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Spontaneous remission of Merkel cell carcinoma presenting with tertiary lymphoid structures in an immunocompetent patient

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Dear Editor,

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin cancer predominantly affecting elderly males, with a median age at diagnosis of 76 years. Its pathogenesis is linked to three main risk factors: UV exposure, Merkel cell polyomavirus (MCPyV) infection, and immunosuppression.[1] Standard management of localized disease (stage I/II) consists of wide local excision with sentinel lymph node biopsy (SLNB), followed by adjuvant radiotherapy according to disease stage.[2] Despite optimal multimodal treatment, prognosis remains poor, with more than 50% of patients progressing to metastatic disease and a median overall survival of approximately 20 months with first-line avelumab.[3]

Spontaneous regression of MCC is a rare but documented phenomenon, reported almost exclusively in immunocompetent, MCPyV-positive patients, often in the context of dense lymphocytic infiltration of the primary tumor.[4,5] We report a case of complete spontaneous regression of a stage IIA MCC following a diagnostic incisional biopsy, with evidence of tertiary lymphoid structures (TLS) in the pathological specimens.

In April 2022, a 70-year-old immunocompetent male presented with a progressively enlarging pink nodule of the left distal thigh. Ultrasonography showed a predominantly vascular lesion without infiltration of surrounding tissues. Contrast-enhanced MRI revealed a 30 mm oval-shaped, homogeneously enhancing subcutaneous mass with irregular margins. Clinical suspicion was initially directed toward a soft tissue sarcoma, and an incisional biopsy was performed. Histology demonstrated sheets and solid nests of small round cells with vesicular nuclei and multiple nucleoli, co-expressing epithelial (CK20, CAM5.2, CK AE1/AE3, Ber-EP4, EMA) and neuroendocrine (chromogranin, synaptophysin, CD56, INSM1) markers, confirming MCC. Staging CT scan showed no evidence of distant metastases (clinical stage IIA) (Figure 1 a-c).

Following multidisciplinary tumor board discussion, wide local excision and SLNB were planned. However, the patient reported progressive nodule reduction after the diagnostic biopsy. At surgery (June 2022), the excision specimen and both sentinel lymph nodes were entirely free of MCC. Negativity for CK20, chromogranin, and synaptophysin confirmed the absence of residual disease. The excision specimen instead showed a dense lymphocytic infiltrate composed of $CD4^+$ helper T cells, $CD8^+$ cytotoxic T cells, and B lymphocytes organized into tertiary lymphoid structures (Figure 1 d-f). Given complete pathological remission, the multidisciplinary team decided against further lymph node dissection or radiotherapy. As of May 2026, the patient is alive with no evidence of disease recurrence at 47 months.

Spontaneous regression of MCC is rare, with a reported incidence of approximately 4.5% in a retrospective series.[5] Reported cases share common features: immunocompetent host, MCPyV positivity, lymphocytic infiltration of the primary tumor, and occurrence following a surgical or needle biopsy. The proposed mechanism involves biopsy-induced trauma triggering $CD8^+$ T cell infiltration, although a translational study on paired biopsy and radicalization specimens did not demonstrate a significant intratumoral increase in $CD8^+$ T cells.[6]

A distinctive feature of our case is the presence of TLS in both the primary biopsy and the radicalization specimen. In a recent study by Nakamura *et al.*, TLS were identified in all cases of spontaneous regression, with RNA sequencing revealing enrichment of B-cell-mediated immunity gene sets in MCPyV-positive, TLS-positive tumors.[7] TLS have also been associated with objective response to anti-PD-(L)1 therapy in metastatic MCC,[8,9] reinforcing their role as a candidate immune biomarker.

This case supports the hypothesis that localized MCC may undergo immune-mediated spontaneous regression in selected patients. The co-occurrence of MCPyV positivity and TLS at diagnostic biopsy may identify a subgroup particularly prone to this phenomenon. A watch-and-wait approach could be considered in immunocompetent patients displaying these features, particularly elderly or frail individuals for whom surgical morbidity is a relevant concern. Prospective studies are needed to validate TLS as a predictive biomarker and to explore treatment de-escalation strategies in this setting.

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Figure 1. a, **b**, **c**) Merkel cell carcinoma with diffuse chromogranin and CK20 staining. **d**, **e**, **f**) regression with detail of tertiary lymphoid structure (arrow), $CD20^{+}$ and $CD3^{+}$ staining.