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Case report

Papillary thyroid carcinoma and strumal carcinoid transformations of a mature cystic teratoma with NRAS codon 61 mutation: A case report

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ABSTRACT

Mature cystic teratoma(MCT)[2] is the most prevalent neoplasm derived from germ cells in females; its progression to malignancy is infrequent. The coexistence of papillary thyroid carcinoma(PTC)[3] and strumal carcinoid derived from MCT is exceptionally rare. To the best of our knowledge, only six cases of this condition have been reported to date, however, the molecular information and immune cell infiltration for the mixture has never been studied. We present a case of a patient exhibiting a combination of these two components in the MCT. The clinical and pathological characteristics of the patient are described in this report. For the first time, we demonstrated that NRAS codon 61 mutations were present in these two elements, and there was no significant difference between cancer-adjacent tissues and malignant tissues in immune cell infiltration. As a unique example of multiple malignant transformations in a single MCT, this case provides a basis for future investigations into MCTs.

1. Introduction

MCT is a prevalent occurrence, constituting approximately 20 % of ovarian tumors [1]. The identification of struma ovarii takes place when an ovarian teratoma specimen encompasses at least 50 % of thyroid tissue. Struma ovarii is a seldom encountered monodermal ovarian teratoma, comprising roughly 2 % of MCT. The malignant transformation of struma ovarii constitutes approximately 0.1 % of MCT [2]. Malignant tumors can be categorized into three types: papillary, follicular variant of papillary, and follicular.

Primary ovarian carcinoids are exceedingly rare, comprising approximately 1 % of all carcinoids and less than < 0.1 % of malignant ovarian tumors [3]. These carcinomas can be classified into four types: insular, strumal, trabecular and mucinous [4]. Strumal carcinoids are characterized by a blend of the thyroid gland and the carcinoid. Moreover, thyroid tissue can transform into various types of malignant tumors. Herein, we present a case of a pre-menopausal patient exhibiting a combination of PTC and strumal carcinoid in the malignant struma ovarii (MSO).[4]

2. Case

The individual seeking medical attention was a middle-aged woman of 47-year-old, who presented with a gradually enlarging pelvic mass in 6 months. Ultrasound revealed a combination of cystic and solid masses located in the left adnexal region, measuring 4.58 × 3.96 cm (Fig. 1**A**). Enhanced computed tomography (CT)[5] images displayed a heterogeneous density shadow with soft tissue, cystic components, and a small number of calcifications (Fig. 1**B**). The mass exhibited clearly defined borders and did not exhibit any noticeable enhancement. Radiological findings were highly suggestive of a teratoma. CEA and CA19–9 levels were within the normal range. Preoperative diagnosis was MCT.

The patient underwent total laparoscopic hysterectomy with bilateral salpingo-oophorectomy, as well as bilateral pelvic and para-aortic

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[2] MCT: mature cystic teratoma

[3] PTC: papillary thyroid carcinoma

[4] MSO: malignant struma ovarii

[5] CT: computed tomography

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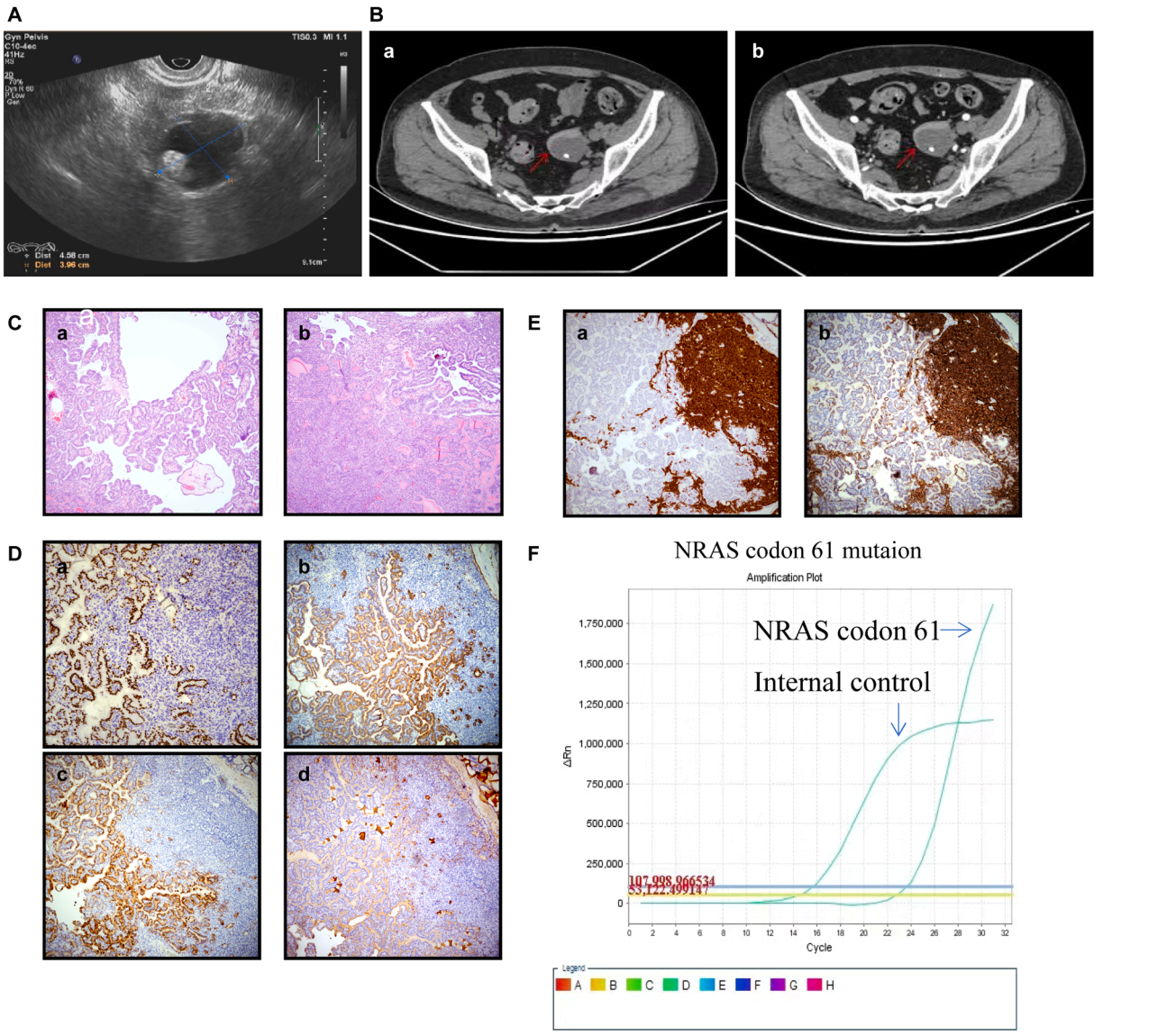

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Fig. 1. Imaging and pathological findings. (A)Ultrasound examination revealed a composite cystic and solid tumor located in the left adnexal area, measuring approximately 4.58×3.96 cm in size. (B) Pre- and post- contrast CT images (a, b) illustrate a heterogeneous density lesion in the left adnexal region, characterized by a combination of soft tissue, cystic components, and a small number of calcifications (red arrow). Following the administration of contrast, no apparent enhancement was observed in the mass as depicted on the enhanced CT scan (b). (C) Representative photomicrographs of HE staining of the tumor areas. (a) Papillary thyroid carcinoma area. Atypical papillary proliferation of thyroid follicular epithelium, 100× magnification. (b) Strumal carcinoid area. A mixture of papillary thyroid carcinoma and carcinoid, 100× magnification. Tumor cells in the strumal carcinoid areas were arranged in insular or trabecular shapes. (D) TTF-1 (a), CK19 (b), Galectin-3 (c), and TG (d) showed positive expression in the PTC area, while exhibiting negative expression in the strumal carcinoid area, 100× magnification. (E) Both Syn (a) and CD56 (b) presented positive expression in the strumal carcinoid area, while displaying negative expression in the strumal carcinoid area, 100× magnification. (F) NRAS codon 61 mutation. Identification of a NRAS codon 61 mutation when fluorescence-based quantitative real-time PCR (RT-qPCR) was employed for the identification of BRAF, KRAS, and NRAS mutations. (G) CD4, CD8, CD20, and CD68 were used for identifying subsets of lymphocytes and monocytes, 200× magnification.

lymph node dissection. Based on these evaluations, there were no obvious signs or indications of the disease having spread to remote anatomical sites.

Pathologic gross examination revealed that the left ovarian cyst measured approximately 3.0 × 3.0 × 0.1 cm in size, with a smooth inner wall. Additionally, a locally protruding nodule measuring approximately 2.0 × 1.0 × 1.0 cm was observed. Hematoxylin and eosin (HE)-stained images showed atypical papillary proliferation of some thyroid follicular epithelia (Fig. 1**C a**). Solid cell nests arranged in an insular or trabecular pattern were observed adjacent to the papillary structures. These nests exhibited gradual transition and intermingling of both elements (Fig. 1**C b**). Morphologically, the cyst was preliminarily diagnosed as PTC or carcinoid. Immunohistochemical analysis was performed to confirm coexistence. In the PTC area, Thyroid Transcription Factor 1 (TTF1)[6], CK19 (Cytokeratin 19)[7], Galectin-3 and thyroglobulin (TG)[8] were positively expressed (Fig. 1**D**), whereas synaptophysin (Syn)[9] and CD56 were negatively expressed (Fig. 1**E**). In the strumal carcinoid area, an inverse result was observed (Fig. 1**D, E**). Gene status analyses were conducted for the KRAS, NRAS, and BRAF genes. The results revealed a NRAS codon 61 mutation (Fig. 1**F**). Additionally, antibodies targeting specific subsets of lymphocytes and monocytes (CD4, CD8, CD20, and CD68) were used. No apparent differences were found between the neoplastic and adjacent normal tissues (Fig. 1**G**). Postoperative recovery was uneventful; however, the patient declined follow-up for additional therapy. The patient has been disease-free for nearly 2 years and will undergo close surveillance.

3. Discussion

MCT of the ovary is the most prevalent germ cell tumor in women, and malignant transformation of this tumor is rare. Moreover, coexistence of both PTC and strumal carcinoid in a mature ovarian cystic teratoma is even more uncommon. To the best of our knowledge, only six cases of this condition have been reported to date. We compiled and summarized these cases, including their clinical and pathological features in Table 1. All patients, including the present case, were adults with a median age of 56 years. With the exception of one patient whose lesion originated in the right ovary, all other lesions were in the left ovary, which is consistent with the literature on MSO [5]. In two patients, the lesion was discovered during physical examination [6,7], while two presented with abdominal pain [8,9], and two others experienced abnormal uterine bleeding [10,11]. In the present case, the patient sought medical attention owing to gradual enlargement of the pelvic mass. Previous studies have identified serum CA-125 levels as a risk factor for the malignant transformation of MCTs [12]. However, among these cases, only three patients underwent serum tumor marker testing, with one showing elevated CA125 levels; the rest did not exhibit any abnormalities. CT and ultrasound examinations can be helpful for preoperative diagnosis; however, these techniques lack specificity. Therefore, histopathological examination is usually necessary for accurate diagnosis and determination of appropriate treatment.

The diagnosis of struma ovarii is established when an ovarian teratoma specimen contains at least 50 % thyroid tissue. In this case, approximately half of the examined tissue was thyroid, confirming the diagnosis of struma ovarii. Histologically, the lesion exhibited well-differentiated thyroid follicles; however, interspersed among these benign follicular structures were papillary proliferations of neoplastic cells displaying significant cytologic atypia (**Fig. 1C a**). These tumor cells featured characteristic ground-glass nuclei with prominent grooves and occasional nuclear pseudo inclusions. Adjacent to the papillary structures, solid cell nests were seen arranged in an insular or trabecular pattern. These nests exhibited gradual transition and intermingling of both elements (**Fig. 1C b**). Histologically, the tumor in our case exhibited the presence of PTC and strumal carcinoid. Additional diagnostic and differential diagnostic procedures were performed using immunohistochemical analyses. The PTC component displayed positive staining for TTF-1, CK19, Ga lectin-3, and TG, but negative staining for Syn and CD56 (**Fig. 1D, E**). In contrast, the strumal carcinoid region exhibited markedly distinct findings compared with those observed in the PTC region. Based on the histopathologic and immunohistochemical characteristics, the present case aligns with the diagnosis of MCT accompanied by PTC and strumal carcinoid.

Limited research has been conducted on genetic modifications in MSO. Certain authors argue that, in addition to exhibiting histological similarities, the thyroid-like carcinomas that emerge in the struma ovarii share genetic characteristics with primary thyroid carcinomas [13]. Nevertheless, some researchers have posited that the gene mutation locations in MSO diverge from those in thyroid cancer [14]. Existing evidence supports the notion that the prevailing genetic alterations in PTC are associated with BRAF and RAS oncogenes [15]. BRAF, a human isoform of RAF, is activated by RAS, resulting in synergistic effects in cells that respond to growth factors [16]. Mutations in BRAF, NRas, KRas [14,15]and HRas [17] have been reported in patients with MSO. To our knowledge, no molecular information pertaining to the mixture of PTC and strumal carcinoid arising from the struma ovarii has hitherto been discerned. This is the first report of an NRAS codon 61 mutation in a combination of these two components (**Fig. 1F**). As the histological states of the two components were mixed, we could not identify them to test their molecular features. Considering the monoclonal origin theory, presence of the NRAS codon 61 mutation, which is a rare mutational event independent of both components, seems unlikely. Moreover, both elements are highly likely to originate from a multipotent epithelial stem cell or a shared multipotent stem cell with neuroendocrine features that undergoes biphenotypic differentiation during the early stages of carcinogenesis. Further research is needed to validate this hypothesis and understand the underlying mechanisms involved.

Immune cells have been documented to engage and interact with tumor cells, thereby influencing the immune microenvironment. A growing body of evidence indicates a favorable correlation between the density of intratumoral lymphocyte infiltrates in solid tumors and enhanced patient survival. Furthermore, various malignancies, such as breast, ovarian, rectal, lung, mesothelioma, and pancreatic cancers,

[6] TTF1: thyroid transcription factor 1
[7] CK19: Cytokeratin 19
[8] TG: thyroglobulin
[9] Syn: synaptophysin

Table 1
Clinical and pathological features of the struma ovarii with PTC and strumal carcinoid.

Case NO	Age	Presentation	Location	Size	Serum tumor marker	Particular clinical manifestation
1[6]	74	Asymptomatic	Right ovary	8.5 cm × 7.3 cm × 5.5 cm	Not mentioned	Not mentioned
2[10]	69	Asymptomatic	Left ovary	21 cm × 17 cm × 14 cm	Not mentioned	With poorly differentiated intraductal carcinoma of the left breast [pTis (DCIS)N0(sn)M0]
3[7]	61	Abdominal pain	Left ovary	23 cm × 18.5 cm × 15.4 cm	CA−125 : 340 U/ml(↑)	With a small to moderate amount of ascites
4[8]	43	Abdominal pain	Left ovary	9 cm × 7 cm × 5 cm	Not mentioned	Not mentioned
5[9]	49	Menstrual irregularity	Left ovary	9.6 cm × 6 cm × 5.5 cm	CA125:18.8 U/ml; CEA:1.6 ng/ml	Not mentioned
6[11]	48	Sharp lower abdominal pain and abnormal uterine bleeding	Left ovary	10 cm × 7.2 cm × 6.0 cm	Not mentioned	Punctate 1–2 mm colloid cysts in the left thyroid gland (Ultrasound)

have exhibited a notable increase in the presence of CD3 or CD8 + lymphocytes following therapy [18], whereas in cervical cancer, CD8 + T-cell rates remain relatively stable[19]. In this case, no obvious immune cell infiltration was detected in malignant tissues compared with cancer-adjacent tissues (**Fig. 1G**), and no significant changes in immune cell infiltration were observed. Though few studies have been conducted on immune-infiltrating cells in the MCT or MSO, substantial infiltration of CD8+ T cells within the tumor has been observed in MCT-SCCs [20]. Moreover, intrathyroidal lymphocyte infiltration is more commonly observed in PTCs than in other types of thyroid cancer [21]. Midgut carcinoid tumors exhibit infiltration by CD4+ and CD8+ T cells [22]. The presence of tumor-infiltrating lymphocytes in both PTCs and carcinoids indicates a favorable prognosis. However, these reports focus solely on single transformations, and there are no previous reports regarding immune cell infiltration in multiple malignancies arising from a single MCT. This study lacked the statistical power to assess the impact of immune cell infiltration on the prognosis of MSO. To evaluate the effect of immune cell infiltration on multiple malignancies originating from a single MCT, more cases are needed. The patient will be followed up continuously until death or for a duration of 10 years, whichever comes first. This case presents a unique example of lymphocyte infiltration with multiple malignant transformations within a single SO, laying the groundwork for future investigations on MSO. Further research is imperative to elucidate the significance of immune cell infiltration in MSO.

4. Conclusion

In summary, we presented a case of MSO with PTC and strumal carcinoid, which present NRAS codon 61 mutations in these two elements, and there was no significant difference between cancer-adjacent tissues and malignant tissues in immune cell infiltration. A multidisciplinary team, along with the patient and her family, decided not to undertake any further supplementary surgical measures. Our team will persist in monitoring her every 3 months to evaluate prognosis, given the presence of PTC and strumal carcinoid. Nearly 2 years post-operatively, the patient's condition continued to be promising, with no indications of illness.

Ethics approval and consent to participate

This study is a non-intervention one, which has been determined exempt, by an independent ethics committee. The patient provided informed consent for the publication of her information.

Consent for publication

The patient gave consent for images and clinical information relating to her case to be reported in this medical publication.

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CRediT authorship contribution statement

Xin Xing: Writing – review & editing. **Liu Heng:** Methodology, Data curation. **Wang Xuejiao:** Methodology, Data curation. **Zhao Jing:** Writing – original draft, Formal analysis. **Zhang Yang:** Writing – original draft, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] M.M. Pineyro, J. Pereda, P. Schou, K. de Los Santos, S. de la Peña, B. Caserta, R. Pisabarro, Papillary thyroid microcarcinoma arising within a mature ovarian teratoma: case report and review of the literature, 1179551417712521, Clin. Med. Insights Endocrinol. Diabetes 10 (2017), https://doi.org/10.1177/1179551417712521.
[2] C.P. DeSimone, S.M. Lele, S.C. Modesitt, Malignant struma ovarii: a case report and analysis of cases reported in the literature with focus on survival and I131 therapy, Gynecol. Oncol. 89 (3) (2003) 543–548, https://doi.org/10.1016/s0090-8258(03)00141-0.
[3] M. Virarkar, S.S. Vulasala, A.C. Morani, R. Waters, D.R. Gopireddy, S. Kumar, P. Bhosale, C. Lall, Neuroendocrine neoplasms of the gynecologic tract, Cancers 14 (7) (2022), https://doi.org/10.3390/cancers14071835.
[4] T. Kurabayashi, T. Minamikawa, S. Nishijima, I. Tsuneki, M. Tamura, T. Yanase, H. Hashidate, H. Shibuya, T. Motoyama, Primary strumal carcinoid tumor of the ovary with multiple bone and breast metastases, J. Obstet. Gynaecol. Res. 36 (3) (2010) 567–571, https://doi.org/10.1111/j.1447-0756.2010.01231.x.
[5] M. Hatami, D. Breining, R.L. Owers, G. Del Priore, G.L. Goldberg, Malignant struma ovarii–a case report and review of the literature, Gynecol. Obstet. Investig. 65 (2) (2008) 104–107, https://doi.org/10.1159/000108654.
[6] H.D. Hinshaw, A.L. Smith, M.M. Desouki, A.B. Olawaiye, Malignant transformation of a mature cystic ovarian teratoma into thyroid carcinoma, mucinous adenocarcinoma, and strumal carcinoid: a case report and literature review, Case Rep. Obstet. Gynecol. 2012 (2012) 269489, https://doi.org/10.1155/2012/269489.
[7] G. Pelosi, A. Sonzogni, J. Rosai, Thyroid-type papillary microcarcinoma in ovarian strumal carcinoid, Int. J. Surg. Pathol. 16 (4) (2008) 435–437, https://doi.org/10.1177/1066896908315819.
[8] H. Williams, E. Salinas, E. Savage, M. Samuelson, M.J. Goodheart, Malignant struma ovarii with insular carcinoma: a case report and literature review, Gynecol. Oncol. Rep. 18 (1-3) (2016), https://doi.org/10.1016/j.gore.2016.08.003.
[9] W. Huang, X. Xu, M. Zheng, L. Wang, J. Hu, Y. Liu, P. Xie, Mature cystic ovarian teratoma with thyroid papillary carcinoma and strumal carcinoid: a case report and review of literature, Int. J. Clin. Exp. Pathol. 9 (2016) 8741–8744.
[10] A.P. Percicote, S.B.B. Hatschbach, S.O. Ioshii, Castilho TJCd, J.A. Bahr, C. G. Zamboni, Papillary thyroid carcinoma in ovarian strumal carcinoid tumor: case report, J. Bras. De. Patol. e Med. Lab. 49 (2013).
[11] K. Cagino, D. Levitan, N. Schatz-Siemers, R. Zarnegar, E. Chapman-Davis, K. Holcomb, M. Frey, Multiple malignant transformations of an ovarian mature cystic teratoma, Ecancermedicalscience 14 (2020) 1009, https://doi.org/10.3332/ecancer.2020.1009.

[12] N. Uddin, K. Minhas, S.T. Arshad, Kayani NJJoC, Histology: Epithelial Malignancies Arising in Ovarian Mature Cystic Teratoma: A Series, of 26 Cases 2016 (2016).
[13] C.J. Gomes-Lima, Y.E. Nikiforov, W. Lee, K.D. Burman, Synchronous independent papillary thyroid carcinomas in struma ovarii and the thyroid gland with different RAS mutations, J. Endocr. Soc. 2 (8) (2018) 944–948, https://doi.org/10.1210/js.2018-00132.
[14] Y. Cui, J. Yao, S. Wang, J. Zhao, J. Dong, L. Liao, The clinical and pathological characteristics of malignant struma ovarii: an analysis of 144 published patients, Front. Oncol. 11 (2021) 645156, https://doi.org/10.3389/fonc.2021.645156.
[15] A. Tan, C.J. Stewart, K.L. Garrett, M. Rye, P.A. Cohen, Novel BRAF and KRAS mutations in papillary thyroid carcinoma arising in struma ovarii, Endocr. Pathol. 26 (4) (2015) 296–301, https://doi.org/10.1007/s12022-015-9394-3.
[16] A. Tannapfel, S. Vomschloss, D. Karhoff, A. Markwarth, U.R. Hengge, C. Wittekind, R. Arnold, D. Hörsch, BRAF gene mutations are rare events in gastroenteropancreatic neuroendocrine tumors, Am. J. Clin. Pathol. 123 (2) (2005) 256–260.
[17] C. Coyne, Y.E. Nikiforov, RAS mutation-positive follicular variant of papillary thyroid carcinoma arising in a struma ovarii, Endocr. Pathol. 21 (2) (2010) 144–147, https://doi.org/10.1007/s12022-009-9097-8.
[18] van den Ende T., van den Boorn H.G., Hoonhout N.M., van Etten-Jamaludin F.S., Meijer S.L., Derks S., de Gruijl T.D., Bijlsma M.F., van Oijen M.G.H., van Laarhoven H.W.M.: Priming the tumor immune microenvironment with chemo(radio)therapy: A systematic review across tumor types. (1879-2561 (Electronic)).
[19] Liang Y., Lü W., Zhang X., Lü B.: Tumor-infiltrating CD8+ and FOXP3+ lymphocytes before and after neoadjuvant chemotherapy in cervical cancer. (1746-1596 (Electronic)).
[20] Tamura R., Yoshihara K.A.-O., Nakaoka H., Yachida N., Yamaguchi M., Suda K., Ishiguro T.A.-O., Nishino K., Ichikawa H., Homma K. *et al*: XCL1 expression correlates with CD8-positive T cells infiltration and PD-L1 expression in squamous cell carcinoma arising from mature cystic teratoma of the ovary. (1476-5594 (Electronic)).
[21] Nagayama Y.: Thyroid Autoimmunity and Thyroid Cancer - The Pathogenic Connection: A 2018 Update. (1439-4286 (Electronic)).
[22] Vikman S., Sommaggio R Fau - De La Torre M., De La Torre M Fau - Oberg K., Oberg K Fau - Essand M., Essand M Fau - Giandomenico V., Giandomenico V Fau - Loskog A., Loskog A Fau - Totterman T.H., Totterman T.H.: Midgut carcinoid patients display increased numbers of regulatory T cells in peripheral blood with infiltration into tumor tissue. (1651-226X (Electronic)).