Int J Clin Exp Pathol 2014;7(6):3456-3459
www.ijcep.com /ISSN:1936-2625/IJCEP0000481

Letter to Editor

Pigmented anal squamous intraepithelial neoplasia: a case report and review of literature

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Received April 9, 2014; Accepted May 26, 2014; Epub May 15, 2014; Published June 1, 2014

Squamous cell carcinoma (SCC) of the anal canal is a rare malignant neoplasm, and non-invasive squamous intraepithelial neoplastic lesion of the anal canal is referred to as anal squamous intraepithelial neoplasia (ASIN), which is considered as a precursor lesion of invasive SCC [1]. Most cases of ASIN and SCC of the anal canal are associated with human papilloma virus (HPV) infection, and acquired immunodeficiency syndrome (HIV)-positive individuals are at high risk of development of ASIN and SCC of the anal canal [1].

Albeit rare, it has been well recognized that various non-melanocytic neoplasms accompany non-neoplastic melanocytes within the tumor, and this phenomenon has been described as "melanocytic colonization" [2-12]. SCC or SCC *in situ* (squamous intraepithelial neoplasia) occasionally accompanies with non-neoplastic melanocytes within the lesion, which is referred to as pigmented SCC or SCC *in situ* [8, 10]. Herein, we describe the first documented case of pigmented high-grade ASIN.

A 43-year-old Japanese male with HIV presented with persistent bloody stool. He had a past history of nontuberculous mycobacterial infection in the lymph nodes. Colorectal endoscopic examination demonstrated a villous lesion from the anal canal to the anus (**Figure 1**). Biopsy was performed under a clinical diagnosis of condyloma acuminatum.

Histopathological study of the biopsy specimen revealed proliferation of atypical squamous cells in the entire layer of the squamous epithelium (**Figure 2A**). These atypical squamous cells had mildly- to moderately-enlarged round nuclei with small nucleoli (**Figure 2B**). Mitotic figures were observed in the upper portion of the squamous epithelium. No invasive growth was noted. A peculiar finding of the present case was the presence of dendritic melanocytes within the neoplastic squamous epithelium (**Figure 2B**). These melanocytes were without atypia, and no mitotic figures were observed (**Figure 2B**).

Immunohistochemical studies were performed using an autostainer (Ventana) by the same method as previously reported [13-17]. The dendritic melanocytes were positive for S-100 protein and Melan-A (**Figure 3A**), and some of them were also positive for HMB-45. The neoplastic squamous cells were diffusely positive for p16 in the entire layer (**Figure 3B**), and Ki-67-positive cells were also observed in the entire layer of the squamous epithelium.

Accordingly, an ultimate diagnosis of pigmented high-grade ASIN was made.

Pigmented intraepithelial squamous neoplasia (SCC *in situ*) has been reported in some organs [2, 8, 18, 19]. Pigmented SCC *in situ* of the skin (pigmented Bowen's disease) has been rarely reported [18, 19]. Ragi *et al*. reported that 7 of 420 lesions of Bowen's disease (1.67%) were pigmented [18]. Moreover, a few cases of pigmented intraepithelial squamous neoplasia have also been reported in organs which normally do not have any non-neoplastic melanocytes, such as the esophagus and uterine cer-

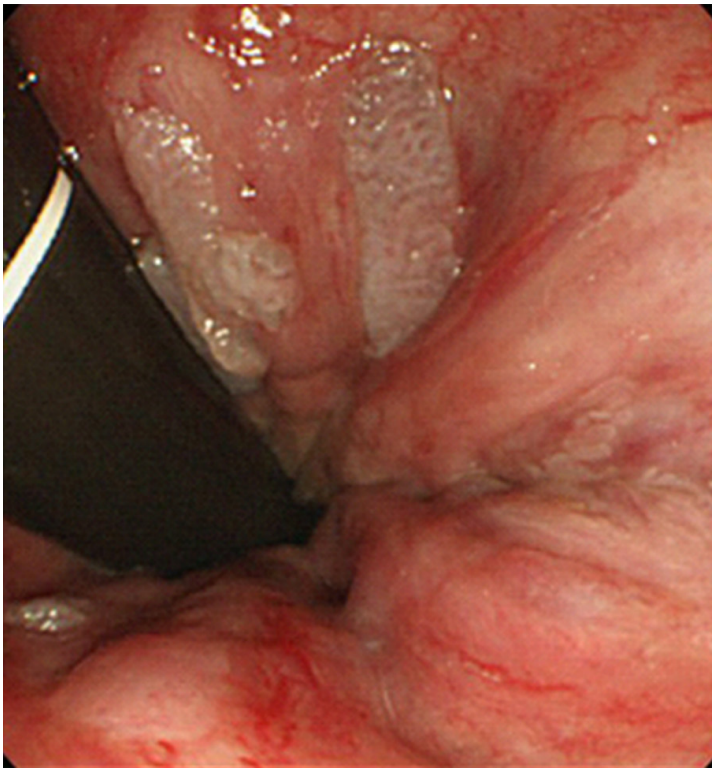

Figure 1. Endoscopic feature showing a villous lesion in the anal canal.

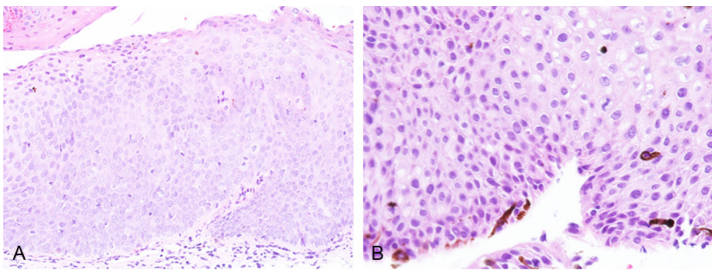

Figure 2. Histopathological features of the biopsy specimen of the anal canal. A. Proliferation of atypical squamous cells is observed in the entire layer of the squamous epithelium. HE, x 200. B. These atypical squamous cells have mildly- to moderately-enlarged nuclei with small nucleoli. Dendritic melanocytes are present within the squamous lesion. HE, x 400.

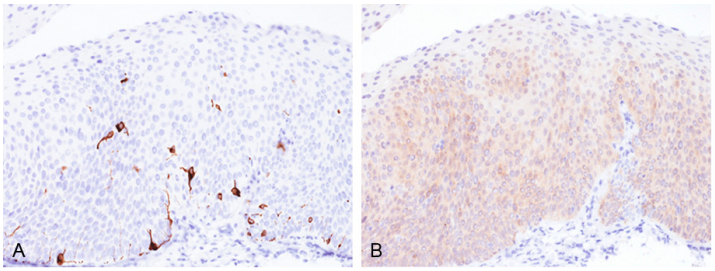

Figure 3. Immunohistochemical findings of the biopsy specimen of the anal canal. A. Melan-A is expressed in the dendritic melanocytes, x 200. B. p16 is diffusely expressed in the entire layer of the neoplastic squamous epithelium, x 200.

vix [2, 8]. Normal anal canal has non-neoplastic melanocytes. Clemmensen and Fenger assessed for the presence of non-neoplastic melanocytes by immunohistochemical methods [20]. Melanocytes are frequently observed in the normal anal squamous zone, and only sporadically in the anal transitional zone, but not in the colorectal zone [20]. The present case is the first documented case of pigmented high-grade ASIN. Non-neoplastic melanocytes may have derived from the surrounding squamous epithelium of the anal canal.

The concise mechanism of melanocytic colonization in the non-melanocytic lesions has not been completely resolved. However, Satomura *et al*. demonstrated that SCC of the oral mucosa can produce melanocyte chemotactic factors, such as stem cell factor and endothelin-1, resulting in melanocytic colonization within the tumor [21]. Additional studies are needed to clarify the mechanism and pathogenesis of melanocytic colonization in non-melanocytic neoplasms in the organs with or without normal non-neoplastic melanocytes.

p16 is a cyclin-dependent kinase inhibitor that prevents phosphorylation of the retinoblastoma tumor suppressor protein, and under normal conditions, inhibits the cell cycle. p16 expression is up-regulated by high-risk HPV infection, and strong and diffuse p16 immunoreactivity is found in almost all cases of SCC and high-grade intraepithelial squamous neoplasms of the cervix [22]. Recent studies revealed that immunostaining for p16 is a very useful marker for diagnosis of high-grade ASIN [23, 24]. Almost all cases of high-grade ASIN show diffuse and strong immunoreactivity for p16, which suggests the presence of high-risk HPV within the lesion [23, 24]. Although the analysis of HPV was not performed in the present case, diffuse immu-

noreactivity of p16 in the present case suggests involvement of high-risk HPV.

Disclosure of conflict of interest

None.

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