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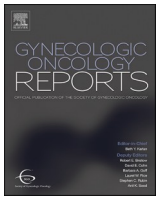

Case report

Ichthyosis uteri: A keratinizing squamous metaplasia of the endometrium with premalignant potential

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1. Introduction

The term ichthyosis uteri is used to describe the rare histopathologic phenomenon of extensive plaque-like keratinization of the surface endometrium (Quick et al., 2018). Several causes and predisposing risk factors have been hypothesized to induce this change, including a hypoestrogenic state, chronic endometritis, uterine prolapse, human papillomavirus (HPV) infection, and iatrogenic introduction of caustic substances and/or instrumentation into the uterine cavity (Baggish & Woodruff, 1967; Sherwood et al., 1997; Fadare, 2006). Though this metaplastic differentiation itself does not portend a malignancy, ichthyosis uteri has been associated with the development of primary squamous cell carcinoma of the endometrium (Seltzer et al., 1977; Murhekar et al., 2008). At baseline, isolated squamous cell differentiation does not independently cause symptoms, and thus diagnosis is most commonly incidental on endometrial sampling obtained for another indication (Wahal & Mardi, 2014). We present a case of ichthyosis uteri confirmed on surgical pathology following hysterectomy for postmenopausal bleeding and persistent vaginal discharge.

2. Case

The patient was an 88-year-old woman, gravida 7 para 6, who first presented to clinic as a referral for a pelvic mass with a two-year history of painless yet bothersome intermittent brown and grey colored vaginal discharge. Her medical history was significant for hypertension, hyperlipidemia, and hyperthyroidism, all well controlled with medication. Her surgical history was significant for a bilateral tubal ligation at age 32. She underwent menopause at age 58 with no history of any hormonal therapy. She denied any abnormal pap smears in the past and had no family history of gynecologic or gastrointestinal cancers.

Prior to her referral, she was treated by her PCP for bacterial vaginosis twice with metronidazole, as well as endometritis with doxycycline with little improvement in her symptoms. Her pelvic exam revealed vaginal atrophy, a mobile uterus measuring approximately 8 cm in size, and no cervical motion tenderness. Her cervix appeared irregular and flush with the vagina; however, no distinct cervical masses were present. A pap smear was performed and returned normal cytology. A pelvic ultrasound revealed a multi-fibroid uterus with a thickened (3.4 cm) endometrial stripe, and an endometrial biopsy was non-diagnostic showing fragments of squamous epithelium with severe acute inflammation. She then underwent a pelvic MRI that was significant for a central circumferentially enhancing uterine mass with an internal air-fluid level measuring 8.6 cm in greatest dimension. Her tumor markers were significant for a normal CA 125 of 12.8 U/mL (RR 0–35 U/mL) and mildly elevated CA 19–9 of 47.4 U/mL (RR 0–37 U/mL); other tumor markers (CEA, LDH, HCG) were normal. Given her otherwise normal labs and clinical presentation, additional workup for her elevated CA 19–9 was not pursued.

She underwent a hysteroscopy, dilation & curettage with evacuation of copious amounts of brown fluid immediately after dilation. There were significant amounts of white plaques and debris noted on the posterior endometrial wall, which was distorted by a known leiomyomata. Fluid cytology and curettage specimens revealed fragments of acutely inflamed and reactive squamous mucosa, without evidence of malignancy. There was no intact normal endometrial tissue seen in any of the samples. After review with the pathologist, the possible diagnosis of ichthyosis uteri was discussed with the patient and family, including an increased risk of concurrent or subsequent carcinoma. As she continued to experience copious vaginal discharge following the hysteroscopy, decision was made to proceed with hysterectomy with plan for intraoperative frozen section to assess for malignancy.

She underwent an uncomplicated total laparoscopic hysterectomy with bilateral salpingo-oophorectomy. Drainage of purulent intrauterine

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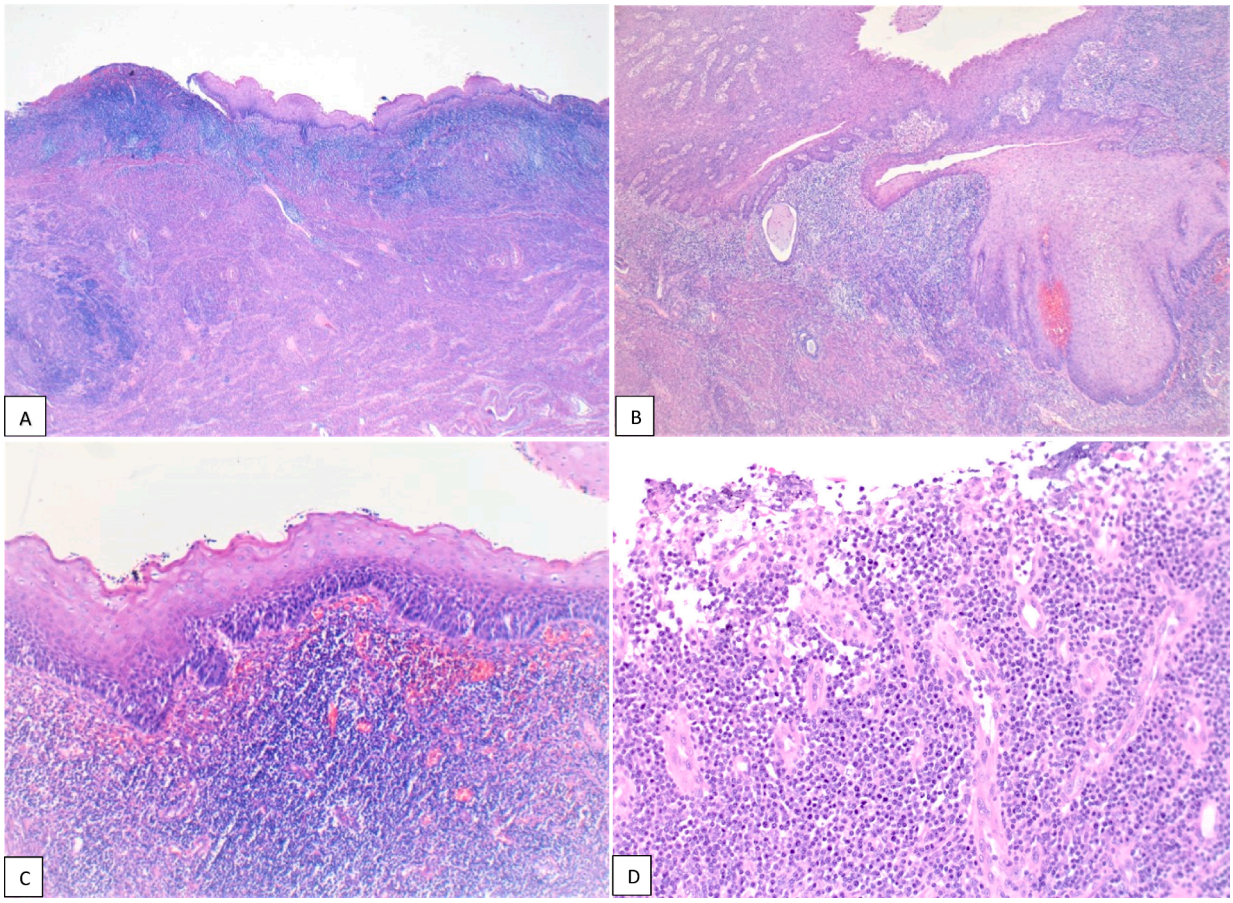

Fig. 1. A. H&E 20x: Section of endomyometrium demonstrating replacement of surface endometrium by plaque-like squamous epithelium with ulceration (left upper corner) and marked subepithelial chronic inflammation, B. H&E 40x: Foci of acanthotic squamous epithelium with invaginations into the underlying stroma and focal residual inactive endometrial glands, C. H&E 100x: Closer view of the keratinizing mature squamous epithelium demonstrating lack of dysplastic changes, D. H&E 200X: High power view of a focus of ulceration with granulation tissue.

material was noted immediately following placement of the uterine manipulator. There was no malignancy detected in the endometrium or cervix on intraoperative frozen pathology. Laparoscopically, her anatomy appeared to be without other significant abnormalities and further staging surgery was deferred. She was discharged home on the same day and had an uneventful recovery. The final surgical pathology

Table 1
Reported cases of primary squamous cell carcinoma of the endometrium associated with ichthyosis uteri.

Author (year)	Age	Presenting symptoms	Descriptive pathology	FIGO Stage	Treatment	Outcomes*
Bagga, et al (2008)	60	Postmenopausal bleeding	Multifocal invasive SCC arising in a background of ichthyosis	NR	Surgery (hysterectomy)	NR
Murhekar, et al (2008)	65	Postmenopausal bleeding	Focally-invasive SCC islands within the myometrium in a background of overlying ichthyosis	IA	Surgery (radical hysterectomy, BSO)	NR
Takeuchi et al (2012)	66	Purulent vaginal discharge	SCC evolving from pre-existing extensive ichthyosis	IIIC1	Surgery (radical hysterectomy, BSO, pelvic LND, omentectomy) followed by adjuvant chemoradiation	Pelvic recurrence at 6 months treated by systemic chemotherapy (carboplatin/paclitaxel); NED at last follow-up (22 months)
Akizawa et al (2020)	68	Watery brown vaginal discharge	Two foci of invasive SCC within widespread ichthyosis	II	Surgery (hysterectomy, BSO) and adjuvant chemotherapy (carboplatin/paclitaxel)	NED at last follow-up (12 months)
Puljiz et al (2022)	62	Postmenopausal bleeding	Invasive SCC nests under endometrial ichthyosis	IA	Surgery (hysterectomy, BSO, pelvic LND)	NED at last follow-up (12 months)
Hopkins et al (2022)	78	Postmenopausal bleeding	Keratinizing SCC with background ichthyosis	II	Surgery (NOS)	DOD (2 months)
	92	Postmenopausal bleeding	Keratinizing SCC with background ichthyosis	II	Surgery (NOS)	NR

* Follow up time reported in months after primary surgery. BSO = bilateral salpingo-oophorectomy; DOD = dead of disease; FIGO = International Federation of Gynecology and Obstetrics; LND = lymph node dissection; NED = no evidence of disease; NOS = not otherwise specified; NR = not reported, or data not available; SCC = squamous cell carcinoma.

of the endometrium revealed confluent plaque-like keratinizing squamous metaplasia replacing the entire endometrium, consistent with ichthyosis uteri (Fig. 1). Extensive sub-epithelial chronic inflammation was noted. Foci of surface ulceration and granulation tissue formation secondary to prior procedural trauma was noted. There was no evidence of squamous dysplasia or carcinoma seen. Additional pathologic findings included adenomyosis, calcified leiomyoma, and chronic cervicitis. At point of last contact, she had recovered well from her surgery, and her discharge had resolved.

3. Discussion

Within the endometrium, squamous metaplasia is relatively common and mostly benign. Small reactive metaplastic foci can be detected secondary to mild insults such as infection or trauma, including iatrogenic procedures and intrauterine devices, and are typically limited and self-contained within the surface epithelium (Quick et al., 2018). In rare cases, there can be extensive replacement of surface endometrium with mature keratinizing squamous epithelium, as seen in our patient in Fig. 1. Ichthyosis uteri is considered morphologically separate from the more commonly seen morular metaplasia, which may be associated with glandular involvement and concern for the premalignant lesion endometrial intraepithelial neoplasia (EIN) (Mutter et al., 2018).

The overall incidence of ichthyosis uteri is difficult to estimate due to its rarity, and literature is limited to scattered case reports and small case series. Though ichthyosis is considered to be benign, primary squamous cell carcinoma of the endometrium have been reported to have a significant association in reported studies (Table 1). Similar to our case, patients typically presented with either postmenopausal bleeding or uterine discharge and found to have air-fluid levels consistent with pyometra on imaging (Bagga et al., 2008; Jain et al., 2017). Most of the time, this was found in association with concurrent postmenopausal cervical stenosis. Patients subsequently underwent hysterectomy, and pathology demonstrated nests of neoplastic cells in a background of ichthyosis metaplasia, thus giving rise to the hypothesis that ichthyosis uteri may have potential for malignant transformation over time.

Superficial endometrial spread of squamous cell carcinoma of the cervix carpeting the endometrium may resemble ichthyosis histologically. The presence of cervical tumor as well as dysplastic changes in the endometrial squamous epithelium will help differentiate this ichthyosis-like change from true ichthyosis uteri (Adler et al., 2007; Bagde et al., 2021). In these cases, microscopic examination of the metaplastic endometrial epithelium revealed extensive koilocytosis, suggesting that the metaplasia was HPV-driven and a result of direct extension of the cervical pathology (Fadare, 2006; Murhekar et al., 2008). Prior to hysterectomy for patients suspected to have ichthyosis uteri, a full cervical dysplasia history should be clarified and updated cervical sampling should be obtained. It is important to note, however, that our patient did not exhibit koilocytosis on histopathology and did not have a history of cervical dysplasia.

Extensive morular metaplasia in endometrioid adenocarcinoma can also resemble ichthyosis morphologically due to the paucity of glandular epithelium. However, a background of hyperplasia and a diligent search for neoplastic glandular epithelium can help differentiate these two possibilities. A single case of concurrent endometrioid carcinoma with overlying ichthyosis has been reported (Bewtra, et al., 2005). The etiology of this is not fully understood, but likely similar to those implicated in primary ichthyosis uteri, such as chronic endometrial trauma, infection, inflammation, and a hypoestrogenic state.

4. Conclusion

Currently, there is a not a consensus on the recommended management of ichthyosis uteri. Though not yet classified as a pre-malignant lesion and the malignant potential is not yet formally established, there seems to be a strong potential association with primary squamous cell carcinoma of the endometrium and other gynecologic malignancies, though it is important to note a potentially significant selection bias in the literature. An incidental diagnosis or suspicion of ichthyosis uteri may warrant a more extensive workup tailored to the individual clinical scenario. Reasonably, an updated evaluation of the uterine cervix should be completed, and endometrial sampling should be obtained, though even surgical curettage may not have great sensitivity in the context of potential squamous cell carcinoma of the endometrium (Goodman et al., 1996; Dijkhuizen et al., 2000). Thus, we would recommend that following complete cervical dysplasia work-up, that a hysterectomy be performed, which provides both diagnostic and therapeutic benefit, especially in the patient who has completed childbearing.

5. Consent

Informed consent was obtained prior to publication of this report.

Author Contributions

YZ and AC developed the idea and performed the initial chart review. YZ performed the literature review and wrote the manuscript, with contributions from ST and GY. RM provided expert consultation. AC supervised this project in its entirety.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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