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Case Report

Rectal clear cell carcinoma of Mullerian origin

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ABSTRACT

Clear cell carcinoma is a malignant tumor arising from paramesonephric ducts such as kidneys, ovaries, cervix and vagina. There are two types of clear cell carcinoma, intestinal and Mullerian type. Primary clear cell carcinoma of rectum is a rare entity. Extra Mullerian involvement of clear cell carcinoma of Mullerian type arises exclusively in the rectum or sigmoid of women. There are case reports of clear cell carcinoma of Mullerian origin arising in endometriosis in multiple sites. We report a case of clear cell carcinoma of Mullerian type in rectum in 63 year old female with no evidence of endometriosis.

1. Introduction

Clear cell carcinoma arises from organs derived from mullerian tract such as uterus and fallopian tubes, cervix, upper portion of vagina and ovaries.[1] There are biologically two different types of clear cell carcinoma; Mullerian and intestinal types; both these types vary widely in clinical and pathological features, diagnostic criteria and treatment necessitating accurate diagnosis and clear identification of the type. Intestinal type shows aggressive clinical behaviour, affects mostly men and has an intestinal type of immunoprofile- Ck7-,CK20+, CEA+, CDX2+ expression while Mullerian type shows an indolent behaviour involving rectum of young women with a mullerian immunoprofile- CK7+ CK20- CEA- and CA125+.[2]

Endometrium and ovary are the common sites of involvement for clear cell carcinoma; primary peritoneal clear cell carcinoma is also reported. Other sites of involvement are cervix and vagina. Women of all ages and children are reported to have Mullerian tract involvement.[3] Extramullerian involvement of clear cell carcinoma is seen in rectum, followed by sigmoid in women. Primary clear cell carcinoma of colon is a very rare entity. 41 cases are reported in literature since 1964.[1] The diagnostic criteria for clear cell carcinoma is presence of more than 50% clear polygonal or columnar cells with central or eccentric nuclei, abundant clear cytoplasm or eccentric marginally located inconspicuous nuclei similar to lipoblasts.[4]

2. Case Presentation

We report a case of perirectal mass with clear cell morphology. A 63 year old lady presented with lower abdominal pain and bleeding per rectum for one and a half months. CT scan showed an enhancing lesion in the right anterolateral wall of rectum showing perirectal stranding with multiple perirectal and inferior mesenteric nodes. Trucut biopsy from the perirectal mass showed cells arranged in a glandular pattern with abundant clear cytoplasm and snouting of nuclei. Focal lipoblast like morphology also noted. The biopsy was reported as clear cell carcinoma followed by immunohistochemistry tests interpreted as CK7+ PAX8+, CK20-, CEA-, Napsin A + and p53 showing diffuse nuclear expression for the

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nuclei and p16 with diffuse block like positivity. Patient underwent diagnostic laparoscopy with total abdominal hysterectomy and bilateral salpingooophorectomy, low anterior resection, cecostomy and bilateral DJ stenting. Per operative observations included 1-8 weeks uterus with sub serous fibroids and normal ovaries, Retroperitoneal rectal mass occupying entire presacral area compressing anterior cervix, rectal mass 7x6cm occupying upper and middle rectum. And no pathology in liver, peritoneum and regional lymph nodes. Resection specimen received as rectum with tumour, a polypoidal tumour with surface ulceration, 6x3.5x2cm, extending trasmurally with multiple perirectal lymph nodes. Microscopy showed extensively necrotic tumour extending trasmurally involving circumferential resection margin and the viable areas showed clear cells arranged in glandular pattern as described above. Uterus, fallopian tubes and ovaries, extensively sampled, even ovaries and fallopian tubes in its entirety showed no tumour. No evidence of endometriosis noted in any of the sections. Repeat immunohistochemistry done on resection specimen showed similar results, except for p53 which was wild type and p16 was negative. Histomorphology and immunohistochemistry test reported as 'Rectal clear cell carcinoma of Mullerian origin'. Molecular tests are not done due to financial constraints. The patient is currently undergoing rectal radiation therapy at 50.4Gy/28f and is currently planned for chemotherapy with Paclitaxel and Carboplatin for 6cycles after radiation therapy.

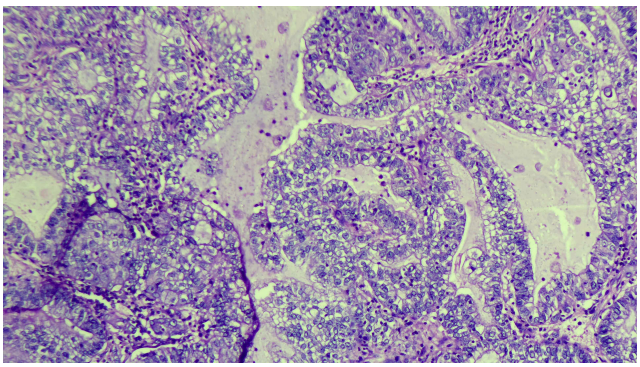

Figure 1: Hematoxylin eosin

3. Discussion

Primary clear cell carcinoma of rectum is a very rare entity in the absence of endometriosis with very few cases reported in literature.[1] Mean age of onset is 56.5yrs and women are affected at a younger age than men. Left colon is more frequently affected than right.[4] Clear cell carcinoma arising from endometriosis is reported in various sites such as diaphragm, peritoneum, and abdominal wall and in foci of scar endometriosis. Diagnosis relies on the clear cell histomorphology which may be in the pure form or composite form mixed with colorectal adenocarcinoma.[2] Some authors require the presence of 50% of clear cells for the diagnosis of clear cell carcinoma.[1] Histomorphological diagnosis is difficult and at the same time crucial which can lead to underreporting of cases; may be the reason for underestimation of cases in literature.[5] Serum tumour markers show increased Ca125 levels in most of the cases and CEA levels are usually unaltered.[6]

Immunohistochemistry results of CK20+ CDX2+ expression is sensitive and specific for the intestinal subtype which shows an aggressive behaviour than Mullerian type.[7] Diagnostic criteria for intestinal type includes a) Composite type with admixed adenocarcinoma or adenomatous pattern b) absence of endometriosis c) intestinal immunoprofile (CK20+ CDX2+ CEA + CK7-). Mullerian type is diagnosed when a) Mullerian immunoprofile (CK7+PAX8+CEA–CA125+) with or without endometriosis and b) exclusion of other primary.[2] Metastatic clear cell renal cell carcinoma is the closest differential for Mullerian type. PAX8 may not help to exclude renal cell carcinoma as both the entities will stain positive for PAX8. CK7 will be helpful in this scenario as Mullerian type of clear cell carcinoma will be diffusely positive for CK7 while clear cell renal cell carcinoma will be negative or may show a focal positivity only. Hepatocyte nuclear factor 1 beta used to be previously utilised as marker for ovarian clear cell carcinoma is no longer used and is replaced by Napsin A which has superior specificity. Napsin A positivity is defined as coarse granular cytoplasmic staining; focal staining can be seen in serous tumours and endometrioid tumours with clear cell change, but diffuse granular staining with Napsin A is typically specific for clear cell carcinoma.[8] Metastatic clear cell carcinoma of ovary and malignant mixed mullerian tumour of uterine origin or even ovarian origin, through rare;[9] also considered in the differential, excluded by the absence of a primary in ovary and uterus.

Molecular characteristics of intestinal type of clear cell carcinoma of rectum is predominantly K-RAS mutations and MMR proficient profile while the molecular characteristics of Mullerian type is yet to be studied.[2]

We observed a heterogeneity in p53 and p16 immunoexpression between trucut biopsy and resection specimen sample of the tumour we reported. Trucut biopsy showed a diffuse p53 expression while resection specimen showed a wild type of expression. Study done by Ahmed Alduaij etal observes that low grade clear cell carcinoma of ovary or uterine wall arising in a background of endometriosis or adenomyosis is unlikely to show p53 alteration; p53 expression is associated with high nuclear grade and is irrespective of the association with endometriosis. He has also observed that clear cell carcinoma showed a high Ki67 proliferation rate irrespective of nuclear grade of the tumour.[3] So the

heterogeneity in p53 expression in the case reported here may also be attributed to the spatial heterogeneity in grade of the tumour.

Embryogenesis explains the predominant involvement of extramullerian clear cell carcinoma in left colon over right side. One of the hypothesis is that the tumour arises from ectopic foci of mullerian cells left behind during ovarian migration in foetal life. Another hypothesis is the inducing role of primordial germ cells in the mesoderm of yolk sac near the allantois diverticulum.[10]

Clear cell carcinoma of intestinal type behaves similar to colorectal carcinoma to treatment and to adjuvant therapy. Targeted therapy is offered according to immunoprofile.[11] Mullerian type is managed by surgical resection of affected segment followed by adjuvant therapy which remains consensual.[1]

4. Conclusion

Primary rectal clear cell carcinoma in the absence of endometriosis is a rare entity. A strong suspicion from histomorphology added on by immunohistochemistry for exact type with a detailed histologic evaluation for involvement of Mullerian organs will aid in conclusive diagnosis. Accurate diagnosis is detrimental as treatment and prognosis differs in intestinal type and mullerian type and is fruitful.

5. Source of Funding

None.

6. Conflict of Interest

None.

References

1. Khefacha F, Triki W, Ayed K, Abbassi I, Baccar A, Baraket O, et al. Right Colon Clear Cell Carcinoma of Müllerian Type. *Case Rep Gastroenterol*. 2022;16(2):469–79.
2. Remo A, Fassan M, Vanoli A, Bonetti LR, Barresi V, Tatangelo F, et al. Morphology and Molecular Features of Rare Colorectal Carcinoma Histotypes. *Cancers (Basel)*. 2019;11(7):1036.
3. Alduaij A, Hansen K, Karim TA, Zhang C, Lomme MM, Sung CJ, et al. Clear cell carcinomas of the mullerian system: does the pathogenesis vary depending on their nuclear grade and their association with endometriosis? An immunohistochemical analysis. *Patholog Res Int*. 2012;2012:674748.
4. Remo A, Grillo F, Mastracci L, Fassan M, Sina S, Zanella C, et al. Clear cell colorectal carcinoma: Time to clarify diagnosis. *Pathol Res Pract*. 2017;213(5):447–52.
5. Saavalainen L, Lassus H, But A, Gissler M, Heikinheimo O, Pukkala E. Incidence of extraovarian clear cell cancers in women with surgically diagnosed endometriosis: A cohort study. *PLoS One*. 2021;16(6):e0253270.
6. Bedell S, Chang Z, Burt C, Khalifa MA, Argenta PA. Incisional carcinoma of Mullerian Origin: A case report and review of literature. *Gynecol Oncol Rep*. 2020;33:100588.
7. Barisella M, Lampis A, Perrone F, Carbone A. Clear cell adenocarcinoma of the colon is a unique morphological variant of intestinal carcinoma: case report with molecular analysis. *World J Gastroenterol*. 2008;14(42):6575–7.
8. Dabbs DJ, editor. Diagnostic immunohistochemistry: theranostic and genomic applications. 5th ed. Philadelphia, PA: Elsevier; 2019. p. 932.
9. Jagtap SV, Jagtap SS, Gudur R, Billawaria S. Primary ovarian malignant mixed Müllerian tumor: a rare case report. *Ther Adv Rare Dis*. 2022;3:26330040221107389.
10. Finkelstein A, Levy GH, Hui P. Clear cell adenocarcinoma of the colon arising in the background of endometriosis: a case report and diagnostic approach. *Lab Med*. 2010;41(2):111–4.
11. Gurzu S, Jung I, Bara T, Bara T, Semester O. Immunohistochemical and molecular features of primary clear cell-adenocarcinoma of the rectum, as predictive factors for individualized therapy. *Rom J Morphol Embryol*. 2014;55(2 Suppl):629–33.

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