A case report on primary cutaneous mucoepidermoid carcinoma of the vulva and its clinico-pathologic identity*

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ABSTRACT

Mucoepidermoid Carcinoma (MEC) is an epithelial malignant tumor that was first described as a salivary gland malignancy. Though common in salivary gland, it is extremely rare in the vulva with only 2 cases reported in the English language literature and none yet in the Philippines. Due to its low incidence, prognosis and definitive management is still unclear.

This is a case of a 68-year-old woman with a history of vulvar pruritus and vulvar mass at the left labia majora. Punch biopsy and review of slides revealed Invasive Squamous Cell Carcinoma, Non-Keratinizing type. She underwent Radical Vulvectomy and Bilateral Lymph Groin Dissection; Wide Excision of Perineal Area; Protective Transverse Loop Colostomy; Gracilis Myocutaneous Flap with Identification of Right and Left Median Circumflex Artery with a final histopathology report of Primary Cutaneous MEC of the vulva with lymph node metastasis.

Keywords: Vulvar Carcinoma, Primary Cutaneous Mucoepidermoid Carcinoma

INTRODUCTION

Mucoepidermoid Carcinoma (MEC) is a distinct type of tumor characterized by mixed epidermoid cells, mucus-secreting cells, and intermediate cells in various proportions. It is a unique entity that was first described in 1945 by Steward et al by reviewing a series of 45 salivary gland tumors[1,2]. This is a relatively common neoplasm of the salivary glands, representing about 30% of all malignant salivary tumors but rarely arises in other sites, including esophagus, anal canal, skin of the breast, lacrymal sac, thymus, thyroid gland, lung or uterine cervix[2,3]. A primary cutaneous MEC is an extremely rare case that has different behavior and prognosis from a metastatic salivary gland MEC[1].

This is a case of a primary cutaneous MEC of the vulva in a 68-year-old woman who presented with a history of intermittent vulvar pruritus and vulvar mass. To the best of our knowledge, this is the first reported case of vulvar carcinoma having this rare pathology in our local setting.

OBJECTIVES

1. To present a case of Primary Cutaneous Mucoepidermoid Carcinoma of the Vulva
2. To describe the clinico-pathologic characteristics of MEC
3. To explain how MEC may occur in the vulva
4. To discuss the management and other treatment options for a primary cutaneous MEC of the vulva

CASE

A 68-year-old, G5P4 (4014), Filipino, widow, sought consult due to a 10-year history of intermittent vulvar pruritus. She had no other symptoms like difficulty of swallowing, weakness, pain or numbness on any part of her face. She is a diagnosed diabetic for around 20 years maintained to Sitagliptin 100 mg/tab OD and has a family history of hypertension, diabetes and breast malignancy, on the maternal side. The patient is a non-smoker and non-alcoholic beverage drinker with no history of elicit drug use. She was regularly menstruating since 12 years old, lasting for 3-4 days, consuming 1-2 pads per day, moderately soaked with no dysmenorrhea. Her first coitus was at 24 years old with one sexual partner with unknown promiscuity. She has no history of oral contraceptive use. Papsmear result was normal. She had 5 pregnancies, 4 of

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which were carried to term, all vaginally delivered, with one abortion. Patient was menopause since age 50.

History started 10 years prior to admission when patient had severe vulvar pruritus. She sought consult with a private physician and was treated with an antifungal ointment which afforded temporary relief. During the years that followed, intermittent vulvar pruritus was observed, even with the antifungal medication.

Four months prior to admission, she noted a 3.0 x 3.0 cm cystic, non-tender lesion on her left labia majora. Consult and biopsy with her OB-GYN revealed Invasive Squamous Cell Carcinoma, Non-Keratinizing type. Review of slides revealed the same findings (Figure 1).

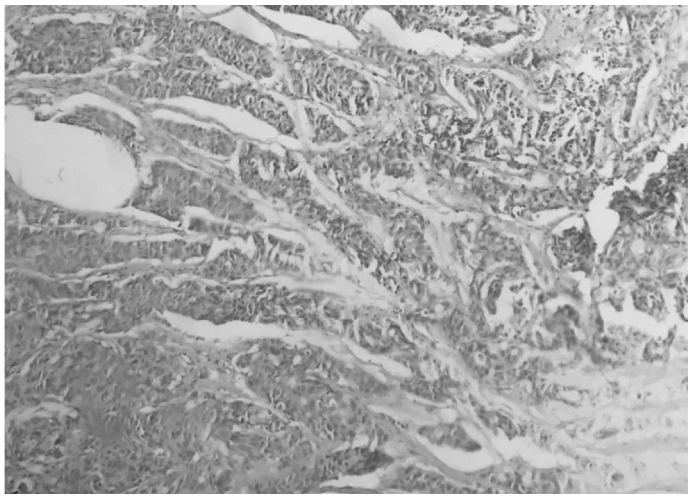
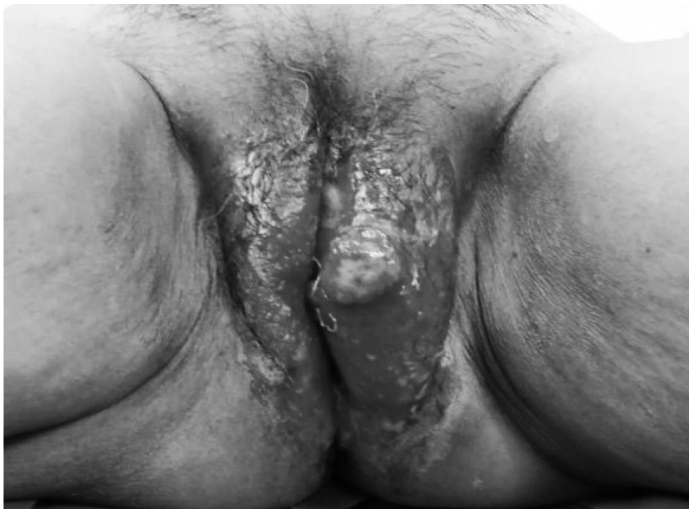


Figure 1. Review of slides with sheets of squamous cells

On pelvic examination, the vulva was erythematous with multiple areas of hypopigmentation from mons pubis down to the anus and extending to the bilateral genital crural folds. There was a 5.0 x 4.0 x 3.0 cm cystic, exophytic, non-tender mass on the left labia majora (Figure 2). Speculum exam revealed a smooth cervix measuring 1.5 x 1.5 cm with no gross lesion. Internal and rectovaginal examination were both unremarkable.

The patient underwent Radical Vulvectomy with Bilateral Groin Node Dissection; Wide Excision of Perineal Area; Protective Transverse Loop Colostomy; Gracilis Myocutaneous Flap with Identification of Right and Left Median Circumflex Artery. (Figures 3 and 4). A Multidisciplinary Team involving Gynecologic Oncology, Colorectal Service and Plastic Surgery, performed the procedure.

The specimen measured 13.0 x 11.0 x 5.5 cm with a fungating, solid mass measuring 5.0 x 4.5 x 4.0 cm on the left labia majora. The external surface of the mass showed tan-brown, roughly ovoid to irregular tissue with tan-white patches (Figure 5). On cut section, the mass showed tan-white, smooth, solid surfaces (Figure 6). The mass was located 4.3 cm anteriorly, 4.5 cm posteriorly, 1.5 cm laterally and 4.5 cm medially. There were inguinal lymph nodes harvested, largest measured 2.0 x 3.4 x 1.6 cm from left deep inguinal node. There was a negative invasion of tumor in anal sphincter and anal canal. Final histopathology



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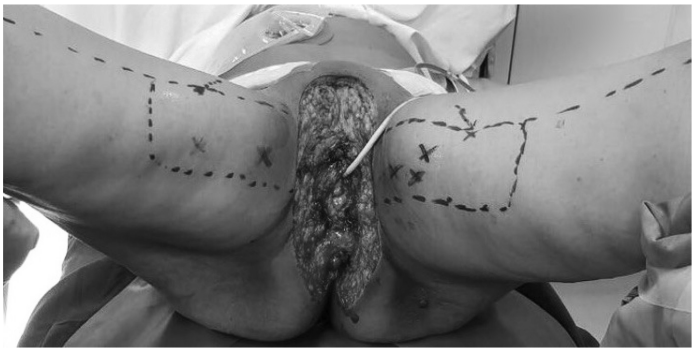

Figure 3. Gracilis Myocutaneous Flap

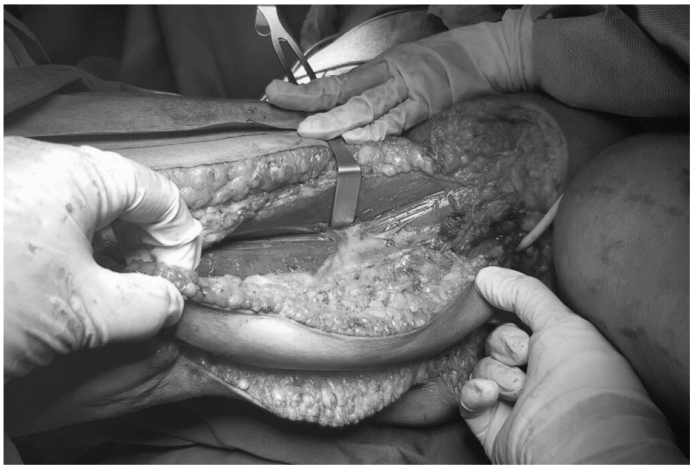

Figure 4. Identification of Right and Left Median Circumflex Artery

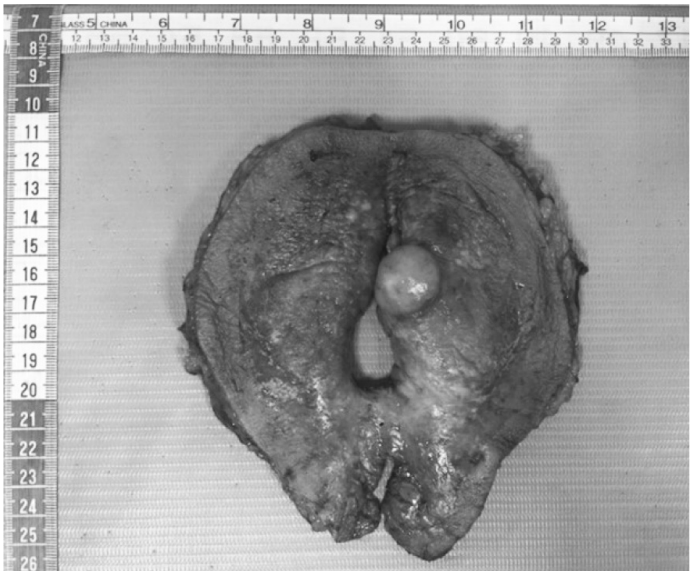

Figure 5. The specimen measured 13.0 x 11.0 x 5.5 cm with a fungating solid mass measuring 5.0 x 4.5 x 4.0 cm on the left labia majora

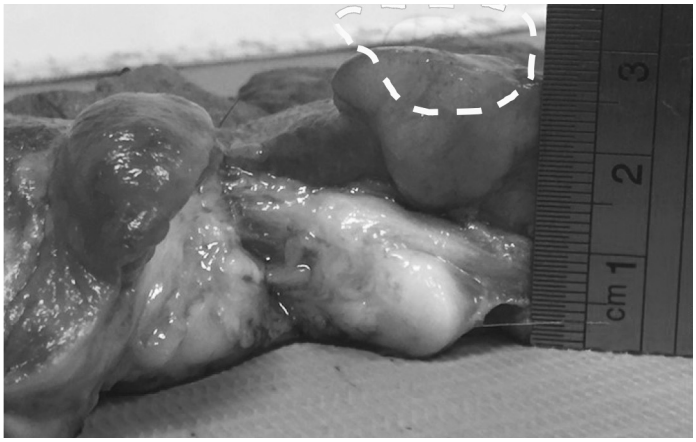

Figure 6. Cut sections through the mass show tan-white, smooth, solid surfaces

DIAGNOSIS:
Radical Vulvectomy with Bilateral Groin Node Dissection.

- **PRIMARY CUTANEOUS MUCOEPIDERMOID CARCINOMA, HIGH GRADE, VULVA.**
- **TUMOR SIZE: 5.0 CM IN WIDEST DIMENSION.**
- **POSITIVE FOR LYMPHOVASCULAR SPACE INVASION.**
- **POSITIVE FOR SKIN ULCERATION.**
- **POSITIVE FOR MALIGNANT CELLS:**
  - **ONE (1) "LEVEL I DEEP FEMORAL LYMPH NODE, LEFT".**
  - **TWO OUT OF FOUR (2/4) "LEVEL II DEEP FEMORAL LYMPH NODES, LEFT", WITH EXTRACAPSULAR TUMOR INVOLVEMENT.**
  - **ONE (1) "LEVEL III DEEP FEMORAL LYMPH NODES, LEFT", WITH EXTRACAPSULAR TUMOR INVOLVEMENT.**
- **NEGATIVE FOR TUMOR INVOLVEMENT:**
  - **CLITORIS.**
  - **ALL SIX (6) SUPERFICIAL LYMPH NODES, LEFT.**
  - **ALL FIVE (5) SUPERFICIAL LYMPH NODES, RIGHT.**
  - **BOTH TWO (2) "LEVEL I DEEP FEMORAL LYMPH NODE, RIGHT".**
  - **BOTH TWO (2) "LEVEL II DEEP FEMORAL LYMPH NODE, RIGHT".**
  - **ALL THREE (3) "LEVEL III DEEP FEMORAL LYMPH NODE, RIGHT".**
  - **ALL SURGICAL MARGINS.**
    - **THE CLOSEST TUMOR-FREE MARGIN IS AT THE BASE MEASURING 0.5 CM.**
- **AJCC: pTIbN2cMx.**
- **FIGO STAGE: IIIC.**

Figure 7. Surgical Pathology Report of the patient

was Primary Cutaneous Mucoepidermoid Carcinoma of the Vulva, High Grade (Figure 7). Microscopically, section of the vulvar mass showed tissues harboring a tumor comprising mostly of solid sheets of atypical squamous (epidermoid) cells (Figure 8) intermingling with intermediate cells and mucin-producing cells without glandular formation (Figure 9), some appearing as signet cells with eccentrically displaced nuclei (Figure 10). More than four mitotic figures were noted in ten high power fields with nuclear atypia (Figure 11). The tumor cells were noted to invade up to 7.5 mm of desmoplastic stroma.

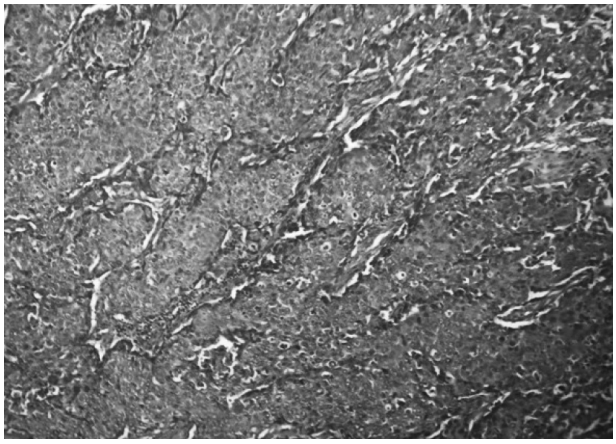

Figure 8. Solid sheets of atypical

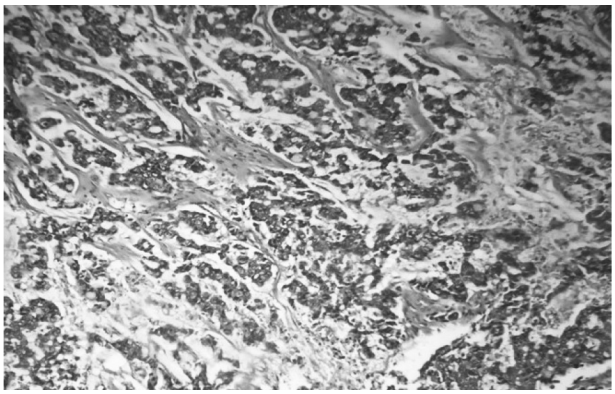

Figure 9. Lakes of mucin from mucin-producing cells

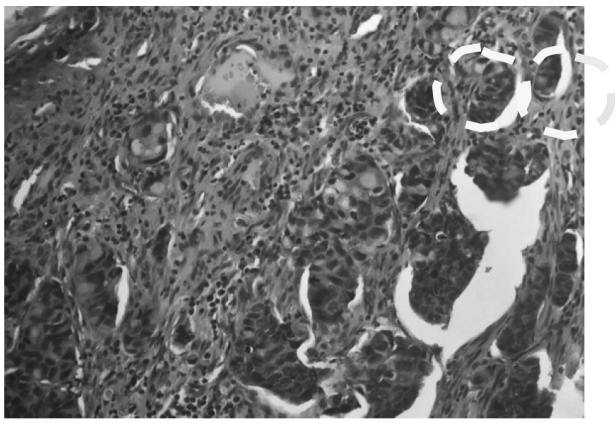

Figure 10. Mucin producing signet cells with eccentrically displaced nuclei

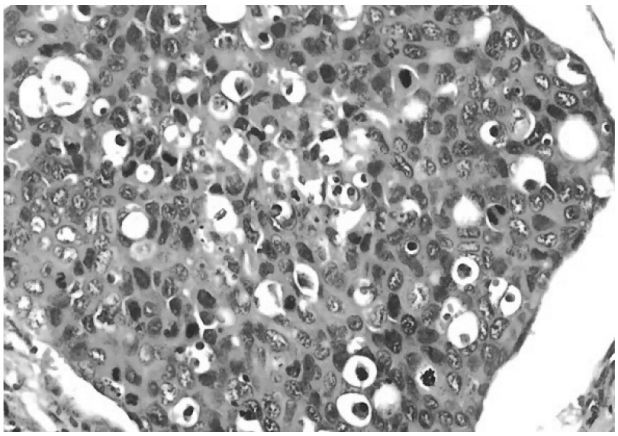

Figure 11. Mitosis (yellow) with nuclear atypia

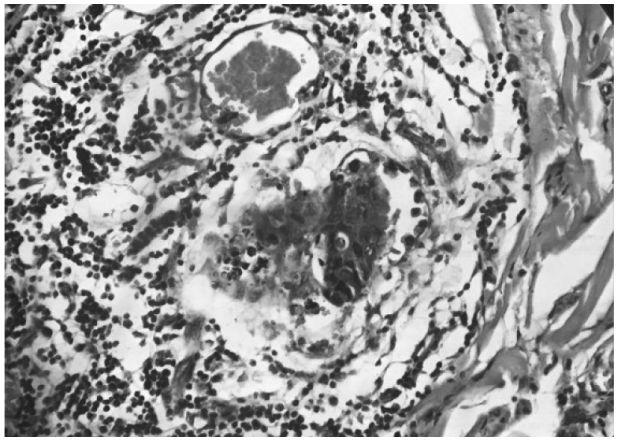

Figure 12. Lymphovascular space invasion was positive for malignant cells

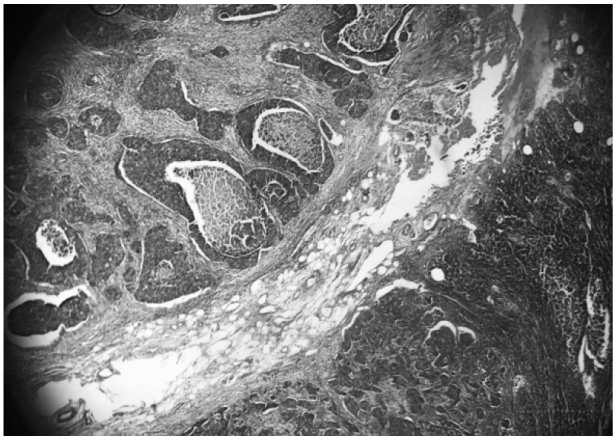

Figure 13. Level I deep femoral lymph node positive for malignant cells with extracapsular spread

Positive for malignant cells were the following: 1.) Lymphovascular space invasion (Figure 12), 2.) Skin ulceration, 3.) 1 Level I deep femoral lymph node, left, 4.) 2 Level II deep femoral lymph node, left, with extracapsular tumor involvement and 5.) 1 Level III deep femoral lymph node, left, with extracapsular tumor involvement (Figure 13).

Post-operatively, the patient was maintained on indwelling foley catheter and was advised to keep both legs abducted at hips level and spread apart (Figure 14). Change of dressing and application of aniti-bacterial ointment was done daily. However, on the 5th post-operative day, the patient was noted to have minimal wound discharge at the apical area of the flap which developed with epidermolysis on both distal ends of the flap. She then underwent wound debridement, suturing and recatheterization (Figure 15) which eventually led to better wound healing until discharge.

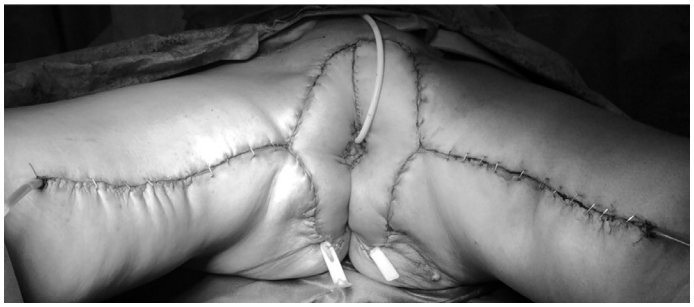

Figure 14. Post-operative

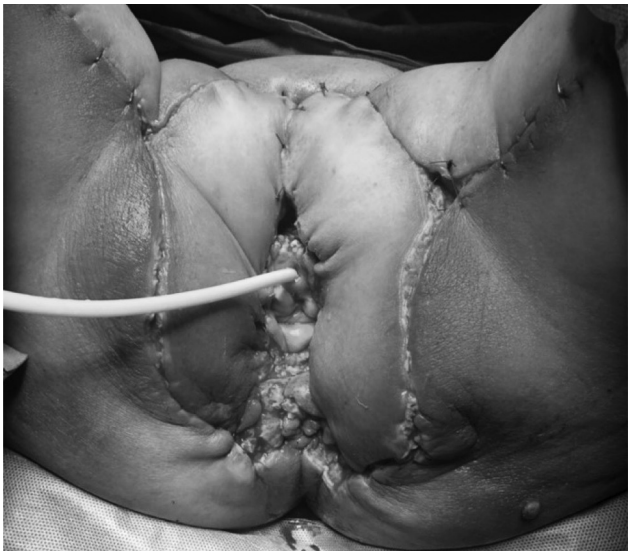

Figure 15. Post wound debridement, suturing and recatheterization

Based on the histopathologic findings, the patient was diagnosed to have Primary Cutaneous Mucoepidermoid Carcinoma of the vulva, stage IIIC (Table 1)[4]. As recommended by the Society of Gynecologic Oncology of the Philippines Clinical Practice Guidelines, this advanced stage disease requires adjuvant chemotherapy and radiation.

The dilemma was to come up with the best mode of treatment for this patient given its rare histopathologic diagnosis and to better understand the behavior of the disease.

Table 1. 2009 FIGO Staging for Vulvar Cancer[4]

Stage I	Tumor confined to the vulva		
	IA	Lesions ≤ 2 cm in size, confined to the vulva or perineum and with stromal invasion ≤ 1.0 mm*, no nodal metastasis	
	IB	Lesions > 2 cm in size or with stromal invasion >1.0mm*, confined to the vulva or perineum, with negative nodes	
Stage II	Tumor of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes		
Stage III	Tumor of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguino-femoral lymph nodes		
	IIIA	(i)	With 1 lymph node metastasis (≥5 mm), *OR*
		(ii)	With 1-2 lymph node metastasis(es) (<5 mm)
	IIIB	(i)	With ≥2 lymph node metastases (≥5 mm), *OR*
		(ii)	With ≥3 lymph node metastases (< 5 mm)
	IIIC	With positive nodes with extracapsular spread	
Stage IV	Tumor invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures		
	IVA	Tumor invades any of the following:	
		(i)	Upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, *OR*
		(ii)	fixed or ulcerated inguino- femoral lymph nodes
	IVB	Any distant metastasis including pelvic lymph nodes	

The depth of invasion is defined as the measurement of the tumor from the epithelialstromal junction to the adjacent most superficial dermal papilla to the deepest point of invasion.

DISCUSSION

Vulvar cancer is a rare disease, representing only 3-5% of all tumors of the female genital tract and 1% of all cancers in female[5]. Ninety to ninety-five percent of them are squamous cell carcinomas (SCC), and the remaining 5-10% being melanomas, sarcomas and basal cell carcinomas[6]. Its annual incidence is 1.5 per 100,000 women per year, increasing constantly with age and the average age at diagnosis being 65-75 years old[7, 8]. The disease is most commonly observed in postmenopausal women presenting primarily with localized pruritus, vulvar mass, bleeding, or pain[5,6]. The prognosis is favorable with a 5-year survival rate of 70-90% for patients with negative nodes compared to 25-41 % for those with lymph nodes metastasis[7,8].

The major risk factors for the development of vulvar cancer include increasing age, smoking, immunosuppressive disease and chronic skin diseases of the vulva such as lichen sclerosus, or Vulvar Intraepithelia Neoplasia but these trends can most likely be attributed to an increasing number of human papillomavirus (HPV) infections[6,9]. The patient's age and immunosuppressive state might have predisposed her to having the disease. And though no histopathologic diagnosis was made, her intermittent vulvar pruritus was suggestive that she might have a chronic skin disease like lichen sclerosus, which is another risk factor for the development of vulvar cancer.

Treatment of vulvar cancer used to be primarily surgical, but radiation therapy and, to a lesser extent, chemotherapy have been progressively integrated into the treatment protocol over the past 20 years. Surgery may involve different methods depending on the stage and lymph node involvement[10]. Not all patients who undergo radical vulvectomy necessitates extensive reconstructive operation such as that of the patient. Further, neoadjuvant or adjuvant treatment may be indicated based on stage and individual patient factors. Therefore, management for vulvar carcinoma has evolved into an individualized multidisciplinary approach[6,10].

Those cases wherein large denudated defects are expected in the perineum following radical vulvectomy or perineal surgery in which primary closure would likely result in post-operative dehiscence of the wound incision are best co-managed with Plastic Surgery for better post-operative outcome. For this patient, a myocutaneous flap was done to cover the vulvar defect with a cutaneous structure having its own non-traumatized blood supply that can produce a healed wound with a normal functioning vulva. This was followed by a prophylactic transverse loop colostomy done by the Colorectal Service to prevent infection in the anal area while the wound is still in the healing process. Post-operatively, the patient acquired wound dehiscence, which is a common complication of a surgical procedure in vulvar carcinoma. Other possible complications include lymphedema and infection, which did not occur in the patient.[10]

The final histopathology revealed primary cutaneous MEC of the vulva. This should be differentiated from a metastatic salivary gland MEC since the latter usually presents with a more aggressive disease and poorer prognosis. In terms of genetic composition, both harbor CREB Related Transcriptional Co-activator 1 (CRCT1) rearrangements. However, Mastermind Like 2 (MAML2) mutations, which were associated with greater metastatic potential and worse prognosis, were only reported in salivary gland MECs[1,11]. In terms of immunohistochemistry, CK7, PanCK, EMA, carcinoembryonic antigen and p63 gene may be used which are all expected to have positive results for primary cutaneous MEC. However, these markers are considered non-specific and of little clinical use[1,3]. Immunohistochemistry was not done to the patient. But review of systems and physical examination, were not suggestive of a primary salivary gland tumor.

Regardless of the primary site, MECs share distinct histopathological features that allow for its straightforward diagnosis[11]. Its unique diagnostic criteria are the predominance of atypical squamous cells or epidermoid cells, scattered or clumped intermediate cells which range from small basal cells with basophilic cytoplasm to larger cells which commonly form clusters with eosinophilic cytoplasm, and cells containing intracytoplasmic mucin without any glandular differentiation. Thus, MEC's distinct

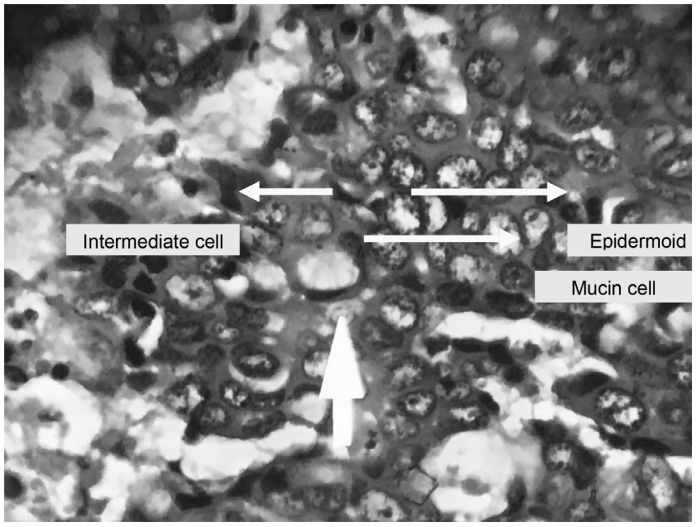

Figure 16. The patient's triphasic cellular morphology of MEC

triphasic cellular morphology includes epidermoid cells, mucus cells, and intermediate cells[1-3,11], which were all seen in the patient (Figure 16).

This complex composition of MEC explains the unmatched results of the patient's vulvar biopsy and review of slides with that of the final histopathology after the radical vulvectomy, implicating that the SCC found in the the first two pathological studies was just a part of the whole vulvar pathology.

Due to its extreme rarity, more precise diagnosis of MEC remains to be a challenge for the pathologists. The most common mimics of MEC are Adenosquamous Carcinoma (ADS) and SCC. MEC may be erroneously interpreted as SCC or ADS when the epidermoid cell population and keratinization were prominent in the tumor[12]. But it can be distinguished from the the SCC or from other mucin producing cells by the presence of three cell types as previously mentioned, and also from ADS by the absence of glandular formation[12,13]. Therefore, Chenevert et al. suggested that thorough search for overlying dysplastic squamous mucosa and increased awareness on the different histopathologic features can improve accurate diagnosis of the disease[13]. In addition, obtaining sufficient tissue from different parts of the lesion should be made to be able to have a more precise diagnosis for these rare cases[1,2].

A clinico-pathologic differentiation of MEC from other vulvar diseases is noteworthy since MEC, are usually more aggressive due to its mucin content, which has a value for the prediction of clinical surveillance. Also, MECs generally have a higher potential for metastasizing to regional lymph nodes than non-mucin-secreting tumors[13]. There were reported cases of MEC in unusual locations such as the liver, ovary and cervix, all presented with recurrences and mortalities despite adjuvant chemotherapy, with or without radiation[2,13,14]. These may signify this type of tumor's aggressive behavior, just like in the patient who presented with a high grade carcinoma, an advanced stage disease and positive lymph node metastasis. Thus, the high grade MEC lesions in other sites having poor prognosis may also hold true for the vulva.

On how a salivary gland tumor appeared in the vulva is unusual and is still unclear. Two hypotheses may explain its etiopathogenesis. First, due to their similarities in embryonic germ layer origin, histologic structures and functions, salivary glands have been suggested to be derived from sweat glands, which are present in labia majora. Thus it can be postulated that the primary cutaneous MEC of the vulva may have been developed from an ectopic salivary gland derived from a sweat gland[1]. However, after thorough examination by the pathologist, no salivary gland was found in the patient's submitted specimen.

Another hypothesis, which is a more plausible explanation for the patient's disease, is that High-Risk Human Papillomavirus (HR-HPV), a known risk factor for vulvar carcinoma, may be involved in the etiology of MEC lesions. In 2013, Isayeva et al. reported that the detection rate of HR-HPV in salivary gland MEC has been increasing over time. Their study had demonstrated the presence of transcriptionally active, biologically relevant, HR-HPV in approximately one-third of MEC. HR-HPV oncoproteins were thought to promote MEC as a later event in multistep carcinogenesis. This could be through the additive impact of the HR-HPV E6 and E7 oncoproteins on overall loss of tumor suppression function[15]. Their study broadens the scope of associations between HR-HPV and head and neck neoplasia, which can aid in the understanding of the etiology of MEC in other sites, especially in the vulva. The patient was not tested for HPV DNA. However, on histopathology, she presented with koilocytes which are squamous epithelial cells that have undergone several structural changes (Figure 17), suggestive of an HPV infection.

Mucoepidermoid carcinoma in salivary glands may be classified into low-, intermediate-, and high-grade, based on scoring of the cystic component, perineural invasion, cellular nuclear atypia and mitotic activity as suggested by the Armed Forces Institute of Pathology (AFIP) / World Health Organiztion (WHO)[3]. Applying this grading system to the patient, she was evaluated to have a high grade tumor due to < 20% cystic component (Figure 8), its mitotic activity of > 4 in ten high power fields and presence of nuclear atypia (Figure 11) (Table 2).

The histological grade, though there is no single grading system accepted universally, is an important survival prognosticator in MEC of salivary gland tumors. The 5-year overall survival (OS) and disease-free survival

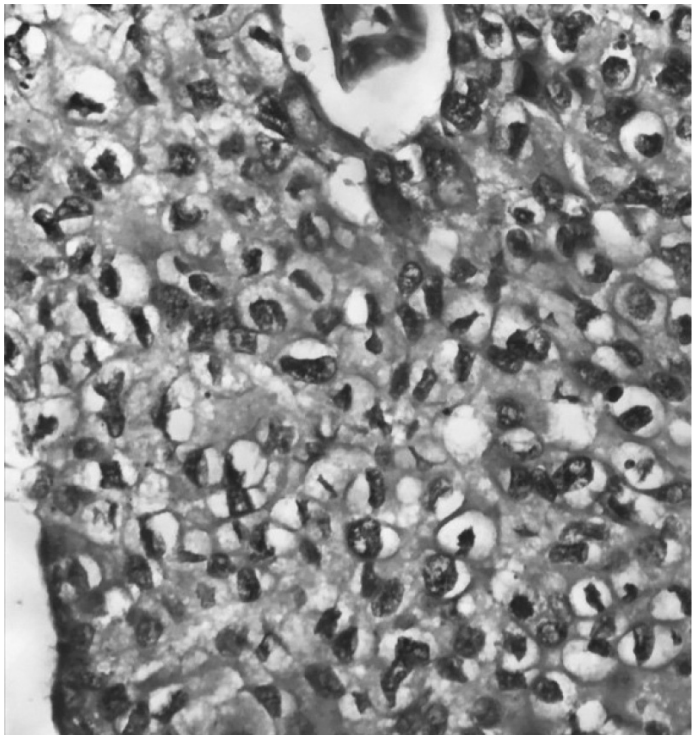

Figure 17. Koilocytes (with moderately enlarged nucleus displaced by a large perinuclear vacuole) as a result of HPV infection

	AFIP
Cystic component	(<20%) 2
Perineural invasion	2
Necrosis	3
≥4 Mitoses per 10 hpf	3
Anaplasia/Nuclear atypia	4
Low-grade:	**0 – 4**
Intermediate-grade:	**5-6**
High-grade:	**≥7**

AFIP - Armed Forces Institute of Pathology

Table 2. Basis of high-grade lesion of the patient based on MEC Grading System suggested by AFIP[3]

(DFS) rates of low-grade and intermediate-grade MEC were 93% and 88%, respectively. Whereas the 5-year OS and DFS rates of high-grade MEC were approximately 40-50% and 20-40%, respectively[3]. Whether or not this observation is applicable in primary cutaneous MEC of the vulva is currently unknown. Further investigation is

Case	Age (years)/sex	Anatomical site and other history	Tumour size (cm)	Histological grade[a]	Treatment and course	t(11;19) by RT-PCR	CRTC1 by FISH	MAML2 by FISH	IHC	Status
Primary cutaneous MEC										
1	51/F	Right cheek lesion	0·5	L	Excision	No	Rearranged	No evidence of rearrangement	NA	LW: 14 years
2	49/F	Adnexal malignancy, left lower eyelid	0·4	L	Block resection after LR	No	Rearranged	No evidence of rearrangement	CK7+ CK20−	LW: 4 years 2 months
3	71/F	Vulval mass	0·4	L	Radical hemivulvectomy	No	Rearranged	No evidence of rearrangement	NA	DU: 6 years 7 months
4	56/M	Recurrent adnexal carcinoma	0·9	L	Mohs surgery	No	Not informative	Not informative	CEA+ CK20−	LW: 19 years
5	77/F	Vulval mass; bone extension by imaging	2·2	H	Radiation therapy after LR	No	Rearranged	No evidence of rearrangement	NA	DOT: 2 months
6	39/M	Skin lesion behind right ear; mastoid process	0·7	L	Biopsy	NA	NA	NA	NA	LW: 2 years 7 months
7	9/M	Occipital mass, scalp[3]	5	L	Excision, LR × 2	No	Rearranged	No evidence of rearrangement	CK7+ CEA+ CK20−	LW: 2 years 10 months
8	79/F	Firm, painless, nonfixed mass, axilla[1]	3·7	L	Excision	NA	NA	NA	CK7+ CEA+ EMA+ CK20−	LW: 5 years 9 months
Noncutaneous MEC[b]										
9	46/F	'Breast cancer', right upper outer quadrant	1·6	NA	Lumpectomy	No	Not informative	Amplified	NA	LW: 7 years 10 months
Glandular MEC metastatic to the skin[c]										
10	58/M	Multiple bone lesions and left mediastinal mass; history of bronchial MEC	> 2	NA	Palliative care	Yes	Rearranged	Rearranged	NA	DOT: 9 months
11	50/F	Shoulder and liver masses; history or parotid MEC	NA	NA	Excision	No	Not informative	Not informative	NA	No FU

[a]Histological grade based on cytological features: high-grade tumours showed focal necrosis, brisk mitotic activity or anaplasia (Fig. 1). [b]The breast can be viewed as a specialized cutaneous appendage; we found MAML2 alterations only in case 9. [c]MEC of the salivary glands can initially present as cutaneous metastasis with identical histological appearance and has been reported in the absence of a recognized head and neck primary tumour or after many years of disease-free interval.[5] We excluded a prior diagnosis of MEC in all cases of primary cutaneous MEC. RT-PCR, reverse transcription-polymerase chain reaction; FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; MEC, mucoepidermoid carcinoma; H, high-grade; L, low-grade; LR, local recurrence; CK, cytokeratin; CEA, carcinoembryonic antigen; EMA, epithelial membrane antigen; LW, living and well; DU, dead, unrelated; DOT, died of tumour; FU, follow-up; NA, not applicable/not available for testing/not tested.

Table 3. Demographics, clinical pattern and treatment outcomes of reported cases of Primary Cutaneous MEC (11)

warranted to determine the prognosticating role of the histological grading to this type of carcinoma.

Due to the limited number of cases presented, primary cutaneous MEC of the vulva follows no therapeutic algorithm and prognosis pattern. In 2014, Ng et al. presented 20 reported cases of Primary Cutaneous MEC and their treatment outcome. Only two of which were found in the vulva, both presented in post menopausal age such as in the patient. The first underwent wide local excision and was diagnosed as low-grade with longer survival time and had no evidence of disease until death. The other was evaluated to have high grade tumor. She underwent radiation after tumor recurrence and died of tumor with only 2 month survival time (Table 3)[1,11].

Due to the rarity of the disease, the specific chemotherapy regimen for primary cutaneous MEC of the vulva has not yet been established. The reported chemotherapy regimens for MEC found in uncommon sites were based on the standards for salivary gland tumors[2]. Reported cases and previous experiences help determine the treatment choice of clinicians. For this case, the patient was given a platinum based chemotherapy with Paclitaxel, following the recommended treatment for advanced stage vulvar carcinoma, which are also used in salivary gland MECs[16].

Currently, some researchers are suggesting that molecular targeted chemotherapy including monoclonal antibodies, anti-epidermal growth factor receptor (EGFR) or anti vascular endothelial growth factor (VEGF) based regimen might be a promising strategy for the treatment of MEC in salivary glands[2]. In a study by Nakano et al and Lujan et al, all high-grade MECs were found to have either HER2 or EGFR gene copy number gains and were associated with poorer prognosis. In contrast, the vast majority of low- and intermediate-grade MECs were negative for such genetic abnormality[3,19]. A model of CRTC1–MAML2-induced activated AREG–EGFR signaling was presented by Chen et al in 2014, suggesting that inhibiting AREG–EGFR signaling with anti-EGFR-targeted therapies, including antibodies that interfere with ligand–EGFR interaction or small molecules that block EGFR tyrosine kinase may block MEC carcinogenesis (Figure 18)[18]. This EGFR signaling was also identified in a recent study by Yan et al, as a promoter of carcinogenesis in MEC, together with p53 mutations. These observations suggest an overall role of EGFR in the pathogenesis of MEC and implicate the pathway as a possible therapeutic target[20].

On the other hand, angiogenesis is an important part in many biological processes, both in physiological and in pathological conditions. Literatures show that the growth and metastasis of solid tumors are dependent on the formation of new blood vessels. And among the known angiogenic factors, it is the vascular endothelial

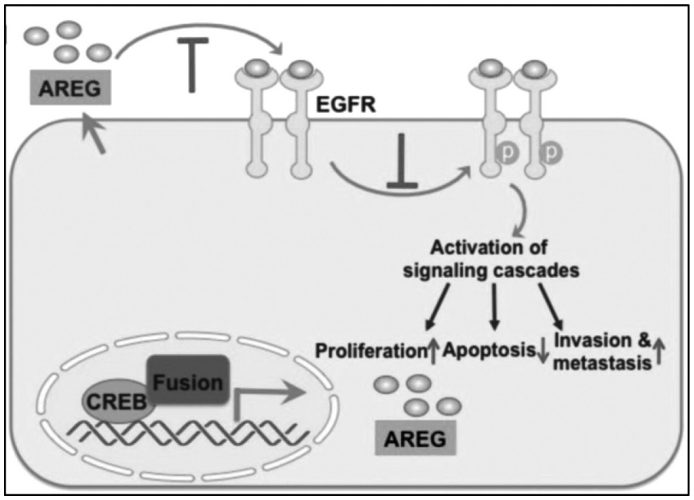

Figure 18. A model of CRTC1–MAML2-induced activated AREG–EGFR. The CRTC1–MAML2 fusion oncoprotein interacts with and coactivates the transcription factor CREB, leading to upregulation of the EGFR ligand AREG expression. The secreted AREG ligand in return activates EGFR signaling in autocrine manner that critically supports fusion- positive MEC cell growth and survival. Consequently, inhibiting AREG–EGFR signaling with anti-EGFR-targeted therapies (including antibodies that interfere with ligand–EGFR interaction or small molecules that block EGFR tyrosine kinase might be an effective approach to block human fusion-positive MEC[(18)].

growth factor (VEGF) that has a central role in controlling the neoplastic angiogenic process. VEGF was found to be significantly more expressed in high grade salivary gland malignancies and its high levels predict a poor prognosis. The use of anti-VEGF may lead to regression of existing tumor vasculature and inhibition of new and recurrent tumor vessel growth, both leading to reduction in tumor size and inhibition of tumor growth[21,22].

These treatment options are more expensive and less available as compared to the more commonly used chemotherapy drugs. However, with further studies, these may eventually lead to good treatment outcome for patients having this rare type of disease.

At present, the patient is ambulatory, voiding freely and with good wound healing. She had her first cycle of chemotherapy with good tolerance and will have her radiation therapy after completion of 6 cycles of chemotherapy. The Colorectal Service will take down her colostomy after 6-8 months.

CONCLUSION

This report of a 68-year-old woman with vulvar pruritus is an additional case to few incidences of vulvar carcinoma with an extremely rare pathology. Due to

limited studies available, tailored management should still be investigated. However, MEC in other primary sites, especially high grade tumors, are reported to be aggressive, have a predilection for metastasizing to lymph nodes and have high risk for recurrence even without any risk factors. For these reasons, the patient was started on adjuvant chemoradiotherapy, as in other histopathologic diagnosis of advanced stage vulvar carcinoma. Other treatment options like monoclonal anti-body, anti-EGFR and anti-VEGF may play a role in the management of this rare case and if possible, should be considered to the patient. ■

REFERENCES

1. Ng C, et al. (2014). Primary Cutaneous Mucoepidermoid Carcinoma. *Case Reports in Clinical Pathology*, 1 (2). DOI: 10.5430/crcp.v1n2p128.

2. Xiao-qin G, et al. (2014). Unusual Mucoepidermoid Carcinoma of the Liver Misdiagnosed as Squamous Cell Carcinoma by Intraoperative Histological Examination. Diagnostic Pathology. 9 (24). doi:10.1186/1746-1596-9-24.

3. Nakano T, et al. (2013). HER2 and EGFR gene copy number alterations are predominant in high-grade salivary mucoepidermoid carcinoma irrespective of MAML2 fusion status. Histopathology, 63(3), 378-392. doi:10.1111/his.12183.

4. Society of Gynecologic Oncologists of the Philippines Clinical Practice Guidelines 2018, 8th edition.

5. Paptheodorou DC, et al. (2017). Bilateral Breast Metastasis from Vulvar Carcinoma: A Case Report and Literature Review. Case Reports in Obstetrics and Gynecology. https://doi.org/10.1155/2017/1357203.

6. Hacker N, et al. (2012) FIGO Report 2012 Cancer of the Vulva. International Journal of Gynecology and Obstetrics S90-S96.

7. Cozma CN, et al (2018). A rare case of vulvar squamous cell carcinoma ; case presentation. *J Clin Invest Surg*. 3(1):32-36. DOI:10.25083/2559.5555 /31.3236.

8. Rauh-Hain JA, et al. (2014). Management and outcomes for elderly women with vulvar cancer over time. BJOG;121:719-727. DOI: 10.1111/1471-0528.12580.

9. Katke RD, et al (2018). Vulvar Carcinoma Survival Outcome: An Institutional Experience. *Cancer Therapy and Oncology International Journal*. 8 (5). DOI: 10.19080/CTOIJ.2018.08.555747.

10. Senn B, et al. (2015). Prevention and Reduction of Complications in Women with Vulvar Cancer: Development of an Algorithm for Safer Multidisciplinary Care. *Journal of Cancer Therapy*. (6), 821-832. doi.org/10.4236/jct.2015.610090.

11. Lennerz J, et al. (2009). CRTC1 Rearrangements in the Absence of t(11;19) in Primary Cutaneous Mucoepidermoid Carcionma. *British Journal of Dermatology*, 161: 925-929. DOI 10.1111/j.1365-2133.2009.09200.x

12. Chenevert J, et al. (2011). Mucoepidermoid carcinoma: A five-decade journey. Virchows Archiv, 458(2), 133-40. doi:http://dx.doi.org.ezproxy.waikato.ac.nz/10.1007/s00428-011-1040-y.

13. Selcuk I, et al. (2015). Mucoepidermoid Carcinoma of Uterine Cervix: A Distinct Pathological and Clinical Entity. *Case Reports In Obstetrics & Gynecology*, 2015,1-4. doi:10.1155/2015/491875.

14. Karateke A, et al. (2006). Mucoepidermoid variant of adenosquamous carcinoma arising in ovarian dermoid cyst: a case report and review of the literature. International Journal Of Gynecological Cancer: *Official Journal Of The International Gynecological Cancer Society*, 16(1), 379-384.

15. Momin YA, et al. (2017). Mucoepidermoid carcinoma in a mature cystic teratoma: A rare case report with review of literature. *Indian Journal Of Pathology & Microbiology*, 60(1), 117-118. doi:10.4103/0377-4929.200038.

16. Isayeva T, et al. (2013). Salivary mucoepidermoid carcinoma: demonstration of transcriptionally active human papillomavirus 16/18. Head Neck Pathol, 7(2), 135-48. doi: 10.1007/s12105-012-0411-2.

17. Lagha A, et al. (2012). Systemic therapy in the management of metastatic or advanced salivary gland cancers. *Head & Neck Oncology*, 4:19.

18. Chen Z, et al. (2014). Aberrantly activated AREG–EGFR signaling is required for the growth and survival of CRTC1–MAML2 fusion-positive mucoepidermoid carcinoma cells. Oncogene 33, 3869-3877

19. Lujan B et al. (2010). Activation of the EGFR/ERK pathway in high-grade mucoepidermoid carcinomas of the salivary glands. *British Journal of Cancer*. 103:510-516.

20. Yan K, et al. (2018). Genomics of Mucoepidermoid and Adenoid Cystic Carcinomas. *Laryngoscope Investigative Otolaryngology*. DOI: 10.1002/lio2.139.

21. Faur A, et al. (2013). Vascular endothelial growth factor (VEGF) expression and microvascular density in salivary gland tumours. APMIS 122:418-426.

22. Zhao S, et al. (2013). Prognostic significance of VEGF immunohistochemical expression in oral cancer: a meta-analysis of the literature. *Tumor Biol*. DOI 10.1007/s13277-013-0886-9.