Uncommon malignancy arising within mature ovarian teratoma: Case report and literature review

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ABSTRACT

Background. Clear cell carcinoma of the ovary developing in the background of an ovarian teratoma represents an extremely rare entity of the gynecologic tract. Giving the rarity of this entity, the histologic challenges, prognosis and the adequate treatment is still uncertain.

Methods. We herein present a case of clear cell carcinoma coexisting with a teratoma, accompanied by a scrutinous literature review. The authors have reviewed all case reports published in the literature (1978-2021), adding our new case, in order to enrich current literature data.

Results. A thorough search of the PubMed/MEDLINE and Google Scholar databases has revealed 7 cases of clear cell carcinoma of the ovary developing in association with a teratoma. Out of the 7 cases, 4 were part of a more complex tumor, including other malignancies (e.g. angiosarcoma, endometrioid carcinoma). The mean size of the tumors was 16 cm and most patients died of disease or suffered multiple recurrences. Additionally, we report a case of a 54-year-old patient who presented with an ovarian tumor and which upon microscopic examination featured a cystic structure lined by squamous keratinizing epithelium and sebaceous glands. Inside the wall of the cyst, a small nodule made out of tubules and papillae lined by clear cells, which invaded the surrounding stroma was identified. Four months later, the patient developed a small nodule in the liver and she has subsequently received adjuvant chemotherapy.

Conclusion. Clear cell carcinoma of the ovary developing in association with a teratoma is an extremely rare entity, that requires thorough sampling of the cyst and which is usually associated with a relatively poor prognosis.

Keywords: clear cell carcinoma, ovarian teratoma, malignancy within teratoma

INTRODUCTION

Malignant tumors developing in association with mature or immature tumors represent rare tumors, comprising less than 2.7% of all teratomas [1,2]. Squamous cell carcinoma is the most common epithelial malignant neoplasm developing within a teratoma, representing 80% of all malignant mature cystic teratomas [1]. In comparison, clear cell carcinoma of the ovary developing in the background of a mature teratoma is an exceptional situation, with only 7 cases reported in the scientific literature in the timeframe 1978-2021. Even though the scientific data regarding this particular entity are scarce, a recent study demonstrated that both
tumors harbor ARID1A deficiency and also PIK3CA mutation [3].

**MATERIAL AND METHOD**

For the purpose of analyzing the particularities of ovarian clear cell carcinoma which coexists with teratoma, we have performed a literature search on the several MESH terms: “ovarian” “clear cell carcinoma”, “teratoma”, “endometriosis”, “mixed germ cell tumor” and “mixed mesodermal tumor”. The entire PubMed®/MEDLINE and Google Scholar databases were analyzed and all relevant scientific papers were reviewed and compared to the case presented below. All the cases were sorted by year and the following information was retrieved: age of the patient, size of tumor, presenting symptoms, surgical and oncological treatment and also the prognosis. PubMed®/MEDLINE data search for case reports revealed 7 cases published in the last 43 years.

**RESULTS**

The performed literature review revealed 7 cases of ovarian clear cell carcinoma coexisting with teratoma, 4 out of which also associated other tumors (e.g. angiosarcoma, endometrioid carcinoma). Mean size of the tumors was 16.18 cm and the most common symptoms were abdominal pain or distension. 83% of all cases underwent total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO) with adjuvant chemotherapy. Out of the scientific papers that reported survival outcome data, 50% died of disease (DOD) in less than 17 months, while the other 50% either featured multiple recurrences, or were disease free after 8 months of follow-up.

**CASE PRESENTATION**

We report a 54-year-old patient, which presented to the hospital for abdominal discomfort, that increased in intensity in the last days. A CT examination was performed, which revealed a large tumor of the right ovary, with a cystic structure. An intraoperative examination has been performed and the preliminary diagnosis was mature teratoma. Upon gross examination, the tumor had a cystic structure with an intact capsule, that featured a thickening of the cyst wall with irregular internal surface and firm consistency. The whole tumor measured 14x12x12 cm, and the thickened area measured 1.7x1.5x0.9 cm. A thorough sampling of the wall cyst and of the area thickened has been performed. Upon microscopic examination, the cystic structure was lined by a squamous keratinizing epithelium, which included with hair follicles and sebaceous glands, representing a mature teratoma. Sampling from the thickened wall cyst revealed a secondary proliferation constituted out of tubule-cystic and papillary structures lined by cuboidal cells with pale or clear cytoplasm and vesicular nuclei and prominent nucleoli (Figure 1). Some of the papillae were lined by cells with a hobnail aspect and had a hyalinized fibrovascular core (Figure 2). Several areas of stromal invasion were noticed, which featured cholesterol clefts, areas of necrosis and psammoma bodies (Figure 3). The described aspects were diagnostic for clear cell carcinoma of the ovary. Immunohistochemical test revealed that the malignant proliferation was positive for PAX8 and Napsin A, and had a proliferative index of 15%. The case has been discussed in the multidisciplinary board meeting and a complex course of adjuvant chemotherapy has been recommended, because the patient had developed liver metastases in less than 2 months from the diagnosis. She is currently closely monitored with imagistic analyses and oncological consults at each 6 months.

**FIGURE 1.** Transition area between squamous epithelium of teratoma and papillary proliferation of clear cell carcinoma (H.E., 40x)

**DISCUSSIONS**

In the recent scientific literature there have been many malignancies reported, which are known to arise in association with a mature teratoma, with the most common entity being represented by squamous cell carcinoma. Additionally, other subtypes reported in the literature are: sebaceous carcinoma, thyroid papillary carcinoma, mucinous adenocarcinoma, mucoepidermoid carcinoma, urothelial car-
acinoma, carcinoid, carcinosarcoma, oligodendro-glioma, neuroblastoma, meningioma, melanoma, undifferentiated pleomorphic sarcoma, leiomyosarcoma, rhabdomyosarcoma, plasmablastic lymphoma, diffuse large B cell lymphoma, follicular lymphoma [4–20]. Cases of teratoma localized in non-ovarian sites have also been reported to be associated with the following tumors: nephroblastoma (retroperitoneum), apocrine carcinoma (mediastinum), signet ring cell carcinoma (sacrococcygeal), salivary gland carcinoma (mediastinum), neuroen-

docrine carcinoma (retroperitoneum), papillary renal cell carcinoma (retroperitoneum) [21-26]. Additionally, Pires et al. have also reported the coexistence of an ovarian teratoma with a uterine adenocarcinoma [27]. One particular scientific article reported the development of a rhabdomyosarcoma inside an ovarian carcinoma, in a patient that had contralateral serous carcinoma [17]. Cagino et al. have reported a case of multiple malignancies arising in a monodermal teratoma, which encompassed papillary thyroid carcinoma and ovarian carcinoid, arising in the background of a struma ovarii [28]. Savitchi et al. have also reported a squamous carcinoma coexisting with a pleomorphic carcinoma, which developed inside a mature cystic teratoma [29]. Myeloid sarcoma has also been reported as a neoplasm arising in a mixed germ cell tumor of a mediastinum, which has a teratomatous component [30].

Notably is the development of several reports of N-methyl-D-aspartate receptor encephalitis in patients with ovarian teratoma [31-33] and also the development of paraneoplastic neuromyelitis [34]. Of significant clinical importance is the observation made by Belge et al., who noticed that microRNA-375-3p serum levels can be used as a reliable biomarker of teratoma [35].

Ovarian teratoma can rarely be part of a mixed germ cell tumor, case in which it can be associated with an embryonal carcinoma [36,37]. Similarly to ovarian teratoma, testicular teratoma can also be part of a mixed germ cell tumor, and can frequently associate a seminoma, an embryonal carcinoma, a choriocarcinoma or a yolk sac tumor component [38]. Similarly, mixed germ cell tumors with a teratomatous component can arise also in the third ventricle and can even cause leptomeningeal spread [39].

Cases of sebaceous carcinoma and squamous cell carcinoma arising in an ovarian teratoma have been demonstrated to harbor mismatch repair deficiencies [40].

The scientific literature has revealed only 7 published cases in the time frame 1978-2021 of clear cell carcinoma coexisting with a teratoma. Out of these 7 cases, only three of them were pure clear cell carcinomas arising from a teratoma (two mature, one immature), the other were part of a more complex tumor and featured tumors such as: one angiosarcoma, one malignant mesodermal tumor, one malignant mixed germ cell tumor (yolk sac tumor, embryonal carcinoma and mature teratoma) and one who also featured other multiple malignancies (endometrioid adenocarcinoma, yolk sac tumor, squamous cell carcinoma and neuroectodermal tumor with rhabdomyosarcomatous differentiation) [3,41-46]. No differences in the overall surviv-

**FIGURE 2.** High magnification view of hyalinized fibro-vascular cores lined by clear cells with hobnail cells and focal calcifications (H.E., 200x)

**FIGURE 3.** Medium power view showing invasive areas with cholesterol clefts lined by polygonal cells with clear cytoplasm and prominent nucleoli (H.E., 100x)
al of patients with only clear cell carcinoma and teratoma and those with clear cell carcinoma, teratoma and other malignancies. The first case described had similarities with the case presented above, namely both featured areas of endometriosis [41]. This finding can support the presumption that both tumors develop from the Mullerian/paramesonephric tissues [41]. Kihara et al. have analyzed the molecular similarities between the clear cell carcinoma and the immature teratoma and noticed that both tumors featured ARID1A deficiency and also PIK3CA mutation [3]. A mesenchymal component with different morphologies (angiosarcoma, rhabdomyosarcomatous and cartilaginous) has been noted in three out of seven cases [41-43].

| Article author          | Age | Size        | Symptoms         | Stage   | Treatment                                                                 | Prognosis                      |
|-------------------------|-----|-------------|------------------|---------|---------------------------------------------------------------------------|--------------------------------|
| Cooper et al. (1978)    | 53  | 16X10X10 cm | Nocturia, low back pain | NA      | NA                                                                        | NA                             |
|                         | 34  | 14 cm       | Abdominal pain   | pT1aN1M0 | Right salpingo-oophorectomy, lymph node dissection, omentectomy, chemotherapy | Multiple recurrences after 5 and 17 months. Alive at 40 months after diagnosis. |
| Ohishi et al. (2007)    | 59  | 16x12x4,5 cm| Abdominal mass   | NA      | TAH, BSO, omentectomy, chemotherapy (paclitaxel, platinum)                | NA                             |
|                         | 55  | 5,1x5x3,4 cm| Lower abdomen discomfort | TAH, BSO, omentectomy, right infundibulopelvic ligament resection and bilateral paracolic sulci peritoneum biopsies, Chemotherapy (bleomycin, etoposide, cisplatin) | NA                             |
| Takahashi et al. (2012) | 49  | 16x10x9,5 cm| Genital bleeding | pT1aN0Mx | TAH, BSO, omentectomy, lymph node dissection, chemotherapy (taxol, carboplatin, | DFS 8 months                   |
|                         | 47  | 30 cm       | Abdominal distension | pT2aNxM1 | TAH, BSO, chemotherapy                                                     | DOD 17 months after diagnosis  |
| Yu et al. (2014)        | 71  | NA          | Abdominal distension | pT1c     | TAH, BSO, lymph node dissection, chemotherapy                             | DOD 9 months after the surgery  |

**CONCLUSIONS**

We presented an extremely rare case of an ovarian clear cell carcinoma developing in association with a mature teratoma, in the background of endometriosis. These rare malignancies are known to have an adverse prognosis with a short disease-free survival and a high mortality rate. This case can emphasize the need to scrutinize analyze the slides when dealing with a teratoma, or with a tumor of Mullerian origin. A malignant component, when present, should always be reported and the pathologists need to be aware of such rare associations.

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**REFERENCES**

1. Li C, Zhang Q, Zhang S, Dong R, Sun C, Qiu C, Zhang Z, Yang X, Kong B. Squamous cell carcinoma transformation in mature cystic teratoma of the ovary: a systematic review. *BMC Cancer*. 2019 Mar 11;19(1):217.

2. Desouki MM, Fadare O, Chamberlain BK, Shakir N, Kanbour-Shakir A. Malignancy associated with ovarian teratomas: frequency, histotypes, and diagnostic accuracy of intraoperative consultation. *Ann Diagn Pathol*. 2015 Jun;19(3):103-6.

3. Kihara A, Iizuka T, Endo S, Hori K, Kanda H, Niki T. Ovarian clear cell carcinoma with an immature teratoma component showing ARID1A deficiency and an identical PIK3CA mutation. *J Obstet Gynaecol Res*. 2021 Sep;47(9):3401-3407.

4. Choi WK, Lee DH, Cho DH, Jang KY, Kim KM. Primary malignant melanoma arising from ruptured ovarian mature cystic teratoma with elevated serum CA 19-9: a case report and review of literature. *BMC Womens Health*. 2019 Nov 27;19(1):149.

5. Liu YY, Liang P, Ji J, Chen KS, Li LM, Gao JB, Yong LL. Meningioma in mature cystic teratoma of the ovary: clinical and computed tomography findings. *Cancer Imaging*. 2020 Feb 5;20(1):15.

6. Rowe JS, Makar G, Holdbrook T, Germaine P. Squamous cell carcinoma arising in a partially ruptured giant mature cystic teratoma: A case report. *Radiol Case Rep*. 2018 Oct 24;14(1):97-102.

7. Pineyro MM, Pereda J, Schou P, de los Santos K, de la Peña S, Caserta B, Pisabarro R. Papillary Thyroid Microcarcinoma Arising Within a Mature Ovarian Teratoma: Case Report and Review of the Literature. *Clin Med Insights Endocrinol Diabetes*. 2017 Jun 6;10:1179551417712521.

8. Angelico G, Santoro A, Inzani F, Martini M, D’Alessandris N, Spadola S, Valente M, Aruizolo D, Sfregola S, Mule’ A, Scambia G, Zannoni GF. When a mimicker wears strange faces: description of an osteogenic melanoma arising within an ovarian teratoma with focus on its late
peritoneal relapse. *Eur Rev Med Pharmacol Sci.* 2020 Jun;24(12):6569-6575.

9. Tewari P, Nigam JS, Kumar T, Singh A, Pandey J. Ovarian Carcinoid Misinterpreted as Endometrioid Adenocarcinoma in Mature Cystic Teratoma. *Cureus.* 2020;12(12):e11948.

10. Lee SY, Jang MH, Koo YJ, Lee DH. Undifferentiated carcinoma arising in ovarian mature cystic teratoma: a case report and literature review. *Int J Clin Exp Pathol.* 2020;13(7):1750-1754.

11. de Lima RB, Jung JE, Joshi SO, Kamli RM. Sebaceous carcinoma in a mature teratoma of the ovary. *Autops Case Rep.* 2018;8(4):e2018060.

12. Kerr SE, Flotte AB, McFalls MJ, Vranas JA, Halling KC, Bell DA. Matching maternal isodisomy in mucinous carcinomas and associated ovarian teratomas provides evidence of germ cell derivation for some mucinous ovarian tumors. *Am J Surg Pathol.* 2013 Aug;37(8):1229-35.

13. Pongsuvareeyakul T, Sukpan K, Chaicharoen S, Khunamornpong S. Leiomyosarcoma and Squamous Cell Carcinoma Arising in Mature Cystic Teratoma of the Ovary. *Case Rep Pathol.* 2017;2017:7907359.

14. Rewusuwan S, Satabongkoch N, Suprasert P, Khunamornpong S. Ovarian Carcinoma and Its Association with Mature Cystic Teratoma and Primary Tubal Carcinoma. *Case Rep Pathol.* 2016;2016:2605045.

15. Chuang HY, Chen YT, Mac TL, Chen YC, Chen HS, Wang WS, Tsai EM. Urothelial carcinoma arising from an ovarian mature cystic teratoma. *Taiwan J Obstet Gynecol.* 2015 Aug;54(4):442-4.

16. Memin YA, Kulkarni MF, Pandav AB, Sulhan KR. Mucoepidermoid carcinoma in a mature cystic teratoma: A rare case report with review of literature. *Indian J Pathol Microbiol.* 2017 Jan-Mar;60(1):117-118.

17. Kefeli M, Kandemir B, Akpolat I, Yildirim A, Akozu A. Rhabdomyosarcoma arising in a mature cystic teratoma with contralateral serous carcinoma: case report and review of the literature. *Int J Gynecol Pathol.* 2009 Jul;28(4):372-5.

18. Hadžišedžić I, Babarović E, Vranić L, Dudelić Načinović A, Lučin K, Krašević M, Jonić N. Unusual presentation of plasmablastic lymphoma involving ovarian mature cystic teratoma: a case report. *Diagn Pathol.* 2017 Nov 29;12(1):83.

19. Tandon N, Sultana S, Sun H, Zhang S. Follicular Lymphoma Arising In a Mature Cystic Teratoma in a 26 Year Old Female. *Ann Clin Lab Sci.* 2016 May;46(3):298-301.

20. Maguire A, Castriciano G, Walker J, Molloy K, et al. Case Study: Diffuse Large B-Cell Lymphoma Arising in Ovarian Mature Cystic Teratoma. *Int J Gynecol Pathol.* 2015 Sep;34(5):459-64.

21. Li Y, Lei C, Xiang B, Wang C, Wang Q, Chen S, Ji Y. Extrarenal teratoma with nephroblastoma in the retroperitoneum: Case report and literature review. *Medicine (Baltimore).* 2017 Nov;96(46):e8670.

22. Sugiyama K, Iwakishi A, Satoh M, Shirashi K, Nozawa K, Kogure Y, Sugiyama M, Moritani S, Kato E, Saka H. Primary Mediastinal HER2-positive Apocrine Carcinoma in Mature Teratoma Treated With Anti-HER2 Therapy and Chemoradiation. *J Med Case Rep.* 2017 Mar;11(1):74.

23. Zhou P, Liu S, Sun H, Zhang S. Follicular Lymphoma Arising In A Mature Cystic Teratoma in a 26 Year Old Female. *Ann Clin Lab Sci.* 2016 May;46(3):298-301.

24. Maguire A, Castriciano G, Walker J, Molloy K, et al. Case Study: Diffuse Large B-Cell Lymphoma Arising in Ovarian Mature Cystic Teratoma. *Int J Gynecol Pathol.* 2015 Sep;34(5):459-64.

25. Li Y, Lei C, Xiang B, Wang C, Wang Q, Chen S, Ji Y. Extrarenal teratoma with nephroblastoma in the retroperitoneum: Case report and literature review. *Medicine (Baltimore).* 2017 Nov;96(46):e8670.

26. Sugiyama K, Iwakishi A, Satoh M, Shirashi K, Nozawa K, Kogure Y, Sugiyama M, Moritani S, Kato E, Saka H. Primary Mediastinal HER2-positive Apocrine Carcinoma in Mature Teratoma Treated With Anti-HER2 Therapy and Chemoradiation. *J Med Case Rep.* 2017 Mar;11(1):74.

27. Zhou P, Liu S, Sun H, Zhang S, Liu X, Liu D. Signet ring cell carcinoma arising from sacrococcygeal teratoma: a case report and review of the literature. *J Int Med Res.* 2019 May;47(5):2234-2239.

28. Zhu YT, Chen Y, Li YH, Chen N, Zhang HW, Xu LM, Liu JY. Coexistence of the BRCA1 and KRAS mutations in a patient with salivary gland carcinoma arising in mediastinal mature teratoma. *Anticancer Drugs.* 2020 Sep;31(8):876-879.

29. Scott AL, Abbassi-Ghadi N, Archer CM, Swamy R, Gupta S. Neuroendocrine carcinoma arising within a retroperitoneal mature teratoma. *Ann R Coll Surg Engl.* 2010 Sep;92(6):WS-5.

30. Scott AL, Abbassi-Ghadi N, Archer CM, Swamy R, Gupta S. Neuroendocrine carcinoma arising within a retroperitoneal mature teratoma. *Ann R Coll Surg Engl.* 2010 Sep;92(6):WS-5.

31. Pires MDA, Catarino JC, Vilhena H, Faim S, Nevés T, Freire A, Seixas F, Orge L, Payan-Carreira R. Co-existing monophasic teratoma and uterine adenocarcinoma in a female dog. *Reprod Domest Anim.* 2019 Jul;54(7):1044-1049.

32. Cagino K, Levitan D, Schatz-Siemers N, Zarnegar R, Chapman-Davis E, Holcomb K, Frey M. Multiple malignant transformations of an ovarian mature cystic teratoma. *E cancer medical science.* 2020 Feb 4;14:1009.