International Cancer Conference Journal (2022) 11:270–274
https://doi.org/10.1007/s13691-022-00558-7

CASE REPORT

Post-pubertal ovarian yolk sac tumor with unusual follicular growth pattern, simulating struma ovarii

Dorsa Ghasemi[1] · **Fatemeh Nili**[1]

Received: 2 February 2022 / Accepted: 24 May 2022 / Published online: 15 June 2022

Abstract

Yolk sac tumors (YST), formerly known as endodermal sinus tumors, are uncommon ovarian neoplasms. They are most common in the second and third decades of life and are rare in women older than 39 years of age. YST exhibit various histologic patterns. Microfollicular pattern resembling thyroid tissue has not been reported. We introduce here a case of yolk sac tumor in a 39 y/o female, presented with pelvic masses and high level of serum Alpha-fetoprotein (Alpha Fetoprotein) (> 1000 IU/ml). The patient underwent left salpingo-oophorectomy. On microscopic study, morphologic findings demonstrated a neoplasm composed of follicular structures with eosinophilic intraluminal content, resembling struma ovarii on low-power field. On Immunohistochemistry study, the tumor cells were positive for Alpha-fetoprotein and Glypican-3. Epithelial Membrane Antigen (EMA), Thyroglobin (TG), Thyroid transcription Factor-1 (TTF1) and sex-cord stromal markers were negative. This case introduces a new histomorphologic pattern of yolk sac tumor in a middle-aged woman. It is important to know that yolk sac tumor can exhibit various histological appearances. Regarding patient's clinical and laboratory findings, this differential diagnosis should be kept in mind for proper diagnosis of similar cases.

Keywords Ovary · Yolk sac tumor · Microfollicular · Struma ovarii

Abbreviations

YST	Yolk sac tumor
AFP	Alpha-fetoprotein
IHC	Immunohistochemistry
EMA	Epithelial Membrane Antigen
TG	Thyroglobin
TTF1	Thyroid transcription Factor-1
CK	Cytokeratin
hCG	Human chorionic gonadotropin
PLAP	Placental alkaline phosphatase
SALL4	Spalt-like 4

Introduction

Germ cell tumors constitute 20% of all ovarian neoplasms. Germ cell tumors account for 20% of all ovarian cancers in western countries [1]. Yolk sac tumors (YST), formerly known as endodermal sinus tumors, are uncommon ovarian neoplasms. They are common in the second and third decades of life, most with a high level of alpha fetoprotein [2]. Yolk sac tumors exhibit various histologic patterns. The endodermal sinus or pseudopapillary pattern is the most distinctive type [3]. However, solid, alveolar-glandular, polyvesicular vitelline, myxomatous, papillary and microcystic patterns are also seen [3]. In addition to these well-defined patterns, further variant with hepatoid differentiation, resembling hepatocellular carcinoma, is also noted [3]. These tumors are usually pure, but may be part of a mixed germ cell tumor, usually with dysgerminoma. In older patients, there is rarely an association with surface epithelial tumors, usually endometrioid carcinoma [2]. Herein, we present a case of middle-aged yolk sac tumor with a different histopathologic feature composed of tubular and follicular structures containing eosinophilic material, resembling struma ovarii.

✉ Fatemeh Nili
f-nili@sina.tums.ac.ir

[1] Department of Pathology, Cancer Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, End of Keshavarz Ave, Tehran, Iran

Case presentation

A 39-year-old female, G2L2 presented with abdominal pain and pelvic masses. On physical examination, vital signs were stable. A left-side mass in left adnexa was identified. Cervix and vagina were unremarkable. On radiologic abdominopelvic MRI study which was performed before surgery, three T1 low and T2 intermediate signal masses measuring 64 × 34 mm, 48 × 33 mm and 33 × 21 mm in left side of pelvic cavity were seen, and in the right side, a 22 × 18 mm mass lesion was identified. Serum levels of tumor markers were also measured. The results showed increase for Alpha-fetoprotein (> 1000 IU/ml) and CA125 (44 IU/ml), while hormone epididymis protein 4 (15.3 pmol/L) and ROMA score (0.511%) were in normal limits.

The patient underwent left salpingo-oophorectomy without frozen section during surgery. Macroscopic examination of the specimen revealed an encapsulated lobulated mass, measuring 9 × 4.5 × 4.5 cm, with solid tan-yellowish cut surface. On microscopic study, morphologic findings demonstrated a neoplasm resembling struma ovarii on low-power examination, whereas at higher magnification, the tumoral growth was composed of malignant pleomorphic cells with abundant eosinophilic cytoplasm and occasional nuclear pseudo-inclusions. The tumoral cells were arranged in follicular structures containing homogeneous eosinophilic material, occasional solid sheets and some tubular structures in the background of myxoid stroma (Figs. 1, 2). Aggregates of luteinized stromal cells were also scattered between the follicular structures (Fig. 2). Typical features of yolk

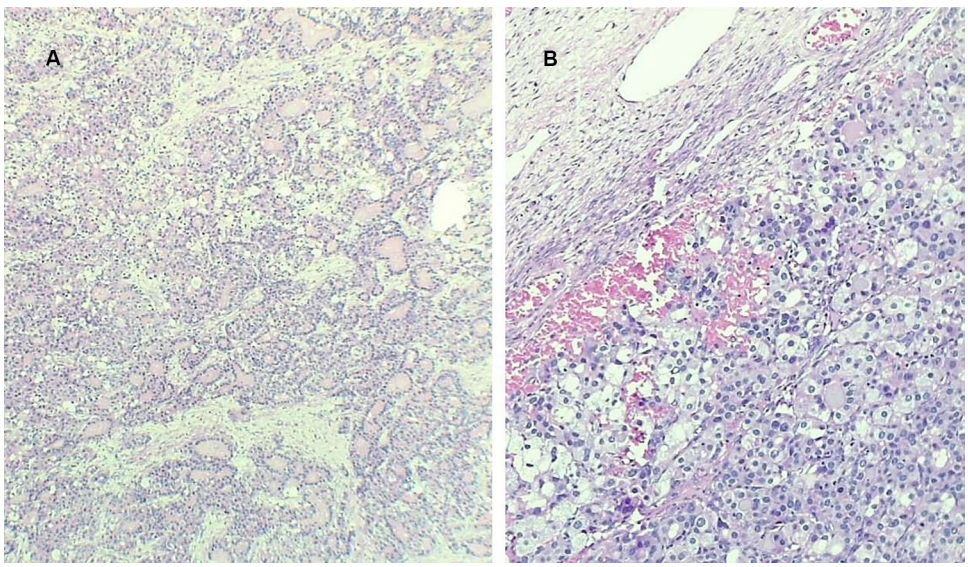

Fig. 1 **a** Microscopic examination shows follicular structures containing eosinophilic intraluminal material in an edematous stroma (40×). **b** In some areas, solid sheets of neoplastic cells are seen (100×)

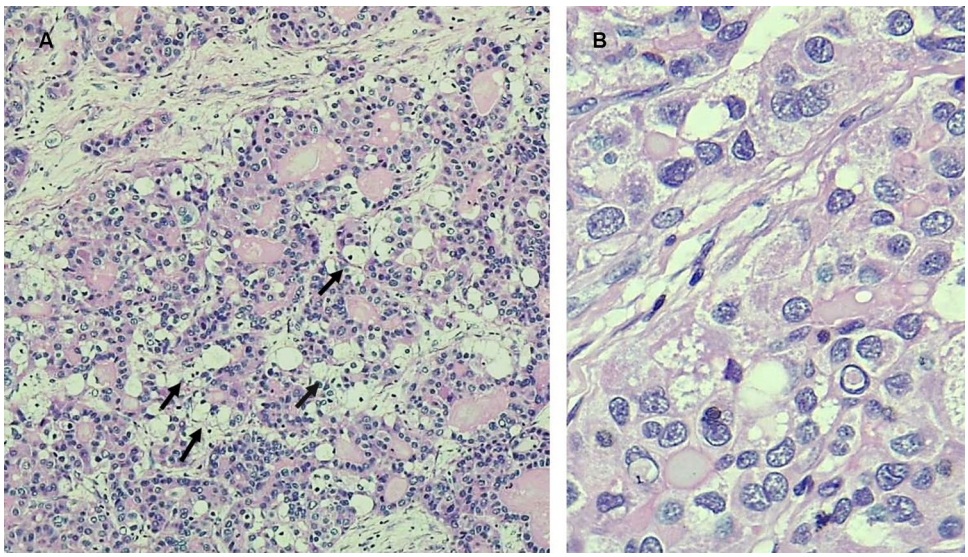

Fig. 2 **a** There are follicular structures lined by cuboidal cells with abundant cytoplasm (100×). There are scattered clear cells between the follicular structures (black arrows), and **b** neoplastic cell show eosinophilic cytoplasm, pleomorphic nuclei and eosinophilic pseudo-inclusions (400×)

sac tumor, or other germ cell tumors were not identified on extensive sampling.

On immunohistochemistry study, thyroid markers including PAX8, thyroglobulin and TTF1 were negative. Inhibin and Calretinin as well as Chromogranin and Synaptophysin showed negative staining. EMA, CA125, PLAP, C-kit and melan-A were also negative. The tumor cells show positive reaction with Glypican-3, SALL4, AFP and focal staining with CK7 and CK19. Ki67 proliferation index was about 20% (Fig. 3a–h). Considering elevated patient's serum level of AFP and IHC findings, yolk sac tumor was suggested as the final diagnosis. Because of COVID-19 pandemic, the patient refused hospitalization for complete surgery. Six cycles of chemotherapy (Bleomycin, Etoposide, Platinum regimen) were done. Now, she is disease-free after 2 year follow-up.

Discussion

Yolk sac tumor is a primitive germ cell tumor with a variety of distinctive patterns that may also exhibit differentiation into epidermal structures ranging from the primitive gut and mesenchyme to the derivatives of extra-embryonal (such as secondary yolk sac and allantois) and embryonal somatic tissues including intestine, liver and mesenchyme [3].

YST is generally a neoplasm of children and young adults [1]. It is very rare in women older than 39 years [4]. Isolated ovarian examples have been found in elderly patients associated with ovarian epithelial–stromal tumors [3]. Conter et al. [5] studied the prognostic significance of "age" in YSTs. There was no obvious correlation between age and probability of events or deaths.

The most common presenting complaints of YSTs are abdominal pain, enlargement or mass. About 10% of patients have acute abdominal symptoms as a result of rupture or torsion of the tumor [4]. Raised serum levels of AFP (> 20 ng/mL) are routinely found which is useful, although not pathognomonic serologic marker for the presence of YST elements in a primary ovarian neoplasm, its metastases and/or recurrences [3].

YSTs are large encapsulated with a mean diameter of 15 cm and usually have a smooth external surface. In cross-section, they characteristically have mixed solid and cystic components. Capsular tears have been described in 27% of cases. In a study by Robert H Young et al., yolk sac tumor and its association with dermoid cyst was identified in 20 out of 150 cases [6].

Microscopically, the tumor cells have primitive appearance with wide spectrum of histologic patterns [7]. Interestingly, there are some evidences that YSTs displaying a diversity of histologic patterns behave less aggressively

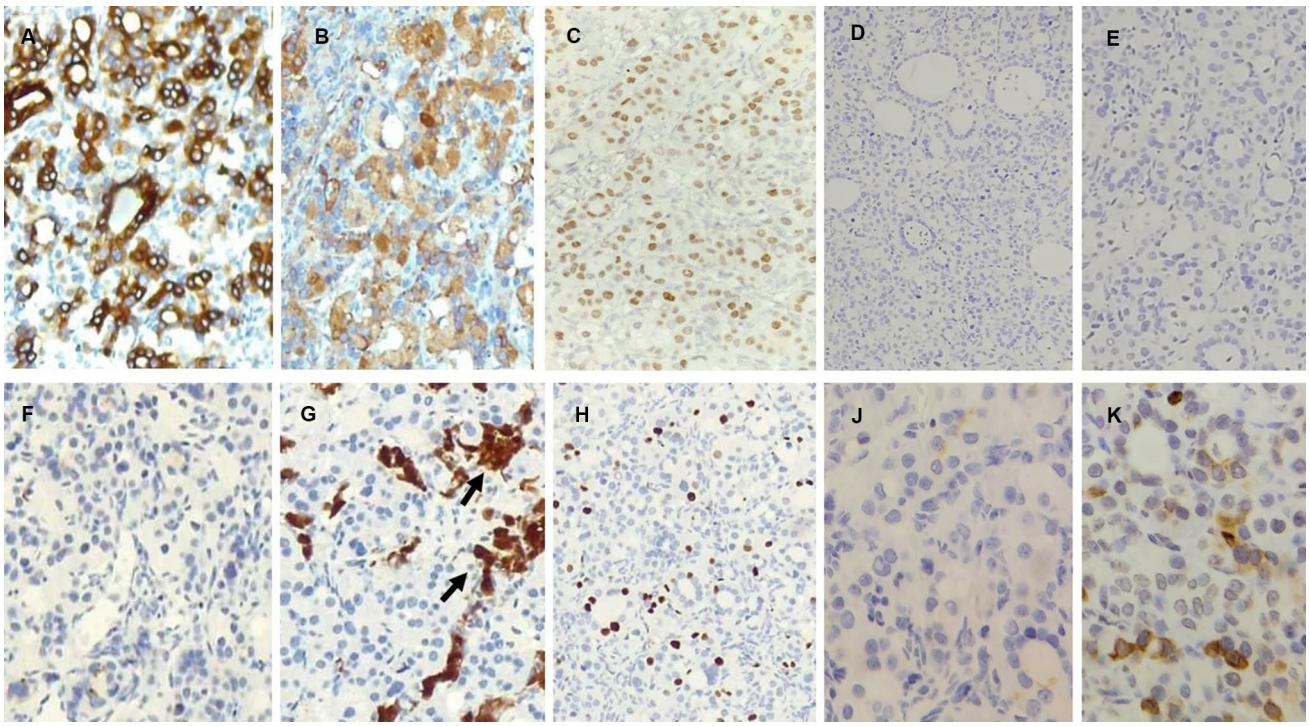

Fig. 3 IHC study shows positive reaction with Glypican-3 (**a**), Alpha-fetoprotein (**b**), SALL4 (**c**) and negative staining PAX8 (**d**), TTF1 (**e**) and TG (**f**). The tumor cells are negative for calretinin/inhibin, but clusters of stromal cells are highlighted (arrows) (**g**). H: ki67 shows about 20% proliferative activity. EMA is negative (**j**). CK7 shows focal staining in some tumor cells (**k**)

than those exhibiting only one or two of histologic patterns [3]. Reticular pattern is the most common architectural pattern characterized by a loose meshwork of spaces lined by primitive tumor cells with large hyperchromatic or vesicular nuclei and prominent nucleoli. Cytoplasm is clear because of glycogen and occasionally lipid content. Focal areas of glandular structures and alveolar spaces can be seen with reticular pattern [3]. The cystic spaces may contain pale proteinaceous PAS-positive material and round eosinophilic hyaline droplets [3]. The characteristic histologic feature of YST is a glomerulus-like structure composed of a central blood vessel enveloped by tumor cells within a space (Schiller-Duval body) [8]. Other histologic patterns that may be observed in YSTs are endodermal sinus, solid, polyvesicular vitelline, myxomatous, papillary, hepatoid and glandular [2]. To the best of knowledge, follicular pattern resembling thyroid tissue and stroma ovarii has not been previously described in the English literature.

The most important immunohistochemical finding in YST is positive staining for AFP. Positive staining is detected in tumor cell cytoplasm, secretory material within cysts and glands and some hyaline bodies. Diffuse strong nuclear staining for the stem cell factor, SALL4, is present in most YSTs. While OCT-4 is positive in dysgerminoma and embryonal carcinoma, this marker shows no immunoreactivity in YST. Glypican-3 stains the cytoplasm of YST cells in nearly all cases. IHC stains for α1-antitrypsine and placental alkaline phosphatase are positive in YST cells. YST is CK positive, but it does not stain for EMA. Immunostains for hCG (human chorionic gonadotropin) are negative except in the rare YSTs that contain syncytiotrophoblastic giant cells [4]. In our case, the first diagnosis based on histopathologic features was struma ovarii with possibility of malignant transformation to papillary thyroid carcinoma because of nuclear features of the tumor cells. Presence of myxoid stroma, high nuclear atypia and negative immune reaction with thyroid markers ruled out its possibility. The other differential diagnosis considering follicular pattern and presence of tumor cells with deeply eosinophilic or foamy cytoplasm was sex-cord stromal tumors such as adult type granulosa or steroid cell tumors. The possibility of them was excluded due to negative immune reaction for inhibin and calretinin as well as melan-A. Neuroendocrine tumors such as stromal carcinoid were also excluded immunohistochemically. Due to absence of immunoreactivity for EMA, CA125, ER, PR and PAX8, Mullerian epithelial nature of the tumor and possibility of clear cell carcinoma, hepatoid carcinoma or endometrioid carcinoma was left out. The possibility of dysgerminoma (negativity for c-kit and PLAP) and metastatic melanoma (negativity for Melan-A) were also eliminated.

Struma ovarii is the expression of the dominant growth of thyroid tissue in a teratoma. The thyroid nature of the lesion has been fully documented by biologic and immunohistochemical studies for TTF1 and thyroglobulin [1]. Most cases occur in the reproductive years with a peak in the early 40 s [3]. This neoplasm may show any of the pathologic changes seen in a normally placed gland, including diffuse or nodular hyperplasia, thyroiditis, papillary carcinoma, follicular carcinoma and malignant lymphoma [1]. In a study by Seung-chul Yoo et al., only two patients out of thirty-four cases of struma ovarii were confirmed with malignant tumor [9]. More frequently than expected, struma ovarii is seen associated with benign Brenner tumors [3].

On the other hand, YST can be a component of a mixed germ cell tumor usually dysgerminoma, immature teratoma and mature teratoma. YSTs can also arise from epithelial tumors, mainly Mullerian adenocarcinoma, mostly in postmenopausal patients [10].

In 2014, Chiho Koi et al. published a case of ovarian YST in a 56 y/o female associated with a poorly differentiated endometrioid adenocarcinoma [11]. Another case of endometrial carcinoma with yolk sac tumor-like differentiation in a 28 y/o female was reported by Ji et al. [12]. In 1999, a case of stage Ia endometrioid-like YST of the ovary, misdiagnosed as a malignant struma ovarii, was described by Kommoss et al. [13] The patient was not treated with adjuvant chemotherapy and after 12 years presented with recurrence.

To summarize, yolk sac tumors have complex nomenclature and histogenesis and this stresses the fact that they are not a discrete entity, but represent a multifaceted group of neoplasms, accounting for their capacity to differentiate into various extra-embryonal and somatic cell types [14]. Their diversity of histological appearances and non-specific clinical pictures highlights the importance of acquiring a thorough knowledge of these tumors.

Conclusion

This case introduces a malignant germ cell tumor (yolk sac tumor) in a middle-aged woman with an unusual histomorphologic pattern. Therefore, it is essential to know that yolk sac tumor can exhibit various histological appearances. Regarding patient's clinical and laboratory findings, this differential diagnosis should be kept in mind for proper diagnosis of similar cases.

Declarations

Conflict of interests 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.

Patient consent statement The patient's informations are not identifiable. Formal constant was taken.

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