

Basal Cell Carcinoma Arising from Xeroderma Pigmentosum: A Case Report and an Immunohistochemical Study

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Key Words

Xeroderma pigmentosum · Basal cell carcinoma · CD163⁺ · M2 macrophages · Foxp3

Abstract

We describe a 26-year-old Japanese patient with basal cell carcinoma arising from xeroderma pigmentosum (XP). Immunohistochemical staining revealed dense infiltration of CD163⁺ M2 macrophages, together with Foxp3⁺ regulatory T cells. Interestingly, MMP9, which was reported as one of the functional markers for immunosuppressive macrophages, was also detected in the CD163⁺ M2 macrophage-infiltrated areas. Our case suggests the immunological background of tumor development in a patient with XP.

Introduction

Xeroderma pigmentosum (XP) is an autosomal recessive disorder characterized by extreme sensitivity to ultraviolet radiation and more than a 1,000-fold increase in the risk of cutaneous malignancy, including basal cell carcinoma (BCC), squamous cell carcinoma, and malignant melanoma in sun-exposed areas [1]. Though previous reports suggest that one of the histopathological findings of XP in the early stage is the variety of infiltrating lymphocytes [2], the precise profiles of these lymphocytes have not been investigated so far.

The roles of regulatory T cells (Tregs) are currently an area of interest in the field of human skin cancer and inextricably connected with immune-tolerance and suppressed

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recognition of tumor antigens in tumor progression and recurrence [3–6]. Together with Tregs, immunosuppressive macrophages, such as myeloid-derived suppressor cells, tumor-associated macrophages and CD163⁺ M2 macrophages, have recently been shown to contribute to establishing the tumor microenvironment in skin cancer [7–11].

Case Report

A 26-year-old male Japanese visited our outpatient clinic with a 2-year history of pigmented nodule on his nose. He has had photosensitivity since he was 3-months old and was diagnosed with XP type A. On his initial visit, physical examination revealed a waxy, blackish-brown nodule with telangiectasia on his nose (fig. 1a). The size of the nodule was approximately 7 × 7 mm in diameter. The dermatoscopic findings revealed multiple blue-gray globules accompanied by arborizing vessels (fig. 1b). Based on the above findings, we clinically diagnosed this patient as having BCC with XP and excised the tumor with a 2-mm surgical margin from the lesion. The histological findings revealed multiple, palisaded basophilic tumor masses surrounded by prominent infiltrating lymphocytes (fig. 1c), confirming our clinical diagnosis. To further evaluate the profiles of the tumor-infiltrating lymphocytes, we employed immunohistochemical staining for CD8, granulysin, TIA-1, CD163⁺, Foxp3 and MMP-9, as previously reported [12]. Immunohistochemical staining revealed dense infiltration of CD8⁺ cells (fig. 2a), CD163⁺ M2 macrophages (fig. 2b) and Foxp3⁺ cells (fig. 2c). MMP9⁺ cells were detected in the CD163⁺ M2 macrophage-infiltrated areas (fig. 2d), and TIA-1⁺ cells were scattered around the tumor (data not shown). A few granulysin⁺ cells were detected, mainly in the CD8⁺ area (data not shown). The number of immunoreactive cells was counted using an ocular grid of 1 cm² at a magnification of ×400 (fig. 3). Staining of the infiltrated lymphocytes was examined in more than 5 random, representative fields from each section.

Discussion

Alternatively activated macrophages, M2 macrophages, have an important role in the responses to parasite infection, tissue remodeling, angiogenesis and tumor progression [13]. Together with Tregs, immunosuppressive macrophages, such as myeloid-derived suppressor cells and CD163⁺ M2 macrophages, promote an immunosuppressive environment in the tumor-bearing host [7–9]. In addition to directly suppressing effector T cells, immunosuppressive macrophages also indirectly suppress effector T cells by several mechanisms through the induction of Tregs and Th2 polarizations [13]. Another report suggested that M2 macrophages produce thymus and activation-regulated chemokine to induce Th2 cells and Tregs [14].

The potential role of Tregs in human disease is currently the focus of intensive research efforts [15]. Indeed, a recent report describes that a Treg population isolated and expanded from normal human skin highly expressed CD25, L-selectin, GITR, Foxp3 and intracellular CTLA-4 as well as the skin homing addressins CLA, CCR4 and CCR6 [16]. Moreover, RANKL expression by keratinocytes alters the function of epidermal Langerhans cells, resulting in systemic increases of Tregs [17], strongly suggesting that Tregs have a crucial function in various inflammatory skin disorders and skin tumors. Indeed, we previously reported the distribution of Foxp3⁺ Tregs in the lesional skin of psoriasis vulgaris and spongiotic

dermatitis [12] as well as extramammary Paget's disease [4] and BCC [18], which might suggest a contribution of Tregs to skin tumors.

XP is a rare autosomal recessive, cancer-prone genodermatosis characterized by a defect in the repair of DNA damage caused by UVR, resulting in a high risk in the development of cutaneous malignancies, including BCCs, squamous cell carcinomas and melanomas on sun-exposed areas [19–21]. Histological criteria of XP are characterized as follows: hyperkeratosis, chronic inflammation in the upper dermis and hyperpigmentation in the early stage, and basophilic degeneration of the collagen and solar elastosis in the upper dermis in the later stage [2]. Though various molecular analyses of the carcinogenesis of XP have been reported previously, and though both CD163⁺ M2 macrophages and Foxp3⁺ Tregs contribute to the progression of conventional non-XP-derived BCC [9, 18, 22], to the best of our knowledge, there is no report focusing on the profiles of immunosuppressive cells in tumors developing from XP. Therefore, we hypothesized that immunosuppressive cells, M2 macrophages and Tregs might contribute to the carcinogenesis of BCC arising from XP. In our present case, CD163⁺ M2 macrophages and Foxp3⁺ Tregs were densely infiltrating around the tumor. In addition, MMP9⁺ cells, also known as functional markers for immunosuppressive macrophages [7], were detected around the tumor mass. In contrast to immunosuppressive cells, few granulysin⁺ cells that lyse various tumors in conjunction with perforin [23] were observed around the tumor. In summary, we described a case of BCC arising from XP. Our present study sheds light on the immunological background of tumor development in a patient with XP.

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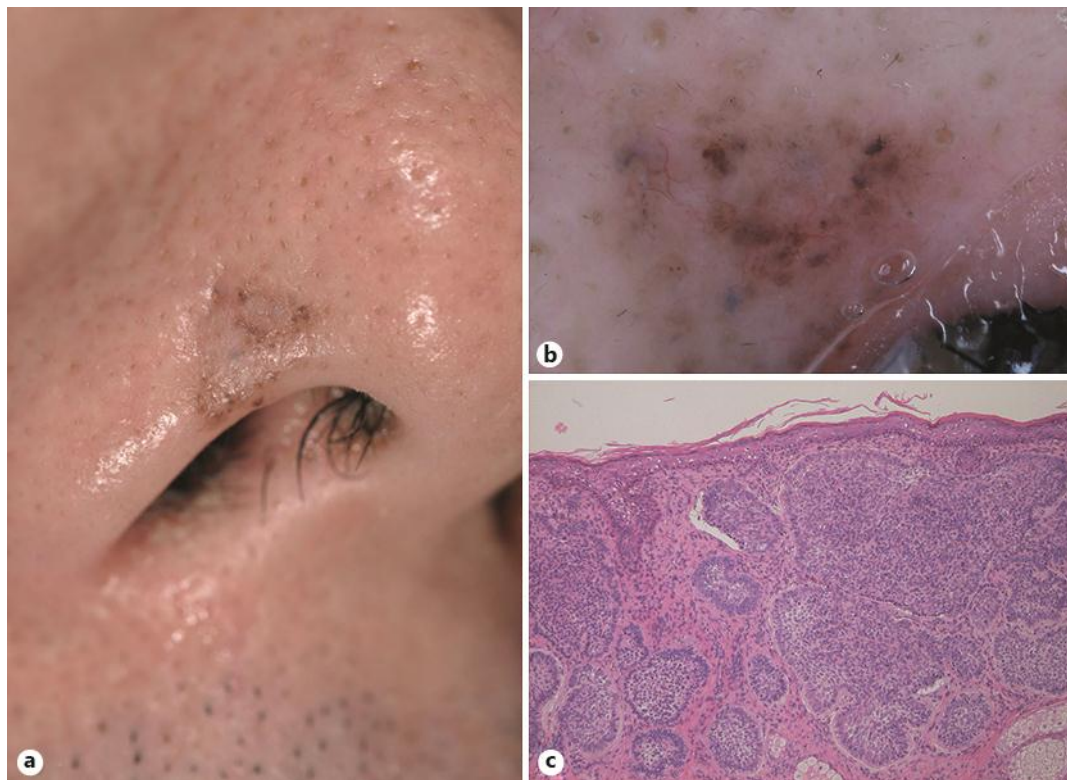


Fig. 1. A waxy, glossy, blackish-brown nodule with telangiectasia on the nose (a). A blue-whitish area with dotted macules is surrounded by arborizing vessels (b). Multiple palisaded basophilic tumor islands are surrounded by infiltrating lymphocytes. Original magnification $\times 100$ (c).

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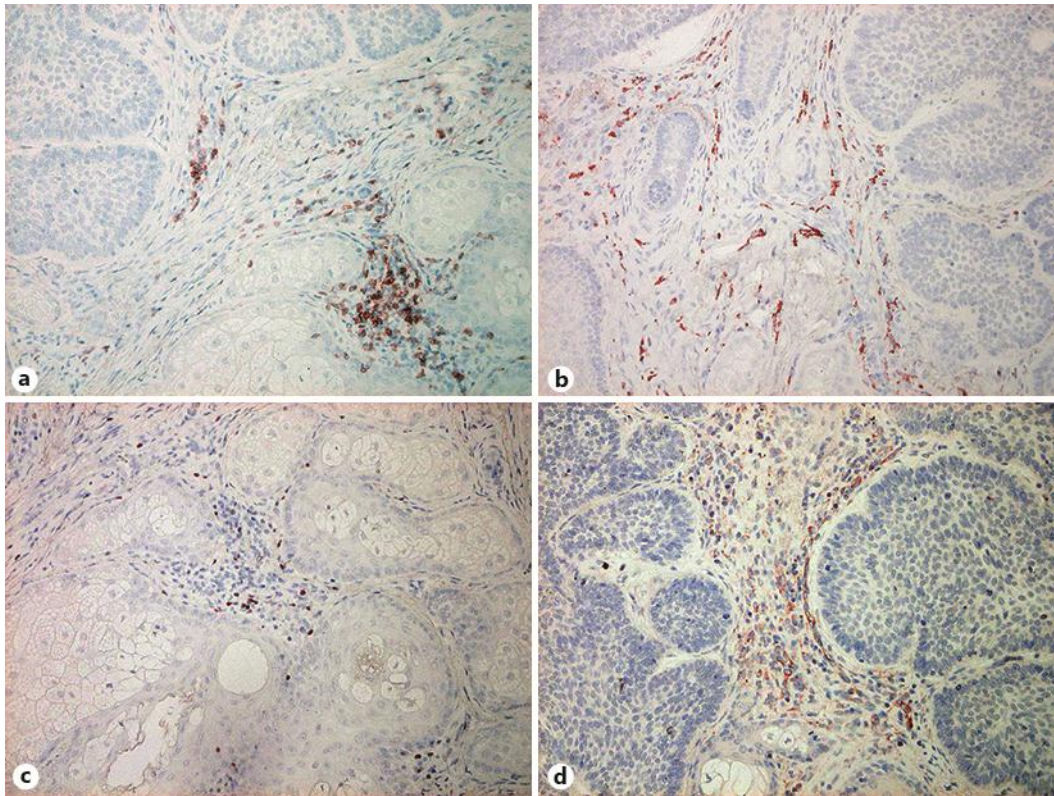


Fig. 2. A paraffin-embedded tissue sample was deparaffinized and stained using anti-CD8 Ab (a), anti-CD163 Ab (b), Foxp3 Ab (c) or anti-MMP9 Ab (d). The sections were developed with liquid permanent red. Original magnification $\times 200$ (a–d).

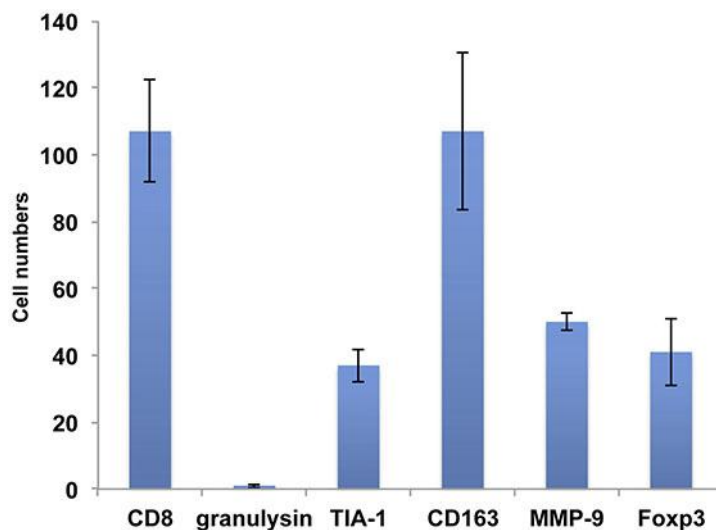


Fig. 3. Summary of the number of immunosuppressive cells versus cytotoxic cells in the tumoral areas. Five representative fields of each section were selected. The number of immunoreactive cells was counted using an ocular grid of 1 cm^2 at a magnification of $\times 400$. Data are expressed as the means \pm SD of the number of immunosuppressive cells versus cytotoxic cells in each tumoral area. * $p < 0.05$.