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Case 19-2008: A 63-Year-Old HIV-Positive Man with Cutaneous Merkel-Cell Carcinoma

Paul M. Busse, M.D., Ph.D., John R. Clark, M.D., Victorine V. Muse, M.D., and Vincent Liu, M.D.

PRESENTATION OF CASE

Dr. Gregory K. Robbins (Infectious Diseases): A 63-year-old man was referred to the clinic for head and neck cancer, a multidisciplinary unit of this hospital, for management of cutaneous Merkel-cell carcinoma. He had been well until 3 months earlier, when he noted a small, painless nodule on the superior, right-central aspect of his forehead. During the next 3 weeks, this nodule grew slowly, and a second, pea-size, painless nodule developed in front of his right ear. Pathological examination of a biopsy specimen of the lesion on the forehead indicated a small-cell carcinoma that was thought to be consistent with Merkel-cell carcinoma. A fine-needle aspiration biopsy of the right preauricular mass revealed malignant cells that were consistent with Merkel-cell carcinoma. The lesion on the forehead, 2.5 cm by 2.2 cm, was excised by means of Mohs procedure; intraoperative frozen-section examination of the specimen led the surgeon to conclude that the final tissue margin was free of tumor. The patient felt well and did not have weight loss, fatigue, fever, or other skin lesions.

A diagnosis of infection with the human immunodeficiency virus (HIV) had been made 12 years earlier, and he was treated with sequential and dual nucleoside therapy. Three years after the initial diagnosis, he was admitted to this hospital with symptoms of congestive heart failure and an ejection fraction of 18%; a diagnosis of *Pneumocystis jiroveci* pneumonia was made. He was successfully treated, and after a long convalescence was able to resume an active physical and professional life. He had hypertension, hyperlipidemia, lipoatrophy, and peripheral neuropathy. As an adolescent, he had received radiation therapy for acne, and 2 years before this evaluation, basal-cell and squamous-cell carcinomas had been removed from his chest and arm. His current medications were zidovudine–lamivudine, lopinavir–ritonavir, trimethoprim–sulfamethoxazole, losartan, and captopril. His mother had died in her fifth decade, and both grandfathers had died of myocardial infarction in their sixth decade. The patient had no siblings. He worked as a radio journalist and university professor and lived alone.

On physical examination, the patient appeared well, with normal vital signs.

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The surgical site on the forehead was healing, and there was a firm, preauricular mass, 3 cm in diameter, on the right side that was inseparable from the parotid gland. There was no facial-nerve weakness. The soft tissue deep to the sternocleidomastoid muscle appeared full, and multiple enlarged lymph nodes were palpable along the right jugular chain. The left parotid gland was normal, and there was no other palpable lymphadenopathy. The oral cavity, pharynx, and larynx were normal, as were the results of the remainder of the physical examination.

Computed tomography (CT) of the head and neck obtained after the administration of contrast material showed a right preauricular soft-tissue mass, 1.6 cm by 2.6 cm; a mass in the right parotid gland, near the angle of the mandible, 1.4 cm by 1.4 cm; and two enlarged lymph nodes anterior to the right jugular vein, each 1.7 cm by 1.1 cm. Lymph nodes in the posterior triangle on the right side were larger than those on the left side. Magnetic resonance imaging (MRI) after the administration of contrast material showed an enhancing lesion, 3.0 cm by 1.5 cm by 2.3 cm, in the right preauricular region, which was inseparable from the superficial lobe of the parotid gland. Multiple, enlarged, abnormally enhancing lymph nodes were present in the right anterior cervical lymph-node chain, extending inferiorly to the level of C5; the largest was 1.6 cm by 2.5 cm. The left parotid gland appeared normal. CT scans of the thorax, abdomen, and pelvis were normal. Lymphoscintigraphy, performed at the site of the lesion on the forehead, showed drainage to lymph nodes in both sides of the neck.

Levels of serum electrolytes, calcium, glucose, creatinine, and urea nitrogen were normal. The hemoglobin was 13.8 g per deciliter, the hematocrit 38.3%, and the white-cell count 5500 per cubic millimeter, with 38% neutrophils and 54% lymphocytes. Flow cytometry indicated the following T-cell counts: CD3-positive cells, 1639 per cubic millimeter; CD4-positive cells, 232 per cubic millimeter; and CD8-positive cells, 1258 per cubic millimeter. The HIV viral load was undetectable. The level of total bilirubin was 1.1 mg per deciliter (18.8 μmol per liter), lactate dehydrogenase 332 U per liter, alanine aminotransferase 48 U per liter, aspartate aminotransferase 64 U per liter, and alkaline phosphatase 116 U per liter. The aminotransferase levels had been stable for several years. A treatment plan was established.

PATHOLOGICAL DISCUSSION

Dr. Vincent Liu: Sections of the punch-biopsy specimen of the forehead nodule revealed a large cellular nodule expanding the dermis (Fig. 1A), which was composed of densely packed, small blue cells dissected by thin fibrous strands (Fig. 1B); the cells had large, open nuclei with salt-and-pepper chromatin. On immunohistochemical staining, the tumor cells were positive for cytokeratin 20 in a dotlike perinuclear pattern (Fig. 1B). Both the morphologic and immunophenotypic features are characteristic of Merkel-cell carcinoma.

Merkel-cell carcinoma is an uncommon skin cancer thought to be derived from Merkel cells,[1] mechanoreceptors that reside in the basal-cell layer of the skin and in the outer root sheath of the hair follicle in the region of the bulge[2] at sites of high hair density, in the glabrous epithelium (the fingers, toes, and lips), and in the oral cavity. The diagnosis can be difficult to establish,

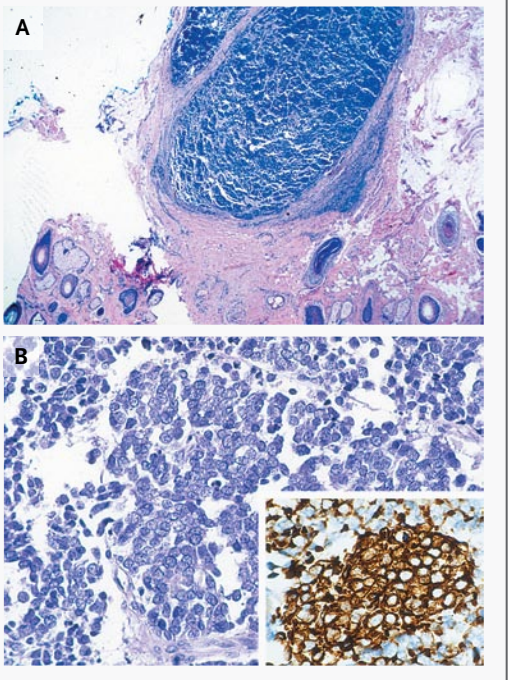

Figure 1. Biopsy Specimen of the Nodule on the Forehead.
A cellular nodule occupies the deep dermis (Panel A, hematoxylin and eosin). At higher magnification, the tumor is seen to be composed of small cells with salt-and-pepper chromatin and scanty cytoplasm (Panel B, hematoxylin and eosin). Immunohistochemical staining for cytokeratin 20 shows a perinuclear, dotlike pattern, confirming the cells to be Merkel cells (Panel B, inset).

because the tumor may resemble metastatic neuroendocrine tumors, lymphoma, leukemia, adnexal tumors, and melanoma, and it may occur in association with other skin tumors.[2] Immunohistochemical studies are helpful in establishing the diagnosis (Table 1).[2,3] Cytogenetic studies have shown the translocation t(1;17) and trisomy 6 in some cases, and gene-expression studies suggest that Merkel-cell carcinoma represents a heterogeneous group of entities.[4] Recently, a novel polyomavirus has been described in a series of Merkel-cell carcinomas, suggesting that such tumors, like other tumors that occur with increased frequency in patients with immunosuppression, may be caused by a virus.[5]

DISCUSSION OF MANAGEMENT

Dr. Paul M. Busse: May we review the radiologic images?

Dr. Victorine V. Muse: CT of the neck obtained after the administration of contrast material shows a preauricular soft-tissue mass (Fig. 2A), 2.6 cm in diameter, with an adjacent enhancing lesion, 1.4 cm in diameter, in the parotid gland (Fig. 2B). Also seen are separate, ipsilateral, enlarged lymph nodes, each 1.7 cm in diameter, anterior to the internal jugular vein (Fig. 2C). MRI of the neck confirmed the findings (Fig. 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org). CT scans of the chest, abdomen, and pelvis were normal. To define the pattern of lymphatic drainage from the site on the forehead, a lymphoscintigram was obtained, which showed drainage to lymph nodes in both sides of the neck (Fig. 2 in the Supplementary Appendix).

Dr. Busse: This 63-year-old HIV-positive man presented with a Merkel-cell carcinoma that had metastasized to regional lymph nodes. Risk factors for this cancer include long-term exposure to the sun, ultraviolet-A treatment for psoriasis, and, as with many other skin cancers, immunosuppression. The risk of Merkel-cell carcinoma is increased by a factor of 40 in recipients of organ transplants, as compared with the general population[6] and by a factor of 13 in patients such as this one, with HIV infection, since both groups of patients are immunosuppressed.[7] This cancer has increased in frequency in the United States, from a historical incidence of about 500 cases per year to 1500 in 2007,[8] probably as a result of sun exposure in a progressively older population in addition to immunosuppression. It typically presents, as in this patient, as a small, painless, firm nodule — rarely exceeding 2 cm in diameter — on a sun-exposed area of the head or neck or, less frequently, on a sun-exposed area of the trunk and limbs.[9]

Despite the typical presentation as a small primary tumor, occult or overt metastases are detected in 10 to 30% of cases at the time of the diagnosis, as they were in this case; in addition, there is a high rate of nodal relapse (50 to 75%) and systemic relapse (30 to 50%) after local treatment.[9] Thus, this tumor has to be regarded not as a localized skin cancer but as a systemic disease.

The staging system for Merkel-cell carcinoma (Table 2) stratifies cases according to the size of the skin lesion, the presence or absence of regional lymph-node involvement, and the presence or absence of distant disease.[10] In patients such as this one, with involvement of regional lymph nodes,[11] the expected 5-year survival rate is about 50%.

DECISION MAKING FOR STAGE II MERKEL-CELL CARCINOMA

What could we offer this patient? The conventional treatment for stage II Merkel-cell carcinoma is wide excision of the primary site, with margins of at least 2 cm and preferably 3 cm, to prevent local recurrence, followed by lymph-node neck dis-

Table 1. Immunohistochemical Differential Diagnosis of Merkel-Cell Carcinoma (Typical Staining Pattern).

Tumor	Cytokeratin 20	Cytokeratin 7	Neurofilament	Neuron-Specific Enolase	Thyroid Transcription Factor 1	S100 Protein	Leukocyte Common Antigen
Merkel-cell carcinoma	Positive	Negative	Positive	Positive	Negative	Negative	Negative
Small-cell carcinoma of the lung	Negative	Positive	Negative	Positive	Positive	Negative	Negative
Small-cell melanoma	Negative	Negative	Negative	Negative	Negative	Positive	Negative
Lymphoma	Negative	Negative	Negative	Negative	Negative	Negative	Positive

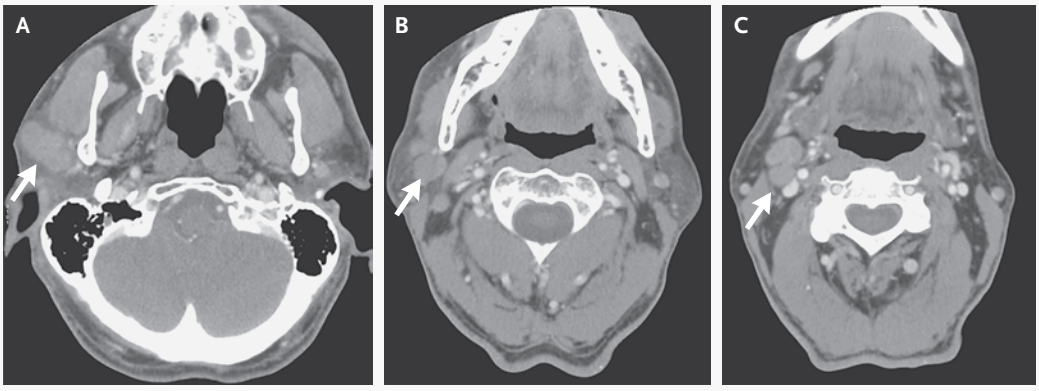

Figure 2. CT Scans of the Head and Neck.
CT scans obtained after the administration of contrast material show a preauricular mass (Panel A, arrow), a mass in the parotid gland (Panel B, arrow), and lymphadenopathy of the internal jugular vein (Panel C, arrow).

section. This is what had been recommended to this patient before we saw him. We considered whether this treatment was sufficient for this patient — whether it addressed the full extent of disease in the head and neck as well as the likelihood of metastatic spread — and what side effects could be expected. First, because excision of a lesion on the forehead with a 3-cm margin is difficult for cosmetic reasons, Mohs surgery is typically used, as it was in this case; however, the local recurrence rate can be as high as 30 to 40% unless the patient is given postoperative radiation therapy.[12,13] Second, in this patient, there was involvement of a lymph node in the superficial parotid gland as well as diffuse lymphadenopathy in the right neck, and lymphoscintigraphy showed bilateral drainage from the primary site. Surgical treatment of the involved nodes would require both parotidectomy and a neck dissection. Among the potential complications of this procedure is a risk of injury to the facial nerve. In addition, there is a high failure rate, even with a full radical neck dissection. Consequently, a full course of postoperative radiation therapy at a fairly high dose (at least 45 Gy) is necessary to reduce the risk of recurrence and may enhance the chance of survival.[13-15] Finally, because of the central location of the tumor in the forehead, we also wondered whether we needed to treat the contralateral portion of the neck, which would result in increased side effects to the mouth, salivary glands, and throat.

If we were to treat this tumor according to its anatomical location, as we would in a case of skin cancer, the emphasis would be on controlling the local–regional tumor with surgery and adjuvant radiation therapy. Instead, we considered whether it should be treated according to its biologic features, which appear to be equivalent to those of a small-cell carcinoma of the lung. For these tumors, surgery has long been abandoned, and the paradigm is combined treatment with chemotherapy and radiation. If we elected the latter approach, we could avoid a parotidectomy and neck dissection, thus reducing the potential for postsurgical complications, but because this man made his living by public speaking, the challenge was to configure the radiation dose through advanced treatment-planning techniques, thereby providing adequate treatment without irradiating the entire mouth, oropharynx, and larynx.

Another factor to consider, if we chose combined treatment with chemotherapy and radia-

Table 2. Staging System and Prognosis for Merkel-Cell Carcinoma.*

Criterion	Stage	Disease-Specific Survival at 5 Yr
		%
Primary lesion ≤2 cm	I	86
Primary lesion >2 cm	II	68
Regional lymph nodes involved	III	49
Distant metastases	IV	0

* Adapted from Greene et al.[10] and Allen et al.[11]

tion, is the patient's HIV infection. In the scanty literature on the treatment of Merkel-cell carcinoma in patients with HIV infection, treatment ranges from local excision to a combination of chemotherapy and radiation, and there is very little information on length of survival. This patient's CD4 cell counts were low but adequate, and although he was physically active and working two jobs, we wondered whether HIV infection would affect his ability to receive a full course of chemotherapy and radiation. In any type of treatment involving a combination of approaches, the dose intensity frequently determines the outcome. If because of the patient's underlying disease his bone marrow reserves were insufficient, the overall treatment time might be protracted, with a potentially adverse effect on the outcome.

Another consideration in this patient was the preservation of his speech and appearance. He had a very recognizable voice that he strongly wished to retain, and he needed to speak for extended periods of time, sometimes for 3 to 4 hours, both on the air and in the classroom.

We decided to offer this man a combination of radiation and chemotherapy, which is what we would use for small-cell lung cancer. Considerations were controlling the primary tumor on the forehead, the metastatic disease in the right side of the neck, and the possible occult metastases in the left side of the neck; minimizing the dose of radiation to normal tissues in the mouth, oropharynx, and larynx; and preserving the quality of speech. The primary tumor had been completely excised, but we decided that additional radiation to the primary site was needed. We discussed whether we needed to treat both sides of the neck, hoping to reduce the side effects. Experience with lymphoscintigraphy and sentinel-node biopsy has shown[16,17] that if a cancer-free sentinel node can be identified on histologic examination, in more than 90% of the cases observation alone may be sufficient. One goal of the lymphoscintigram was to find a sentinel node on the left side that might help to dictate treatment, but a sentinel node was not found. We thus believed it was most prudent to treat both sides of the neck.

We next considered how to minimize the dose of radiation to the oral cavity, oropharynx, and larynx in order to reduce the side effects of the radiation therapy. Classic radiation therapy uses two opposing lateral fields, so that the oropharynx, oral cavity, and larynx receive the same dose as the lymph nodes that are the intended target. Intensity-modulated radiation therapy (IMRT) uses CT-based, three-dimensional planning and nonuniform radiation delivery to produce a treatment plan in which the tumor is treated, but with a relative sparing of uninvolved normal tissue (Fig. 3, and Fig. 3, 4, and 5 in the Supplementary Appendix). IMRT was administered, with 60 Gy to the right parotid gland and the right side of the neck, 50 Gy to the left parotid gland and the left side of the neck, and 66 Gy to the grossly abnormal lymph nodes. The forehead received 50 Gy of superficial radiation with electrons through a separate, en-face field. Dr. Clark will discuss the chemotherapy regimen.

Dr. John R. Clark: Although in most patients Merkel-cell carcinoma appears at presentation to be a local–regional disease, it is in fact a systemic disease, with recurrences at nodal and systemic sites in the majority of patients; systemic therapy was therefore appropriate for this patient. Chemotherapy for Merkel-cell carcinoma[18,19] results in an overall response rate (including complete and partial responses) of about 60% and in a complete-response rate of 40% — results similar to

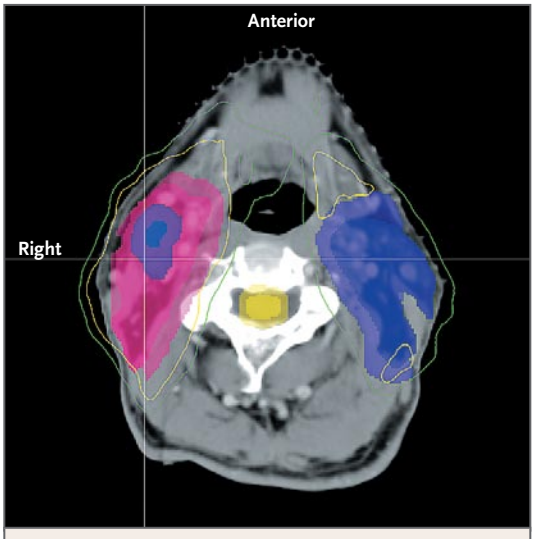

Figure 3. Treatment Planning for Intensity-Modulated Radiation.

An axial image through the neck shows the area treated with a dose of 60 Gy, outlined in yellow, and a dose of 50 Gy, outlined in green; the lymphatic target volumes are indicated by the fully colored areas. The enlarged lymph nodes on the right are included in the region receiving 60 Gy, whereas the at-risk lymph nodes on the left receive 66 Gy; the structures in the center are thus spared.

those seen with chemotherapy for small-cell lung cancer. Current guidelines published by the National Comprehensive Cancer Network[20] state that Merkel-cell carcinomas, regardless of stage, should be treated according to paradigms established for small-cell lung cancer.

The recommended treatment for a patient with locally advanced small-cell lung carcinoma is chemotherapy consisting of cisplatin or carboplatin and etoposide for four cycles with concurrent radiation therapy.[21,22] Because of the rarity of the disease, this treatment has not been evaluated in randomized clinical trials. In a nonrandomized trial, consisting of 53 patients with high-risk disease,[23] the overall and relapse-free actuarial survival rate at 3 years was 75%. Thus, we treated this patient with four cycles of carboplatin and etoposide, with radiation given during the first two cycles.

Dr. Busse: The patient had the anticipated side effects of treatment with chemotherapy and radiation to the head and neck, including severe oral mucositis and an erythematous skin reaction as well as poor oral intake. He also had recurrent infections that required three admissions to this hospital for parenteral nutrition and antibiotic therapy during the course of 3 months. There was complete regression of clinically evident disease within 4 weeks from the start of therapy (Fig. 6 in the Supplementary Appendix). He had a full recovery, and at the completion of treatment, he was able to return to broadcasting and lecturing, with no appreciable change in his voice. Unfortunately, 12 months after completion of treatment, he was admitted to the hospital with anorexia, pain in the right flank, and jaundice.

Dr. Muse: Ultrasound examination of the liver (Fig. 4A) showed almost complete replacement of the parenchyma by echogenic nodules. A percutaneous biopsy of a lesion in the right lobe was performed.

Dr. Liu: A specimen from a core biopsy of the liver showed foci of malignant cells within the liver parenchyma (Fig. 4B), with positive staining for cytokeratin 20, chromogranin, and neuron-specific enolase, confirming the diagnosis of metastatic Merkel-cell carcinoma.

Dr. Busse: The patient died at this hospital 1 week later, which was 15 months after the initial diagnosis of Merkel-cell carcinoma. Although he was not cured of his aggressive cancer, he had an excellent quality of life for 1 year and was spared a parotidectomy and a neck dissection. It is important to realize that this disease is a form of small-cell cancer that should be treated not as a simple skin cancer that tends to go to lymph nodes but in the same way as a small-cell carcinoma of the lung, with a combination of chemotherapy and radiation therapy.

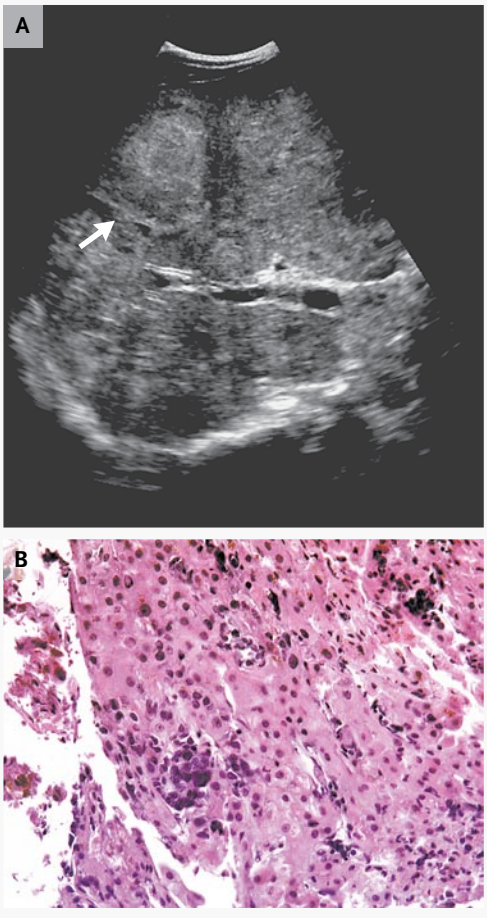

Figure 4. Examination of the Liver 12 Months after Treatment.

An ultrasonogram of the liver (Panel A) shows numerous echogenic nodules. A lesion in the right lobe (arrow) was targeted for percutaneous biopsy. The core-biopsy specimen of the liver shows nests of malignant cells within the liver parenchyma (Panel B, hematoxylin and eosin).

Dr. Robbins: As an adolescent, this patient received radiation therapy to the face for severe acne vulgaris. Is radiation therapy known to be a risk factor for Merkel-cell carcinoma?

Dr. Busse: I am not aware of any data addressing this question, but since the risk is increased by sun exposure, it would not be surprising if it was increased by radiation therapy.

Dr. Robbins: This patient received highly active

antiretroviral therapy (HAART) for more than 8 years, and for the past 5 years, he had no detectable viral genomes in the blood. However, his CD4 cell count never rose above 250 per cubic millimeter. Immune reconstitution is important for the control of opportunistic infections as well as for the successful treatment of HIV-related lymphomas, so I wonder whether the low CD4 cell count may have increased the risk of Merkel-cell carcinoma and the risk of relapse after treatment.

Dr. Busse: I think this patient's low CD4 cell count may have had a role in both the development and progression of the cancer. There has been one reported case of a patient with chronic HIV infection and a disseminated Merkel-cell carcinoma who declined systemic therapy, but while that patient was receiving HAART, the CD4 cell count returned to normal and the cancer regressed.[24]

ANATOMICAL DIAGNOSIS

Merkel-cell carcinoma, stage III.

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