

## Case report

## A rare case of ovarian carcinoid on mature cystic teratoma in a 36-year-old patient

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## 1. Introduction

Mature cystic teratoma (MCT) is the most common tumor in the ovary. The tumor is benign but presents a risk of malignant transformation, reported occurs in 1–3% of all MCT (Rathore et al., 2018; Maeda et al., 2018). Teratoma with malignant transformation (TMT) is dominant to squamous cell carcinoma type (75% of cases), followed by other types which have less frequent malignancies, including adenocarcinoma, thyroid carcinoma, sebaceous carcinoma, malignant melanoma, sarcoma, and carcinoid (Maeda et al., 2018; Gadducci et al., 2019). Carcinoid tumors are rare tumors of the diffuse neuroendocrine system, representing about 0,3% of all ovarian neoplasms. Incidents of carcinoid tumors are usually reported in postmenopausal women, mostly detected postoperatively and confirmed by a histological examination (Salhi et al., 2017). The occasion of carcinoid tumors arising from MCT is very rare, with only a few numbers of published cases (Tosuner et al., 2015). We report an original case of a carcinoid tumor arising from an MCT in a 36-year-old woman.

## 2. Case report

A 36-year-old woman, presented with the chief complaint of an asymptomatic abdominal mass that had increased in size since nearly two years before admission. No abnormality was found in defecation or micturition. Adnexal mass was detected during the physical examination, which was confirmed by an ultrasound. The ultrasonography examination revealed a cystic mass approximately >15 cm derived from the ovary, characterized by hypochoic heterogeneity. Further investigation of the patient was performed, including laboratory tests and computed tomography (CT of the abdomen). Hematology, renal

function, electrolytes, coagulation profile, liver function, tumor marker values alpha-fetoprotein, human chorionic gonadotropin, carcinoembryonic antigen, and CA-125 were all within normal limits. CT scan confirmed the presence of tumors in both ovaries (see Fig. 1).

She underwent an exploratory laparotomy with a salpingo-oophorectomy bilateral procedure. The ovaries were cystically enlarged to 20 × 15 cm and 15 × 15 cm. Macroscopic surgical specimen revealed the left adnexa with a fallopian tube 6 cm in length and a cystic enlarged ovary mass containing sebaceous material, hair, and bony structures, measuring 25 × 23 × 8 cm. Similarly, the right ovary showed a cystic mass filled with viscous sebaceous material and hair, measuring 21 × 20 × 9 cm. The ovarian tumor consists of tissues from 3 germ layers on microscopic examination, including ectoderm, mesoderm, and endoderm. The ectoderm component consists of a flattened epithelium with skin adnexa, sebaceous glands, and hair roots. The components of the mesoderm consist of cartilage, adipose tissue, and smooth muscle, which have been observed. The endoderm component consists of the salivary glands and thyroid. No immature neuroepithelial tissue component was seen. Morphologically, these findings were consistent with a mature cystic teratoma. There is also a tumor cell formed in compacting trabeculae bands consisting of one to several layers of cells between the stroma of the collagen connective tissue with tubular/insular structures and a rosette. Tumor cells were relatively uniform with a round to oval nuclei, vesicular, fine-grained chromatin resembling “salt and pepper”, partially solid, eosinophilic cytoplasm, without mitotic figure (see Fig. 2).

The histopathology results have shown a mature ovarian teratoma and carcinoid, with no lymphovascular invasion. Immunohistochemical staining showed positive staining for synaptophysin, chromogranin, NSE, and CD56. Diffuse intense immunoreactivity of synaptophysin and

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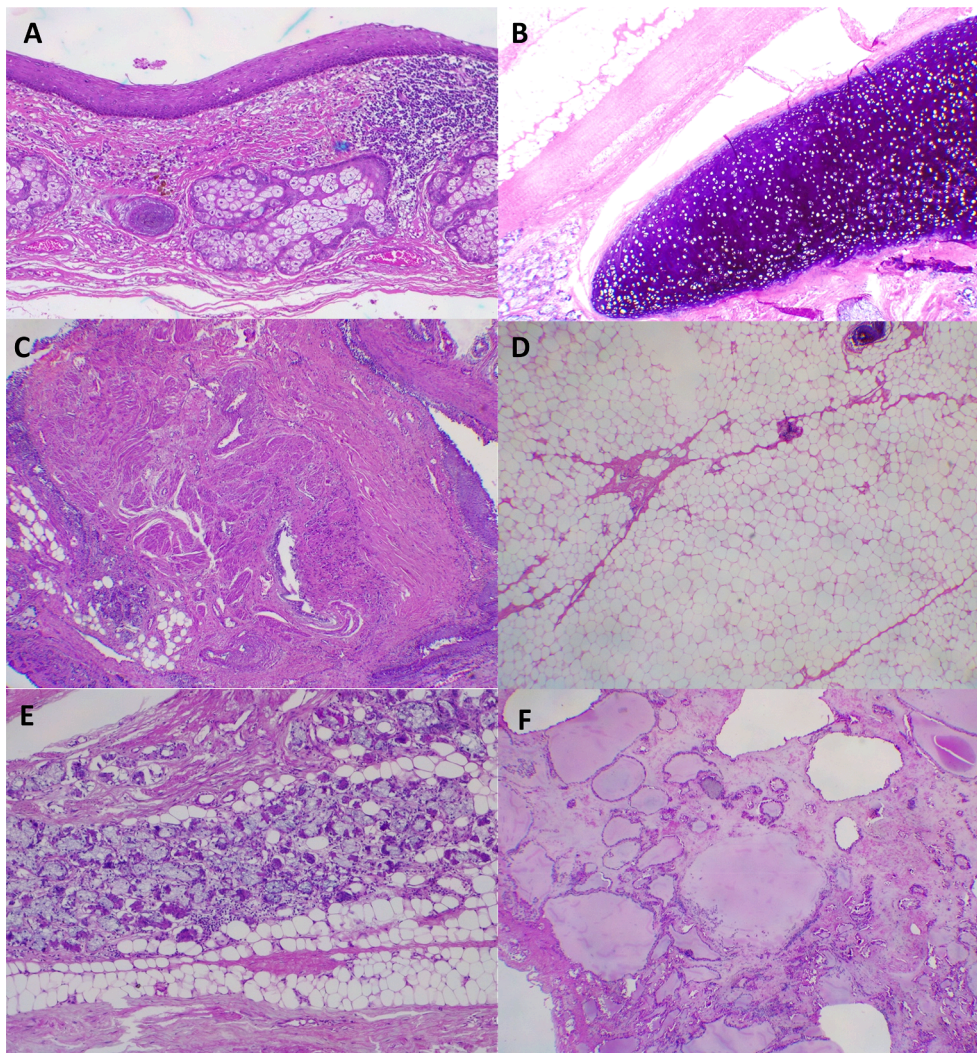
chromogranin was present, indicating that the tumor was of neuroendocrine origin. Based on the pathological features, strengthened by immunohistochemical staining, the tumor was diagnosed as a carcinoid tumor within a mature cystic teratoma. The patient received no further treatment and was set for a follow-up examination, which included a gynecological examination and ultrasound imaging every three months for three times and every six months after that. She did not present with carcinoid syndrome. No evidence of recurrence disease or metastasis was detected on the whole abdomen, pelvic computer tomography (CT), and MRI after 28 months of follow-up (see Fig. 3).

### 3. Discussion

Malignant transformation of ovarian MCT is an exceedingly rare phenomenon, reported in the literature from 1.5% of all malignant ovarian tumors. (Maeda et al., 2018) The majority of these cases are dominantly squamous cell carcinoma on histological type of coexisting tumor. Carcinoid tumors arising within ovarian teratoma are unusual and even rarer, representing 0,3% of all carcinoid tumors and less than 0,1% of ovarian cancers. (Valencia-west et al.) In addition, these changes usually occur in elderly women around menopause and remain exceptionally and unusually observed in young women. (Tosuner et al., 2015) The coexistence of a carcinoid tumor within an ovarian teratoma

is extremely rare in young patients. To our knowledge, our case represents potentially one amongst the very few that have occurred in women less than 40 years old.

Carcinoid tumor is a kind of epithelial neoplasm that is mainly differentiated from neuroendocrine cells. This neuroendocrine tumor is usually seen in the gastrointestinal tract and bronchopulmonary systems, with other locations like a gynecologic system which is far less common (Linhas et al., 2018). The ovarian carcinoids are divided into four histological types (Table 1): the insular, mucinous, trabecular, struma, and mixed types (insular and trabecular). (Valencia-west et al.) The most common type is the insular, followed by the struma and trabecular types, while mucinous types are the least common. Insular carcinoids are morphologically identical to midgut carcinoids and are composed of nested/insular arrangements, sometimes with small acinar or tubular formations (Analysis AC) The tumor cells are polygonal with round or oval nuclei with a so-called "salt and pepper" chromatin and abundant cytoplasm. Eosinophilic cytoplasmic granules may be seen. There may be seen slight nuclear atypia, and mitotic activity is low. The tumor cells are often set in a conspicuous stroma with a rather hyaline appearance, occasionally with psammomatous calcification. Trabecular carcinoids are composed of parallel trabecular/wavy ribboned arrangements of regular cells with similar nuclear features to those seen in insular carcinoids and set within a fibrous stroma (Carcinoid, 1982);



**Fig. 1.** Mature Cystic Teratoma A: The ectoderm component consists of flattened epithelium layered with skin adnexa, sebaceous glands, and hair roots (HE x100); B: The mesoderm consists of cartilage (x40), C: smooth muscle (x100), D: adipose tissue (x100); E: the endoderm includes the salivary glands (x100) F: thyroid glands (40x).

they are morphologically identical to hindgut carcinoids. Strumal carcinoids are an admixture of carcinoid elements (usually either insular or trabecular in type, with the latter more common) and thyroid tissue (Dikman and Toker, 1971). The two components may be spatially separate or intimately admixed. Intestinal-type mucinous glands are often present (40% of cases). Mucinous (goblet cell) carcinoid is the rarest primary ovarian carcinoid tumor. It is composed of small glands or acini lined by columnar or cuboidal epithelium with abundant intracytoplasmic mucin and variable numbers of goblet cells (Baker et al., 2001).

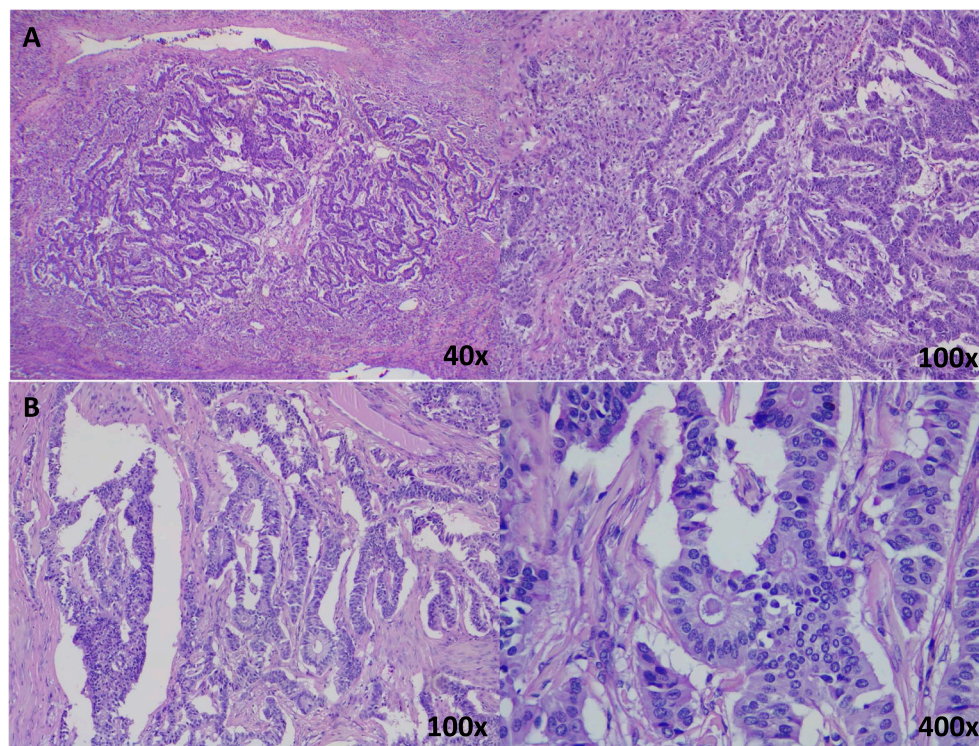
Carcinoid tumors secrete various neurohumoral substances such as serotonin, histamine, bradykinin, catecholamines, and prostaglandins. (Tosuner et al., 2015) Persistent body exposure to large quantities of these hormones and amines results in carcinoid syndrome with the classical triad of; flushing of the upper extremities and face, wheezes, and diarrhea. The insular type is often associated with carcinoid syndrome and rarely affects patients with trabecular types. (Metwally et al., 2016) However, carcinoid tumors are often unrecognized and underdiagnosed. It is conceivable to suspect the presence of a carcinoid tumor preoperatively if the patient presents symptoms, but our patient did not present with carcinoid syndrome. In most cases, a definitive diagnosis is incidentally detected on postoperative examination by the histological finding of the operative specimens. (Kim, 2016) Similarly to our case, the tumor was identified incidentally hence the patient did not have any symptoms of carcinoid syndrome for the previous two years.

Carcinoid tumor can be seen in the ovary as metastasis of a primary tumor located in the gastrointestinal tract or elsewhere, as a component of mature cystic teratoma, or as a pure primary neoplasm of this organ. (Zhai et al., 2020) The large majority of primary ovarian carcinoids are unilateral, but in 16% of cases, the contralateral ovary is involved by a cystic teratoma or a mucinous neoplasm (Report et al., 2018) The established criteria used for differentiating metastatic tumors of the ovary or primary ovarian tumors are the presence of multiple ovarian nodules and the finding of a primary tumor in the gastrointestinal tract,

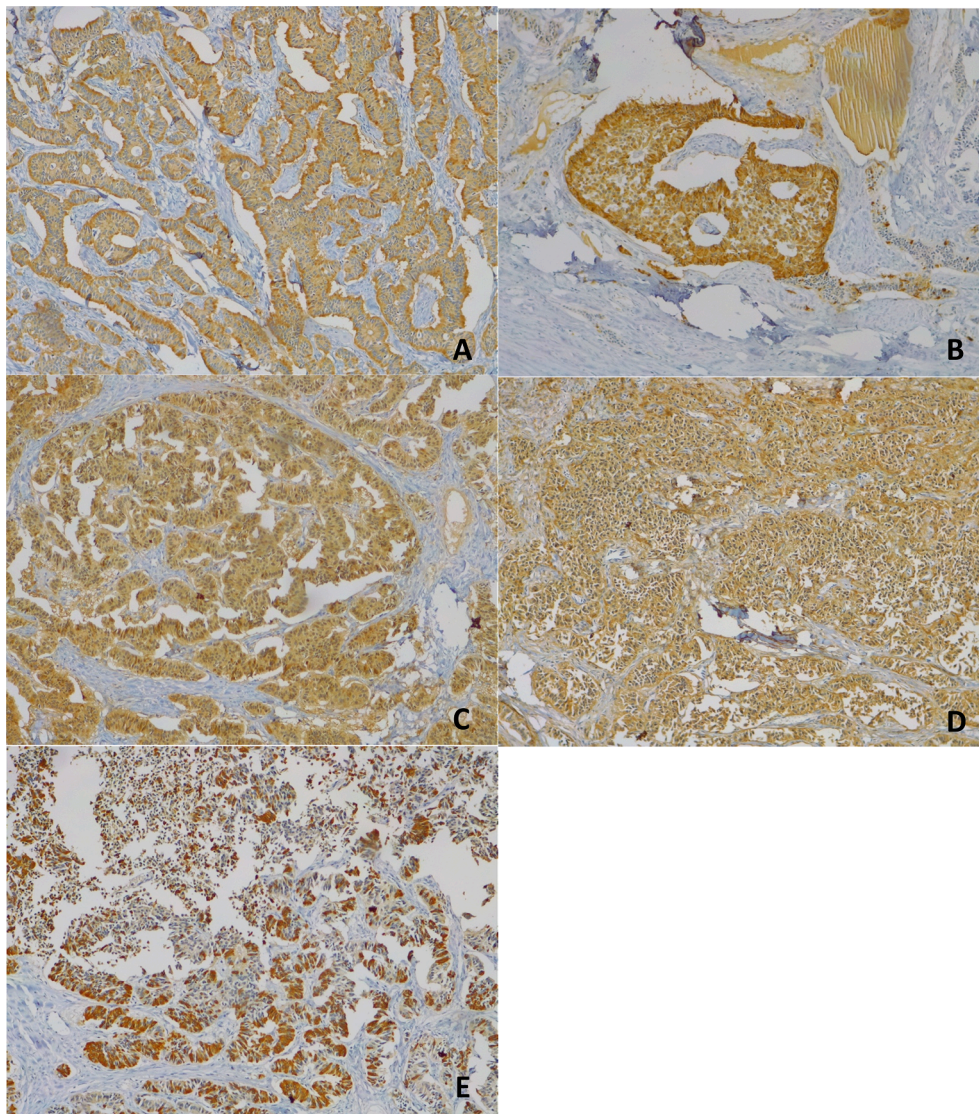
all favor metastasis to the ovary (Valencia-west et al.). Our patient has a primary carcinoid tumor because the tumor capsule was intact, without a vascular invasion or other suspicious lesions in the abdominal cavity. Immunohistochemistry is necessary to diagnose primary carcinoid tumors of the ovary. Tumor cells revealed immunoreactivity for the neuroendocrine markers following chromogranin, synaptophysin, NSE, and CD56, and these findings are typical of carcinoid tumors (Metwally et al., 2016). Previous literature reports both insular and trabecular variants typically diffuse positivity with neuroendocrine immunohistochemical stains such as Synaptophysin, Chromogranin, and CD56, although trabecular carcinoids may be chromogranin negative (Howitt et al., 2017; Rabban et al., 2009). This reflects that they are analogous to hindgut carcinoids which are often chromogranin negative (Rabban et al., 2009). Both insular and trabecular carcinoids stain positively with CK7 and negatively with CK20. In contrast, Mucinous carcinoids are often CK20 positive and CK7 negative. Insular and mucinous carcinoids may be positive with CDX2 (Howitt et al., 2017; Rabban et al., 2009). Stromal carcinoids exhibit positive staining with neuroendocrine markers (carcinoid component) and thyroglobulin and thyroid transcription factor (TTF1) (thyroid component) (Howitt et al., 2017).

There is no consensus in the literature on the treatment and follow-up. It is difficult to establish an optimal surgical treatment because it is rare. An attempt is made to adapt the surgical aggressiveness according to the patient's age, fertility preservation, and prevention of further malignancy progression. However, a thorough intraoperative assessment of extra-ovarian involvement is advised. Peri- and premenopausal patients may be offered total abdominal hysterectomy and bilateral salpingo-oophorectomy. Mucinous carcinoids are rare but may exhibit aggressive behavior with extra ovarian spread. Hence, omentectomy and para-aortic lymph node dissection may be indicated in patients with a mucinous variant of primary ovarian carcinoid. There is currently no evidence for the use of adjuvant therapy (McGrath and Nicklin, 2016).

The neoplasm's clinical and histopathologic prognostic factors represent the primary determinants of the therapeutic strategy in such



**Fig. 2.** Carcinoid Tumor A: Tumor cell formed in compacting trabeculae bands consisting of one to several layers of cells between the stroma of the collagen connective tissue with tubular/insular structures and a rosette (HE x40 x100); B: Tumor cells with round to oval nuclei, vesicular, fine-grained chromatin resembling “salt and pepper”, partially solid, eosinophilic cytoplasm, without mitotic figure (x100 x400).



**Fig. 3.** Tumor cells showing diffuse intense immunoreactivity of (A) synaptophysin, (B) chromogranin, (C) NSE, (D) CD56, (E) AE1/AE3 staining were positive partially (Magnification, x 100).

rare cases without evidence-based guidelines. Cyst wall invasion, intraoperative rupture of the ovarian mass, tumor dissemination, and adhesions are unfavourable prognostic factors (Zhai et al., 2020). Conservative surgery (adnexectomy) or unilateral oophorectomy is reserved for young women, especially nulliparous or those who wish to preserve fertility. However, total abdominal hysterectomy and bilateral salpingo-oophorectomy are considered to be the most appropriate surgical option for postmenopausal women or for women who have no intention of further childbirth (Cokmez et al., 2019). Adjuvant chemotherapy may sometimes be indicated, particularly in advanced stages (Gadducci et al., 2019). According to the literature, the prognosis of tumors is excellent for primary ovarian carcinoid tumors, and the 10-year survival rates are approximately 100%. However, the 5-year survival rate decreases to 33% in the advanced stage (Gadducci et al., 2019).

#### 4. Conclusion

The occasion of primary carcinoid tumors arising within a mature teratoma in a young patient is an extremely rare phenomenon. Moreover, it is difficult to diagnose TMT of the ovary preoperatively. A thorough histopathological examination of the tumor is mandatory to detect malignant transformation within solid tumor components, which

were not detected either on gross examination or radiologic findings. Clinical examination, histopathology, and imaging support are needed to decide whether or not to give further therapy.

#### Informed consent

Written informed consent was obtained from the patient for anonymized publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

#### CRediT authorship contribution statement

**Tricia Dewi Anggraeni:** Conceptualization, Methodology, Investigation, Resources, Supervision. **Gatot Purwoto:** Validation, Writing – review & editing. **Kartiwa Hadi Nuryanto:** Validation, Writing – review & editing. **Intan Winta Pratiwi:** Writing – original draft, Visualization. **Hartono Tjahjadi:** Resources.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial

**Table 1**  
Differences of histological type of carcinoid.

	Insular	Trabecular	Struma	Mucinous	Case
Characterized	Composed of nested/insular arrangements, with small acinar/tubular formations. Polygonal cells have round or ovoid nuclei "salt and pepper" chromatin and a lot of cytoplasm. There may be eosinophilic cytoplasmic granules, nuclear atypia, and minimal mitotic activity	Composed of parallel trabecular/wavy ribboned arrangements of regular cells with similar nuclear features to those seen in insular carcinoids and set within a fibrous stroma	Composed of an admixture of carcinoid elements (usually either insular or trabecular in type with the latter more common) and occasional thyroid tissue	Composed of small glands or acini lined by columnar or cuboidal epithelium with abundant intracytoplasmic mucin and variable numbers of goblet cells	Composed of compacting trabecular bands consisting of one to several layers of cells between the stroma of the collagen connective tissue with tubular/insular structures and a rosette. Tumor cells with round to oval nuclei, vesicular, fine-grained chromatin resembling "salt and pepper", partially solid, eosinophilic cytoplasm, without mitotic figure
Derivation	midgut	Foregut/ hindgut	Foregut/ hindgut	midgut	-
Carcinoid Syndrome	++	+/-	+/-	+/-	-
Incidence	Most common	Rarely than insular	rare	rarest	rare
Immunohistochemistry					
Choromogranin	++	+/-			++
Synaptophysin	++	++			++
CD56	++	++			++
CK7	+	+		-	N/A
CK20	-	-		+	N/A
CDX2	+	-		+	N/A
TTF1			+/-		N/A
Ki67	<1%	<1%	<1%		N/A
Treatment Strategy	TAH + BSO	TAH + BSO		Omentectomy + para-aortic lymphadenectomy	BSO
Prognosis	good	good	good	worse	good

interests or personal relationships that could have appeared to influence the work reported in this paper.

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gore.2022.100999>.

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Analysis AC. INSULAR CARCINOID PRIMARY I N T H E OVARY.  
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