Pregnancy after atypical placental site nodule; a case-report

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Background

Gestational trophoblastic disease (GTD) refers to a group of rare tumors originating in the syncytiotrophoblast, cytotrophoblast or intermediate trophoblast of the placenta. Epitheloid Trophoblastic Tumor

(ETT) and Placental Site Trophoblastic Tumor (PSTT) are malignant forms of GTD that both originate in the intermediate trophoblast. Their benign counterparts are respectively placental site nodule (PSN) and exaggerated placental site reaction (EPSR). PSN can present with abnormal vaginal blood loss, amenorrhea or as an incidental finding in postpartum endometrium sampling[1]. A minority of these PSNs have an atypical appearance for which a new entity called Atypical Placental Site Nodule (APSN) is suggested. To the best of our knowledge, only one cohort of patients with APSN has been described in literature by Kaur et al., consisting of twenty-one registered cases between 2005-2013 at the Charing Cross Gestational Trophoblastic Disease Centre of which three (14%) progressed to or co-existed with GTN[2].

Histological diagnosis of APSN should be considered when a PSN lesion displays increased cellularity, mild atypia and larger lesion size. An index of the marker of proliferation Ki-67 between 8 and 10-12% is indicative for APSN, while a Ki-67 index below 8% corresponds to PSN and above 12% to ETT[3]. APSN is not acknowledged by the World Health Organization since no consensus on the histological definition has been reached yet.

Due to its rarity, the clinical significance of APSN is not well known and therefore recommendations on treatment and follow-up are lacking. However, it is important to learn more about the risk of ETT or PSTT development, as these malignant forms of GTD are less responsive to chemotherapy and have a lower overall survival after 5 and 10 years of respectively 80% and 75%4. Prognostic factors for reduced overall survival in ETT and PSTT were also determined by Froeling et al. The hazard ratio (HR) in the group of patients with >48 months from antecedent pregnancy to start of treatment was 14.57 (95% CI 4.17–50.96, $p < 0.001$), which highlights the importance of avoiding delays in treatment4.

In addition, the incidence and outcome of pregnancy following the diagnosis of APSN are unknown, which makes it difficult to counsel patients. Knowledge of the course of pregnancy and its effect on APSN is necessary to better understand this entity. In this case-report, we describe a woman with two pregnancies after the diagnosis of APSN, which was considered fully resected by hysteroscopy prior to these pregnancies. After fulfilling her child wish a hysterectomy was performed and a clinically and radiologically undetected persistent APSN was found in the final hysterectomy specimen. We have written permission from our patient to publish her case.

Case-presentation

A 32-year-old woman presented in 2019 with secondary subfertility two years after a full-term pregnancy. Her first pregnancy was complicated by a preeclampsia. In October 2016, at 36 weeks and 6 days, she delivered a daughter vaginally after induction of labor. The placenta was retained and removed manually, which was complicated by post-partum hemorrhage. In January 2017 a hysteroscopy was performed due to complaints of irregular vaginal bleeding and suspicion of retained products of pregnancy. A suspected remnant of the placenta was removed hysteroscopically and an intra uterine device (IUD Mirena) was inserted as a contraceptive. The pathology report described normal placental tissue. The IUD was removed in the beginning of 2018 because of a renewed child wish. In March 2019, a hysteroscopy was performed because of secondary subfertility and the suspicion of Asherman's syndrome. Before the procedure, no abnormalities were seen on transvaginal ultrasound in the myometrium. The endometrial thickness was relatively thin (2.7mm) postovulatory. During the hysteroscopy a small lesion of placenta-like tissue (1cm) was resected. The histologic examination showed linear, superficial linear lesional tissue of 1 cm, with a thickness of 1.2 mm, consisting of hyalinized eosinophilic material with interspersed hyperchromatic, pleomorphic and intermediate type trophoblast. The cells had mainly clear cytoplasm and focally contained eosinophilic cytoplasm. The trophoblastic cells were arranged in cords and small nests. Mitoses and necrosis were not present in the hysterectomy specimen but were seen in the previous histology sample. Some chorionic villi were seen to suggest trophoblast accompanying products of conception. Immunohistochemistry showed that these cells were positive for p63 and showed a Ki-67 or MIB-1 proliferation index of 8-10%. Immunophenotype was that of proliferating intermediate trophoblast. These characteristics were consistent with the diagnosis of APSN.

Following the pathology result, hCG-levels were determined and found to be below the cut-off limits. A CT-scan chest/abdomen and MRI pelvis were performed to exclude an infiltrating, malignant mass, no abnormalities or lesions suspected of metastases were seen. An expectant approach was discussed as the woman wished to conceive again. She was counseled about the association of APSN with PSTT and ETT. Her case was discussed in a national and international multi-disciplinary team. Consensus was to perform three-montly monitoring using serum hCG-levels, transvaginal ultrasound and alternating MRI/hysteroscopy if not pregnant. None of the tests used showed abnormalities during follow-up. The woman achieved two full-term pregnancies two years apart from each other, the pregnancies were uneventful except for a retained placenta in both deliveries resulting in a manual removal of the placenta. Histological examination of both placenta's did not show any signs of abnormality. The MRI scans performed during the pregnancies were discussed with a specialist in placental MRI scans.

In May 2022, six months after the last pregnancy, a hysterectomy was performed. An atypical, linear and superficial lesion of 1.1 cm was found in the endometrium and pathology results remained consistent for APSN with a Ki-67 proliferation rate of 8-10%. Macroscopically the lesion could not be detected. The woman was discharged from follow-up.

Discussion

This is the first case-report of a woman with APSN, who carried two pregnancies after this diagnosis. A hysterectomy after completion of her family, revealed on histological examination a persistent APSN that was prior clinically and radiologically undetectable. The impossibility to detect the lesion on scans and hysteroscopy is due to its linear appearance and small width.

Five articles have reported cases of APSN, describing a total of 26 patients [2, 5-8]. However, no subsequent pregnancies have been reported before. At the moment of diagnosis, maternal age ranged between 31 and 43 years old. The presentation of symptoms in our case is similar to that of other cases described in literature. Most patients presented with complaints of irregular vaginal bleeding (n=18), two patients presented with a pelvic mass and pelvic pain, the other cases (n=6) were incidental findings of APSN after curettage or hysterectomy. In four patients, ultrasound abnormalities were described consisting of a cystic mass in utero. In the remaining 22 patients, results of imaging were not described. All hCG-levels at the moment of diagnosis of APSN or GTN were low or below detection threshold, as in our case.

Four of the 26 patients (15%) with APSN were diagnosed with GTN synchronously or during follow-up [2,5]. Two patients had a mixed tumor consisting of APSN and PSTT or APSN, PSTT and ETT. One patient developed ETT six months after APSN diagnosis, another patient developed PSTT 16 months after APSN diagnosis. All patients diagnosed with GTN were treated only with hysterectomy, no additional chemotherapy was needed.

In contrast to our case, seven patients opted for immediate treatment after diagnosis of APSN and underwent a hysterectomy. Four patients underwent surgery for other reasons than APSN and unexpected diagnosis of APSN was based on tissue from the hysterectomy, they did not receive other additional treatment. Two patients were treated with a wedge resection, in one patient no follow-up was described and the other patient was followed for 12 months without displaying complications 6,8. Nine patients were diagnosed with APSN based on material retrieved during suction curettage and did not receive additional surgical removal of any kind. Of these patients, four did not display signs of recurrence during follow-up (length of follow-up not described), the other five patients were lost to follow-up. In none of these patients a subsequent pregnancy was reported.

To the best of our knowledge, no literature exists on patients with APSN and subsequent pregnancies. No previous literature has been published on fertility sparing (surgical) treatment in APSN and in case of ETT or PSTT fertility sparing treatment is uncommon9. This is the first case-report of a woman still wishing to conceive and in whom an expectant management was installed rather than performing a hysterectomy immediately. Patients should be counseled on the risk of GTN development. Postponement of treatment and watchful waiting in order to fulfill a child wish could be an option as 85% of this patient population

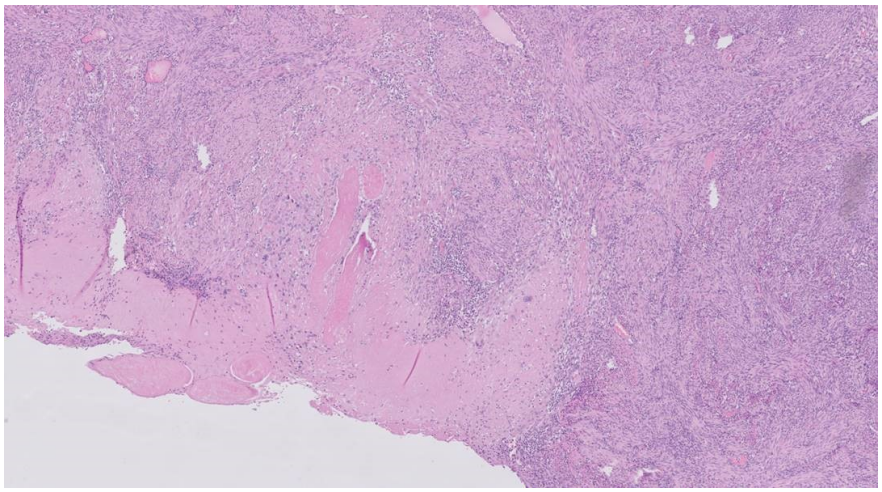
does not develop GTN, just as we demonstrate with our case. However, reliable diagnostics to monitor this period have not yet been found.

Monitoring with hCG serum level measurements, transvaginal ultrasound, hysteroscopy and MRI could be considered. However, the absence of an abnormality does not exclude the presence of APSN as is clear from our case. It was very remarkable that during the three years of monitoring none of the diagnostics displayed anything abnormal, which can be explained afterwards by the linear formation of the lesion. On MRI imaging linear structures are difficult to detect, especially if the lesion does not display malignant characteristics like restriction or contrast-enhancement. In addition, experience is needed for the adequate interpretation of placental MRI. Previous research showed a significantly higher accuracy for placental MRI interpretation by experienced radiologists compared to juniors, as juniors underestimated the degree of placental infiltration (18.5% vs 0%, p=0.006) [1]0. Taking these findings together, further research is needed to determine the role of MRI in monitoring this patient population.

Currently, not enough is known about the reliability of hCG-levels and diagnostic imaging to detect APSN progression to GTN. This legitimizes a hysterectomy, even in the absence of increased hCG and/or abnormalities on imaging. Further research should clarify which APSN progresses to ETT or PSTT in order to establish protocols for monitoring and to establish recommendations for follow-up if pregnancy is desired. A better understanding of the clinical significance of APSN is needed in order to prevent unnecessary (early) hysterectomies and to improve patient counselling about the risks of postponing hysterectomy.

In conclusion, we demonstrate that pregnancy is possible after resection of APSN but that APSN can remain present and undetectable for many years. Further research is needed to form monitoring and treatment recommendations for this rare and young patient group.

Image



Histology report of microscopic examination: *Endometrial tissue with a linear, superficial nodule (see box in image) consisting of hyalinized eosinophilic material with interspersed hyperchromatic, pleomorphic and intermediate type trophoblast. Immunohistochemistry showed that these cells were positive for p63.*

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Declaration section

Consent for publication

Our patient has given written permission to publish her case in the British Journal of Gynecology and Obstetrics. She also agrees to share histology images of hysterectomy tissue.

Disclosure of interests

Nothing to disclose

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Contribution to Authorship

Writing – Original draft L.T.A. Coopmans

Writing – Review & editing C.A.R. Lok, M. Bol, A. Bruining, A.M.H. Koning, V.T.H.B.M. Smit,

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