Case Report

Metastatic merkel cell carcinoma in the bone marrow of a patient with plasma cell myeloma and therapy-related myelodysplastic syndrome

Megan Kiett Kressin1,2,3, Annette S Kim1

1Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, TN, USA; 2Department of Pathology & Laboratory Medicine, Tennessee Valley Healthcare System Veterans Affairs, Nashville, TN, USA; 3Current address: Austin Pathology Associates, 901 W. Ben White Blvd., Austin, TX, USA

Received August 30, 2012; Accepted September 21, 2012; Epub October 20, 2012; Published October 30, 2012

Abstract: Merkel cell carcinoma is an aggressive neoplasm of the skin that shows frequent lymph node metastases, but has only rarely been reported in the bone marrow. Herein we report a case of a 64-year-old male with a history of plasma cell myeloma and recent skin diagnosis of Merkel cell carcinoma who presented for a routine follow-up bone marrow to assess his myeloma. The biopsy showed persistent plasma cell myeloma, trilineage dysplasia, and clusters of neuroendocrine cells consistent with metastatic Merkel cell carcinoma. Discussion of this case, a review of metastatic Merkel cell carcinoma, and identification of clinical settings in which staging bone marrow biopsy may be warranted are presented.

Keywords: Merkel cell, bone marrow metastases, plasma cell myeloma

Introduction

Merkel cell carcinoma is known to be an aggressive tumor with a high rate of metastasis and mortality. However, bone marrow metastases are rare, and a staging bone marrow biopsy is not routinely performed. We describe herein a patient who received a bone marrow biopsy for routine follow-up of plasma cell myeloma, previously treated with thalidomide, melphalan, dexamethasone, and autologous stem cell transplantation, who had also had a recent skin resection for Merkel cell carcinoma. His marrow demonstrated persistent plasma cell myeloma, trilineage dysplasia with complex cytogenetics consistent with therapy-related myelodysplasia, and clusters of neuroendocrine cells consistent with metastatic Merkel cell carcinoma. Review of the literature suggests that, while Merkel cell carcinoma is known to be an aggressive neoplasm of the skin, it has only rarely been reported to metastasize to the bone marrow. To the best of our knowledge, this is the first reported case of metastatic Merkel cell carcinoma involving the bone marrow in the setting of plasma cell myeloma. This case suggests that the bone marrow may be an under-recognized site of metastases for this tumor, especially when there is exogenous immunosuppression or underlying hematopoietic disease causing secondary immunosuppression.

Case presentation

The patient was a 64-year-old male who had been diagnosed 13 years prior with plasma cell myeloma, management of which included two autologous peripheral blood stem cell transplants and prior chemotherapy which involved thalidomide, melphalan, and dexamethasone. The most recent therapy prior to presentation had been the second autologous stem cell transplantation 7 months previous. In addition, three months prior to the current presentation, the patient underwent a wide local excision of a Merkel cell carcinoma (MCC) on his forehead. This carcinoma measured 1.6 cm in greatest extent, extended to within 1 mm of the inked margin, and showed a metastatic focus in one
Merkel cell carcinoma in the bone marrow

Three months later, the patient presented for evaluation of thrombocytopenia and follow-up care of his plasma cell myeloma, including a bone marrow study. A CBC obtained at the time of bone marrow biopsy showed WBC 3.6 K cells/μL, hemoglobin 8.0 g/dL, hematocrit 22.6 %, platelets 9 K cells/μL, and MCV 103.6 fL. The bone marrow study showed a normocellular marrow (40-50% cellularity) with small sheets of plasma cells on the core biopsy which accounted for 10-20% of total cellularity (Figure 1A and 1B), although plasma cells accounted for less than 1% of the cellularity on the aspirate smears. By flow cytometry, the neoplastic plasma cells strongly expressed CD138 and CD56, partially expressed CD38, and expressed monotypic lambda light chain.

In addition, the biopsy also demonstrated trilineage hematopoiesis with geographic disarray. Although there was no increase in blasts, occasional small, monolobate megakaryocytes were identified on the biopsy (Figure 1A). The aspirate smears (Figure 1C) showed dysplastic changes in the erythroid elements, including irregular nuclear contours, mild left shift, and megaloblastoid change. The granulocytic lineage also demonstrated aberrant maturation with increased promyelocytes and dysplastic features including hypogranulated neutrophils.

Although no large metastatic tumor deposits were initially identified by hematoxylin and eosin (H&E) staining of the biopsy and particle preparation, in the background of the trilineage dysplasia seen on the aspirate smear were scattered groups of cohesive large cells with round nuclei, occasional nuclear molding, fine chromatin, and scant cytoplasm, consistent with metastatic MCC (Wright Giemsa, 100x). Large areas of tumor necrosis were present on the biopsy section (H&E, 20x). Inconspicuous clusters of atypical cells on the particle preparation were consistent with metastatic tumor (H&E, 40x). Staining with neuron specific enolase (NSE) highlighted small clusters of metastatic MCC (NSE immunostain, 100x). CK20 was positive in a dot-like Golgi distribution on the MCC cells (CK20 immunostain, 100x).

Immunohistochemical studies performed on the bone marrow biopsy and particle preparation revealed several minute foci of cohesive cells, with crush artifact. These cells were uniformly positive for Cam 5.2 (cytokeratin 8,18, not shown) and neuron specific enolase (NSE), and several of the minute foci showed apparent dot-like paranuclear staining with cytokeratin 20 (Figure 1G and 1H, stain interpretation limited by the limited tumor burden and crush artifact).

Chromosomal studies were performed with routine metaphase cytogenetics, and demonstrated a complex karyotype including monosomy 5 and 7: 46, Y, der(X)t(X; 7)(p22.3; p15),...
Merkel cell carcinoma in the bone marrow

-5, add(6)(p23), -7, add(18)(p11.2), add(21)(q22), +r1, +r2[12/46, Y, der(X)t(X; 7)(p22.3;p15), del(4)(q21q31.1), -5, add(6)(p23), -7, add(21)(q22), +r2, +r3[7]/46, XY[1].

Fluorescent in-situ hybridization (FISH) studies demonstrated monosomy 5 in 50.5%, loss of 5q31 in 28.5%, and 3~4 copies of 5p15.2 in 13% of 200 cells as well as monosomy 7 in 36.5% and loss of 7q31 in 43% of 200 cells.

In summary, the bone marrow findings identified 3 neoplastic processes: 1) persistent plasmacytoid myeloma after 2 autologous stem cells transplantations and chemotherapy, 2) therapy-related myelodysplastic syndrome with complex karyotype including monosomy 5 and 7, and 3) metastatic MCC.

The patient was continued on maintenance lenalidomide, and was too ill to make his follow-up appointment. There was no documented treatment of the myelodysplastic syndrome or further treatment for metastatic MCC. He died at an outside hospital 3 months following this bone marrow biopsy. The cause of death is unknown.

Discussion

In 1972, Cyril Toker described a “trabecular cell carcinoma of the skin”, which was subsequently shown to have the ultrastructure of Merkel cells. [1] MCC is a rare, aggressive skin cancer with a strong predilection for sun-exposed areas, typically the head and neck or extremities. However, it is often asymptomatic at presentation, albeit demonstrating rapid expansion, and is easily initially misdiagnosed as a benign process. [2] Risk factors include advancing age, fair skin, and immunosuppression. Recent years have seen a steady increase in the diagnosis of MCC, with the incidence tripling between 1986 and 2001. [1, 3] The mortality rate for MCC is high and overall survival ranges between 30% and 75%. [4] Survival is even further decreased in patients with a history of organ transplantation. [5]

Histologically, MCC is comprised of a monotonous proliferation of intermediate-sized cells with high nuclear-to-cytoplasmic ratios, finely granular chromatin, and multiple small or inconspicuous nucleoli, arranged in sheets, nests or cords in the dermis. [6] There is significant morphologic overlap with small cell carcinoma, although it can less commonly mimic lymphoma, with dyshesive round cells, or show plasmacytoid, clear cell, anaplastic, or spindle cell morphology. [3] Mitotic figures and apoptotic debris are common, and larger tumors may demonstrate necrosis.

Recently, a polyoma virus has been identified in the genome of Merkel cell carcinoma, and appears to play a role in the pathogenesis of the tumor. [4] This Merkel cell polyoma virus (MCPyV) has been shown to be frequently reactivated in the more common skin cancers in immunocompromised patients as well, such as squamous cell carcinoma and basal cell carcinoma, suggesting more widespread virus reactivation in patients with immunosuppression. [7] This potential infectious etiology supports the finding that the tumor is more common among immunosuppressed individuals, and may explain the increased incidence of the cancer in recent years.

By immunohistochemistry, the tumor cells express epithelial markers, including EMA and cytokeratins, neuroendocrine markers, including chromogranin and synaptophysin, as well as neural markers such as neurofilament and CD56. The majority of cases are also at least focally positive for cytokeratin 20 in a paranuclear dot-like pattern. TTF-1 is usually negative, and can help distinguish between primary skin cancers and lung metastases. [3]

At the time of presentation, MCC has frequently invaded dermal lymphatics, warranting sentinel lymph node biopsy at the time of wide-local excision. Local lymph node metastasis occurs in approximately one-third of cases, and is treated with lymphadenectomy and/or radiation therapy. [1] Visceral involvement occurs in between 30 and 50% of patients, most commonly to the lymph nodes (27%), liver (13%), lung (10%), bone (10%) and brain (6%). [3, 8]

In contrast to bone involvement, actual involvement of the bone marrow is rare, most commonly occurring as direct extension of the primary tumor rather than as a distant metastasis, as indicated by the standard American Joint Committee on Cancer staging criteria for MCC. [9] Of the latter, there are 8 reported cases, including the current case (Table 1). Of these 8 cases, 5 are clearly associated with a history of...
therapy-induced immunosuppression—two for solid organ transplantation, and three for autoimmune disease. The listed agents used to induce and immunosuppressed state in these patients include agents which target both B and T cells (corticosteroids, azathioprine, mycophenolate mofetil), as well as agents which target T cells more specifically (methotrexate, cyclosporine). Each of the 5 patients had received some corticosteroid treatment. In two cases no past medical history is reported.

In the largest single series of MCC cases to date involving 195 patients, immunosuppression was implicated in 7.8% of cases. [2] Of those, the single most common cause of immunosuppression was concomitant chronic lymphocytic leukemia (CLL). In fact, the prevalence of MCC is 30-fold higher in patients with CLL. [2] Solid organ transplantation is the second most common cause of immunodeficiency-associated MCC, with a 10-fold increase in prevalence, and among HIV+ patients, the risk for MCC is increased 13-fold. [3] While both HIV and solid organ transplantation implicate decreased T cell immunity in the pathogenesis of MCC, CLL is a B cell neoplasm. Although CLL can be associated with hypogammaglobulinemia, it is unclear whether its association with MCC is due to a B cell defect or a possible T cell defect. While CLL itself causes increases in both CD4+ and CD8+ T cells with increased cytotoxic function, the common use of fludarabine in the treatment of CLL can cause a profound and persistent T cell suppression. [14]

In the current case, the bone marrow biopsy was performed for evaluation of thrombocytopenia and routine follow-up of the patient’s known plasma cell myeloma. Marrow metastasis of his MCC was not suspected. While pancytopenia was present at the time of biopsy, the tumor burden for both his myeloma and carcinoma was low. Therapy-related myelodysplastic syndrome is a well-known complication of therapy for myeloma. [15] The morphologically evident trilineage dysplasia, cytopenias disproportionate to the marrow involvement by myeloma and carcinoma, and the patient’s long treatment history for myeloma together favor a therapy-related myelodysplastic syndrome as the cause for this patient’s low peripheral counts.

However, this finding of metastatic MCC in this marrow raises the question of the nature of the association between the patient’s immune status and the bone marrow involvement by MCC. Unlike the other patients listed in Table 1, this patient had not received any corticosteroids or other immunosuppressive agents in the previous 7 months, at the time of the patient’s second autologous stem cell transplantation. Leukocyte count recovery was achieved by the tenth day after transplantation. A day 100 bone marrow biopsy, obtained one month prior to the diagnosis of MCC in the skin, showed no evidence of MCC and lymphocytes were within the normal range. Lymphocyte counts continued to be within the normal range at the time of diagnosis of MCC until the last record available. Thus, there was never a point in time when the patient was overtly lymphopenic or immunosuppressed either at the time of diagnosis of MCC or thereafter. However, the patient demonstrated persistently low levels of quantitative

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Time from presentation of MCC to bone marrow metastasis</th>
<th>Immuno-suppressive agent</th>
<th>Disease resulting in immunosuppression</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current case</td>
<td>M</td>
<td>64</td>
<td>3 months</td>
<td>No therapy in past 7 months</td>
<td>Myeloma</td>
</tr>
<tr>
<td>Nemoto [8]</td>
<td>F</td>
<td>73</td>
<td>7 months</td>
<td>Prednisolone, methotrexate</td>
<td>SLE/Sjögrens</td>
</tr>
<tr>
<td>Lentz [6]</td>
<td>M</td>
<td>55</td>
<td>3 weeks</td>
<td>Prednisone</td>
<td>SLE</td>
</tr>
<tr>
<td>Gooptu [10]</td>
<td>F</td>
<td>68</td>
<td>unknown</td>
<td>Prednisolone, azathioprine</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Tam [12]</td>
<td>M</td>
<td>66</td>
<td>6 months</td>
<td>Agents not reported</td>
<td>Heart transplant</td>
</tr>
<tr>
<td>Tam [12]</td>
<td>M</td>
<td>55</td>
<td>MCC recently diagnosed</td>
<td>none</td>
<td>n/a</td>
</tr>
<tr>
<td>Smadja [13]</td>
<td>F</td>
<td>33</td>
<td>4 months</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Merkel cell carcinoma in the bone marrow

IgG and IgM during the year leading up to presentation until the patient’s demise. Thus, although there does not appear to be a definitive T cell suppression which could be associated with the MCC, a B cell immune paresis may be implicated.

In conclusion, we have reported a case of a bone marrow involved by metastatic Merkel cell carcinoma. To the best of our knowledge, this is the first reported case of metastatic Merkel cell carcinoma in the marrow in the setting of plasma cell myeloma and in the setting where no T cell suppression can be implicated. Bone marrow involvement by MCC is rare and highly associated with immunosuppression. While this was an unexpected finding in a biopsy performed to assess for involvement by plasma cell myeloma, plasma cell myeloma can cause the development of immune paresis (hypogammaglobulinemia other than the neoplastic clone), or a B cell-based immune defect. Although CLL can also cause hypogammaglobulinemia, its association with MCC may actually be secondary to the profound T cell suppression caused by the treatment of CLL. In our patient’s case, no T cell suppressive treatment was evident in the 7 months prior to the patient’s presentation. Thus, this case represents the first case of MCC associated with a hematologic condition that is not accounted for by a T cell deficiency. In addition, the rare finding of bone marrow involvement is also noteworthy. Bone marrow biopsies are not typically performed to stage MCC, so the true incidence of bone marrow metastases is likely to be under-reported. Given the new understanding of the role polyoma virus plays in the carcinogenesis of MCC, as well as the increasing incidence of MCC, it may be helpful to include bone marrow biopsy as part of the staging process in all immunocompromised patients with MCC, including those with hematologic malignancies, such as CLL and myeloma, associated with a secondary immunodeficiency states affecting both B and T cell function.

Conflicts of interest statement

Nothing to declare.

Address correspondence to: Dr. Annette S Kim, Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, 1301 Medical Center Dr, 4603A TVC, Nashville, TN 37232-5310, USA. Phone: 615-343-7745; Fax: 615-343-7961; E-mail: annette.s.kim@Vanderbilt.Edu

References

Merkel cell carcinoma in the bone marrow

