Spontaneous regression of Merkel cell carcinoma: A case report and review of the literature

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1. Introduction

Merkel cells are primarily located in the basal layer of the epidermis and concentrated in touch-sensitive areas of the skin.1 Their most noticeable ultrastructural characteristics are the dense-core secretory granules accumulated near the nerve fibre junction, which may contribute to its indefinite neuroendocrine function.2 Merkel cell carcinoma (MCC) was first described by Toker3 in 1972 as trabecular carcinoma of the skin. 85% of all MCCs appear on sun-exposed areas4 with the head and neck region most frequently affected, accounting for 35–47% of these cases.5,6 The prognosis is poor, with a 5-year survival rate of around 60%.7 Owing to the common involvement of regional lymph nodes (10–45%) at initial presentation, of which 50–75% of patients develop regional lymph node metastases at some time.8–12 Distant metastases commonly affect 50% of patients with common sites being the lymph nodes, liver, bone, brain, lung and skin.8–10,13,14

O’Rourke and Bell15 first described complete spontaneous regression (CSR) of MCC in 1986. Thereafter, 21 additional cases have been reported. This present study presents a case of complete spontaneous regression of MCC with an immunohistochemistry study of the region in which the tumour was located.

2. Presentation of case

An 86-year-old female patient presented with a violaceous lump on the left side of the nose measuring 25 × 25 mm. An incisional biopsy was performed and histology showed a dense infiltrate of small tumour cells with hyperchromatic nuclei and little cytoplasm (Fig. 1). Immunohistochemistry confirmed the diagnosis of MCC, with positive staining for cytokeratin 20 (CK20) (Fig. 2), neuron-specific enolase (Fig. 3), synaptophysin and negative staining for cytokeratin 5/6T, TTF1 and MelanA. The patient attended for an excision 8 weeks after her initial biopsy and showed no presence of lump prior to excision (Fig. 4). Histology of the excised specimen showed severely sun-damaged skin with mild epidermal atrophy. There was a patchy chronic inflammatory cell infiltrate with focal fibrosis and foreign body giant cell reaction with no evidence of any residual MCC. Immunohistochemistry demonstrated a mixture of both T and B cells with positive staining for CD4, CD3, CD5, and
CD8 with CD4 slightly more than CD20 and CD79a. In addition, the specimen revealed admixed macrophages, which stained with CD68.

### 3. Discussion

Spontaneous regression among all neoplastic diseases has been estimated to be 1 case per 60,000 to 100,000 neoplasms. Complete spontaneous regression (CSR) of MCC is rare and predicted to be 0.0013%. To date, 15 cases of complete MCC regression following incisional biopsy have been reported (Table 1), along with 7 cases of regression occurring after local or regional recurrence of the carcinoma (Table 2). In the group of MCCs with primary CSR most neoplasms were located on the cheek. In contrast, none of the cases of MCCs with CSR after local recurrence or metastasis were primarily located on the cheek. In both groups of patients the majority were female (15 cases) and the mean age was 79 years old. Our patient presented the typical characteristics of patients with primary CSR of MCC i.e. female sex, elderly and regression after incisional biopsy.

The histopathologic study of the biopsy following CSR in our patient demonstrated results similar to other reports. The biopsy showed accumulation of chronic inflammatory cells, mainly T cells. Other studies of both primary and secondary MCC demonstrated infiltration by CD4+, CD8+ and CD3+ T lymphocytes and foamy macrophages. The mechanism of CSR remains unclear, however, along with our findings, it suggests that T-cell-mediated immunity plays an important role in tumour regression. This could be attributed to the initial incisional biopsy of MCC (15 cases), which may have triggered tumour regression via stimulation of the immune system. In addition, the majority of patients were elderly with poor health status and various co-morbidities, which may suggest other unknown mechanisms, could be involved.
### Table 1
Cases reported with primary complete spontaneous regression of Merkel cell carcinomas.

| Author                  | Sex/age | Co-morbidities                                                                 | Tumour Site          | Treatment | Immunological study after regression                                                                 | Disease free period |
|-------------------------|---------|--------------------------------------------------------------------------------|----------------------|-----------|-------------------------------------------------------------------------------------------------------|---------------------|
| Kayashima et al.        | F/68    |                                                                                   | Forehead Biopsy      |           | CD3 and CD5 (pan-T cells) cells heavily infiltrated and few CD19 cells (B cells). CD4 cells were in the majority. CD1 (Langerhans) cells also present Infiltrates of inflammatory cells (chiefly lymphocytes) | 11 years            |
| Kayashima et al.        | F/86    | Hypertension Cerebral atherosclerosis, IDDM                                        | Cheek Biopsy         |           |                                                                                                      | 36 months           |
| Djilali-Bouzina et al.  | F/83    |                                                                                   | Cheek Biopsy         |           |                                                                                                      | 1 year              |
| Duncan and Tschen       | M/79    |                                                                                   | Scalp Biopsy         |           |                                                                                                      | 28 months           |
| Tanita et al.           | F/75    |                                                                                   | Cheek Biopsy         |           |                                                                                                      | 1 year              |
| Sato et al.             | M/87    |                                                                                   | Cheek Biopsy         |           |                                                                                                      | 2 months            |
| Maruo et al.            | F/82    | Cervical spinal cord injury and complete paresis, Cerebral atherosclerosis and Neurosis | Cheek Biopsy         |           | Large number of KP-1+ foamy cells (macrophages). Infiltration of lymphocytes, numerous lymphoid follicles and T cells | 1 year              |
| Connelly et al.         | F/71    |                                                                                   | Cheek Biopsy         |           |                                                                                                      | 11 months           |
| Sais et al.             | F/78    |                                                                                   | Cheek Biopsy         |           |                                                                                                      | 40 months           |
| Junquera et al.         | F/79    |                                                                                   | Cheek Biopsy         |           |                                                                                                      | 6 years             |
| Vesely et al.           | F/67    |                                                                                   | Cheek Biopsy         |           |                                                                                                      | 6 months            |
| Missotten et al.        | M/90    |                                                                                   | Eyelid Biopsy        |           | Granulomatous inflammation consisting of many histiocytes and lymphocytes                            | 18 months           |
| Ciudad et al.           | F/81    |                                                                                   | Eyelid Biopsy        |           | Moderate lymphocytic infiltrate. Most lymphocytes were T cells                                       | 2 years             |
| Ciudad et al.           | F/86    |                                                                                   | Cheek Biopsy         |           |                                                                                                      | 18 months           |
| Present Study           | F/86    | Osteoarthritis, COPD, Hypertension, AF, PPM (pacemaker)                           | Nose Biopsy          |           | Lymphocyte infiltrate staining for CD4+, CD3+, CD5+ with CD4+ slightly more than CD20+ and CD79a. Also admixed macrophages present staining for CD68                             |                    |

### Table 2
Cases reported with complete spontaneous regression of recurrences or metastasis of Merkel cell carcinomas.

| Author                  | Sex/age | Co-morbidities                                                                 | Tumour site          | Treatment                                                                                              | Metastasis                                                                 | Immunological study after regression | Disease free period |
|-------------------------|---------|--------------------------------------------------------------------------------|----------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------|---------------------|
| O'Rourke and Bell       | F/90    | Cerebral atherosclerosis, SCC upper sternum                                     | Pre-auricular area   | Surgery, radiotherapy, chemotherapy, surgery                                                          | Skin                                                                      | Cervical lymphadenopathy and Skin | 18 months           |
| Bayrou et al.           | F/69    | Dilated cardiomyopathy, Mitral insufficiency, Hypertension, Atrial fibrillation, Transient ischaemic attacks, Chronic renal failure, Abdominal aortic aneurysm | Temple               | Surgery                                                                                                |                                                                           |                                      | 15 years            |
| Yanguas et al.          | M/65    | Dilated cardiomyopathy, Mitral insufficiency, Hypertension, Atrial fibrillation | Ear                  | Surgery                                                                                                | Cervical lymphadenopathy and Skin |                                                                           | 18 months           |
| Richetta et al.         | F/76    |                                                                                   | Eyebrow Biopsy       | Regional lymph nodes and Skin                                                                           | Fibrosis, vascular congestion and modest lymphocytic infiltrate           |                                      | 13 months           |
| Wooff et al.            | F/94    |                                                                                   | Eyebrow Biopsy       | Regional lymph nodes                                                                 | Extensive fibrosis with accumulation of foamy macrophages and other chronic inflammatory cells including many T lymphocytes |                                      |                    |
4. Conclusion

In summary, we report one patient with CSR of MCC. To the best of our knowledge, this is the first described case of MCC with primary CSR of the nose. The findings are in concordance with many other studies most notably an incisional biopsy before regression and an infiltrate of T cells after regression. Although, this is only a proposed mechanism it certainly is an area that requires further research with the possibility of developing immune modulating therapy in treating such cancers.

Conflict of interest

None.

Funding

None.

Ethical approval

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Author contributions

Calver Pang – data collection, data analysis, writing; Deepika Sharma – histopathological and immunohistochemistry studies including figures; Thangasamy Sankar – study design, patient details.
Key learning points

- Merkel cell carcinoma is a rare disease with a high metastatic rate and poor prognosis.
- Spontaneous regression of Merkel cell carcinoma is an extremely rare event.
- In this case report, regression occurred following incisional biopsy.
- Biopsy showed mainly T cells suggesting immunity plays an important role in tumour regression which may be attributed to the incision which triggered an immune response.
- Mechanism of regression is still unclear but research into immune modulating therapy may help in managing such cancers.

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