Case Report

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Double Trouble: A case of synchronous high-grade serous carcinoma of the fallopian tube and borderline mucinous tumor of the ovary

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Abstract:

A 55-year-old, Gravida 2 Para 2 (2002), presented with postmenopausal vaginal bleeding. Workups pointed toward ovarian malignancy with distant metastasis (pleural effusion). Exploratory laparotomy, bilateral salpingo-oophorectomy, surgical staging, and appendectomy were performed. On histopathological examination, synchronous high-grade serous carcinoma of the right fallopian tube and borderline mucinous tumor of the left ovary were diagnosed. Primary fallopian tube carcinomas are very uncommon, while synchronous tumors of the female genital tract are extremely rare. Furthermore, there is a paucity of literature discussing the occurrence of synchronous primary malignancies arising from the fallopian tube and the ovary. It is crucial to differentiate primary malignancies from metastatic cancers to determine accurate staging and prognosis, as well as to assign appropriate treatment strategies. Immunohistochemistry and molecular testing play vital roles as adjunctive diagnostic tools to histologic examination in determining the origins of these tumors and distinguishing primary tumors from metastasis.

Keywords:

Borderline mucinous tumor of the ovary, fallopian tube carcinoma, high-grade serous carcinoma, synchronous primary malignancies

Introduction

Primary fallopian tube cancer (FTC) is rare, comprising 0.2% of malignancies in women in the United States.[1] The main risk factor has been identified in women who are positive for the *BRCA1 and BRCA2* tumor suppressor gene inherited mutations. Other associated risk factors include a history of infertility, low parity, early menarche, and late menopause. Of primary fallopian tube carcinomas, one or more synchronous independent tumors of different sites and histology in the same individual may arise. Synchronous primary tumors were found to account for 0.7%–1.8% of all gynecological neoplasms.[2]

Borderline ovarian tumors, also known as tumors of low malignant potential, on the other hand, were found to comprise 25% of ovarian tumors and up to 10% of ovarian malignancies.[2] These tumors most often confer a favorable prognosis, regardless of the stage. Borderline tumors are usually classified under two histologic types – serous and mucinous. Mucinous borderline tumors and carcinomas are often found in patients in the 4th to 7th decade of life. Molecular studies have shown *KRAS* mutations and *HER-2* gene amplifications in 18%–40% of cases.

Synchronous tumors have been described by Singh accounting for 1%–2% of gynecological cancers, defined as having two or more simultaneous independent tumors of the female reproductive tract. The most common combination for such phenomena involves endometrial and

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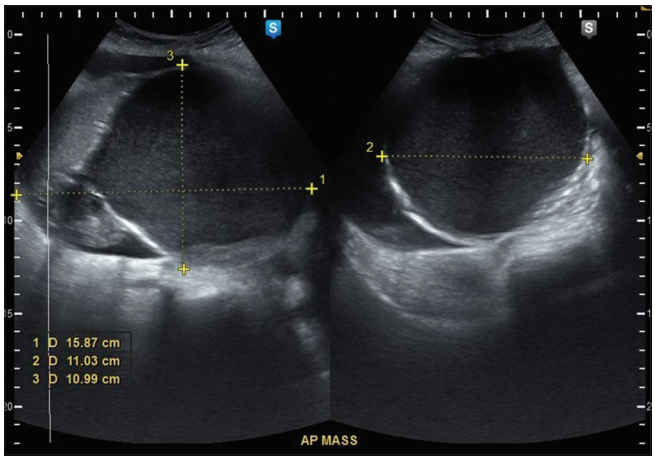

Figure 1: Transvaginal ultrasound images, with anteroposterior view (left) and transverse view, revealing an abdominopelvic mass with low-level echo fluid, measuring 15.9 cm × 11.0 cm × 11.0 cm

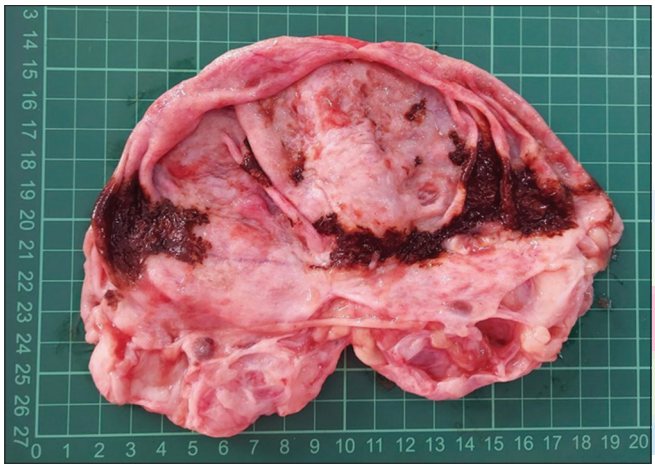

Figure 3: Left ovary, cut section

ovarian malignancies accounting for 50%–70% of synchronous tumors.[3] From an exhaustive literature review, data and cases of simultaneous primary ovarian cancer and borderline mucinous tumor arising independently have yet to be described in case reports globally.

This report aims to discuss a case of a 55-year-old postmenopausal woman with synchronous primary tumors of the fallopian tube and the ovary and the corresponding diagnostic and management strategies and challenges for such uncommon cases.

Case Report

This is a case of a 55-year-old, Gravida 2 Para 2 (2002), who was admitted for the difficulty of breathing. The patient is a known hypertensive since 2019 which was well controlled with antihypertensive medications. She had no prior history of cardiopulmonary, liver, kidney, or gynecologic disease. She had an unremarkable

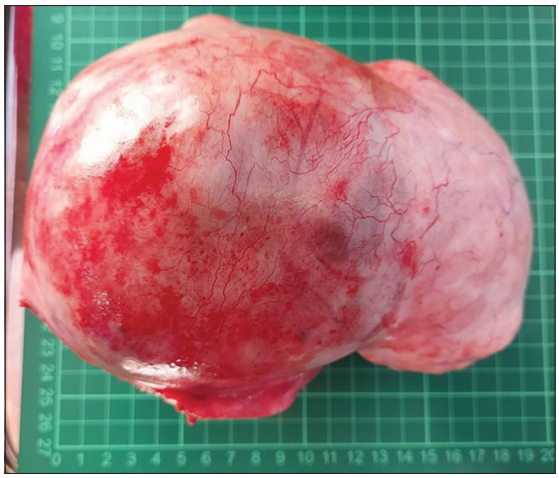

Figure 2: Left ovary

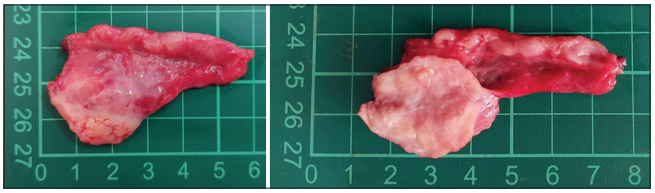

Figure 4: (a) (Left) and (b) (right) – Intact and cut right ovary with fallopian tubes, respectively

family medical, personal, social, menstrual, and sexual history.

The patient's present illness started 5 months before the consult when she reported gradually progressive exertional dyspnea. It was accompanied by gradual and painless abdominal enlargement with associated postmenopausal intermittent vaginal bleeding which lasted for 3 days consuming two regular sanitary pads per day. There was no associated abdominal pain, abnormal vaginal discharge, as well as gastrointestinal or urinary symptoms. Due to her progressing dyspnea, she consulted at the emergency room of a local hospital. The assessment was abdominopelvic mass of ovarian etiology. There was also pleural effusion on the left for which she underwent tube thoracostomy. She was discharged improved with the plan for further work up of the abdominopelvic mass.

On the day of On the day of re-admission, 14 days from the discharge, she had recurrence of dyspnea and orthopnea. Due to her progressing difficulty of breathing, she was advised admission.

Upon admission, the patient was assessed to have a patent airway and speaks in sentences. She was tachypneic at 22 cycles per minute and had decreased breath sounds upon auscultation of the bilateral lower lung fields. She had oxygen desaturations as low as 92% on room air by oximetry which was relieved with oxygen

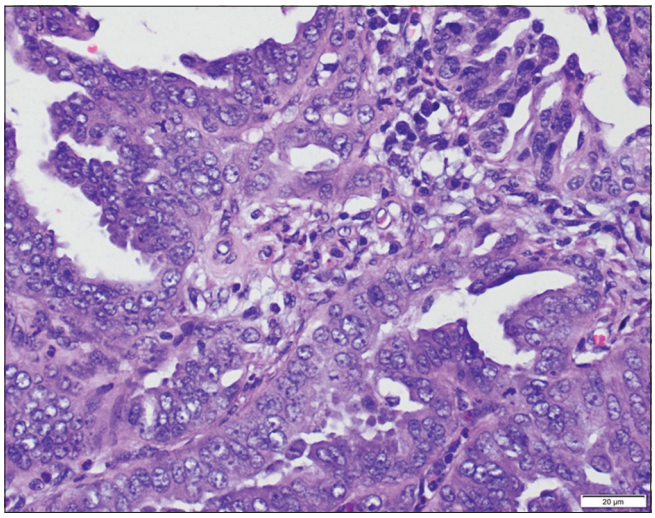

Figure 5: Right fallopian tube (×400), stained with hematoxylin and eosin, showing high-grade serous carcinoma, with the presence of mitotic figures, cellular atypia, increased nucleus-to-cell body ratio, and hyperchromatic nucleoli

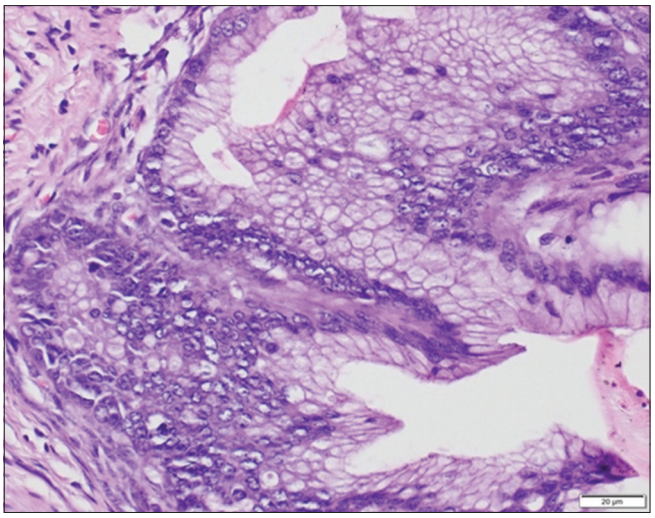

Figure 6: Bladder implant (×100), stained with hematoxylin and eosin, showing high-grade serous carcinoma with similar histomorphology as the right fallopian tube tumor

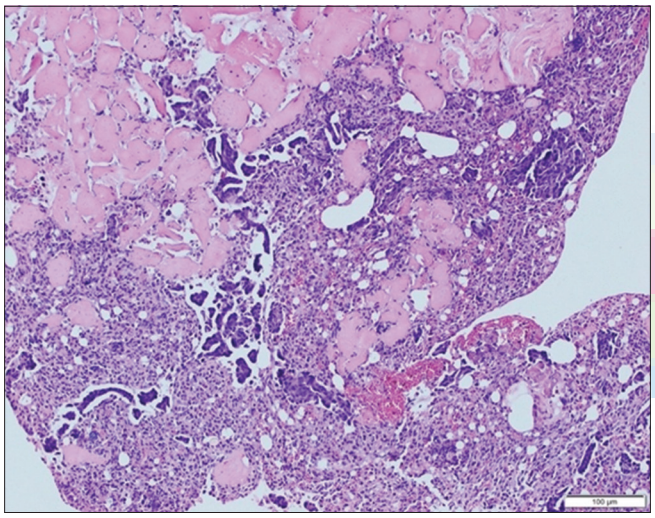

Figure 7: Left ovary (×400), showing mucinous borderline tumor, with the presence of cellular atypia, increased nucleus-to-cell body ratio, and hyperchromatic nucleoli

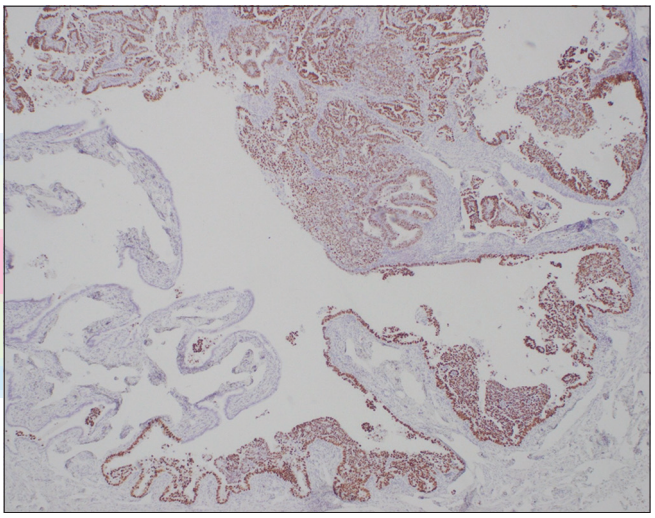

Figure 8: Right fallopian tube (×40), stained with p53, showing diffusely staining cells confirming complete p53 mutation or absence with associated serous tubal intraepithelial carcinoma seen as staining of single layer of epithelium

supplementation by face mask. She was tachycardic at 136 beats/min. Her blood pressure was 135/85 mm mercury (mmHg). She had a chest tube in place on her left hemithorax, which drained no output. She was 150 cm tall and 41 kg in weight.

Her abdomen was distended, nontender, with a girth measuring 97 centimeters with an absent fluid wave. There was a palpable solid mass measuring 18 cm × 15 cm occupying the anterior hypogastric area, fixed to the left abdominal sidewall. She had normal external genitalia, smooth, parous vagina, with a smooth cervix measuring 2 cm × 2 cm. The uterine corpus was small. Bilateral parametria were smooth and pliable. There was no blood per examining finger.

Transvaginal ultrasound [Figure 1] showed a normal-sized uterus and thin endometrium. An abdominal mass was found, with consideration of a right ovarian new growth, measuring 16.0 cm × 11.0 cm × 11.0 cm, with mixed echo fluid with fluid-fluid leveling and echogenic debris within. There were no solid areas or papillary excrescences seen. The septum and capsule measured 0.2 cm and 0.3 cm, respectively. The impression was abdominopelvic mass, benign by the subjective assessment, with a 13.2% risk of malignancy by the International Ovarian Tumor Association (IOTA) (cutoff: 10%) and a 1.5% relative risk of the borderline tumor by IOTA ADNEX model.

Serum tumor markers extracted upon admission revealed elevated cancer antigen 125 at 661.9 international units

per milliliter (U/mL; reference value [*n*] <35 U/mL) and CA 19-9 at 92.08 U/mL (*n* <37 U/mL). Serum alpha-fetoprotein, carcinoembryonic antigen, and beta-human chorionic gonadotropin were all within normal values of their respective laboratory reference standards.

A computed tomography scan of the chest and abdomen was also done, revealing a right adnexal mass, measuring 17.0 cm × 11.6 cm × 11.0 cm, which was likely ovarian in origin. There was also a finding of moderate ascites and bilateral pleural effusion.

She was assessed to have ovarian new growth, probably malignant, community-acquired pneumonia–moderate risk, pericardial effusion, bilateral exudative pleural effusion, and left-sided empyema thoracis. She underwent left tube thoracostomy reinsertion, draining 800 mL of serosanguinous fluid. Pleural fluid cytology was found to be negative for malignancy and was assessed to be infectious in nature.

The patient's pneumonia and exudative pleural effusion were treated with intravenous antibiotics, and the pleural effusion was monitored and drained using a Jackson-Pratt (JP) drain. She also underwent nutritional upbuilding. She was subsequently referred to the pulmonology, cardiology, and infectious diseases specialties.

On her 29th day of admission, she underwent right intrajugular catheter insertion, preoperative cystoscopy and bilateral ureteral double-J stenting, exploratory laparotomy, evacuation of ascites, bilateral salpingo-oophorectomy, a biopsy of bladder implant, infracolic omentectomy, appendectomy, and JP drain insertion under general endotracheal anesthesia.

Operative findings include the following. There was 500 mL of cloudy straw-colored ascitic fluid. The peritoneal surfaces from the pelvis up to the subdiaphragmatic area, large intestinal serosa, small intestinal serosa, mesentery, and uterine surface were studded with subcentimeter implants. There was an implant measuring 1.0 cm × 0.5 cm × 0.5 cm on the sigmoid serosal surface. The liver, gallbladder, spleen, kidneys, and stomach were grossly normal.

The left ovary [Figure 2] was enlarged to a cystic mass measuring 18.0 cm × 11.0 cm × 10.0 cm with a smooth and intact capsule. On the cut section [Figure 3], it was multiloculated and multiseptated containing mucoid chocolate-colored fluid within. There was a solid area measuring 3.0 cm × 2.0 cm × 2.0 cm. The thickest septum measured 0.3 cm, while the thickest capsule measured 0.1 cm. The left fallopian tube measured 5.0 cm × 0.5 cm and was grossly normal.

The right ovary [Figure 4a] measured 3.0 cm × 1.5 cm × 1.5 cm, while the right fallopian tube measured 5 cm × 0.5 cm. Both were grossly normal. There was a bladder implant measuring 1.0 cm × 0.5 cm × 0.5 cm, which detached spontaneously. The omentum was friable, measuring 50.0 cm × 9.0 cm × 1.0 cm, with no gross tumor. The appendix measured 4.5 cm × 0.5 cm × 0.7 cm and was grossly normal. The uterus was small. There was minimal blood loss. Residual tumors were multiple subcentimeter tissue implants on the peritoneal surfaces from the pelvis up to the subdiaphragmatic area, large intestinal serosa, small intestinal serosa, mesentery, and uterine surface; and an implant measuring 1.0 cm × 0.5 cm × 0.5 cm on the sigmoid serosal surface. The intraoperative diagnosis was ovarian new growth, malignant, intraoperative stage IIIC.

On histopathological examination, two distinct synchronous tumors were described. First is a high-grade serous carcinoma with associated serous intraepithelial carcinoma [Figure 5], 0.4 centimeters in the greatest tumor dimension of the right fallopian tube. The left ovary, left fallopian tube, appendix, and the tissues harvested from the bladder and omentum were also found to be positive for the tumor [Figure 6]. The peritoneal fluid was also found to be positive for malignant cells as well. The right ovary was negative for the said tumor.

The second tumor was of the left ovary, a mucinous borderline tumor [Figure 7], 15 cm in greatest diameter, apart from the presence of the tumor described of the left fallopian tube.

Immunohistochemical stains were also performed [Figure 8] to confirm the diagnosis of high-grade serous carcinoma (HGSC). The results showed diffuse, moderate, nuclear staining in neoplastic cells with the Wilms tumor protein, while there was strong nuclear staining in >90% of neoplastic cells with *p53.* Staining with Ki-67 also showed a 30%–40% proliferative index in neoplastic cells. These immunohistomorphologic findings were interpreted to be supportive of an HGSC with an associated intraepithelial carcinoma.

Postoperatively, the patient had stable hemodynamic parameters, but still complained of dyspnea and had episodes of oxygen desaturations. She underwent completion of treatment of complicated pneumonia and exudative pleural effusion through IV antibiotics. She also developed acute kidney injury from multifactorial causes, which was closely managed by the nephrology service. She was discharged on the 13th day after surgery. She was followed up as an outpatient at the same institution's cancer institute. She was originally scheduled for chemotherapy with a carboplatin–paclitaxel regimen, but during the course of her follow-up, she was assessed

to have decreasing trends of glomerular filtration rate, as well as recurrent pleural effusion. The patient was then lost to follow-up and was then reported to have expired at home, 2 months postoperatively.

Discussion

Primary FTC has been historically defined to be a rare gynecologic malignancy. In 1950, Hu *et al*. proposed the conventional diagnostic criteria of FTC in gross and histopathologic features and accordingly modified by Sedlis *et al*. in 1978.[4] More recent studies have identified precursor lesions of ovarian cancer in the fallopian tube, referred to as serous tubal intraepithelial carcinoma (STIC), which are distinguished histologically from normal mucosa as dysplastic tubal cells, and adjunctively diagnosed through immunohistochemistry.

A model presented by several studies divides epithelial ovarian carcinomas into a dualistic model of carcinogenesis, named Type I and Type II.[5] Type I tumors are neoplasms of low malignant activity and are found to arise from borderline tumors. These include mucinous carcinoma, micropapillary serous carcinoma, endometrioid carcinoma, and clear cell carcinoma. On the other hand, Type II tumors present aggressively and with a high grade from inception. HGSCs are included in this subset of tumors. They present with an invasive growth pattern, high-grade nuclear atypia, and highly active mitotic activity.

In such emerging paradigms, high-grade serous ovarian carcinomas (HGSCs) have been described by several literature over the past decade to originate from carcinogenic processes from the fallopian tube as opposed to the ovary. Molecularly, STIC and HGSC are theorized to be clonally related and express identical TP53 mutations with a high frequency.[6] The precise cell and tissue of origin for HGSC are, however, contentious, and it remains to be the only epithelial cancer without a clearly defined precursor lesion.

High-grade serous carcinoma (HGSC) is the most common and is associated with the highest mortality rate among ovarian cancers. The main reason for its deadly course is its common presentation and diagnosis at such an advanced stage. Most cases have been diagnosed at Stages III and IV, of over 75% of cases seen at such stages.[7]

Central to its aggressive presentation is its distinct mechanism of dissemination, which has been typically described as direct extension or the migration of cells from the primary tumor to attach and invade adjacent organs within the peritoneal cavity. The cells arising from the ovary and fallopian tube encounter no anatomical barriers to their dissemination, hence being characterized by a pattern of metastasis that is subservient to the flow of fluid around the peritoneal cavity.[8] Among the organs within the peritoneal cavity, HGSC cells appear to have a predilection for implanting to the omentum, with at least 80% of patients with the disease presenting with omental metastases on harvested samples in surgical staging.[9]

The case reported is a rare occurrence of synchronous adnexal tumors of distinct mechanisms of carcinogenesis: A large borderline mucinous tumor of the left ovary and a subcentimeter HGSC identified in the right fallopian tube with metastasis to the left ovary, fallopian tube, appendix, bladder, and omentum. On presentation, the behavior of a malignant adnexal neoplasm with peritoneal dissemination was apparent with the clinical presentation. The culprit for the peritoneal dissemination, however, appeared to arise as a microscopic lesion from the unilateral fallopian tube, histologically distinct from the abdominal mass that was grossly appreciable.

Even more peculiar for this case is the development of a mucinous, rather than serious, borderline tumor in the background of STIC. Unlike serous borderline tumors, mucinous tumors are more often linked with its corresponding carcinoma. Studies have elucidated the malignant transformation of mucinous cystadenoma to a borderline tumor, which appears to progress to an intraepithelial carcinoma. The molecular association has also been described as an increased frequency of *KRAS* mutations at codons 12 and 13, found to be identical in mucinous cystadenomas, borderline tumors, and mucinous carcinomas, in more than 60% of cases.[10,11]

Immunohistochemical analysis for each of these tumors and the sampled implants would be crucial in further characterizing the peritoneal involvement, as the origin of borderline mucinous tumor or a possible coexistence of another secondary neoplasm must be ruled out and is important in defining prognosis and treatment. *TP53*, with its surrogate marker, p53, would be a useful stain in clinching HGSC, approaching 100% specificity in detecting TP53 mutation, as well as having a high negative predictive value in excluding low-grade serous carcinomas.

The therapeutic approach may also be greatly impacted by the diagnosis of peritoneal carcinomatosis originating from HGSC. Nearly one-fifth of HGSC are associated with *BRCA1/BRC2* mutations. These tumors are highly responsive to poly (ADP-Ribose) polymerase inhibitors and show improved survival comparing to those without the mutation. For this patient, a multi-agent adjuvant

chemotherapy regimen of carboplatin and paclitaxel had been originally planned as per recommendation by the local gynecologic oncology society guidelines as the standard postoperative treatment. In the absence of molecular and genetic (somatic or germline) testing done for the patient, the decision was based on the frontline chemotherapy combination for advanced-stage ovarian cancers. Primary response rates may exceed 90% in Stage III cases, but the survival rate is reported to be <30%.[12] Strong evidence has supported genetic testing for women with high-grade epithelial, nonmucinous ovarian, or tubal cancer.[13]

Conclusion

There exists a challenging conundrum and a lack of published case reports in the diagnosis and treatment of borderline tumors with coexisting peritoneal dissemination and high-grade serous carcinomas of primary fallopian tube origin. Any incongruency in the clinical presentation of a patient, coupled with tumor markers, imaging parameters, and malignancy scoring must prompt further investigation of a more aggressive, yet obscure neoplasm. An accurate histopathological and immunohistochemical examination is invaluable in delineating the optimal treatment plan and prognosis for such cases, and the standardization of testing protocols would probably be of benefit to such patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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