Case Report
Volume 11:2, 2021

Clinical Case Reports

ISSN: 2165-7920 Open Access

Clear Cell Carcinoma Arising on the Surface of Atypical Polypoid Adenomyoma in a Young Female with Confirmed Diagnosis of Cowden Syndrome

Shireen R. Abdullah[1]*, Tim Duncan[2] and Chrysoula Liakou[2]
[1]*Department of Histopathology, Norfolk and Norwich University Hospital, UK*
[2]*Department of Gynaecologic Oncology, Norfolk and Norwich University Hospital, UK*

Abstract

Atypical Polypoid Adenomyoma (APA) is a rare uterine polypoid biphasic tumour that is typically seen in fertile age. Patients present with abnormal uterine bleeding. Although considered as a benign tumour the literature review reveals a risk for recurrence when conservatively treated and an association with endometrial hyperplasia and carcinoma. Hence, the current views suggest the possibility that APA might be a localised form of atypical hyperplasia. Cowden syndrome is an often difficult to recognize hereditary cancer predisposition syndrome caused by mutations in Phosphatase and Tensin Homologue Gene (PTEN) located on chromosome-10. Affected individuals are predisposed to hamartomatous growths as well as malignancy in multiple organ systems including female breast, endometrium, thyroid, colon and kidney. We describe a first case of clear cell carcinoma arising on the surface of atypical polypoid adenomyoma in a 26 years old female. The tumour was confined to the surface of atypical polypoid adenomyoma of the lower uterine segment with no underlying myometrial invasion; lymphovascular permeation or distant metastasis. The patient was also suggested as having Cowden syndrome based on the clinical circumstances "age and the previous history of follicular thyroid adenoma". Molecular (PTEN gene) analysis performed later-on confirmed the clinical diagnosis of PTEN hamartoma tumour syndrome. This is the second reported case of atypical polypoid adenomyoma within the context of Cowden syndrome highlighting the possible association between the two. The additional pathological finding of clear cell carcinoma in our case would imply that coexisting/associated endometrial adenocarcinoma with APA could be of either endometrioid or non-endometrioid histo-type.

Keywords: Atypical polypoid adenomyoma • Cowden syndrome • Endometrial cancer

Introduction

Atypical Polypoid Adenomyoma (APA) is a rare uterine polypoid tumour that was first reported as a new disease concept by Mazur in 1981. Typically, it is found in fertile age, but some cases are also described in postmenopausal period. In most cases patients present with abnormal uterine bleeding. Because of its presentation in young women with possible infertility; conservative treatment has been considered as a valid choice. However, recurrences are common as well as coexistence or subsequent development of atypical endometrial hyperplasia or endometrial cancer [1,2]. Histologically, Atypical Polypoid Adenomyoma (APA) is a biphasic tumour composed of endometrioid-type glands embedded in a myomatous or fibromyomatous stroma. It is most located in the lower uterine segment, although may involve fundus, uterine body or even endocervix. The tumour is typically polypoid with a broad base. At low-power examination, the tumour shows haphazardly arranged endometrioid-type glands that may be crowded, or widely separated with a vague lobular architecture. The glands may be tubular or show complex branching and not infrequently contain squamous morules that may show central necrosis. The glands exhibit mild or, at most, moderate cytological atypia; are set in an abundant myoid or fibromyomatous stroma which is often arranged in short interlacing fascicles with minimal cytologic atypia and only occasional mitotic figures [3]. Cowden Syndrome (CS) is a rare, autosomal dominant disorder affecting approximately 1 in every 200,000 people. CS involves a germline mutation in the Phosphatase and Tensin (PTEN) homolog gene, which encodes a tumor suppressor antagonizing the phosphatidylinositol 3-kinase (PI3K/AKT) and Mitogen-Activated Protein Kinase (MAPK) pathway. Loss of PTEN function results in a downstream effect of increased cell proliferation and survival, leading to tumorigenesis. CS is associated with the development of hamartomas, as well as an increased lifetime risk of breast (25-50%), thyroid (10%), renal (13-34%), colorectal (16%) and endometrial carcinomas (13-19%); forming the prototype of the PTEN Hamartoma Tumor Syndrome (PHTS). Physical manifestations may include macrocephaly, trichilemmomas and papillomatous papules [4,5].

Somatic PTEN mutations are found in a variety of cancers, including breast and endometrial cancers and melanoma. However, germline PTEN mutations are rare in individuals with these cancers and additional phenotypic features associated with PHTS are almost always identified in these cases [6]. Within families, PTEN mutations are passed on in an autosomal dominant pattern of inheritance. Thus, each child of an individual with a molecular diagnosis of CS has a 50% chance of having CS as well. As many as 45% of cases of CS may be due to *de novo* PTEN mutations. A much smaller number of cases are believed to be due to PTEN mutation mosaicism. Due to its phenotypic variability, CS can present a dilemma for clinicians, and affected individuals often undergo numerous medical evaluations before a diagnosis is made. Germline mutations in the PTEN gene are known to cause CS. However, studies have shown great variability, with PTEN mutation detection rates ranging from 11% to 80% for patients meeting the clinical diagnostic criteria set forth in 1996. Subsets of CS/CSL individuals with no germline PTEN mutations were found to have germline SDHB/C/D variation and KLLN promoter methylation "Succinate Dehydrogenase (SDH) belongs to mitochondrial complex II that participates in both the electron transport chain and Krebs cycle". Germline SDHB/C/D variation was found in 8% of PTEN mutation negative CS/CSL individuals. Individuals with SDHB/C/D variants have higher risks of breast and

***Address for Correspondence:** Abdullah SR, Department of Histopathology and Cytopathology, The Cotman Centre, Norfolk and Norwich University Hospital, Colney Lane, Norwich, NR4 7UB, UK, E-mail: shireen.abdullah@nnuh.nhs.uk*

***Copyright:** © 2021 Abdullah SR, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.*

Received 13 January 2021; **Accepted** 27 January 2021; **Published** 03 February 2021

thyroid cancers compared to those with germline PTEN mutation [7]. Among CS/CSL individuals with no germline PTEN or SDH alteration, 37% were found to have germline KLLN promoter methylation with higher prevalence of breast and renal cancers compared to those with germline PTEN mutations "KLLN is a p53-regulated gene located upstream of PTEN and shares a bidirectional promoter region" [7].

Endometrial cancer is the only known gynecologic cancer significantly associated with CS. Reported lifetime risks for endometrial cancer in CS range from 5% to 28%. The risk for endometrial cancer appears to start around age 25 years. However, two case reports of endometrial cancer in adolescence have been reported in individuals with CS, with both patients having germline PTEN mutations [4,8]. In this paper we describe a case of clear cell carcinoma arising on atypical polypoid adenomyoma of lower uterine segment in a young female with genetically confirmed diagnosis of Cowden syndrome.

Case Report

A 26-year-old female presented with a history of sudden onset unprovoked heavy vaginal bleeding, requiring 3 units of blood transfusion. She also reported pelvic pain with normal bladder and bowel function. Her menstrual cycles prior to that episode have been regular every 28 days and she had never been sexually active. Her medical history included mild asthma and anxiety and her surgical history included thyroidectomy for follicular thyroid adenoma. On examination her abdomen was soft and non-tender. On speculum examination a large polypoid vascular mass was seen protruding through the cervix engaging the upper part of the vagina. A biopsy of the lesion was taken, and an urgent MRI of the pelvis was arranged. The histopathological examination suggested clear cell carcinoma. The MRI showed that the tumour was arising from the endometrium, protruding through the cervix and filling the upper part of the vagina, hence giving the impression of being cervical in origin.

Management

The case was discussed at the Gynaecologic Oncology multidisciplinary team meeting and referral to fertility services prior to surgical management was recommended. Fertility services suggested two-part surgery, with hysterectomy and pelvic lymphadenectomy first, to allow for safe egg retrieval due to the size and location of the tumour, which was engaging vaginal fornixes, and thereafter salpingo-ophorectomy and adjuvant treatment. The patient underwent total abdominal hysterectomy and pelvic lymphadenectomy and has had egg collection.

Pathologic findings

Macroscopic examination of the hysterectomy specimen revealed a uterus with cervix and attached left fallopian tube. The uterus and cervix measured 85 mm fundus to os × 55 mm cornu to cornu × 40 mm anterior to posterior. There was a polypoid lesion blocking the external os of cervix. On opening the uterus, uterine wall thickness was 18 mm with the polypoid tumour 40 mm × 30 mm which appeared attached to the lower uterine segment and protruding through the external os of the cervix (Figure 1). Furthermore, a smaller polypoid lesion was identified at the fundus measuring 7 mm in max. dimension (Figure 1). Histological sections of the polypoid lesion revealed a biphasic tumour arising from the lower uterine segment comprising endometrioid type glands in a benign fibromyomatous stroma (Figure 2). The glandular component displayed crowding with architectural complexity and mild to moderate cytologic atypia. Abundant squamous morules were present with some showing central necrosis (Figure 2). Focally on the surface of the polypoid lesion (Figure 2), glandular and short hyalinized papillary structures were seen (Figure 3). These were lined by markedly atypical hobnail type cells with pleomorphic large nuclei and clear to eosinophilic cytoplasm (Figure 3), consistent with clear cell carcinoma. Immunohistochemistry revealed positive expression of HNF1B (Figure 4) with patchy positivity for Napsin A and AMACR (Figure 4) within the area showing morphological features of clear cell carcinoma. In addition, p16 was diffuse strong positive, p53 showed wild type pattern and ER was negative (Figure 4). Immunohistochemistry for mismatch repair proteins revealed retained nuclear expression for MLH1, PMS2, MSH2 and MSH6. The background endometrium showed proliferative phase pattern with a small polypoid lesion at the fundus showing features of hyperplasia with atypia (Figure 5). The final pathological analysis of the hysterectomy specimen was that of clear cell carcinoma arising on and confined to the surface of atypical polypoid adenomyoma, with no evidence of underlying myometrial invasion or lympho-vascular permeation, FIGO stage IA. The pelvic lymph nodes were negative for malignancy.

Further management

Based on the clinical circumstances (including patient's age and the previous history of follicular thyroid adenoma) together with the pathological findings the possibility of Cowden's syndrome was suggested. Hence, following histological diagnosis and egg retrieval, the patient had gastroscopy and colonoscopy together with breast assessment to exclude the presence of GI polyps/hamartomas and benign or malignant pathologies of the breast. She was then found to have macrocephaly and skin-coloured facial lesions. Later, she was referred for PTEN gene analysis. The sequence analysis of the PTEN gene identified a heterozygous C to T base substitution at nucleotide position 445 (c.445C>T) with the resulting substitution of the amino acid glutamine at position 149 for a stop codon p. The result confirmed the clinical diagnosis of PTEN hamartoma tumour syndrome. Further evaluation revealed that her brother has had macrocephaly and Asperger syndrome, for which the patient herself is awaiting assessment, but there is no other relevant family history. Currently under the care of the oncology team, the patient is receiving carboplatin-paclitaxel chemotherapy treatment with an aim of completing 6 cycles. After its completion bilateral salpingo-ophorectomy will be arranged.

Discussion

Endometrial cancer is a feature commonly seen in families with a hereditary cancer syndrome known as Lynch syndrome. Therefore, On 28th October 2020, the National Institute of Health and Care Excellence (NICE)

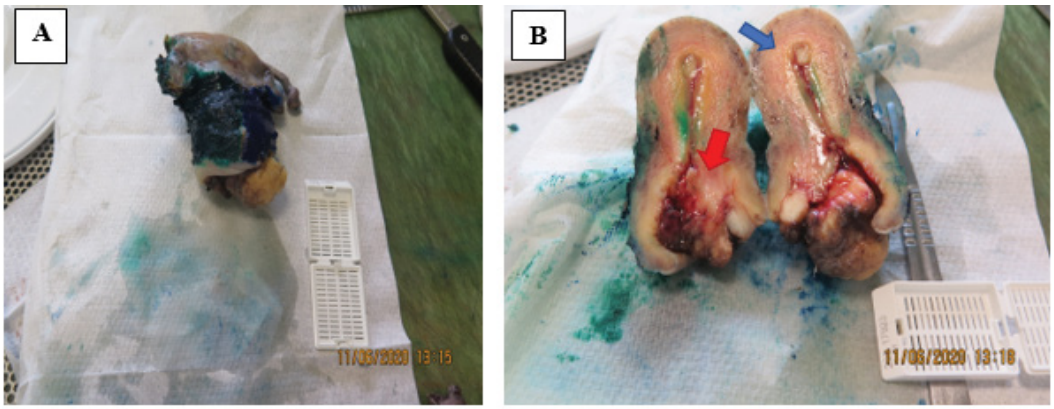

Figure 1. Gross appearances of the hysterectomy specimen showing a polypoid lesion blocking the external OS of cervix in (A). On opening, the polypoid lesion appears to be arising from lower uterine segment indicted by red arrow in (B). A smaller polypoid lesion is also identified at the fundus indicted by blue arrow in (B).

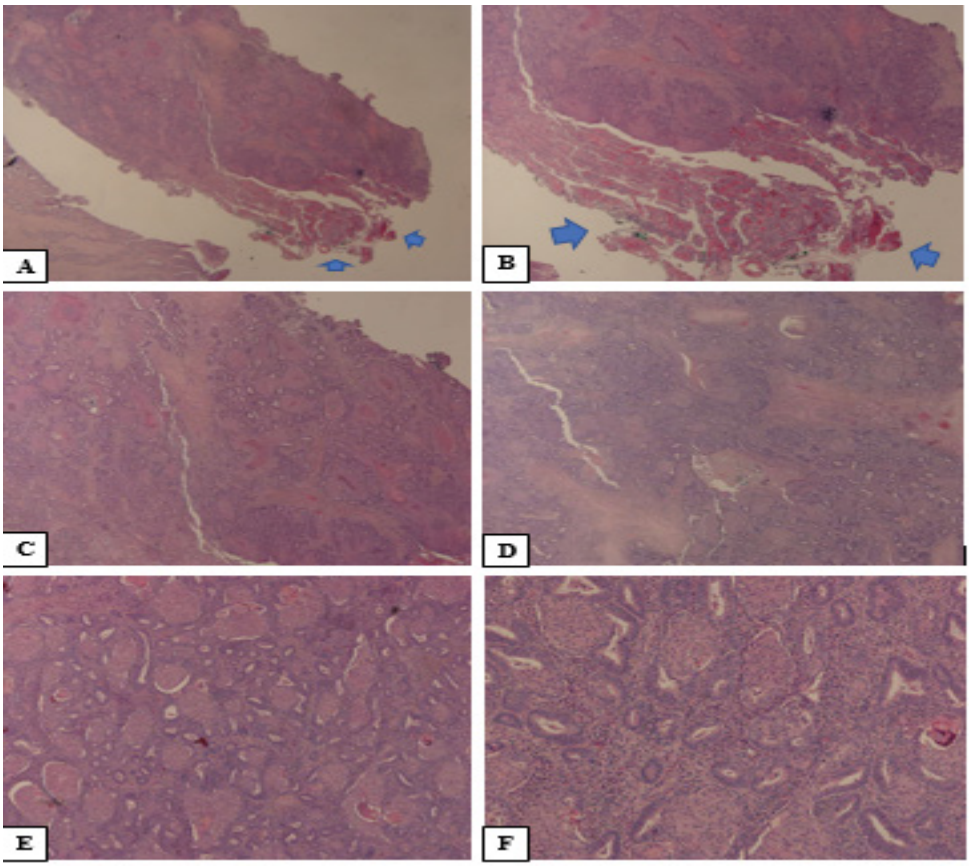

Figure 2. (A and B) Atypical polypoid adenomyoma with a focal area of associated clear cell carcinoma indicated by arrows. (C and D) Low power view of atypical polypoid adenomyoma showing haphazardly arranged endometrioid-type glands embedded in a myomatous/fibromyomatous stroma with a vague lobular architecture. (E and F) On higher magnification, APA comprises irregular and architecturally complex endometrioid type glands with abundant squamous morules. Haematoxylin-eosin, original magnifications 10x (A); 20x (B, C, D); 40x (E) and 100x (F).

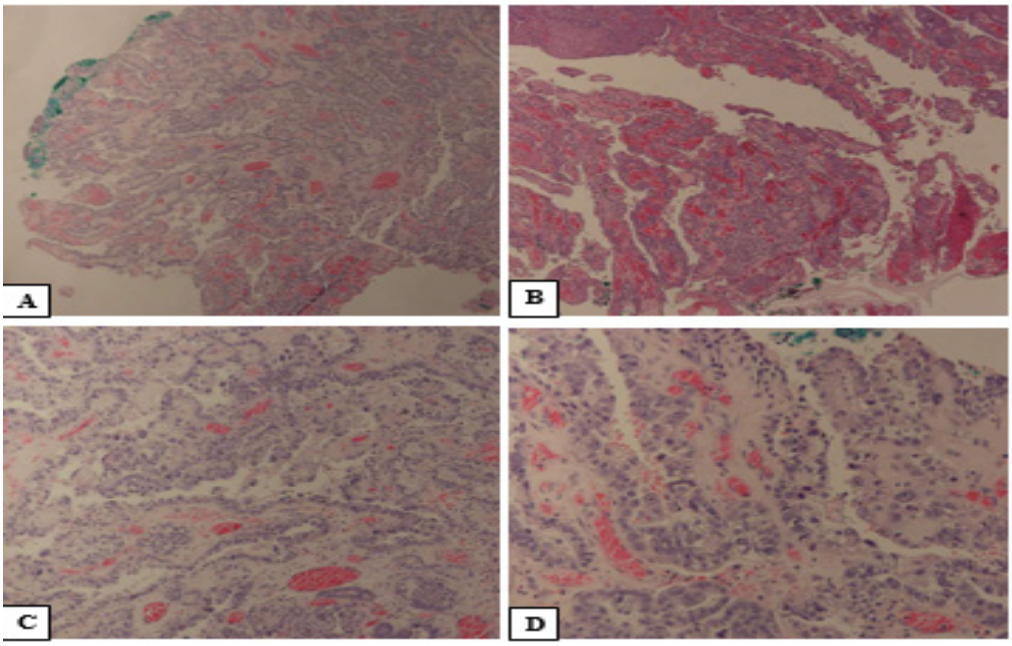

Figure 3. (A and B) Low power view of the focal area of clear cell carcinoma comprising glandular and short hyalinized papillary structures. (C and D) High power magnification of clear cell carcinoma showing the markedly atypical hobnail type cells with pleomorphic large nuclei and clear to eosinophilic cytoplasm Haematoxylin-eosin, original magnifications 40x (A and B); 100x (C) and 200x (D).

published a document stating that testing for Lynch syndrome should be offered when a person is diagnosed with endometrial cancer. However, the reported instances of strikingly early-onset endometrial cancer in CS should remind clinicians to think beyond Lynch syndrome when evaluating these patients [6,9]. The majority of reports indicate endometrioid carcinoma to be most common subtype to afflict women with CS [10]. However, in a large prospective multicenter study involving 371 CS and CS-like patients with endometrial carcinoma, only 42% were noted to have carcinoma of the endometrioid subtype. The remaining 58% were reported to been diagnosed with a non-endometrioid carcinoma, of which 50% were labeled as endometrial

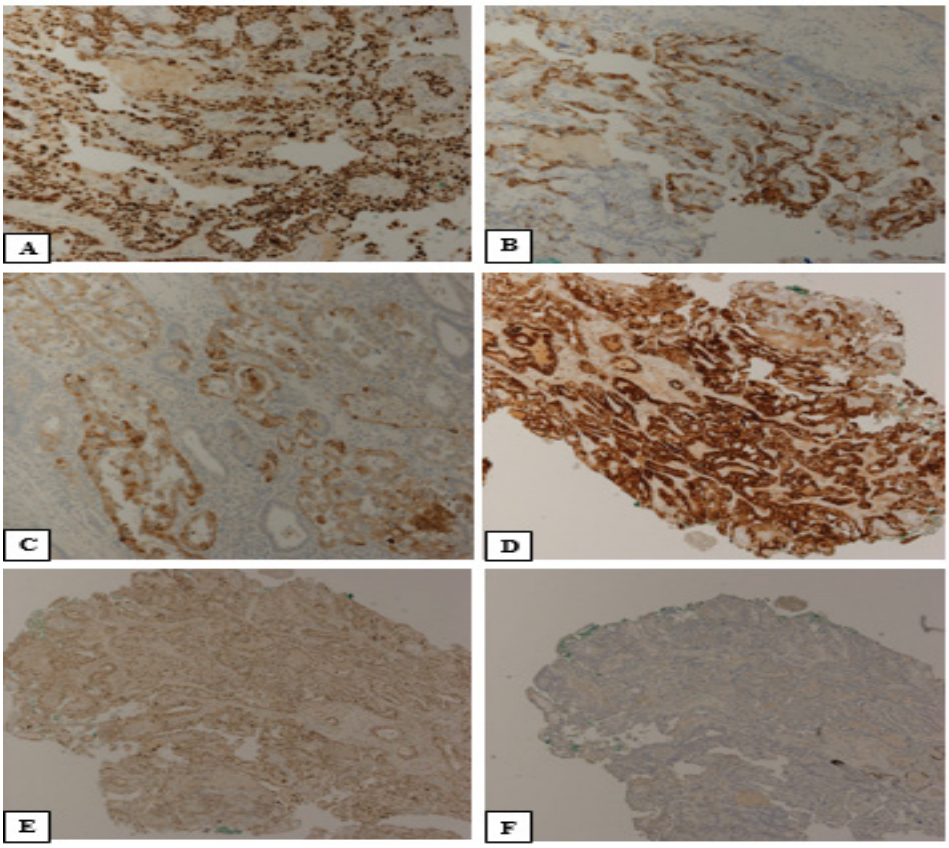

Figure 4. Immunohistochemistry of the focal area with morphological features of clear cell carcinoma. (A) Positive expression of HNF1B. (B and C) Patchy positivity for Napsin A and AMACR. (D) Diffuse strong expression of p16. (E) Wild type p53. F, ER is negative. Original magnifications 100x (A, B and C) and 40x (D, E and F).

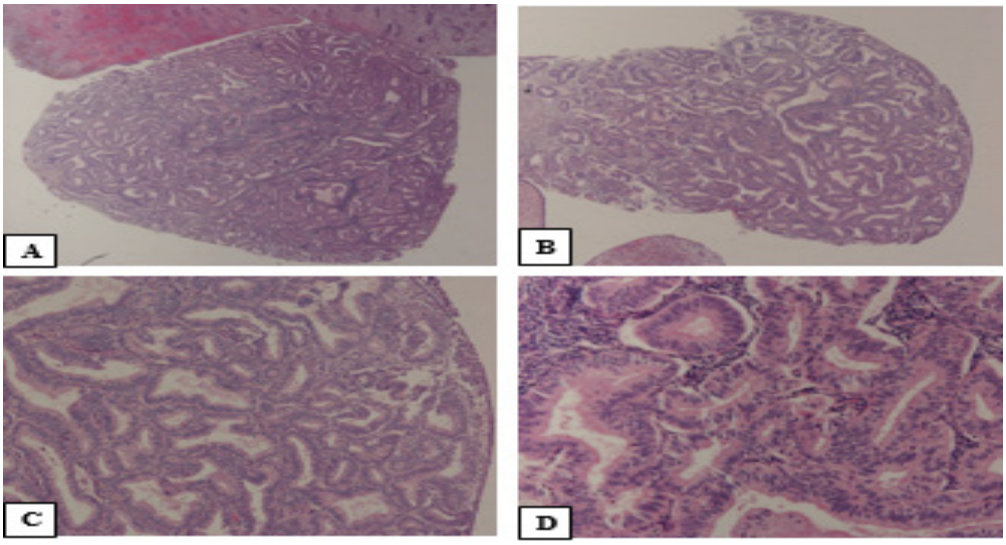

Figure 5. (A-D) Smaller polypoid lesion at the fundus showing features of hyperplasia with atypia. Haematoxylin-eosin, original magnifications 20x (A); 40x (B); 100x (C) and 200x (D).

carcinoma, NOS. Serous/clear cell carcinoma (5%), mucinous carcinoma (0.3%), and sarcoma (2.7%) were shown to account for the other malignancies in the non-endometrioid carcinoma group [7].

Atypical polypoid adenomyoma is a rare uterine tumour, less than 500 cases have been reported in the literature up to now. Although considered as a benign tumour, the literature review reveals a risk for recurrence when conservatively treated, and an association with endometrial hyperplasia and carcinoma [11]. Heatley in a 2006 review, concluded that where incompletely excised atypical polypoid adenomyomas are associated with 30% risk of recurrent or residual disease and 8.8% risk of association with endometrial hyperplasia and adenocarcinoma. The carcinomas were located in the adjacent endometrium, within the atypical polypoid adenomyoma or in association with its base [12].

A more recent systematic review and meta-analysis study has mentioned a prevalence for APA relapses during follow-up as 44% with a significantly lower prevalence in cases treated with operative hysteroscopy 22% versus 38% for the cases treated with dilatation, curettage and polypectomy. It was also noted that recurrences occur even after several years, with a 10 years cumulative recurrence of 59%. Moreover, the association with endometrial cancer was 16%, concurrent with APA diagnosis in 12% and during follow-up in 14%. Respectively, the association with endometrial hyperplasia was 15%; 10% (concomitant with APA diagnosis), and 11% (during follow up) [2]. Cases of co-existing endometrioid adenocarcinoma have been described both at the time of the initial treatment of atypical polypoid adenomyoma and after several years of follow-up [13-16]. Based on the above findings including the association of APA with atypical hyperplasia and/or endometrial carcinoma.

The current views suggest the possibility that APA might be a localised form of atypical hyperplasia [3,17].

Having said that, a case of co-existing (non-endometrioid) serous adenocarcinoma of the endometrium with atypical polypoid adenomyoma has been reported in a post-menopausal woman [18]. And our case which shows co-existing clear cell carcinoma. The latter findings would imply that co-existing/associated endometrial adenocarcinoma with APA could be of either endometrioid or non-endometrioid histo-type. The precise mechanism underlying the development of adenocarcinoma in APA has yet to be understood. Therefore, further studies are required to better understand the clinico-pathologic features and underlying molecular events of endometrial carcinomas co-existing with atypical polypoid adenomyoma. While, atypical polypoid adenomyoma has not been previously described as a manifestation of Cowden syndrome in the English literature. This is the second case of atypical polypoid adenomyoma being reported within the context of this syndrome. The previous case had a coexisting endometrioid carcinoma and our case has an associated clear cell carcinoma [13]. The development of APA may be affected by oestrogen because the disease often develops in premenopausal and nulligravid women, and the endometrium shows endometrial hyperplasia or proliferation. Furthermore, concomitant development of APA has been reported in a patient with Turner's syndrome who was receiving long-term administration of an estrogenic drug, suggesting a relationship between long term oestrogen stimulation and this polypoid tumour [19]. There is limited information regarding the molecular events underlying the development of atypical polypoid adenomyoma. However, a few studies have reported a common finding of PTEN loss [20]. This would suggest that the background genetic abnormality in Cowden syndrome may represent a fertile soil for the development of atypical polypoid adenomyoma.

Conclusion

Clinicians/gynaecologists need to be aware of the diagnostic criteria for Cowden syndrome and identify potential cases especially in young females presenting with uterine cancer. Identifying PTEN-related endometrial cancers is important because of the increased risks of other cancers and implications for family members, with the potential for gene-directed cancer prevention. Therefore, it is important to identify those at high-risk of germline PTEN mutation for referral to genetics specialists for gene testing and gene-informed medical management and high-risk surveillance. Awareness of the association of atypical polypoid adenomyoma with endometrial adenocarcinoma of either endometrioid or non-endometrioid histo-type. Therefore, meticulous pathological assessment of this uncommon uterine lesion is essential. Further studies are required to better understand the clinico-pathologic features and underlying molecular events of endometrial cancer co-existing with atypical polypoid adenomyoma. Future studies may further clarify the possible association between atypical polypoid adenomyoma and Cowden syndrome.

References

1. Iori Kisu, Kouji Banno, Megumi Yanokura and Yusuke Kobayashi, et al. "Atypical Polypoid Adenomyoma (APAM) of the Uterine: Relationship with Endometrial Cancer." *J Cancer Ther* 2 (2011): 458-462.
2. Anna Biasioli, Ambrogio P. Londero, Maria Orsaria and Federica Scrimin, et al. "Atypical Polypoid Adenomyoma Follow-Up and Management: Systematic Review of Case Reports and Series and Meta-Analysis. *Med* 26 (2020): 20491.
3. Anthony T. Williams and Raji Ganesan. A Practical Approach to the Diagnosis of Mixed Epithelial and Mesenchymal Tumours of the Uterus." *Mod Pathol* 29 (2016): 78-91.
4. Adam C. ElNaggar, Sheri L. Spunt, William Smith and Morgan Depas, et al. "Endometrial Cancer in a 15-Year-Old Girl: A Complication of Cowden Syndrome." *Gynecol Oncol Case Rep* 3 (2012): 18-19.
5. Amanda Gammon, Kory Jasperson, Wendy Kohlmann and Randall W. Burt. "Hamartomatous Polyposis Syndromes." *Best Pract Res Clin Gastroenterol* 23 (2009): 219-231.
6. Amanda Gammon, Kory Jasperson and Marjan Champine. "Genetic Basis of Cowden Syndrome and its Implications for Clinical Practice and Risk Management." *Appl Clin Genet* 9 (2016): 83-92.
7. Haider Mahdi, Jessica L. Mester, Emily A. Nizialek and Joanne Ngeow, et al. "Germline PTEN, SDHB-D, and KLLN Alterations in Endometrial Cancer Patients with Cowden and Cowden-Like Syndromes: An International, Multicenter, Prospective Study." *Cancer* 121 (2015): 688-696.
8. William David Baker, Andrew Patrick Soisson and Mark Kane Dodson. "Endometrial Cancer in a 14-Year-Old Girl with Cowden Syndrome: A Case Report." *J Obstet Gynaecol Res* 39 (2013): 876-878.
9. Adam C. ElNaggar, Sheri L. Spunt, William Smith and Morgan Depas, et al. "Endometrial Cancer in a 15-Year-Old Girl: A Complication of Cowden Syndrome." *Gynecol Oncol Case Rep* 3 (2013): 18-19.
10. Adele Wong and Joanne Ngeow. "Hereditary Syndromes Manifesting as Endometrial Carcinoma: How Can Pathological Features Aid Risk Assessment?." *Bio Med Res Int* 12 (2015): 17.
11. Antonio Raffone, Antonio Travaglino, Gabriele Saccone and Carlo Alviggi, et al. "Management of Women with Atypical Polypoid Adenomyoma of Uterus: A Quantitative Systematic Review." *Acta Obstet Gynecol Scand* 98 (2019): 842-855.
12. Heatley, Ma. "Atypical Polypoid Adenomyoma: A Systematic Review of the English Literature." *Histopathol* 48 (2006): 609-610.
13. James M. Edwards, Skylar Alsop and Susan C. Modesitt. "Coexisting Atypical Polypoid Adenomyoma and Endometrioid Endometrial Carcinoma in a Young Woman with Cowden Syndrome: Case Report and Implications for Screening and Prevention." *Gynecol Oncol Case Rep* 2 (2012): 29-31.
14. Nejkovic, Lan. "Atypical Polypoid Adenomyoma Mixed with Endometrioid Carcinoma: A Case Report." *Eur J Gynaecol Oncol* 34 (2013): 101-103.
15. Sonoyama, Aaan. "Coexistence of Endometrioid Adenocarcinoma in Atypical Polypoid Adenomyoma." *Kobe J Med Sci* 60 (2014): 74-77.
16. Kayo Inoue, Hiroshi Tsubamoto, Masateru Hori and Toshitada Ogasawara, et al. "A Case of Endometrioid Adenocarcinoma Developing 8 Years after Conservative Management for Atypical Polypoid Adenomyoma." *Gynecol Oncol Case Rep* 8 (2014): 21-23.
17. Kristýna Němejcová, Sarah L. Kenny, Jan Laco and Petr Skapa, et al. "Atypical Polypoid Adenomyoma of the Uterus: An Immunohistochemical and Molecular Study of 21 Cases." *Am J Surg Pathol* 39 (2015): 1148-1155.
18. Dah-Ching Ding, Chiu-Shih Cheng, Yu-Chi Wei and Tang-Yuan Chu. "Serous Adenocarcinoma of Endometrium Coexistence with Atypical Polypoid Adenomyoma in a Postmenopausal Woman: A Rare Case." *J Med Sci* 36 (2016): 162-164.
19. Bo Ma, Yingjun Zhu and Yixin Liu. "Management of Atypical Polypoid Adenomyoma of the Uterus: A Single Center's Experience." *Med* 97 (2018): 135.
20. Antonio Travaglino, Antonio Raffone, Gabriele Saccone and Mariano Fuggi. "Immunophenotype of Atypical Polypoid Adenomyoma of the Uterus: Diagnostic Value and Insight on Pathogenesis." *Appl Immunohistochem Mol Morphol* 6 (2019): 842-855.

How to cite this article: Shireen R. Abdullah, Tim Duncan, and Chrysoula Liakou. "Clear Cell Carcinoma Arising on the Surface of Atypical Polypoid Adenomyoma in a Young Female with Confirmed Diagnosis of Cowden Syndrome." *Clin Case Rep* 11 (2021): 1414.