Merkel Cell Carcinoma of the Head and Neck: A Clinical and Histopathological Approach

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Introduction
Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine carcinoma arising within the skin. The head and neck is the most common site affected and it usually presents in elderly patients. MCC has a high propensity to spread to regional and distant sites. Ultraviolet B radiation exposure and immunosuppression are the primary etiologic factors. Merkel cell polyomavirus (MCPyV) may represent another etiologic factor. Histologically, MCC can be challenging to distinguish from other small cell tumors that can be found in the skin, e.g. small cell carcinoma of the lung, lymphoma, carcinoid, neuroblastoma, etc. Independent histopathologic parameters may further elucidate the best treatment management for the disease.

Objectives
The aim of the study is to identify and confirm any new or suggested independent histopathologic predictors correlated with outcome.

The data analysis uses a new protocol for the examination of MCC developed by the College of American Pathologists [Rao P]. The protocol relies on published potential relevant histopathological parameters, such as mitotic index or the presence of tumor-infiltrating lymphocytes (TILs), etc.

Results I
- Median tumor size: 1.2 cm (range, 0.4–10 cm), median tumor thickness: 6.5 mm (1.5–40 mm)
- Overall negative surgical margins: 19/39 cases (49%)
  - Negative peripheral margins: 70%
  - Negative deep margins: 51%
- LVI present in 68%, PNI present in 24%, TILs present in 28%, spindle cells present in 15%
- Median mitotic-index: 57 mitoses/mm² (range, 9–141)
- Nodular growth pattern in 67%
- CK 20 positive in 91%, synaptophysin positive in 74%, chromogranin A positive in 45%

Results II
- Median follow-up was 19 months (range, 1–168)
  - Overall recurrence: 34.6%
  - Local recurrence: 13.5%
  - Regional recurrence: 26.9%
  - Distant disease occurrence: 25.9%
  - Nodal recurrence risk factors:
    - Positive deep resection margin: significantly correlated with nodal recurrence (p=0.02)
  - No other parameters significantly associated with outcome

Discussion
- A change has been made in the way MCC is evaluated histopathologically. In analogy to malignant melanoma of the skin, a defined protocol needs to be used for pathological examination of MCC.
- The often combined treatment approach (surgery plus radiotherapy) may not be valid for all of the patients, since many patients are aged or immunosuppressed.
- 66% of the included patients presented with early stage disease with a 5-year disease specific survival of 63.6% showing a need to identify independent predictors, especially in early stage disease.
- Conflicting findings about tumor size and outcome exist. Since most of head and neck MCC are small at time of diagnosis, size may be less important than thickness. Again, conflicting data exists.
- Other histopathologic parameters previously reported to be associated with poorer prognosis, e.g. mitotic-index, and TILs were not found to be related to outcome in our series.
- The high rate of positive deep margins is concerning. A frozen section of the deep margin is crucial. While MCC is radiosensitive, it does not justify for not obtaining a clear deep margin.
- A positive deep margin is an independent predictor for nodal recurrence, therefore revision surgery is indicated in case of a positive deep margin before the planned adjuvant radiotherapy.
- The importance of the deep margin is underlined by the fact that MCC tends to grow particularly in a vertical way as shown in our series and other reports.

References

Conclusions
With a single institutional series, although large, we are not able to identify or confirm predictive histological factors. Multicenter, and prospective studies are warranted. A clear deep surgical margin of the primary is of utmost importance in this disease mostly growing vertical. Adjuvant radiotherapy can not replace a re-resection in case of a positive deep resection margin, although MCC is highly radiosensitive.

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