Current Opinion in Gynecology and Obstetrics

Struma Ovarii. Can we face this Challenge? A Case Report

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Received date: May 07, 2019; Accepted date: May 31, 2019; Published date: June 05, 2019

Abstract

Struma ovarii is an uncommon and sometimes aggressive tumor that must be recognized from the early beginning in order to be treated properly. We want to report a case of a woman whose tumor was wrong labeled at first sight, but even redirecting the diagnosis afterwards and finding a good treatment, toxicity was unfortunately the cause of death. Further investigation on these tumors is necessary.

Keywords: Struma, Oncology, Diagnosis, Treatment

Case Presentation

A 57-year-old woman presented polyhydramnios with simple endometrial hyperplasia and bilateral adnexal images compatible with long-standing polycystic cells as the only personal history. No family history of cancer interest.

In the last gynecological review, the adnexal images were visualized with a hyperrefringent-solid pole in the newly appearing left ovary. Bilateral adnexectomy and hysterectomy were performed finding two tumors: 5-6 cm in the left ovary and 3-4 cm in the right one. They were firmly attached to the posterior uterine surface.

The result of the anatomopathological analysis was a grade 2 bilateral endometrioid adenocarcinoma with areas of clear cell carcinoma (<10%). The tumor surpassed the ovarian capsule without vasculolymphatic invasion.

Surgery was performed to complete the staging: pT3a2N0M0 (stage IIIA2 FIGO 2014). Cytoreduction was optimal.

The patient received adjuvant chemotherapy treatment according to carboplatin-paclitaxel scheme, 6 cycles. In the first radiological re-evaluation (disease-free interval, ILE <6 months) peritoneal recurrence was observed with perihedral (Morrison and subphrenic capsule) and peritoneal implants. We administrated liposomal doxorubicin, 4 cycles, with again progression as peritoneal carcinomatosis. We started Bevacizumab-Paclitaxel, giving 4 cycles, with a decrease in the number and size of most peritoneal implants. She continued with the same scheme for 6 months, maintaining partial response. It is necessary to emphasize that our patient did not present CA 125 marker elevation at any time in the evolution.

In the multidisciplinary committee, it was decided to perform cytoreductive surgery with PCI 13 (peritonectomy of the right diaphragm, omentectomy, exeresis of 2 lesions of 2 cm and one of 6 cm in left Morrison-paravertebral capsule, 1 cm lesion in parietal peritoneum, various implants <1 cm in the small intestine and a right pelvic lesion of 5 cm). Surprisingly, the new morphological and
immunohistochemical pathological study of the surgical specimens was found to be associated with a peritoneal involvement by a papillary carcinoma of thyroid tissue (struma ovarii). Positivity was observed for TTF-1 (> 70%), PAX8 (> 90%) and thyroglobulin (2%) and absence of p53 expression in all samples (Figure 1).

**Figure 1:** (left-right, up-down) 1. Ovarian neoplasm glandular pattern; 2. Columnar epithelium; 3. Relapse with papillary pattern; 4. Classic pattern of papillary thyroid carcinoma.

Total thyroidectomy was performed, without synchronous thyroid carcinoma findings, and a dose with 200 mCi of I131 was administrated. The posterior body scan showed a cervical deposit in relation to the thyroid remnant. Treatment with levothyroxine was indicated to keep TSH levels suppressed and the study was repeated at six months, having disappeared thyroid uptake. In our patient, antithyroglobulin antibodies were positive, which made it impossible to monitor and evaluate the thyroglobulin response. One year after debulking surgery, a tumor recurrence with liver metastases and peritoneal implants was detected by TC scan. A new ablative dose of 200 mCi of I131 was administered, with a subsequent gamma scan without clear pathological uptake (Figure 2).

In view of the refractoriness to radioactive iodine, we decided to treat with lenvatinib 20mg/day, with good clinical tolerance and acceptable toxicity (weight loss due to hyporexia, mild mucositis and hypertension). We saw partial response after 3 months of treatment so we keep same administration and dosage (Figure 3).

**Figure 2:** Left: Pathological uptake at the moment of progression. Right: Non pathological uptake.

A few months later the patient came to the emergency room relating severe abdominal pain and showing septic symptoms. The diagnosis was intestinal perforation and a possible mesenteric ischemia, with no evidence of associated tumor progression in the performed TC scan. Given the poor clinical situation of the patient, surgical intervention was ruled out. Her decease finally occurred,

**Figure 3:** Tumor response after last treatment with lenvatinib.
3 years after the initial diagnosis of the ovarian neoplasia.

**Discussion**

Struma ovarii (SO) is a rare variation of monodermal teratoma, whose composition of mature thyroid tissue is more than 50 percent of the overall tissue. Malignant transformation of SO is reported in < 5% of all cases and metastases are uncommon, occurring in 5-20% of cases, mostly contained within the abdomen. They are usually found in 5th-6th decade of life. In most cases the tumor is unilateral (94%), and apparently involves the left ovary more commonly than the right one [1].

It is a tumor difficult to diagnose on clinical basis and imaging, and just a few cases are published in the literature. Clinical presentation is nonspecific, but similar to other ovarian tumors. However, incidental discovery during the performance of pelvic imaging or surgery occurs in more than 50% of cases [2,3].

The diagnosis of SO is not always exhaustive and it can be a challenge to recognize the morphology of the thyroid tissue architecturally and cytologically. In the present case, the morphology in the initial biopsy corresponded to the columnar variant of papillary carcinoma. This variant is infrequent in normal thyroid tissue and ovarian findings cause diagnostic problems.

In our case, the tumor was in an advanced stage and lacking in both teratoma residues and recognizable differentiation of thyroid tissue, as classic characteristics of typical thyroid gland carcinomas. The columnar variant, which was the exclusive pattern of the initial biopsy, as mentioned in the fourth edition of the WHO Classification of Endocrine Organ Tumors, imitates endometrioid adenocarcinoma. This variant is infrequent in normal thyroid tissue and ovarian findings cause diagnostic problems.

Differential diagnosis includes other ovarian lesions such as endometrioid or mucinous adenocarcinoma, Sertoli-Leydig cell tumors or metastatic microacinar carcinomas. Immunohistochemical staining for thyroglobulin and TTF-1 are helpful for confirming the presence of differentiated thyroid-type tissue. Also serum thyroglobulin can be used as a valuable tumor marker for monitoring both SO and thyroid cancer, even indicating metastatic disease when level is high [5].

Due to its rarity, there is no consensus on stratifying risk or establishing optimal treatment for malignant SO. After the second surgery we were facing a metastatic scenario of malignant SO, in which many authors suggest the same management as differentiated thyroid cancer [6]. According to this, we performed surgical removal of the tumor as the initial step, followed by prophylactic total thyroidectomy (eliminating all possibilities of hidden thyroid primary malignancy). After we gave radiotherapy treatment with radio-iodine (131I) in order to minimize recurrence risk. A radiiodine scan performed before and after the treatment allows detecting additional areas of metastases with active thyroid function.

An interesting fact in our case is the absence of uptake in the post-131I body scan at the time of peritoneal and hepatic recurrence showed by PET-TC one year after surgery, without having observed a poorly differentiated component in the pathological exam. 131I is a teragnostic agent that allows us to identify a molecular target on which to act in a therapeutical way. The presence of differentiated thyroid cells is necessary for the effective treatment with iodine of thyroid cancer. However, there are patients who develop metastases losing the ability to capture iodine and become refractory to treatment. BRAF V600E mutation found in our patient is an example of possible causes of resistance to radioiodine [7].

In fact, the content of thyroid tissue in the tumor doesn't correspond to the symptoms of hyperthyroidism. These symptoms are observed only in 5-8% of cases, with unknown pathophysiology. We have found two main theories to connect hyperthyroidism and SO: the capacity of the ovarian malignant tissue of producing thyroid hormone, having radioiodine activity in metastatic locations and not in cervical area; and the coexistence of Grave's disease and SO, when TSH-antibodies are present due to ectopic production. For us this resulted a problem, because we couldn't use thyroglobulin for monitoring, due to the presence of these antibodies.

In case of progressive distant relapse refractory to iodine 131 treatment [8], it should be treated as a thyroid carcinoma with tyrosine kinase inhibitors. These drugs can stabilize progressive metastatic
disease, what has changed the standard approach of these patients. Lenvatinib is a novel potent multikinase inhibitor that selectively blocks the kinase activity of vascular endothelium, RET and fibroblast growth factors receptors. It is approved for the treatment of refractory differentiated thyroid cancer based on results of a phase III trial (SELECT) [9]. This study showed that treatment with lenvatinib was associated with the improvement of progression-free survival and response rates (64.8% vs. 1.5% compared to placebo).

However, as many adverse effects of lenvatinib have been reported, dose reduction is common. The most frequent are hypertension, diarrhea, proteinuria and hyporexia. Dosage levels are 24 mg, 20 mg, or 14 mg once per day. In our case, facing a pre-multi treated patient, we started with a “first reduction dosage” of 20 mg per day. However, a rare side effect as a gastrointestinal perforation caused finally our patient’s death, but having partial tumoral response while receiving this treatment [10].

The risk of gastrointestinal perforation with other anti-angiogenic treatments like bevacizumab is well known. In metastatic ovarian cancer different factors can be involved in this complication: necrosis of malignant ovarian cells infiltrating the bowel, and increased pressure due to abdominal carcinomatosis, or micro-perforations of little adhesions in vulnerable areas of the bowel. These underlying mechanisms and risk factors might account for other anti-angiogenic TKI therapies as well. Actually, we have found in the literature some case reports.

Retrospectively, in our case certain warning signs such as the free interval <6 months after adjuvant chemotherapy, the lack of response to anthracyclines and a normal CA 125 value, should have made us suspect that it was not an epithelial carcinoma of ovary. On the other hand, the tumor response obtained with the bevacizumab-paclitaxel regimen, which allowed us a second cytoreduction surgery, is related to the antiangiogenic effect of this combination. It is known the efficacy of the antiangiogenic activity by the inhibition of vascular endothelial growth factor receptor (VEGFR), and the effect of other drugs (thalidomide or lenalidomide) in metastatic thyroid cancer [11-13].

Conclusion

We do believe that our case raises some interesting considerations. First of all, as the introduction to the fourth edition of the WHO Endocrine Organ Tumor Classification published in 2017 reminds us, there is no more difficult classification than that of thyroid carcinomas. We therefore believe that our case warns of the difficulty that could be associated with this diagnosis and urges the need to optimize its recognition in extra-thyroidal location. Second, it was initially treated with chemotherapy focusing on a ovarian cancer, and it was only after bevacizumab treatment when we obtained a partial response, so we could finally set up surgery. This is why we think a further investigation about this antiangiogenic drug is important. Third, the 131I scan should include PET/TC imaging, which can demonstrate additional areas of metastases missed on planar imaging, allows for accurate anatomic correlation of metastatic lesions, and can have impact in treatment decisions. Fourth, subsequent management was carried out in an adequate manner according to refractory 131I thyroid cancer treatment guidelines, with a good response of the tumour to levantinib. However, drug toxicity was sadly the cause of the death of our patient.

We need more studies to determine the best management of this neoplasms and dose adjustment, and we consider that sharing our experience can definitely help.

References

1. Roth LM, Miller AW, Talerman A. Typical thyroid-type carcinoma arising in struma ovarii: A report of 4 cases and review of the literature. Int J Gynecol Pathol. 2008;27(4):496-506. Doi: https://doi.org/10.1097/PGP.0b013e31816a74c6
2. Goffredo P, Sawka AM, Pura J, et al. Malignant struma ovarii: A population-level analysis of a large series of 68 patients. Thyroid. 2015;25(2):211-215. Doi: https://doi.org/10.1089/thy.2014.0328
3. Shaco-Levy R, Bean SM, Bentley RC, et al. Natural history of biologically malignant struma ovarii: Analysis of 27 cases with extranodal spread. Int J Gynecol Pathol. 2010;29(3):212-227. Doi: https://doi.org/10.1097/PGP.0b013e3181bfb133
4. Zhu Y, Wang C, Zhang GN, et al. Papillary thyroid cancer located in malignant struma ovarii with omentum metastasis: A case report and review of the literature. World J Surg Oncol. 2016;14(1). Doi: https://doi.org/10.1186/s12957-016-0776-x
5. Leite IT, Cunha TM, Figueiredo JP, et al. Papillary carcinoma arising in struma ovarii versus ovarian metastasis from primary thyroid carcinoma: A case report and review of the literature. J Radiol Case Rep. 2013;7(10):24-33. Doi: https://doi.org/10.3941/jrcr.
6. Luo J, Xie C, Li Z. Treatment for malignant struma ovarii in the eyes of thyroid surgeons: A case report and study of Chinese cases reported in the literature. *Medicine*. 2014;93(26):e147. Doi: https://doi.org/10.1097/MD.0000000000000147

7. Huillard O, Tenenbaum F, Clerc J, et al. Restoring radioiodine uptake in BRAF V600E-mutated papillary thyroid cancer. *J Endocr Soc*. 2017;1(4):285-287. Doi: https://doi.org/10.1210/js.2016-1114

8. DeSimone CP, Lele SM, Modesitt SC. Malignant struma ovarii: A case report and analysis of cases reported in the literature with focus on survival and I131 therapy. *Gynecol Oncol*. 2003;89(3):543-548. https://www.ncbi.nlm.nih.gov/pubmed/12798728

9. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med*. 2015;372(7):621-630. Doi: https://doi.org/10.1056/NEJMoa1406470

10. Date E, Okamoto K, Fumita S, et al. Gastrointestinal perforation related to lenvatinib, an anti-angiogenic inhibitor that targets multiple receptor tyrosine kinases, in a patient with metastatic thyroid cancer. *Invest New Drugs*. 2018;36(2):350-353. Doi: https://doi.org/10.1007/s10637-017-0522-4

11. Ukita M, Nakai H, Kotani Y, et al. Long-term survival in metastatic malignant struma ovarii treated with oral chemotherapy: A case report. *Oncol Lett*. 2014;8(6):2458-2462. Doi: https://doi.org/10.3892/ol.2014.2587

12. Aguilera BG, Vázquez RG, Herguido NG, et al. The lack of consensus in management of malignant struma ovarii. *Gynecol Endocrinol*. 2015;31(4):258-259. Doi: https://doi.org/10.3109/09513590.2014.995616

13. Oudoux A, Leblanc E, Beaujot J, et al. Treatment and follow-up of malignant struma ovarii: Regarding two cases. *Gynecol Oncol Rep*. 2016;17:56-59. Doi: https://doi.org/10.1016/j.gore.2016.05.014

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