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# Reflectance confocal microscopy of mammary Paget disease

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**ABSTRACT** Mammary Paget disease is the intraepidermal adenocarcinoma of the nipple area which is characterized usually by a well-demarcated eczematous plaque. Reflectance confocal microscopy (RCM), is an in vivo noninvasive diagnostic tool with a high-resolution imaging of the skin, almost comparable to conventional histology. RCM findings of Paget disease are limited in the literature. Most of the reported cases are the extramammary type. In this report, we aimed to evaluate the RCM findings of a non-pigmented mammary Paget disease in a 65 year-old woman.

## Introduction

Mammary Paget disease (MPD) is an intraepidermal adenocarcinoma of the nipple area usually characterized by a well-demarcated eczema-like plaque. It may be associated with an underlying malignancy of the breast. Reflectance confocal microscopy (RCM) is an in vivo noninvasive diagnostic tool with high-resolution imaging of the skin, almost comparable to conventional histology [1-4]. In this report, we aimed to evaluate the confocal microscopic findings of the mammary Paget disease.

## Report

A 65-year-old woman was admitted with a one-year history of an erythematous, asymptomatic, slowly enlarging plaque on the left nipple area. She had a history of hemorrhagic discharge 13 years ago from the left breast. The subsequent mammography had revealed segmental microcalcification behind the areola extending to the periphery; thus, surgery was performed in 2001. The histopathology revealed ductal intraepithelial neoplasia IA (intraductal hyperplasia). Six months later the hemorrhagic discharge recurred. Surgery

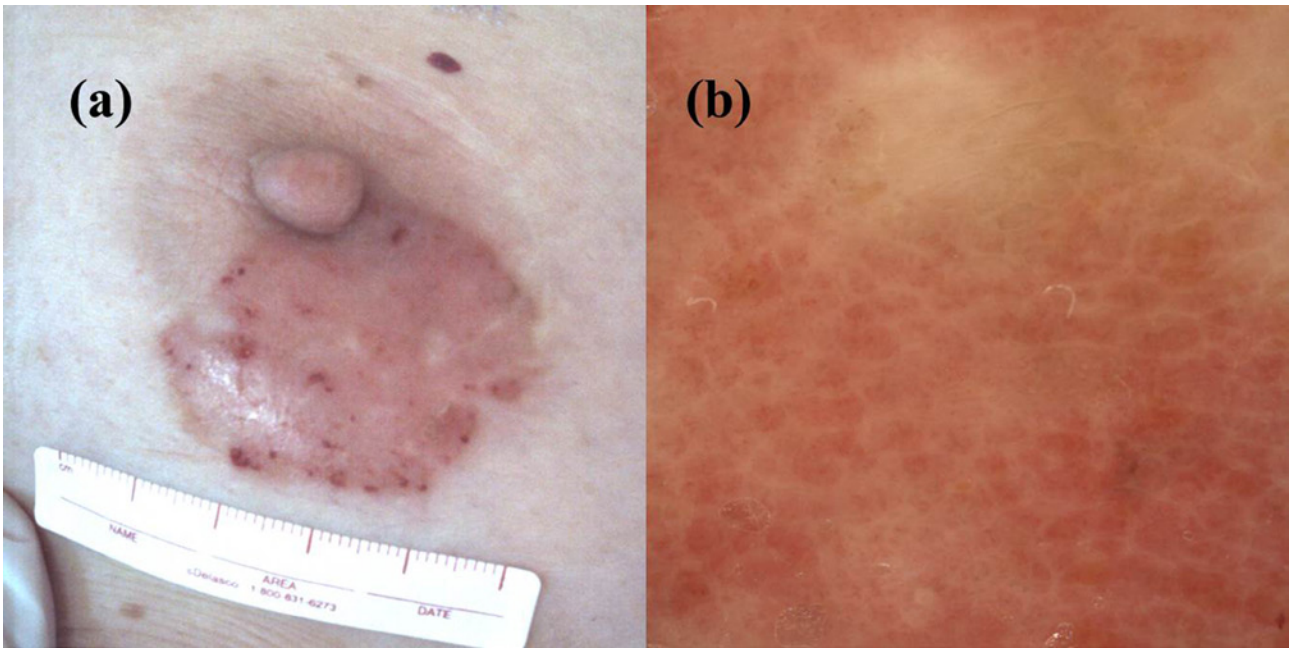


**Figure 1.** (**a**) Erythematous plaque with punctate hemorrhagic crusts and minimal scales, 4.0 x 2.6 cm in diameter on the nipple. (**b**) Background erythema (vascular blush) separated with whitish reticulation in most of the lesion and some linear and comma-like vessels. [Copyright: ©2017 Ozdemir et al.]

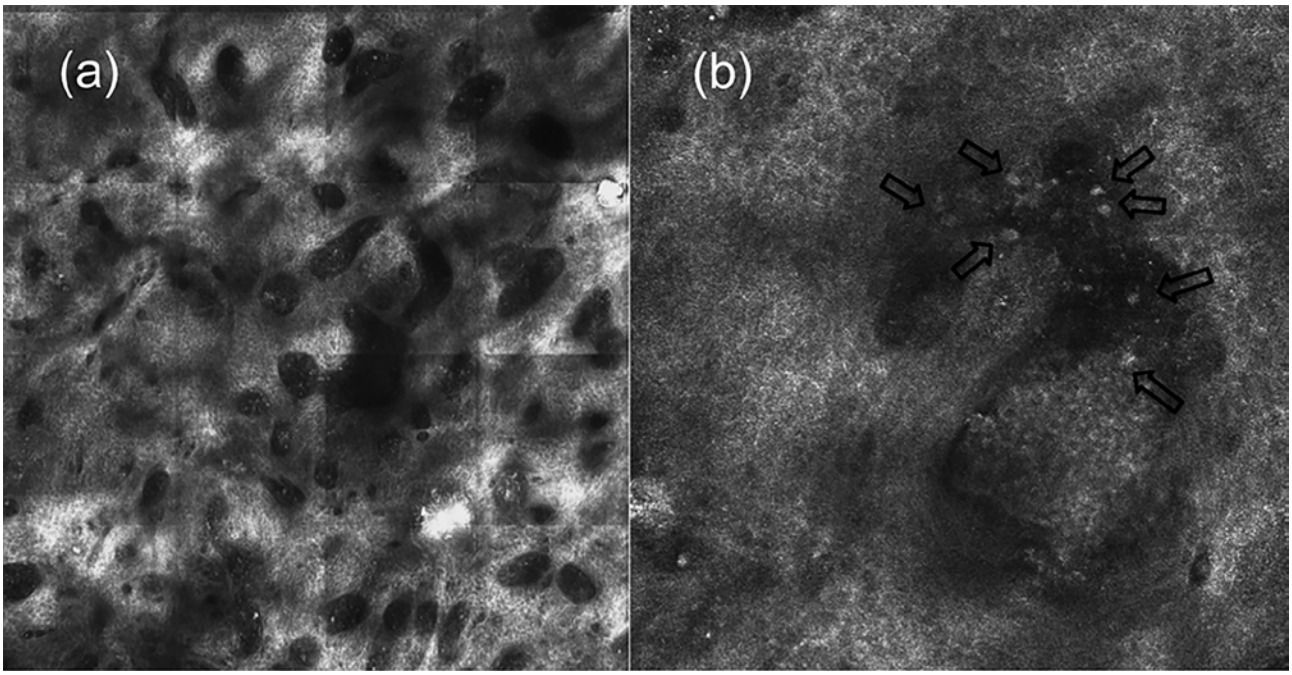


**Figure 2.** Reflectance confocal microscopy: (**a**) Dense tumor nests, simulating dark silhouettes that varied in size and shape in the partially spared honeycomb pattern of the epidermis (mosaic, 2 x 2 mm). (b) One of these nests; composed of hyporeflective tumor cells (Paget cells), larger than the keratinocytes with abundant, pale cytoplasm and small, mildly bright nuclei (black arrows) (mosaic, 0.5 x 0.5 mm). [Copyright: ©2017 Ozdemir et al.]

was repeated, and a histopathological diagnosis of atypical ductal hyperplasia and atypical intraductal papilloma was made Periodic follow-up examinations with mammography and ultrasonography have been performed yearly without any pathologic findings.

On dermatologic examination there was an erythematous plaque with multiple punctate hemorrhagic crusts and minimal scales, 4.0 x 2.6 cm in diameter involving some of the nipple of the left breast (Figure 1a). Before the biopsy, the lesion was examined using dermoscopy (DermLite DL3;

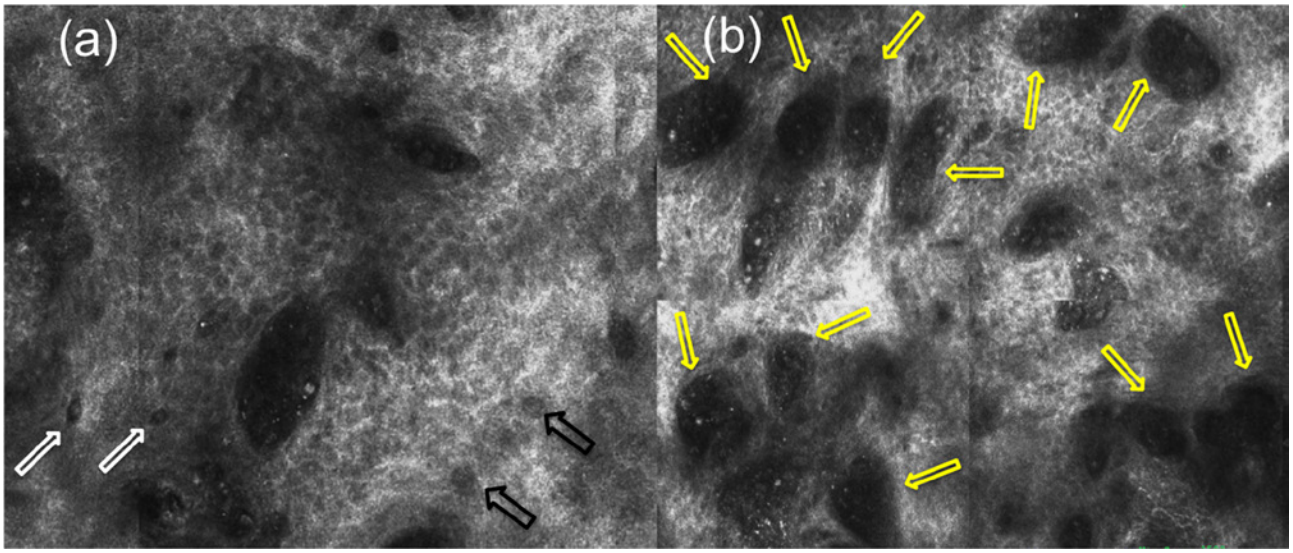


**Figure 3.** Reflectance confocal microscopy: (**a**) Pagetoid spread of single tumor cells scattered focally within the epidermis, some big and poorly reflected (black arrows), and some smaller and darker ones (white arrows) (mosaic, 0.65 x 0.5 mm). (**b**) Numerous, large tumor cell nests simulating dark silhouettes (yellow arrows) at the lower epidermis, close to dermoepidermal junction level (mosaic, 1.0 x 0.8 mm).

3Gen LLC, San Juan Capistrano, CA, USA) and in vivo RCM (Vivascope 1500 Multilaser, Lucid, Rochester, NY, USA, distributed by Mavig, Munich).

On dermoscopy, the background erythema (vascular blush) was separated with whitish reticulation due to the sulci of the areola in most of the lesion. Some linear and comma-like vessels were present (Figure 1b).

RCM images were recorded at different levels to a maximum depth of 200 µm on the mostly infiltrated part of the lesion with three mosaics (VivaBlocks) (epidermal layer, dermal-epidermal junction, and upper dermis) with the maximum area of 8 x 8 mm. The epidermal layers were characterized by partially spared honeycomb pattern with bright reflective dots (inflammatory cell groups) and dense tumor nests, simulating dark silhouettes that varied in size and shape (Figure 2a). These nests were composed of hyporeflective tumor cells that were larger than the keratinocytes with abundant, pale cytoplasm and small, mildly bright nuclei (Figure 2b).

In addition, pagetoid spread of single tumor cells was scattered focally within the epidermis. Some of the single cells were big and poorly reflected, and some were smaller and darker (Figure 3a). At the lower epidermis, close to the dermo-epidermal junction, many large, dense tumor nests simulating dark silhouettes were present also; however, these tumor nests were more abundant than the ones in the upper epidermis (Figure 3b). At the papillary dermis, there was increased vascularity due to horizontal and looped vessels with rapid blood flow, and some perivascular inflammatory cells were observed.

Histopathology of the shave biopsy revealed epidermal infiltration of tumor cells with abundant pale cytoplasm.

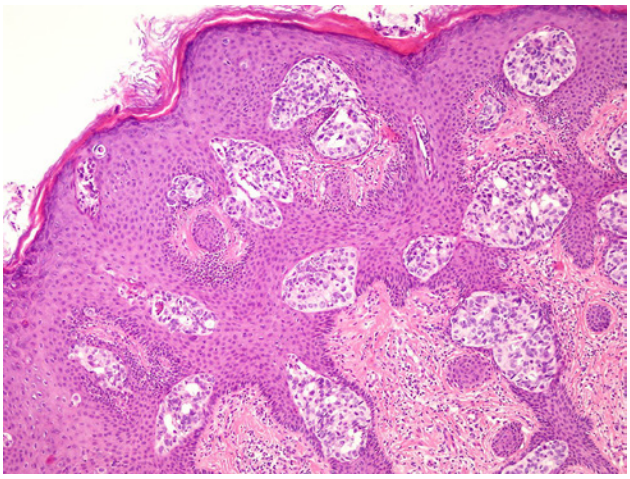

**Figure 4.** A few scattered single tumor cells in the upper epidermis, and tumor cell groups mostly in the lower epidermis (H&E, x100) [Copyright: ©2017 Ozdemir et al.]

Tumor cells were arranged in small groups and focally with glandular formation. The epidermis was hyperplastic and a few scattered single tumor cells were seen in the upper epidermis; however, most of tumor cell groups were in the lower epidermis (Figure 4).

With immunoperoxidase techniques, the tumor cells stained diffuse positive for MFGP-1, EMA, e-cadherin, and c-erbB2. They were negative for Melan-A, and HMB-45. With these histological and immunohistochemical findings, Paget disease was diagnosed.

Mammography and breast ultrasonography were normal. The patient had breast surgery, after which the pathology revealed Paget disease without any associated malignancy of the breast.

## Discussion

RCM findings of Paget disease are limited in the literature [1-8]. Some of the reported cases are extramammary type [3,4,6,7]. RCM findings of mammary Paget disease were reported in four articles [1,2,5,8] in total of eight cases. The first case reported by Longo et al. was a 70-year-old woman with pigmented MPD. In this report, Paget cells were described as large, round cells with reflective cytoplasms and dark nuclei, similar to pagetoid melanocytes suggestive of melanoma [1]. Richtig et al. described these cells as scattered bright nucleated cells in different sizes and shapes and varying reflectivity at the epidermal level, and pointed out that they resembled the pagetoid cells reported by Longo et al. and to melanoma [2]. However, later, Pan et al. described Paget cells in extramammary lesions as large cells having dark cytoplasm and mild bright nuclei, each separated from the surrounding by a black halo. In addition, they observed that nests of Paget cells formed dark glandular structures at the basal layer. They also suggested that Paget cells could be discriminated from the pagetoid cells of melanoma by their low refractivity and round to oval shape [3]. A further report by Guitera et al. clarified that Paget cells of extramammary type were poorly reflective cells observed as dark "holes." Sometimes, single or small clusters of these cells appeared as "target" structures with round, bright centers and surrounding dark halos. Some nested cells appeared as "palisading" nodules also, similar to nodular basal cell carcinoma (BCC) [4]. Cinnoti et al. have also described the isolated Paget cells as hyper-reflective cells with a dark halo in a targetoid appearance at the superficial layers together with hyporeflective, roundish, large cells at the basal layer [5]. Oliveira et al. have also described RCM findings of five cases of MPD, similar to the report by Guitera et al, as target structures and dark holes [8]. They reported that on RCM, Paget cells were seen as 1.5–2 times larger the keratinocytes and explained that these cells observed as dark holes were poorly reflective due to their abundant pale cytoplasm, and that the bright central area seen in target structures were related with their pleomorphic nuclei [8]. All the MPD cases are summarized in Table 1.

In our case, hyporeflective Paget cells with abundant, pale cytoplasm and small, mildly bright nuclei within dense tumor nests or scattered as single cells observed on RCM were in accordance with the recent literature [3,4,8]. They were clearly different from the pagetoid cells of melanoma, which have bright cytoplasm and dark nucleus. The single, hyporeflective cells scattered focally within the epidermis seen on RCM corresponded to the single tumor cells scattered in the upper epidermis on histology. Paget cells forming large, dense tumor nests simulating dark silhouettes on RCM corresponded to tumor cell groups with glandular formation mostly in the lower epidermis.

Paget cells contain intracytoplasmic mucin [9-12], a mixture of acid mucopolysaccharides. Fraga-Braghiroli et al. have shown that mucin located areas in dermal mucinosis were seen as darker areas on RCM [13]. Likewise, Ulrich et al. have shown that the peritumoral cleft-like spaces seen in BCC on histopathology exist in vivo, and correspond to the peritumoral mucin deposition which also demonstrates that mucin appear dark on RCM [14]. This may be due to the lower refractive index (RI) of mucin compared to melanin (1.72), keratin (1.51) or collagen (1.43) all of which have much higher refractive index than water (1.33) and, therefore they are hyper-reflective and appear brighter under RCM. We think this may be the reason of the hyporeflective nests of Paget's cells in our case.

This case was more likely to be a mammary Paget disease considering the history and required early surgical intervention. However, the clinical differential diagnosis of solitary erythematous patch on the breast may range from inflammatory lesions such as eczema to malignancy such as amelanotic melanoma, Bowen's disease or superficial BCC [15]. In this case, unfortunately, dermoscopic findings were nonspecific also for the differential diagnosis.

At first glance on RCM the presence of numerous large, and dense nests simulating dark silhouettes excluded the diagnosis of eczema. In detailed examination, together with numerous dense nests, hyporeflective cells with pale cytoplasm and bright nuclei seen all through the epidermis made it possible to exclude a melanoma characterized by atypical cells with bright cytoplasm and dark nuclei. Large, round nucleated cells representing dyskeratotic cells at the spinogranular layer, and tightly coiled vessels are characteristic features of Bowen's disease on RCM. However, neither dyskeratotic cells nor coiled vessels were seen in this case. The dense tumor nests we have seen on RCM were actually similar to the morphology of dark silhouettes of BCC. However, the lack of typical peritumoral cleft-like spaces and localization of the nests through the epidermal layer were the features opposing this diagnosis.

The main limitation of RCM in the diagnosis of Paget's disease may be due to the hyporeflective cells. If the tumor cells are not abundant, and arrange in smaller groups with lesser glandular formation, RCM features may not be as obvious as they are in this case. So it may not always be possible to reach an accurate diagnosis easily. Surely histopathological examination will be the gold standard in challenging RCM features.

In conclusion, this case highlights the confocal findings of a typical MPD, which is similar to extramammary counterpart. The characteristic appearance of Paget cells and their distinctive nest formation on RCM, may aid the clinical differential diagnosis by discerning it from inflammatory imitators like eczema. In addition, RCM is likely to improve

**TABLE 1.** All the cases of Mammary Paget Disease

| | Case number | Presentation | Dermoscopy | RCM findings of Paget disease |
|---|---|---|---|---|
| Longo et al, 2007 [1] | 1 case | Partially pigmented plaque on the superior quadrant of the breast | Lighter portion: whitish-pink area with irregular linear vessels Darker portion: light brown diffuse pigmentation with irregular black dots and small gray-blue structures | Superficial epidermal layers: Disarranged pattern, large, round, atypical cells with reflective cytoplasms and dark nuclei together with bright reflective particles + Within the stratum corneum numerous large, reflective cells with long dendritic branches |
| Richting et al, 2011 [2] | 1 case | Erosion on the center of the mamilla | Glomerular, linear-irregular and comma-like vessels | Disorganized epidermal architecture with multiple bright, nucleated cells of varying size, shape and reflectivity seen focally |
| Guitera et al, 2013 [4] | 1 case (the same case in Longo et al, 2007, the coauthor of this article) + 9 extramammary cases | Partially pigmented plaque | The pigmented part is described as light brown pigmentation, some irregular black dots and small gray-blue structures | Dense nests in the epidermal layer and some dendritic structures, dark round-oval areas, probably representing nuclei in some cells |
| Cinotti et al, 2013 [5] | 1 case | 2 mm, papular lesion | Non-specific findings | Hyper-reflective cells with a dark halo corresponding to isolated Paget cells in the epidermal layers + Roundish, large, hyporeflective cell groups at the basal layer |
| Oliveira et al, 2016 [8] | 5 cases | Eczema-like plaques in 4 cases, and in patient #5 partially pigmented nodule | Pink-whitish to red background (in all cases), polymorphous vessels, erosions, yellow scales, and shiny-white streaks (in some cases), and in patient # 5: polymorphous vessels within red-yellow-whitish background, brown dots and structureless areas of grey pigmentation | Loss of epidermal architecture and pagetoid spread of poorly reflective round cells (Paged cells), surrounded by a dark stroma seen as dark holes, + Single cells or small nests of cells with a bright central area and a peripheral large dark halo seen as target structures |
| Ozdemir et al, 2017 (this article) | 1 case | Eczematous reddish plaque involving some of the nipple area | Background erythema mostly separated with whitish reticulation, together with some linear and comma-like vessels | Partially spared honeycomb pattern with dense tumor nests, simulating dark silhouettes, composed of hyporeflective tumor cells, larger than keratinocytes with abundant, pale cytoplasm and small, mildly bright nuclei + Pagetoid spread of single tumor cells, some big and poorly reflected and some smaller and darker, scattered focally |

the accuracy of the clinical diagnosis especially in patients who refuse biopsy in this sensitive area, the mammilla. This noninvasive technique can be also used to outline the surgical margins of MPD when necessary. As a summary, RCM may be applied as an adjuvant diagnostic tool for the diagnosis and management of MPD.

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