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Merkel cell polyomavirus on primary Merkel cell carcinoma of the skin with partial regression after biopsy

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ABSTRACT

Introduction: Merkel cell carcinoma (MCC) is an uncommon primary cutaneous tumour. The majority of these tumour (about 80%) have integration of the polyomavirus DNA into the genome of Merkel cell carcinoma. Reports about at least nine cases of partial regression in primary and or metastatic lesions have been published. It is likely that regression is an immunological response mediated by T cells. **Case Report:** We report an 81year old woman who presented with a rapidly growing tumor in the left thigh. An incisional biopsy of the lesion was performed. Histopathologic and immunohistochemically diagnosis were consistent with Merkel cell carcinoma. Scant peritumoral lymphocytic infiltrate was CD3+, CD4+, and scant CD8+ was observed. The reporter test polymerase chain reaction (PCR) for Merkel virus yielded a positive result. Twenty days after the initial biopsy the lesion began to regress. **Conclusion:** Merkel cell carcinoma is a rare and aggressive tumour. At least nine cases of partial regression on primary and or metastatic lesions have been published. It is likely that regression is a T cell-mediated immunological response. A reporter test (PCR) for Merkel virus and both types of lymphocytic infiltrate and distribution (intratumoral and peritumoral) in our case very important as there are several known mechanisms that can contribute to cellular immune escape in MCP y V positive Merkel cell carcinoma. Study of integration and regulation of the immunological system implies future development of individually of different immunological therapies.

Keywords: Skin, Merkel cell polyomavirus, Merkel cell carcinoma, partial regression, biopsy

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INTRODUCTION

Merkel cell carcinoma (MCC) is a rare and aggressive tumour with an incidence rate of 0, 44 out of 100,000 people affected per year [1]. The most frequent form of clinical presentation is a cutaneous lesion in the form of single, fast-growing painless lump, with a red to purple color and superficial telangiectasias. MCC etiology is unknown, although ultraviolet radiation, immunosuppression, and viral oncogenesis (Merkel cell polyomavirus) (MCP y V) have all been implicated in its development. Feng et al discovered a new species of the genus polyomavirus named MCPyV [2]. The majority of these tumors (about 80%) have integration of the polyomavirus DNA into the genome. The oncogenicity of MCPyV in MCC has been described by recent reports in which it has been suggested that MCPyV with truncated mutations of the large T antigen (LT) region is integrated into the MCC host genome and that the interaction of MCPyV- LT and retinoblastoma protein or the presence of the MCPyV small T antigen is essential for sustained tumor growth [3]. At least nine cases of partial regression in primary and or metastatic lesions have been published [4-8]. It seems likely that regression is a T cell-mediated immunological response [7-10].

CASE REPORT

This case involved an 81 year-old woman who presented with a rapidly growing, lobulated, non-ulcerated violet 4x2 cm tumor in her left thigh (Figure 1A). An incisional biopsy of the lesion was performed and revealed MCC. Twenty days after the initial biopsy the lesion began to regress (Figure 1B). Microscopic examination of the incisional biopsy revealed a tumour with a solid and trabecular pattern that was located in the dermis without any connection to the epidermis. Cells have hyperchromatic nuclei and finely dispersed granular chromatin with scanty peritumoral lymphocytic infiltrate (Figure 2A). Immunohistochemically study revealed it was keratin 20 and chromogranin A positive (Figures 2B and C). The peritumoral lymphocytic infiltrate was cluster of differentiation CD3 and CD4 positive with scant CD8 (Figures 2D-F). Thyroid transcription factor-1(TTF-1), Keratin 7, and CD20 were negative. Tests for Merkel virus were carried out using a paraffin block. This yielded positive results, indicating a virus (Figure 3). The patient did not return for the initial excision of the lesion. Six months later she returned due to the persistency of the lesion, which had grown, and increased pain during the previous week. Complete excision was performed at another center.

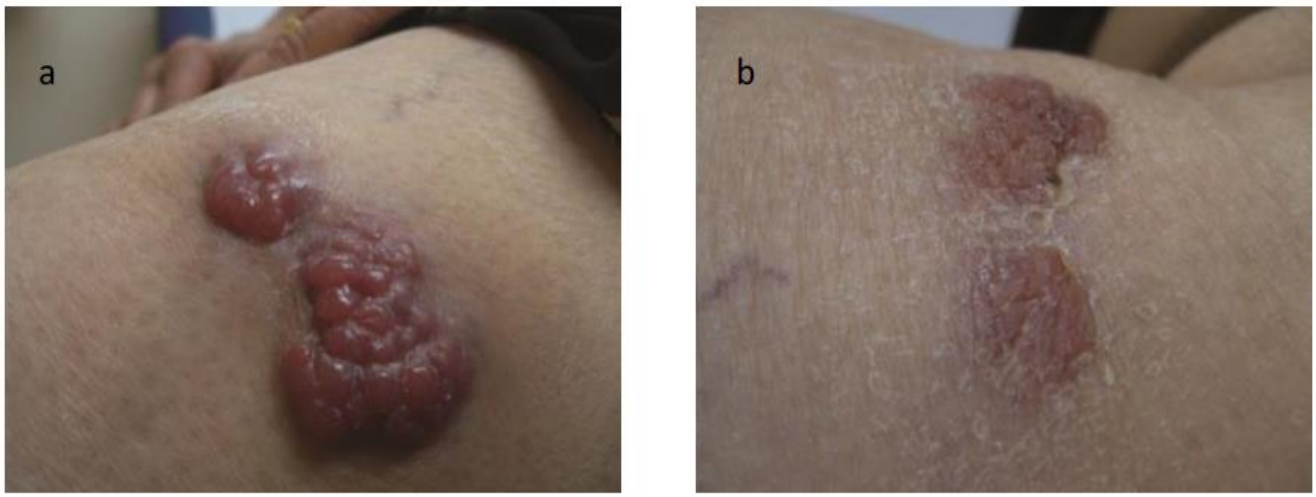

Figure 1. Clinical appearance of tumor on the first visit (a) and twenty days after incisional biopsy (b).

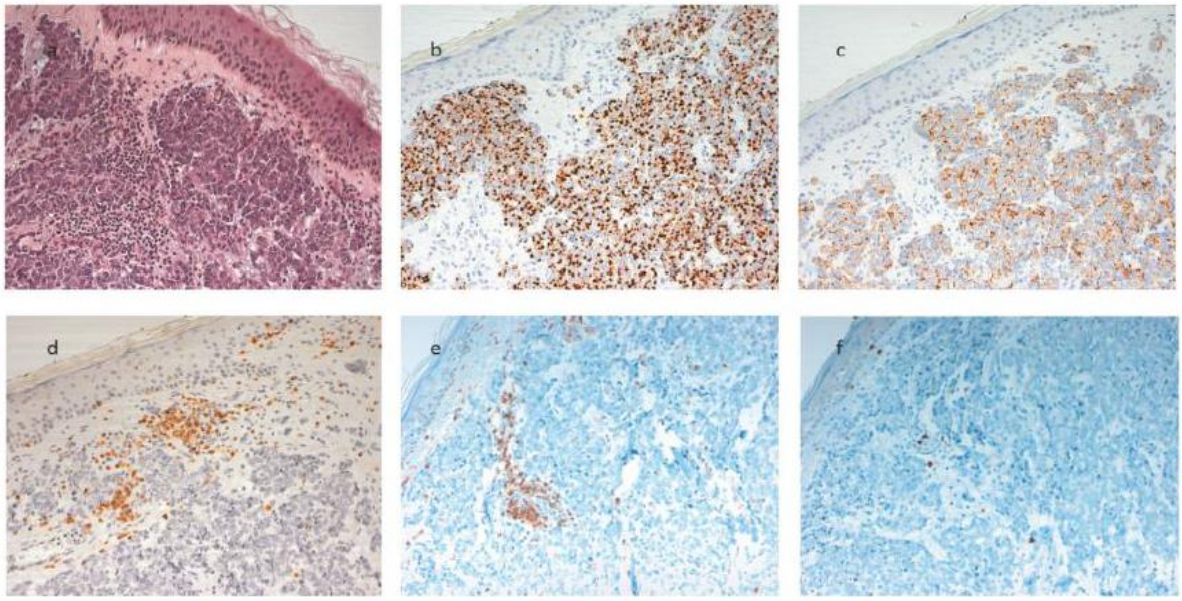

Figure 2. Tumor located in the dermis without connection to the epidermis, consisting of medium sized cells and hyperchromatic nuclei with a finely dispersed granular chromatin. Multiple nucleoli of small size and scant cytoplasm. In the dermis, mild superficial inflammatory infiltrate consisting of lymphocytes with a peritumoral distribution (a). (Hematoxylin and eosin x 200). Immunohistochemical analysis, keratin 20 positive with distribution paranuclear in drop (b). Cytoplasmatic granulate positive for chromogranin A (c). CD3 positive in peritumoral T lymphocytes (d) and CD4 + (e) with scant CD8+ (f). (Immuhistochemical stain x 200).

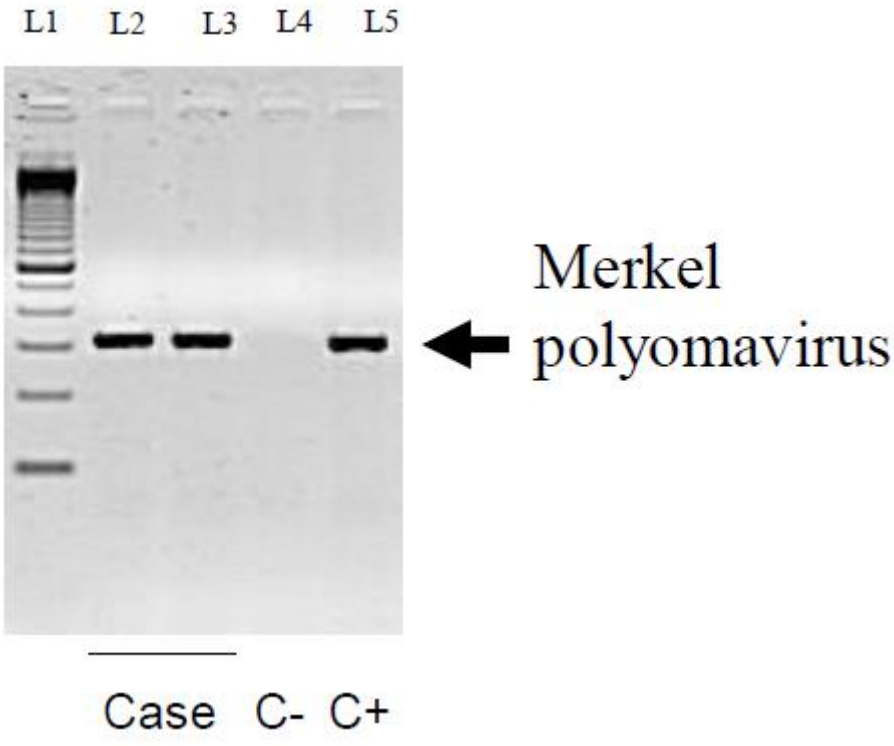

Figure 3. Electrophoresis separation of fragments of the Merkel cell polyomavirus (309 bp) amplified by means of PCR with primers corresponding to the LT3 region from the DNA genomic. Line 1 corresponds to the molecular weight ladder, lines 2 and 3 case problem, line 4 negative control, and line 5 positive control. Electrophoresis agarose gel (2%) and ethidium bromide staining.

DISCUSSION

Complete spontaneous regression was first described in 1986 by O'Rourke and Bell [11]. The estimated rate of regression was shown to be 1.4% [12]. The mechanism by which this process takes place is unknown, although an immunological T cell-mediated response, which could induce apoptosis and replacement by foamy cells, has been postulated [7-10]. In the majority of cases described, there was a prior biopsy/fine needle aspiration trauma to the lesion, as had occurred in our case; therefore, this could be the triggering factor for this process [7, 13-15]. There have been cases of spontaneous regression without a prior external physical or chemical agents [16]. The presence of intratumoral T cells has been associated with patient survival in MCC, and intratumoral CD8+ lymphocytes have been reported to be associated with favorable prognosis as an independent predictor of survival [17, 18]. In our case, the scant peritumoral lymphocytic infiltrate indicated CD3+ and CD4+ with scant CD8+. There are several known mechanisms that can contribute to cellular immune escape and diminished lymphocyte infiltration in MCPyV positive Merkel cell carcinoma such as HLA-I expression down-regulation on tumor cells (similar to other virally associated cancers), dysfunctional endogenous MCPyV specific CD8+ cells responses with expression of phenotype PD-1+/Tim3+ expression and low E-Selectin expression in vessels [19-21]. Such mechanisms could explain why tumor regression is only partial or does not happen. Therefore, more than one trigger factor could contribute to cellular immune escape in MCPyV Merkel cell carcinoma. The study of integration and regulation of immunological system implies future development of individualized immunological therapies.

Conclusion

Merkel cell carcinoma is a rare and aggressive tumour. At least nine cases of partial regression in primary and or metastatic lesions have been published. It is likely that regression is a T cell-mediated immunological response. The reporter test (PCR) for Merkel virus and types of lymphocytic infiltrate and distribution (intratumoral and peritumoral) in our case are very important as there are several known mechanisms that can contribute to cellular immune escape in MCP y V positive Merkel cell carcinoma. Study of integration and regulation of the immunological systemimplies future development of individualized immunological therapies.

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