ARC Journal of Cancer Science
Volume 9, Issue 1, 2024, PP 1-5
ISSN (Online): 2455-6009
DOI: https://doi.org/10.20431/2455-6009.0901001
www.arcjournals.org

Triple Pathologies of the Breast in a Known Case of Polyposis Coli and Multinodular Goiter: Rare Associations and Manifestations

Ayda Hussein[1*], Alaaddin Salih[2*], Azza Abdalsatir[3]

[1]*Associate Professor, Faculty of Medicine, Neelain University, Khartoum, Sudan.*

[2]*Associate Research Fellow, Academy of Health Sciences, Khartoum, Sudan.*

[3]*Senior Pathologist, Pathology and Histopathology Center, Khartoum, Sudan.*

**Both authors contributed equally to this manuscript as first authors.*

Corresponding Author:** ***Alaaddin Salih, *Associate Research Fellow, Academy of Health Sciences, Khartoum, Sudan*

Abstract

Background: *Invasive micropapillary carcinoma (IMPC) is a rare, aggressive histological subtype that is still not fully understood.*

Case Presentation: *Here, we present a case report of all rarities on multiple levels. First, 2 out of our patient's 3 conditions, IMPC and PASH, are relatively rare. Second, unheard of combination or concurrences between different conditions (IMPC and colorectal polyposis) and histopathological diagnoses too (IMPC, PASH, and fibroadenoma). Third, the contradictions in IMPC biological behavior (lack of lymphatic metastasis despite IMPC tendency for lymphogenic invasion, beside the massively fungating lesion out of a relatively small tumor size).*

Conclusion: *This is a report of a rare triad of IMPC of the breast, PASH, and fibroadenoma in a known case of multinodular goiter and colorectal polyps. Since mammary pathologies could be a little complicated in colorectal polyps patients, doctors' approach should presume malignancy till it is proven otherwise.*

Keywords: *IMPC, PASH, fibroadenoma, MNG, colorectal polyposis.*

1. Introduction

Here we present a case of all rarities. **Invasive micropapillary carcinoma (**IMPC) mixed with Pseudoangiomatous Stroma Hyperplasia (PASH) and fibroadenoma was diagnosed in a patient known to have adenomatous polyposis coli and thyroid multinodular goitor. This is the first ever report that defines: a new form of multiple polyposis that combines IMPC and polyposis coli; a subtype of IMPC that is mixed with PASH; a potential transformation of fibroadenoma into 2 histologically differentiated benign and malignant tumors; and supports suggested association between multinodular goiter and polyposis coli. To the best of our knowledge, existence of such relations has never been reported in medical literature.

These findings are supportive of the presumed association between breast cancer and adenomatous polyps coli. They favor consideration of PASH as a differential for phylloid tumor. Finally, given contradicting cytological results, surgeons should rely on clinical diagnosis and support it with the more sensitive and specific histopathology.

2. Case Presentation

A 40-year-old female presented to our unit complaining of ulcerated right breast lump for 1 year associated with ipsilateral breast pain for the last 2 months (Fig.1). The mass initially pursued a steady growth rate followed by a remarkable one during the last 6 months. 4 months ago, patient developed right breast pain. It is of gradual onset, moderate severity, burning nature, not radiating or associated with specific relieving or aggravating factors. 2 weeks ago, the mass fungated and a minimal bloody discharge came out intermittently. There was no history of trauma, nipple discharge, itchy, fever, malaise, weight loss, or symptoms suggestive of

metastasis. Past medical history is significant for bilateral multiple fibroadenoma of the breast diagnosed 20yr ago, adenomatous polyposis coli managed by total colectomy with preservation of rectum and iliorectal anastomosis, and simple multinodular goiter removed by total thyroidectomy. Both excisional surgeries were done 18 and 4 years ago, respectively. Multiple fulgurations and snare polypectomy were done for newly developed rectal polyps. No family history of similar condition, familial adenomatous polyposis, and breast or colorectal cancers. Menarche age is 13yr. She has regular cycles with average bleeding and cyclic pain. Her Kata is 7/30. She is single with no prior pregnancies (Gravida 0, Para 0+0).

On examination, 6×4.5cm oval ulcer in the upper inner quadrant overlying enlarged right breast. Palpation revealed 18×11.5cm multilobulated mass in lower outer quadrant while the smaller 3×3cm is found in the upper inner one. Both of them have hard consistence, rough surface, irregular margins, attached to skin and partially fixed to underlying structures. 2 significantly enlarged lymph nodes in the medial group of right axilla. No abnormalities detected in left breast and axilla.

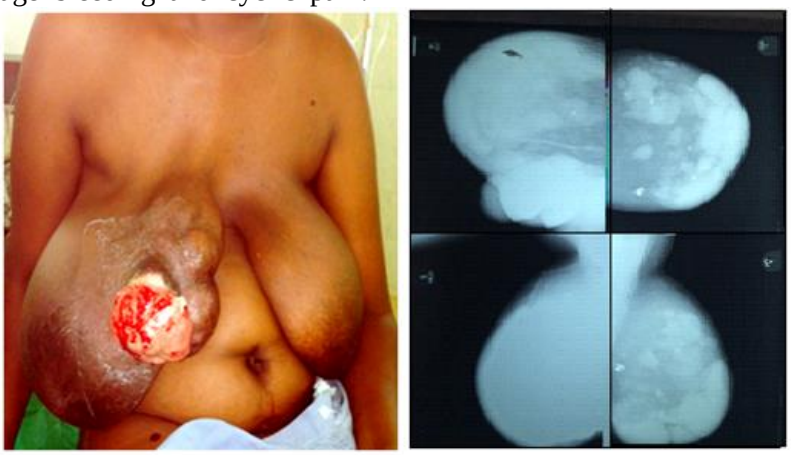

Fig 1. *Pre-Operative Assessment.*

Left (At Presentation): enlarged Rt breast with fungaing hugely lobulated mass occupying the medial half. The ulcer is vertically oval, measuring 6.5×5.2 cm, 3.4 cm is the maximum height of the protruded fleshy tumor that oozes blood. Buckering and tethering of the overlying skin are present. Infra-umbilical midline coloctomy scar (yellow arrow) and thyroidectomy scar (blue arrow) could be seen.

Right (Pre-Op Mammogram): showing heterogenous multicenteric hyperdensities with the largest measuring 6×4.5cm in the medial of Rt CC. Lt breast has scattered hyperdensity that accumulate retroareolarly to form 3 interlinked masses.

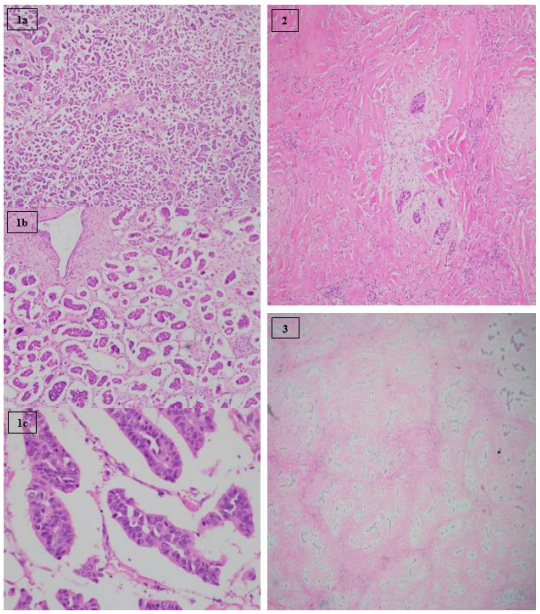

Fig 2. *Histopathology Findings.*

Left: IMPC as it appears on 3 different views. (1a) micropapillary carcinoma, field view; (1b) micropapillary carcinoma, low power image, showing micropapillae floating in rich stromal space; (1c) micropapillae composed of cells with moderate pleomorphism and high mitotic activity.

Rights-upper: (2) PASH composed of networks of anastomosing spaces in the interlobular & intralobular stroma.

Rights-lower: (3) Fibroadenoma showing proliferating stroma compressing ducts lumens.

Baseline hematological and biochemical investigations are normal. Ultrasonography showed 2 hypoechoic parenchymal masses suggestive of malignancy. Mammogram showed multicenteric hyperdense mass. Fine needle aspiration cytology (FNAC) aspirated malignant cells. Tru-cut biopsy showed suspected benign phylloid tumor. Whole bone scan and CT chest\abdomen\pelvis were unremarkable. The patient underwent combined right radical mastectomy with axillary dissection (level I-III). The excised lump measured 15 cm x 13 cm and weighed 600 g. Specimen sent for histopathology which reported IMPC (0.6×0.5 cm) on top of PASH with clear lymph nodes (Fig.2). Further essential workup could not be done because of financial barriers to the patient. Postoperative course was unremarkable.

3. DISCUSSION

IMPC is a rare aggressive histological subtype that counts for 1.7-2.7% of all breast cancers[1]. 2 forms are known, pure and mixed, 78.3% of the later are mixed with Invasive Ductal Carcinoma (IDC)[2]. It is described as a tightly cohesive nests of eosinophilic neoplastic cells with intermediate to high grade nuclei arranging in solid, morular, or tubular clusters[3]. A clear space separates them from the surrounding loose fibrocollagenous stroma[4, 5].

Early lymphovascular invasion, lymph node metastasis, perineural invasion and poor prognosis are the most important features of this tumor[6]. Reported mean tumor size is 4 cm with IMPC compartment constituting <20% of that volume in 53% of cases[7]. Obviously, our mass is much sizable with minimal IMPC portion, 0.6 cm only.

Characteristically, primary IMPC is usually positive for ER (90%), PR (70%), HERS-2/neu (60%)[8] and MFGP-1, while it classically shows TTF-1 negativity[4]. Moreover, IMPC has reverse polarity, i.e. "inside-out" growth, which may count for its aggressive behavior[3, 9]. The micropapillary pattern is primarily due to MUC1 that detaches cells from stroma[10].

In our case, there is a triangle of relationships (Fig.3). Firstly, the association between Familial Polyposis Coli (FAP) and Multinodular Goiter (MNG) and thyroid nodules has been previously reported; Secondly, there is an established link between MNG and Pure Mucinous Carcinoma (PMC) of the breast and subsequently its differentials like Pure Mucinous Carcinoma with Micropapillary Pattern (MUMPC) and IMPC. Thirdly, our search for a relation between our patient's breast cancer and APC came across what has been reported in many observational studies. Jouin *et al.*[13] perform screening colonoscopy for the presence of intestinal polyps in 161 breast cancer patients and 147 controls. They found it in 14.2% and 4.7% of cases and controls, respectively, with a statistically significant difference (*p*-value <0.01). Similarly, Bremond *et al.* reported a significant increase in adenomatous colonic polyps among breast cancer patients in their study of 289 case and control (*OR* 2.65; Confidence limit 1.56 and 3.74)[14]. On the other hand, concomitance of polyposis coli and IMPC, as a histological variant, was investigated by Verdú *et al*. in a case series in which they found adenoma in 30% of participants with colorectal IMPC[15].

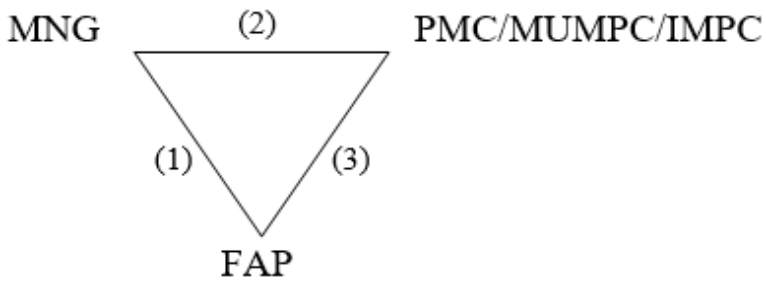

Fig 3. *Relationship between our case's 3 conditions IMPC (FAP, MNG, and) reported in literature.*

To interpret our case findings the best, we suggest the molecular approach. Kuraguchi *et al.* stated that mutant APC proteins enhance tumors by controlling Wnt/β-catenin signaling to a level that is optimal for the specific tumor and varies between tissues depending on its type[16]. *APC* mutations produce high levels of β-catenin preferentially produce intestinal polyposis, while those result in moderate levels give rise to breast tumors[17]. Furthermore, Kuraguchi *et al.* assume presence of positive selection for truncating somatic mutations that down-regulate β-catenin signaling[16], thereby, achieving intermediate levels of β-catenin that favor breast carcinogenesis. Our patient could not run the appropriate genetic tests to identify such somatic mutations in *APC* gene, because of financial barriers.

Geyer *et al.* suggested that *APC* deletions, mutations and promoter methylation as promoters for Wnt/β-catenin activation[18]. Heterogeneous deletion was least associated with luminal B subtypes, as IMPC[19]. *APC* mutations are rare Furuuchi *et al.*[20] exceptionally detect it in 18% of breast cancer patients, e.g. R2714L detected in IMPC[21]. Jin *et al.*[22] detect hypermethylation of *APC* 5' promoter CpG island in 36% of their sample. Such a high frequency of this cancer-specific epigenic modulation may have a greater role in *APC* silencing seen in breast cancer when compared to the less frequent somatic mutations. In contrast, none of the known 51 3'UTR short nucleotide polymorphism (SNPs) of the 3' region found to have a damaging effect[23].

4. Conclusion

Breast cancer should be considered in patient with colonic polyps. IMPC of the breast remains one of the differentials in such patients. Despite an absence of supportive cytological findings, surgical management of highly suspicious breast masses remains a choice given patients consent. Larger studies are needed to further understand the clinically and biologically complex nature of this tumor.

Consent: Written informed consent was obtained from the patient for both writing and publishing this report and any accompanying images.

Abbreviations: APC: Adenomatous Polyposis Coli; IMPC: Invasive Micropapillary Carcinoma; PASH: Pseudoangiomatous Stroma Hyperplasia.

Competing interests: None declared.

Authors' contributions: AH and AS participated in the design of the manuscript; AH has obtained necessary documents and consent; AS has reviewed the literature and patient's clinical data and lead the drafting; AA and AS have reviewed pathological workup and findings; All authors have approved the final manuscript.

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Citation: *Ayda Hussein, Alaaddin Salih et al. Triple Pathologies of the Breast in a Known Case of Polyposis Coli and Multinodular Goiter: Rare Associations and Manifestations. ARC Journal of Cancer Science. 2024; 9(1):1-5. DOI: http://dx.doi.org/10.20431/2455-6009.0901001.*