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Case report

Invasive acantholytic anaplastic extramammary Paget disease: A previously unreported neoplasm in the vulva and review of the literature

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ABSTRACT

This report describes the first documented invasive acantholytic anaplastic extramammary Paget disease (AAEMPD) of the vulva. An 87-year-old female presented with a recurrent vulvar lesion refractory to topical imiquimod and treated with multiple wide local excisions (WLE). Microscopic examination of the final WLE specimen revealed unique histologic features, primarily supra-basal intraepidermal acantholysis with epidermal papillomatosis and hyperkeratosis. The epidermis, composed of two distinct cell populations, exhibited full-thickness atypia. Paget cells with high mitotic activity were present in the basal and parabasal layers surrounding benign squamous cells in the mid-squamous mucosa. The histologic features were suspicious of the EMPD involving a warty lesion and/or invasive squamous cell carcinoma. In addition to the intraepidermal component, dermal invasion was also present with lymphovascular space invasion. Immunohistochemical studies (KRT7, HER2, and GATA3 reactivity in Paget cells, p63 negativity, and rare mucin in Paget cells) supported the diagnosis of acantholytic anaplastic EMPD. AAEMPD, a rare variant of EMPD, shares similar prognosis and behavior with the classic Paget disease. Recognition and accurate diagnosis of this subtype is crucial for optimal patient management, given distinct treatment strategies compared with other entities in the differential diagnosis.

1. Introduction

Extramammary Paget disease (EMPD), most frequently seen in the vulva, primarily affects postmenopausal women with a mean age of approximately 65 years (Elder et al., 2018; Crum et al., 2018). Invasion occurs in 4–19 % of EMPD cases (Borghi et al., 2018).

Rayne and Santa Cruz (Rayne and Santa Cruz, 1992) first described anaplastic Paget disease (APD), a rare subtype of Paget disease (PD), in six cases confined to the nipple. Due to the associated acantholysis, APD and acantholytic anaplastic (extramammary) PD (AAPD or AAEMPD) have been used interchangeably. This entity has previously been reported in mammary (Rayne and Santa Cruz, 1992; Mobini, 2009; Batalla et al., 2014) and extramammary locations (Oh et al., 2011; Lin et al., 2019; Satomi et al., 2024) (Table 1). In our review of existing English literature, this is the first case of AAPD in the vulva. The presence of invasion in this rare PD variant underscores the unique nature of this case with important implications for management.

2. Case presentation

An 87-year-old female presented with a 3-year history of recurrent vulvar Paget's disease. The lesion was initially discovered when she sought consultation for vaginal bleeding despite her history of hysterectomy for benign indications years prior. On physical examination, a large, beefy red vulvar lesion in the bilateral labia minora and clitoris extending across the midline and anteriorly was discovered. Biopsy of the vulvar lesion from an outside institution revealed EMPD. The patient was treated with topical imiquimod 5 % with partial response. Follow-up at 4 months revealed a similar lesion despite continued treatment. Eventually, WLE of the anterior vulva, including bilateral labia majora and clitoris was performed. Microscopic examination revealed EMPD with associated ulceration and acantholysis. Skin adnexal and surgical margin involvement was identified. Prominent acantholysis with villous-like projections into the acantholytic spaces was identified. The possibility of EMPD involving an existing warty dyskeratoma or

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acantholytic dermatosis was raised.

A recurrent erythematous plaque measuring 2 cm developed 6 months after initial excision in the right labia majora, at the previous positive margin site. Topical imiquimod was trialed for 8 weeks without response. Due to the increase in tumor size (3.0 cm), the patient decided to proceed with surgery.

WLE of the lesion was performed nine months after recurrence. Microscopic examination confirmed extensive EMPD with associated ulceration, marked chronic inflammation of the dermoepidermal junction, and stromal fibrosis. Adnexal and surgical margin involvement was seen. EMPD involving pseudoepitheliomatous hyperplasia, or a warty lesion were included in the differential diagnoses.

A second recurrent lesion, a U-shaped erythematous plaque, developed in the posterior perineum two months later. Despite initial topical imiquimod treatment, rapid lesion progression resulted in difficulties with urination. Physical examination revealed large beefy-red raised lesions, one protruding along the left (4 x 4 cm) and right vulva (2 x 2 cm). Rapid lesion enlargement necessitated WLE of the right and left vulva. Gross examination of both specimens revealed irregular tan, exophytic skin lesion, abutting the surgical margins (Fig. 1A). Histologic examination showed marked papillomatosis of the epidermis with acantholysis, acanthosis, hyperkeratosis (Fig. 1B), ulceration and granulation tissue (Fig. 1D). Prominent acantholysis, forming parabasal cleft- and fissure-like spaces was observed (Fig. 1C). The epidermis demonstrated full thickness cellular atypia, composed of an intimate admixture of two distinct cell populations: Paget cells and benign squamous cells (Fig. 1C, 2A, 2E and 2H). Solid sheets and clusters of Paget cells exhibiting round, vesicular nuclei, occasional prominent nucleoli, pale amphophilic cytoplasm, and brisk mitotic activity (1 to 5 mitotic figures per high power field; Fig. 1D) occupied the basal and parabasal portion of the epithelium. The distribution (single cells, solid nests, or gland-like structures) typical for PD was not observed. Whorls, nests, and sheets of bland squamous cells with small nuclei, inconspicuous nucleoli, prominent cell borders and low mitotic activity were seen in the mid-portion of the epithelium (Fig. 1C and 1D). Invasive tumor (Fig. 1E and 1F), arranged singly or in small irregular clusters, were identified in the dermis, The tumor cells have round, vesicular nuclei, prominent nucleoli, and eosinophilic cytoplasm. The greatest horizontal tumor dimension measured 2 mm, while the maximum depth of invasion measured 3 mm. Lymphovascular invasion (Fig. 1E) was noted.

Differential diagnoses included EMPD involving a warty lesion and squamous cell carcinoma. Immunostaining revealed strong KRT7 (Fig. 2B), HER2 (Fig. 2C) and GATA3 (Fig. 2I) staining in the Paget cells, while p63 antibody highlighted only the basal cells and benign squamous component (Fig. 2F). Alcian blue (Fig. 2G), mucicarmine and PAS-D highlighted mucin in rare Paget cells. KRT20, p16 (Fig. 2D) and SOX10 were negative in both components. Based on the histomorphology and IHC profile, acantholytic anaplastic extramammary Paget disease was favored.

The patient's post-operative recovery was unremarkable. Left inguinal lymphadenectomy was proposed for staging purposes, however, given the patient's advanced age and overall frailty, the patient declined the procedure.

3. Discussion

The vulva is the most common extramammary site for Paget disease (PD). PD can be primary, originating in apocrine or eccrine glands, or secondary when arising from underlying vulvar or extra-vulvar carcinoma. The majority of vulvar PD are not associated with carcinoma. EMPD usually manifests as an erythematous plaque or patch with associated scaling, exudation, and pruritus. Multicentricity and recurrence are frequent (Elder et al., 2018; Crum et al., 2018).

Extramammary Paget cells are postulated to originate either from the intraepidermal cells of apocrine gland ducts or from pluripotent keratinocyte stem cells (Orlandi et al., 2001; Matsumoto et al., 2007; Baldovini et al., 2015). Microscopically, the intraepithelial neoplastic cells (Paget cells) are disposed singly, in solid nests or gland-forming structures. The cells display vesicular nuclei, prominent nucleoli and abundant basophilic to amphophilic cytoplasm. Involvement of adnexal structures is common. In primary EMPD, Paget cells are consistently positive for KRT7 and CAM5.2, and often express CEA, GCDFP15, HER2,

Table 1
Clinical and pathologic features of previously reported cases of acantholytic anaplastic extramammary Paget disease.

Author/s	Number of cases	Age	Gender	Location	Clinical findings	Associated malignancy	Immunohistochemistry			Special stains
							Positive staining	Negative staining	Variable staining	Mucicarmine /Alcian blue/ PAS-D)
Rayne [4]	6	40–85	female	nipple	scaly erythematous lesions	yes	–	–	CEA, EMA, AE1/AE3	neg
Mobini [5]	2	51–98	female	nipple/ areola	oozing plaque	yes	AE1/AE3, KRT7, HER2, CAM5.2, HMWCK, p16	CEA, GCDFP-15, ER, PR	–	neg
Batalla [6]	1	81	female	nipple	erythema, erosion, crusted with exudate	yes	CEA, KRT7, CAM5.2, Ki67, E-cadherin	ER, PR, KRT20	–	–
Oh [7]	1	79	male	scrotum	pruritic erythematous plaque, verrucous papule	no	CEA, CAM5.2, EMA, KRT7, AE1/AE3, GCDFP-15	KRT20	–	neg
Lin [8]	1	63	male	esophagus	dysphagia	no	KRT7, KRT8/ 18, CEA, Ki67 and HER2	S100, HMB45, KRT5/6, p63, GCDFP-15	–	neg
Detweiler [14]	1	78	male	genito-crural crease	tender, erythematous plaque	no	KRT7, CEA, AE1/AE3, LMWCK	KRT20	–	–
Satomi [9]	1	83	male	esophagus	Rough esophageal epithelium	no	KRT7, CAM5.2, E-cadherin (weak)	p40, p63, KRT20	–	–

HMWCK – high molecular weight cytokeratin; LMWCK - low molecular weight cytokeratin; ER- estrogen receptor; PR- progesterone receptor; KRT- cytokeratin; EMA – epithelial membrane antigen; neg - negative.

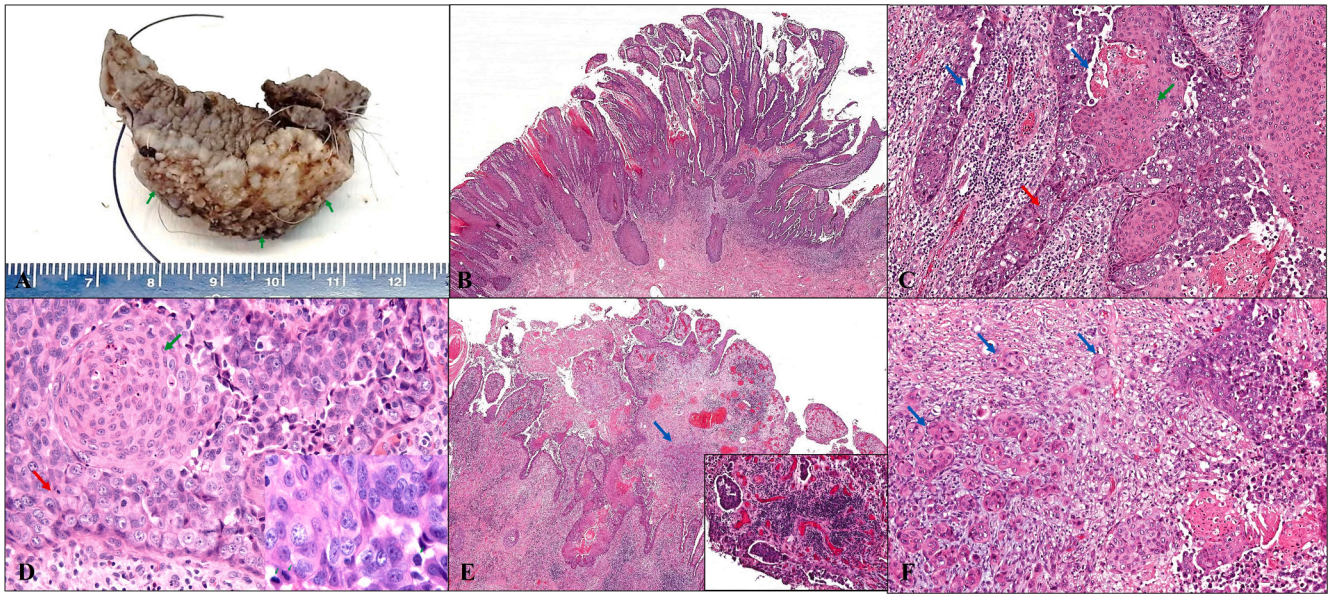

Fig. 1. A.) Wide local excision of the vulva shows irregular, tan exophytic skin lesion (green arrows), abutting the edge of the skin. B.) Microscopic examination reveals papillomatosis with marked acanthosis, hyperkeratosis and acantholysis of the epidermis, H&E, 10x. C.) Paget cells (basal and parabasal; red arrow) and benign squamous (middle of the epithelium; green arrow) along with acantholysis (blue arrow), H&E, 100x. D.) The Paget cells with round, vesicular nuclei, occasional prominent nucleoli, and pale cytoplasm (red arrows) are intermixed with whorls of bland squamous cells (green arrow) and numerous mitotic figures (green arrows; inset, H&E, 400x), H&E, 200x. E.) Both non-invasive and invasive components; invasive tumor cell clusters in the dermis (blue arrow) and lymphovascular invasion (inset; H&E, 100x) G.) Higher magnification shows invasive tumor cells (blue arrows) H&E, 100x. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

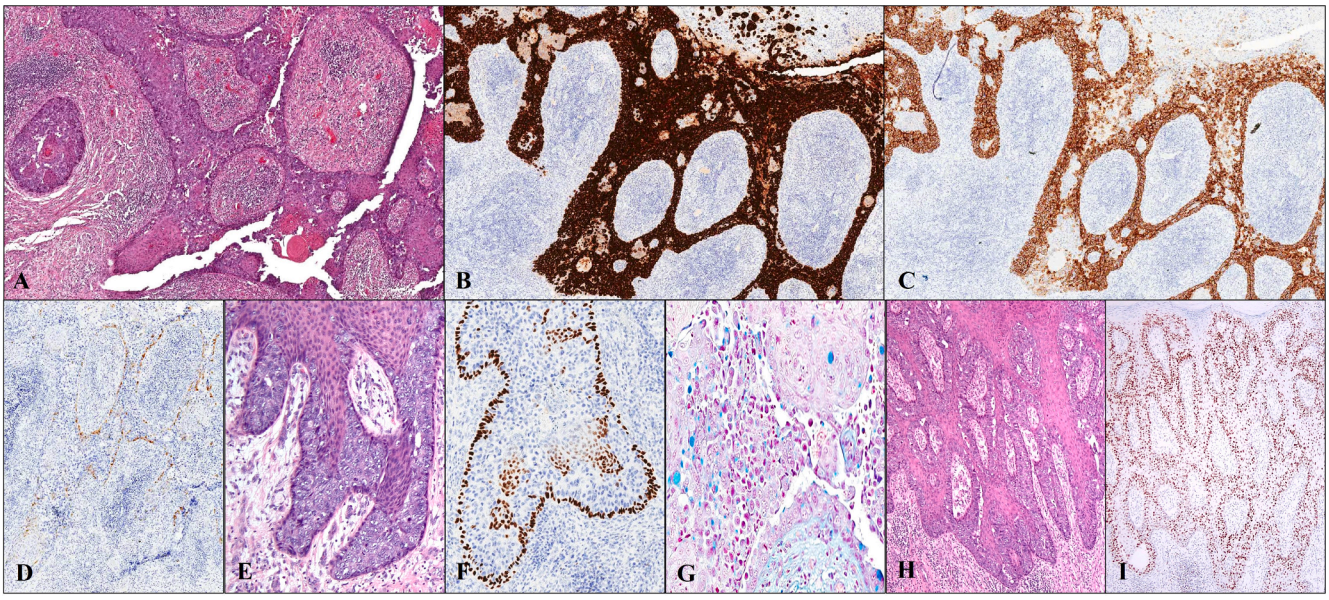

Fig. 2. A.) The epidermis demonstrates full thickness atypia and acantholysis, H&E, 40x. B.) Cytokeratin 7 (KRT7) and C.) HER2 immunostains (IHC) showing overexpression in Paget cells, while negative in the benign squamous components, 40x. D.) Both the Paget cells and squamous cells are negative for p16 antigen, 40x. E.) Two distinct cell types are present in the epidermis, with associated mixed dermal inflammation, H&E, 100x. E.) Benign basal cells and squamous cells display p63 IHC reactivity, 100x. G.) Mucin in rare Paget cells is highlighted by the Alcian blue stain, 200x. H.) Acanthosis and acantholysis of the epidermis, H&E, 40x I.) GATA3 antibody stains the Paget cells, 40x. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

CA125 and androgen receptor. Mucin in Paget cells is highlighted by Alcian blue, mucicarmine and PAS-D stains (Elder et al., 2018). Expression of high molecular weight cytokeratin (HMWCK; KRT5/6), melanocytic antigens, estrogen receptor and progesterone receptor is usually not seen in Paget cells (Detweiler et al., 2019).

Invasion in EMPD is defined as the presence of isolated Paget cells, clusters, glands, and sheets within the dermis. Invasive EMPD is associated with an unfavorable prognosis and a propensity for lymph node metastasis. Depth of invasion is one of the most important prognostic indicators of nodal metastasis, disease recurrence and survival in invasive EMPD (Elder et al., 2018; Hoang et al., 2022).

Anaplastic Paget disease (APD), first described by Rayne and Santa Cruz in 1992 (Rayne and Santa Cruz, 1992) in the breast, is a rare subtype of PD histologically resembling “Bowen disease”/human

papillomavirus (HPV)-associated high grade squamous intraepithelial lesion (HSIL). Half of their cases had invasive ductal carcinoma. APD exhibits full-thickness disorganized epithelial growth with marked cytologic atypia. "Anaplasia" was defined as moderate to marked cellular pleomorphism characterized by evidently hyperchromatic nuclei, prominent nucleoli, and increased nuclear-to-cytoplasmic ratio. Some cases lack the classic nesting architecture and relatively monotonous appearance typical of PD. Microscopic features that overlap with HSIL include full thickness epidermal atypia, loss of nuclear polarity, and cytologic anaplasia. Intraepidermal cleft-like acantholysis, absence of dyskeratotic cells, and basal layer preservation differentiate APD from HSIL. Acantholysis is the diagnostic hallmark of APD. Other features include associated ductal carcinoma or classic PD and intracellular lumina. Mucicarmine was uniformly negative in all 6 cases, and in contrast to classic EMPD, immunostaining (IHC) results (CEA, EMA, and KRTAE1/AE3) were variable.

Mobini (Mobini, 2009) reported 2 cases of AAPD presenting as scaly erythematous plaques in the nipple and areola. The mucin negativity and variable CEA staining previously described were confirmed (Rayne and Santa Cruz, 1992), and the cases demonstrated KRT7, HER2 and unusual p16 IHC positivity, with GCDFP-15 and HPV in-situ hybridization negativity. Ductal carcinoma in situ was present in both cases.

Lin et al. (Lin et al., 2019) described the first case of invasive AAEMPD with nodal metastasis in the esophagus. Initial biopsy of their patient was misdiagnosed as squamous cell carcinoma. Paget cells were KRT7, KRT8/18, CEA, and HER-2 positive, but were KRT5/6 and p63 negative.

While AAPD has been documented in both mammary and extramammary sites (Table 1), including the nipple (Rayne and Santa Cruz, 1992; Mobini, 2009; Batalla et al., 2014), scrotum (Oh et al., 2011), genitocrural crease (Detweiler et al., 2019) and esophagus (Lin et al., 2019; Satomi et al., 2024), this rare entity is unprecedented in the vulva. Microscopic features in our case were consistent with the original description, except for the presence of dyskeratosis and dermal and lymphovascular invasion. The diagnostic challenge arises from the intimate admixture of squamous proliferation and the presence of acantholysis. The IHC profile of AAEMPD shows some deviation and inconsistencies compared with classic EMPD (Table 1 and Table 2). Differential diagnoses include squamous cell carcinoma, nevoid melanoma, HSIL/vulvar intraepithelial neoplasia (VIN II or III) with pagetoid pattern (VIN III-P), warty dyskeratoma and pemphigus vulgaris. Immunostaining may aid in the diagnosis of difficult cases (Table 2).

Squamous cell carcinoma (SCC) is the primary differential diagnosis due to the full-thickness epithelial atypia and invasion. However, SCC lacks the bland squamous cells and acantholysis seen in AAEMPD. While KRT7 and HER2 are sensitive diagnostic markers for EMPD, they lack specificity and can also be expressed in squamous cell carcinoma (Elder et al., 2018; Orlandi et al., 2001; Williamson et al., 2000; Raju et al., 2003).

VIN III-P is a histologic variant of SCC in situ that can mimic AAEMPD on histologic sections because of similar histologic features, e.g., cytologically atypical cells with pale vacuolated cytoplasm in a pagetoid distribution. VIN III-P can be distinguished from AAEMPD by the absence of intraepidermal acantholysis and p63 and p16 positivity (Table 2) (Orlandi et al., 2001; Williamson et al., 2000; Raju et al., 2003; Memezawa et al., 2008; WHO, 2020). Neoplastic cells in VIN III-P and benign keratinocytes are highlighted by p63 immunostaining, hence, p63 can serve as a marker to differentiate AAEMPD from PBD (Memezawa et al., 2008). In our case, the Paget cells were p63 negative while p63 IHC reactivity is seen in benign keratinocytes.

Nevoid melanoma may display papillomatous growth and mimic AAEMPD but can be readily confirmed by the expression of melanocytic IHC markers (Elder et al., 2018).

Warty dyskeratoma presents as a benign keratinocyte proliferation with well-circumscribed cup-shaped epidermal invagination, acantholysis with suprabasal clefting, dyskeratosis, and mitoses. Unlike AAEMPD, it exhibits a connection with the pilosebaceous unit, keratinocytes lack cellular atypia and are the only population of cells seen (Elder et al., 2018).

Pemphigus vulgaris shows supra-basal intraepidermal acantholysis of keratinocytes but lacks cytologic atypia and Paget cells (Radoš, 2011).

HSIL-like features in EMPD (Quinn et al., 2004) and VIN III-P (Baldovini et al., 2015; Williamson et al., 2000; Raju et al., 2003) have been reported in male and female external genitalia. These cases lack the marked acantholysis, acanthosis and papillomatosis seen in AAEMPD. The coexistence of invasive and non-invasive EMPD with VIN has been reported (Orlandi et al., 2001; Matsumoto et al., 2007). This phenomenon is potentially explained by the presence of pluripotent stem cells, capable of squamous and glandular differentiation (Orlandi et al., 2001; Matsumoto et al., 2007; Baldovini et al., 2015).

Surgical resection with curative intent is the primary treatment modality for EMPD. Vulvar EMPD demonstrates a significant association with primary and extra-vulvar malignancies, primarily involving the lower gastrointestinal or urinary tract (Elder et al., 2018; Crum et al., 2018; Borghi et al., 2018). Consequently, standard management protocols incorporate imaging studies to exclude occult malignancies (Borghi et al., 2018; Kibbi et al., 2022). Conversely, autoimmune blistering disease are managed medically, while laser ablation represents a potential treatment option for VIN (Committee Opinion, 2017).

In conclusion, AAEMPD is a distinct variant of EMPD, characterized by epidermal acantholysis, papillomatosis, and acanthosis, in conjunction with intraepithelial proliferation of atypical glandular (Paget) and benign squamous cells. Microscopic features often overlap with other dermatologic entities, posing diagnostic challenges. Although associated with an increased risk of underlying malignancy, AAEMPD does not necessarily confer a poorer prognosis compared to classic PD. Definitive diagnosis demands a thorough assessment integrating histopathologic, immunohistochemical, and clinical findings. Due to divergent management options compared with other entities, pathologists must maintain a high index of suspicion for AAEMPD to avoid diagnostic misinterpretation.

Consent statement

Written informed consent was obtained from the patient for the publication of de-identified patient data and images for research and

Table 2
Immunohistochemical profile of acantholytic anaplastic Paget disease (AAPD) and its differential diagnoses.

	Mucin	AE1/AE3	CAM5.2	KRT7, KRT20	p63	GCDFP-15	CEA	HER2	Melan A, S100	Others
AAPD	−	+	+	+, −	−	+/-	+/-	+	−, −	See Table 1
Extramammary Paget Disease	+(40–90 %)	+	+	+,+/-	−	+/-	+	+	−, −	KRT13, KRT19, KRT8
Squamous cell carcinoma	−	+	−	−/+, −	+	−	−	−/+	−, −	p40, EMA, KRT5/6, MNF116, HMWCK 34βE12
VIN III with pagetoid pattern	−	+	−	+/-, −	+	−	−/+	−	−, −	HMWCK 34βE12, KRT5/6, p16, KRT19, KRT13
Melanoma	−	−	−	−, −	−	−	−	−	+, +	HMB-45, SOX10, tyrosinase

educational purposes.

CRediT authorship contribution statement

Flora Mae G. Sta. Ines: Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Julia R. Salinaro:** Writing – review & editing, Methodology. **Mary Marchese:** Writing – review & editing, Methodology. **Cara A. Mathews:** Writing – review & editing, Methodology. **M. Ruhul Quddus:** Writing – review & editing, Visualization, Supervision, Methodology, Formal analysis, Conceptualization.

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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