14 (48%) of 29 borderline cases, and 15 (38%) of 39 cases of carcinomas. In previous studies, the distribution of the BMI in mucinous neoplasms is not clear [19,20].

The outcome of the patients with mucinous carcinomas in this cohort was in keeping with previous reports as the seven patients with intraepithelial carcinoma did not experience recurrences, whereas recurrences or death was seen in 9.5% of the patients with mucinous carcinoma (expansile pattern) and in 72.7% of the patients with invasive mucinous carcinoma (infiltrative pattern) [21,22].

The novel findings of our study are the constellation of features in the background ovarian tissue in cases of primary ovarian mucinous neoplasms, as described in the following sections.

4.1. Capsule around the tumor

Intestinal mucinous neoplasms have a connective tissue capsule composed of tissue that can be fibrous/hypocellular and hypercellular or composed of immature ovarian tissue. A fibrous capsule was also seen in low-grade serous tumors, but serous carcinoma and metastases to the ovaries, even mucinous metastases, do not have a fibrous capsule.

The cells in the capsule are most probably important in the development of these neoplasms because (1) they are positive for estrogen and progesterone receptors and (2) they are the enzymatically active stromal cells described by Fienberg and Cohen [13] and Scully and Cohen [14] beneath the glandular epithelium in mucinous neoplasms of the ovary. These cells are believed to play a role in steroid hormone production [13,14] and may play an active part in

the development of mucinous neoplasms as a mesenchymal epithelial effect. A similar effect could explain the presence of a hypercellular stroma in mucinous neoplasms in other locations, for example, in the pancreas, where some mucinous neoplasms have an *ovarian-type of stroma* [23].

4.2. Ovarian cortex

The ovarian cortex, a very active part of the ovary, is where steroid hormones are metabolized in enzymatically active stromal cells, resulting in metabolization of estrogens. A defect in this part of the ovary creates an imbalanced hormonal environment that facilitates the development of ovarian neoplasms [13,14]. Different studies in the 1960s and 1970s have shown that ovarian *fibroblasts* are important cells in the endocrine activity of the ovary. Studies by Fienberg, Cohen, Scully, and Reeves have shown the presence of lipid vacuoles and enzymes involved in the synthesis of cholesterol-producing steroid hormones. Based on these studies, some of the spindle cells have been named *enzymatic active stromal cells*, and because they also contribute to the formation of the theca, some authors refer to them as *stromal theca cells*. It has been suggested that their participation in the production of steroid hormones becomes more important during premenopause, when the follicles decrease in number. In summary, these previous studies have shown that spindle stromal cells of the ovary are not just supporting cells, but they have an active specialized role in the synthesis of steroid hormones, very important for proper function of the Mullerian system. It is possible that the absence of the hypercellular cortex, in mucinous tumors, intestinal type, may be an important factor in the development of this neoplasm, different from all other Mullerian histotypes [13,14,24]. The ovarian cortex was normal in only 9 (4%) of 196 cases, was fibrotic/hypocellular in 104 (53%) cases, and consisted of ovarian tissue without distinction between the cortex and medulla in 83 (42%) cases.

Of note, all 9 cases with a normal ovarian cortex were cystadenomas, and the ovarian tissue without distinction between the cortex and medulla increased from the cystadenomas to the borderline cases and to the carcinomas. We are certain that this tissue represents ovarian tissue, and it is not reactive stroma to the neoplasm because of the following facts: (1) It is unrelated to the size of the neoplasm. (2) The cells in this tissue are not fibroblasts with haphazard distribution but smaller cells, positive for ER and PR and with equidistant distribution. (3) This ovarian tissue without distinction between the cortex and medulla is seen almost in only mucinous intestinal tumors in 17% of cystadenomas, in 45% of borderline cases, and in 73% of carcinomas. This ovarian tissue without distinction between the cortex and medulla was seen in only 1 of 85 serous tumors and was never seen in 29 metastases to the ovaries, even in mucinous metastases. Figs. 3 and 4 show foci of serous borderline tumors, a primitive neuroectodermal tumor, and several mucinous metastases without a capsule and in a background of the hypercellular ovarian cortex.

4.3. Primordial follicles

The reason for the paucity of primordial follicles is uncertain. Our review of normal ovaries showed that only 8 of 54 (14%) cases had less than 0.5 primordial follicles per low-power field. By way of contrast, 158 of 196 (81%) mucinous tumors had less than 0.5 primordial follicles per low-power field. In primary mucinous tumors, the low number of primordial follicles is not related to the size of the tumors (Table 6). We also compared the number of primordial follicles in mucinous tumors with the primordial follicles in the ovaries with metastatic tumors and with serous tumors. Less than 0.5 primordial follicles per low-power field was seen in 5 of 29 (17%) metastases, similar to that seen in normal ovaries, even when metastases were larger than 10 cm, and in 38 of 85 (45%) of serous tumors. It is possible that the paucity of primordial follicles found in primary epithelial ovarian neoplasms, with the lowest number in mucinous tumors, may have an important role in their development; however, a prospective study to further evaluate these findings is necessary.

Follicular cysts are found in only 8% of these neoplasms; by way of contrast, we found follicular cysts in 28 of 39 (72%) normal ovaries, in 40 of 85 (47%) serous neoplasms, and in 14 of 29 (48%) metastases.

All the features we are reporting can be used in the differential diagnosis of mucinous tumors in the ovary, in addition to previously recognized important features [3,25]. However, to use these features in the differential diagnosis, it would be important during the grossing of mucinous neoplasms in the ovary to include the possible residual ovary in the sections submitted for histologic diagnosis.

The possibility that all of the tissue between the tumor and the ovarian surface could be due to edema created by occlusion of vessels is improbable because 178 cases showed, at least focally, three distinct layers: capsule, medulla, and a tissue replacing the cortex.

The presence of peculiar calcifications likely has a different explanation than the calcifications in serous neoplasms because they do not have the classic round shape of psammoma bodies; the unusual calcifications are rectangular and angulated and have sharp ends. They are present more frequently in cystadenomas (45%) than in carcinomas (22%). These findings are further evidence that calcifications in ovarian epithelial neoplasms are unrelated to papillae or necrosis but are probably related to a metabolic process [26].

In 39 cases in which the contralateral ovary was resected, the architecture appeared normal. This may explain why intestinal mucinous neoplasms are usually unilateral, they develop in abnormal ovaries, and the presence of an abnormal ovary is not detected clinically because one

normal ovary suffices to meet the hormonal needs of patients.

Another very interesting fact is that in patients with gonadal dysgenesis, the most extreme example of an abnormal ovary, completely replaced with fibrous tissue, the common neoplasms are germ cell neoplasms. However, two epithelial ovarian neoplasms have been reported as arising in these abnormal gonads: Brenner neoplasms and mucinous tumors [27–30].

We believe that recognizing these neoplasms arise in abnormal ovaries is the first step toward designing new studies to explore how intestinal mucinous neoplasms develop in the ovaries, possibly leading to a change in treatment and in poor prognosis of malignant cases.

Author contribution

E.S., A.M., A.R., P.R., G.K., R.B., A.S.-B., and I.A.-C. contributed to cases, data curation, and final analysis. E.S., A.M., A.R., P.R., G.K., S.L., S.K., and A.S.-B. contributed to writing and editing the manuscript. M.L.M.-P. and G.C. contributed to statistical analyses. D.M.G. contributed to clinical analysis of all cases.

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