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Melanosis of the vagina and human papillomavirus infection, an uncommon pathology: Case Report.

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Key words: Melanosis, human papillomavirus, vaginal pathology.

Abstract. Benign melanotic lesions of the vagina are uncommon and only a few cases have been reported in the literature. A 34-year-old woman was referred because of a Vaginal Intraepithelial Neoplasia 1 biopsy result. On the gynecological examination, two different hyperpigmented areas were noted in the vagina. The colposcopic visualization of the cervix and vagina found an aceto-white lesion at the right lateral wall of the upper third of the vagina. Biopsies from three areas were taken. Histological study reported a melanosis of the vagina and HPV infection. An immunohistochemical panel of epithelial markers was performed in vaginal samples, such as Cytokeratin AE1/AE3 and epithelial membrane antigen, mesenchymal marker: vimentin; melanocytic makers: protein S-100 and HMB45 (Human Melanoma Black); proliferating cell marker: proliferating cell nuclear antigen (PCNA), and P-53 oncoprotein. High Risk (16, 18, 31, 45) and Low Risk (6, 11) HPV types were studied by In Situ Hybridization using the same vaginal samples. CK, EMA and Vimentin were 2+. Melanocytic markers, HMB45 and S100, and PCNA were 1+ in basal cell layer. P-53 was negative. The melanotic tissue and acetowhite lesion were positives to HPV Types 6,11. In conclusion, melanosis of the vagina is a uncommon benign pathology. Usually, melanosis is present in women over 40 years old. We present a case of melanosis of the vagina in a young woman infected with low-risk HPV types and review the literature.

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Melanosis de la vagina e infección por virus del papiloma humano, una patología poco común: Reporte de un Caso.
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Palabras clave: Melanosis, virus del papiloma humano, patología vaginal.

Resumen. Las lesiones melanóticas de la vagina son infrecuentes. y Solo pocos casos han sido reportados. Se presenta el caso de una mujer de 34 años quien es referida con diagnóstico de una Neoplasia Intraepitelial Vaginal 1. Al examen ginecológico, se encontraron dos áreas hiperpigmentadas en la vagina. La exploración colposcópica del cuello uterino y vagina reveló la presencia de una lesión aceto-blanca en la pared lateral derecha del tercio superior de la vagina. Muestras de biopsias fueron tomadas en dichas áreas. El estudio histológico reportó una melanosis de la vagina y una infección por el virus del Papiloma Humano (VPH). Se realizó un panel de estudio inmunohistoquímico de marcadores epiteliales en las muestras vaginales: tales como citoqueratina AE1/AE3 y antígeno epitelial de membrana; marcador mesenquimal: vimentin; marcadores melanóticos: proteina S-100 y HMB45 (Human Melanoma Black); marcadores de proliferación celular: antígeno de proliferación nuclear (PCNA), y la oncoproteína P-53. Se realizó Hibridización In Situ para establecer los tipos de alto (16, 18, 31, 45) y bajo (6, 11) riesgo de VPH en las muestras vaginales. Los marcadores CK, EMA y Vimentin fueron 2+. Los marcadores melanótico, el HMB45 y el S100, y el PCNA fueron 1+ en la capa basal. P-53 fue negativo. El tejido melanótico y la lesión acetoblanca fueron positivos al VPH 6,11. En conclusión, la melanosis vaginal es una patología poco frecuente. Usualmente, se ha reportado en mujeres mayores de 40 años. Presentamos un caso de una melanosis de la vagina infectada con un tipo de VPH de bajo riesgo en una mujer joven y una revisión de la literatura.

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INTRODUCTION

Melanosis is a term given to lesions showing an increased number of normal melanocytes confined to the basal layer of the squamous epithelium in which the pigment melanin is confined and on visual inspection it may have an appearance similar to malignant melanoma (1, 2). The majority of such lesions should be regarded as malignant until proved otherwise (2). Although relatively common in the oral and gastrointestinal tract, melanosis is an uncommon finding in the female genital tract and especially rare in the vagina, with few cases reported in the medical literature (1-3).

Nigogosyan *et al.,* in 1964 studied the vaginal mucosa of 100 random autopsies and found melanotic lesions in three cases (4). Most recently, it has been reported the association between multiple-type Human Papillomavirus (HPV) infection in a malignant melanoma of the vulvar region. The role of HPV could be either direct through infection of melanocytes or indirect as a cofactor with free radicals chronic inflammatory vulvar disease such a lichen sclerosus

(5). Some authors (3, 10, 11) have suggested that melanotic vaginal lesions are a precursor of malignant melanoma and have considered melanotic lesions like premalignant lesions.

CASE REPORT

A 34-year-old woman, gravid 7, parity 7, was referred to the Cervical Pathology Out-Patient Clinic at the Manuel Noriega-Trigo Hospital because of a Vaginal Intraepithelial Neoplasia 1 biopsy result. On the gynecological examination, two different hyperpigmented areas were noted in the vagina. One area was surrounding the *portio vaginalis* and extended to the right lateral wall of the lower third of the vagina, measuring about 4 cm in length and 2.5 cm in width (Fig. 1a). The other melanotic area was at the anterior wall and upper third of vagina, measuring 1.5 × 0.5 cm. Both areas were neither raised nor firm. No ulceration was found. On palpation, melanotic areas were flat, having the contour of normal vagina, and were not indurated or tender. The colposcopic visualization of the cervix and vagina found an aceto-white lesion at the right lateral wall of the upper third of the vagina. Biopsies from three areas were taken. The patient did not have any melanotic lesion at other mucocutaneous sites of the body; also, she denied any family history of pigmentary disorders.

Fixed vaginal specimens were paraffin-embedded, and 3 μm sections were obtained and were stained with hematoxylin and eosin (HE). Biopsies of the hyper-

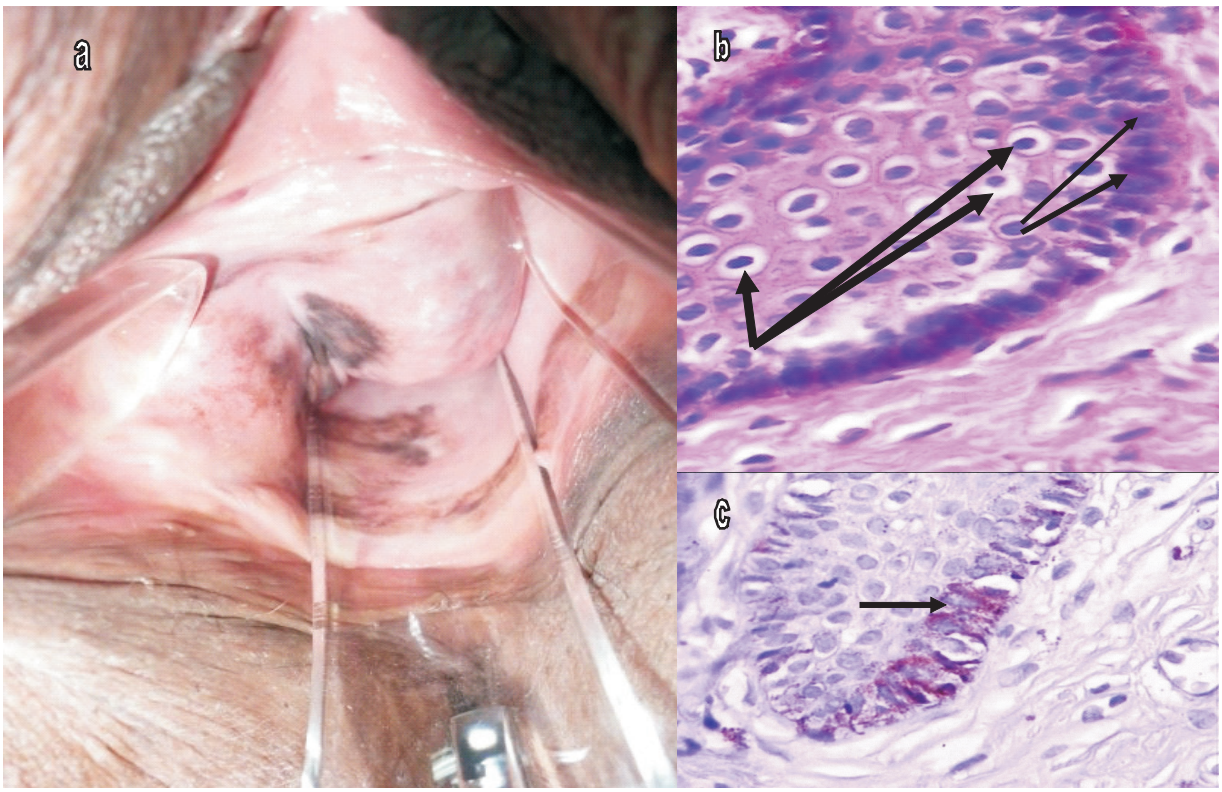

Fig. 1. a.- Melanotic tissue at the *portio vaginalis*; b.- Melanosis (high-power field 400x, hematoxilin and eosin) Thin arrows indicates hyperpigmentation of the basal layer with increases of the melanocytes. Thick arrows shows koilocytic atypia; c.- Immunohistochemical stain for HMB45 (400x), a marker of melanocytic cell (arrow).

pigmented areas revealed an acanthotic, parakeratotic and hyperkeratotic squamous epithelium with hyperpigmentation of the basal layer of the epithelium with increased number of melanocytes (Fig. 1b). Also, superficial or intermediate mature squamous cells had a large perinuclear cavity associated with a peripheral rim of thickened cytoplasm. The peripheral cytoplasm was very dense and irregularly stained. The nucleus was dense, irregular, hyperchromatic, and pyknotic. Binucleation was observed (Figs.1b, 2a, 2b, 2c). Biopsy of vaginal aceto-white lesion showed a flat condyloma.

Immunohistochemical panel of epithelial markers: Cytokeratin AE1/AE3 (CK) and epithelial membrane antigen (EMA), mesenchymal marker: vimentin, melanocytic makers: protein S-100(S100) and HMB45(Human Melanoma Black), proliferating cell marker: proliferating cell nuclear antigen (PCNA), and P-53 oncoprotein were performed. CK, EMA and Vimentin were 2+. Melanocytic markers, HMB45 (Fig. 1c) and S100, and PCNA were 1+ in the basal cell layer. P-53 was negative. High Risk (16, 18, 31, 33) and Low Risk (6, 11) HPV types were studied by In Situ Hybridization using the same vaginal samples. The melanotic tissue and acetowhite lesion were positives to HPV Types 6, 11 (Figs. 2a, 2b, 2c).

The patient has been followed every 6 months since the diagnosis was done in September 2009. During the last follow-up, the melanotic areas remain without changes, the aceto-white lesion at right lateral wall of the upper third of the vagina vanished and, a new and extended leucoplasic lesion which compromises the

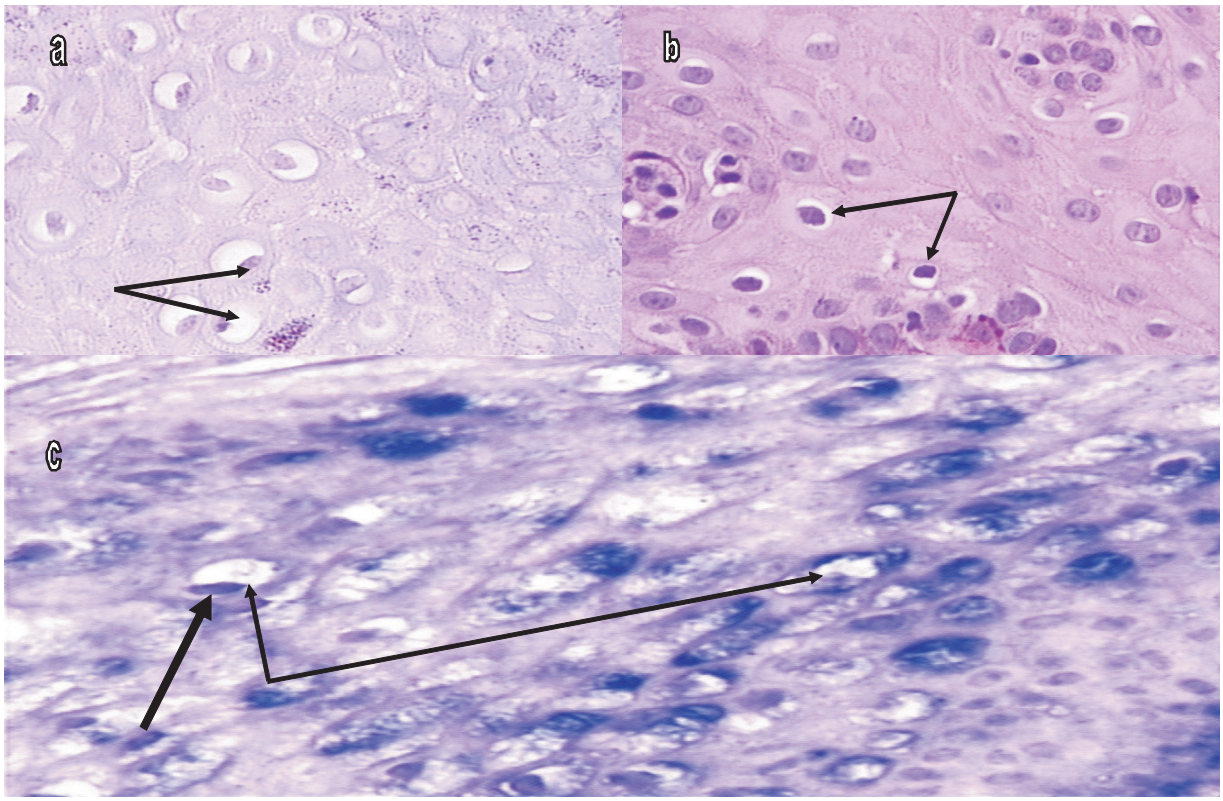

Fig. 2. a.- In Situ Hybridization HPV types 31-33: negative; b.- In Situ Hybridization HPV types 16-18: negative; c.- In Situ Hybridization HPV types 6-11: positive (thick arrow: blue staining to nitroblue tetrazolium chromogen) Koilocitic atypias (thin arrows).

posterior labium of the cervix and the posterior fornix of the vagina was observed. Biopsies were taken from vagina and cervix. They were fixed in 10% formalin, embedded in paraffin for the realization of 3μ wide cuts and stained with HE. The anatomo-pathologycal study showed an exophitic condyloma

DISCUSSION

Vaginal hyperpigmented lesions can be present, such as melanosis, lentigo, blue nevi, pigmented nevi, melanoma or malignant blue nevi (3).

Benign melanotic lesions of the vagina and/or cervix are uncommon and only few cases have been reported (2, 6). The earliest cases of melanosis of the vagina found in English literature were Nigogosyan *et al*. (5) who reported the first three cases of melanosis of the vagina in elderly white women in 1964. They found this benign melanotic lesion in 100 random autopsies. In 1966, Norris *et al*. (6) reported two benign melanotic lesions in the vagina. Other authors such as Tsukada (2) in 1976, Karney *et al*. (1) in 2001 and Burgos *et al*. (3) in 2004 have reported melanotic lesions of the vagina. Different authors (1-3) have reported melanosis of the vagina in patients over 40 years old. This case is the youngest patient with melanosis of vagina ever reported.

Melanosis of the vagina could be a risk factor for the development of genital melanomas (3, 8, 9). Rohwedder *et al.* (5, 9) reported that cutaneous HPV and *epidermodysplasia verruciformis* (EV) could play a role in the pathogenesis of genital melanoma either as a direct and primary agent, via oncogenic interactions, or as a cofactor, via activation of melanocytes (melanosis) or chronic fibroinflammatory states (eg, *lichen sclerosus*). Two-thirds of primary malignant melanomas of the oral cavity have been associated with oral melanosis (10). Vaginal melanomas and other mucosal melanomas are similar histologically to *acral lentiginuos* melanomas (10). Bottles *et al.* (10) reported a 63-years-old woman with an extensive pigmentation of the vagina and the histological study showed an atypical melanocytic hyperplasia. The authors (10) presented the case as a possible precursor of a malignant melanoma. Lee *et al.* (11) reported a case of malignant melanoma of the vagina which progressed from pre-existing melanosis. Burgos *et al.* (3) found melanosis of the vagina three years after a radical vulvectomy because of a malignant melanoma of the vulva. Different authors (3,10,11) have considered that vaginal melanosis is a risk factor for the development of malignant melanoma of the vagina.

We found in this case, two kinds of HPV infections: 1. a flat condyloma, a HPV expression of clinical infection, and 2. a koilocytic atypias in the melanotic tissue, an expression of cytological infection (Fig. 1b). The *in situ* hybridization technique showed the presence of HPV types6 and 11. After reviewing the literature of melanosis of the vagina, this is the first report of a case in which benign melanosis lesions of the vagina are infected by low risk HPV types. Rohwedder *et al*. (9) mentioned that the presence of HPV infection can induce pigmentation in lesions such as pigmented flat warts, pigmented condyloma, pityriasis versicolor-like lesions in *epidermodysplasia verruciformis*, and pigmented Bowen disease, indicating the potential to activate the melanocytes. Also, Rohwwedder *et al.* (5, 9) said there is evidence that HPV can infect the melanocytes and induce tumor formation, and HPV infection could be a factor, either as a primary agent-direct infection of melanocytes or as a cofactor, producing a carcinogenic effect in vulva and vagina.

Once the diagnosis of melanosis is made, conservative management is indicated, with periodic examinations documenting the size, shape and colour of the lesion.

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REFERENCES

1. **Karney Y, Cassidy MS, Zahn CM, Snyder RR.** Melanosis of the vagina: A case report. J Reprod Med 2001; 46:389-391.
2. **Tsukada Y.** Benign melanosis of the vagina and cervix. Am J Obstetric Gynecol 1976; 124 (2):211-212.
3. **Burgos JJ, López JC, Burgos J, Diez J, Rivera JM.** Benign vaginal melanosis associated to primary melanoma of the vulva. Case report Rev Esp Patol 2004; 37(4): 423-428.
4. **Nigogosyan G, De La Pava S, Pickren JW.** Melanoblasts in vaginal mucosa. Origin for primary malignant melanoma. Cancer 1964; 17:912-913.
5. **Rohwedder A, Brooke P, Malfetano J, Kredentzer D, Carlson JA.** Vulvar malignant melanoma associated with human papillomavirus DNA: Report of two cases and review of literature. Am J Dermatopathol 2002; 24(3):230-240.
6. **Kaplan PA, Griffo MD, Diaz-Arias AA.** Melanosis of the uterine cervix. J Reprod Med 2005; 50(11): 867-870.
7. **Norris HJ, Taylor HB**. Melanoma of the vagina. Am J Clin Pathol 1966; 46(4): 420-426.
8. **Lee RB, Buttoni L, Dhru K, Tamini H.** Malignant melanoma of the vagina: a case report of progression from preexisting melanosis. Gynecol Oncol. 1984; 19:238-245.
9. **Rohwedder A, Slominski A, Wolff M, Kredeentser D, Carlson A.** Epidermodysplasia verruciformis and cutaneous human papillomavirus DNA, but not genital human papillomavirus DNAs, are frequently detected in vulvar and vaginal melanoma. Am J Dermatopathol. 2007; 29(1): 13-17.
10. **Bottles K, Lacey CG, Miller TR.** Atypical melanocytic hyperplasia of the vagina. Gynecol Oncol 1984; 19:226-230.
11. **Lee RB, Buttoni L Jr, Dhru K, Tamini H.** Malignant6 melanoma of the vagina: a case report of progression from existing melanosis. Gynecol Oncol 1984:19:238-245.