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CASE REPORT

Concomitant chronic lymphocytic leukemia and Merkel cell carcinoma

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ABSTRACT

We present the case of a 69-year-old Caucasian man with a 5-year history of untreated chronic lymphocytic leukemia who presented with Merkel cell carcinoma on the right gluteal region. Six months after surgical treatment of Merkel cell carcinoma, we detected massive lymphadenopathy in the right retroperitoneum descending to the inguinum. A lymph node biopsy confirmed Merkel cell carcinoma relapse, and the patient was unsuccessfully treated with radiotherapy. As patients with chronic lymphocytic leukemia have a risk for developing a secondary malignancy, skin lesions need to be carefully examined and new lymphadenopathy must be pathohistologically evaluated.

Introduction

Chronic lymphocytic leukemia (CLL) is a B lymphocyte-derived neoplasia and the most common adult leukemia, with an incidence rate of three to five cases per 100,000.[1] Usually, CLL has a protracted course, but sometimes it is complicated by the occurrence of secondary malignancies.[2] Merkel cell carcinoma (MCC) is a rare, highly aggressive, primary cutaneous neuroendocrine malignant tumor, which occurs with an estimated incidence rate of 0.18–0.41 cases per 100,000 persons and has a high mortality rate of 33% at 3 years following diagnosis.[3,4] Both malignancies tend to occur in the elderly population, with a median age at diagnosis of 70 years for MCC and 72 years for CLL.[5,6] MCC frequently occurs in cancer survivors as well as in association with hematologic malignancies, particularly B lymphoproliferative disorders.[5] Indeed, there is growing evidence that patients with CLL have a high risk for developing MCC as a secondary malignancy.[2,5,7–11]

In addition, both CLL and MCC can present with lymphadenopathy. MCC metastasizes principally via the lymphatics in a stepwise fashion, with an initial involvement of the regional lymph nodes and subsequent systemic spread.[3] Lymphadenopathy occurring in a patient with concomitant CLL and MCC presents a clinical problem in terms of the differential diagnosis.

Here, we present a case of a patient, previously diagnosed with both CLL and MCC, presenting with mass lymphadenopathy.

Case Report

A 69-year-old Caucasian man previously diagnosed with CLL was referred to our clinic in April 2012 for a routine follow-up examination. At that time, he had CLL for 5 years (Rai 0) and did not require any specific or supporting therapy. Physical examination revealed an oval, red, firm, verrucous lesion (3×4 cm^2) in the right gluteal region, which the patient had noticed 4 months earlier and which was growing rapidly. Other than this lesion, his physical examination was unremarkable. With the exception of leukocytosis (22.6×10^9/L) and mild creatinine elevation (139 μmol/L) due to previously diagnosed chronic renal failure, his laboratory analyses were normal. The skin tumor was completely excised (margins were tumor free), and pathohistological analysis confirmed MCC. The tumor was located in the dermis and had infiltrated the subcutaneous tissue. The tumor cells were monomorphic, with a

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minimal amount of cytoplasm and uniform nuclei. The predominant histological pattern was diffuse (Figure 1A). Immunohistochemical analysis revealed that many of the tumor cells were positive for synaptophysin (clone SP11; Thermo Lab Vision, Fremont, California, USA) (Figure 1B), CK20 (clone Ks20.8; Thermo Lab Vision) (Figure 1C), NSE (clone E27; Dako, Glostrup, Denmark) (Figure 1D), chromogranin A (clone LK2H10; Thermo Lab Vision), and AE1/AE3 (clone AE1/AE3; Thermo Lab Vision); there was focal positivity for CD57 (clone NK1; Thermo Lab Vision) and EMA (focal) (clone E29; Thermo Lab Vision). None of the tumor cells were positive for LCA (clone PD7/26+2B11; Thermo Lab Vision), CD10 (clone 56C6; Thermo Lab Vision), CD30 (clone Ber-H2; Thermo Lab Vision), CD43 (clone DF-T1; Thermo Lab Vision), CD20 (clone L26; Thermo Lab Vision), CD3 (clone SP7; Thermo Lab Vision), ALK (clone SP8; Thermo Lab Vision), vimentin (clone V9; Thermo Lab Vision), aktin (clone 1A4; Thermo Lab Vision), desmin (clone D33; Thermo Lab Vision), S100 (polyclonal; Thermo Lab Vision), CD34 (clone QBEnd10; Thermo Lab Vision), and PSA (clone 35H9; Novocastra, Nussloch, Germany). The proliferative fraction, as detected by Ki-67 staining (clone SP6; Thermo Lab Vision), was greater than 50% in some high power field (HPF).

After surgery, adjuvant therapy was not advised. Six months later, the patient presented with painless right inguinal lymphadenopathy and right leg edema. Computed tomography of abdomen revealed a large ($19 \times 2.5 \times 10.8$ cm^3) lobulated mass, which enveloped the iliac blood vessels like a muff and descended through the right inguinal region (Figure 2). His blood count was stable, and there was no organomegaly. However, a clinical dilemma with regard to the differential diagnosis of lymphadenopathy arose (CLL transformation vs. MCC metastasis). Therefore, pathohistological analysis was required, and MCC infiltration of the lymph nodes was confirmed. As the tumor was inoperable, local radiotherapy (total dose 36 Gy) was performed. However, a control computed tomography scan showed local disease progression with bladder infiltration. The patient was then treated with only palliative symptomatic therapy.

Discussion

Patients with CLL have a risk of developing a second neoplasm, particularly skin or lung cancer.[2,12] The appearance of any suspicious extranodal lesions and rapid lymph node enlargement require urgent histological confirmation in order to differentiate between disease transformation (Richter syndrome) and secondary malignancy. MCC is a relatively newly identified malignancy that has occurred with increasing prevalence in the past decade.[3,13] One of the hallmarks of MCC is its tendency to occur in association with other neoplasms, particularly B lymphoproliferative disorders.[4,5,7,9,14] A great number of case reports, as well as some larger population studies, unequivocally showed that patients with CLL were at increased risk for developing MCC, and vice versa.[5,8,9,14] Despite extensive research, knowledge of the etiopathogenesis of MCC is still limited. It has been postulated that exposure to ultraviolet light and immunosuppression are risk factors for development of MCC.[3] Indeed, patients with chronic immunosuppression are approximately 15 times more likely to develop MCC than age-matched controls.[15] On the other hand, immunosuppression is one of the well-known features of CLL. Although CLL is primarily a B lymphocyte-derived neoplasia, it alters both cellular and humoral immunity, including B- and T-lymphocytic, granulocytic, and monocytic functions; natural killer cell and complement activity; as well as cytokine balance.[16] The recent discovery of the association of Merkel cell polyomavirus (MCV) with MCC was a major contribution to an improved understanding of this rare neoplasm's

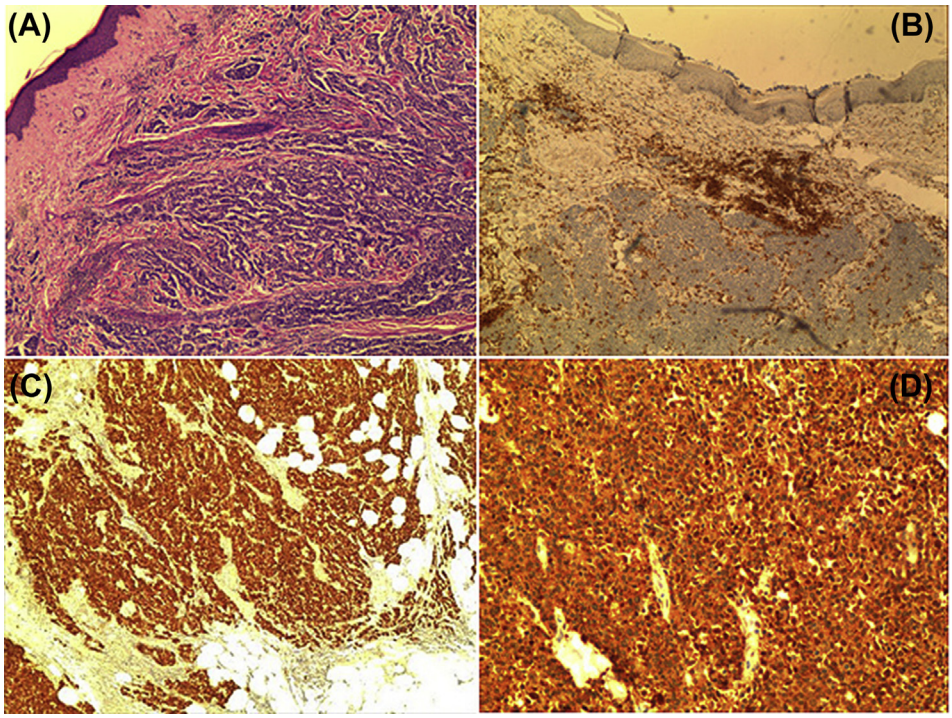

Figure 1 Pathohistological and immunohistochemical features. (A) Low-power view showed tumor growth in the dermis and infiltration of the subcutaneous tissue. The tumor cells were monomorphic, with a minimal amount of cytoplasm and uniform nuclei. The predominant histological pattern was diffuse (original magnification, 100×). (B) Many tumor cells showed strong immunoreactivity for synaptophysin (original magnification, 100×). (C) Strong staining for CK20 with infiltration of adipose tissue (original magnification, 200×). (D) Many tumor cells showed strong immunoreactivity for NSE (original magnification, 100×).

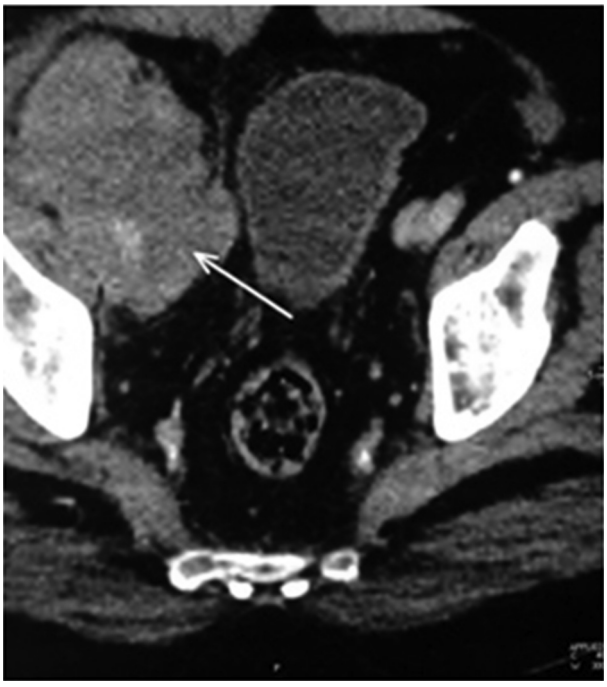

Figure 2 Abdominal computed tomography showed a lobulated mass, which enveloped the iliac blood vessels like a muff and descended through the right inguinal region.

pathogenesis.[17] Namely, it has been repeatedly proved that approximately 70–80% of MCCs harbor MCV.[8,17–19] More importantly, this virus could be the missing link between MCC and CLL. Indeed, recent studies demonstrated the presence of MCV in 27–33% of patients with CLL.[19,20] Additionally, immunosuppression in CLL may favor the colonization of MCV, which can induce MCC development.[8,21]

In our patient, MCC developed in the context of a 5-year history of untreated CLL. This sequence of disease occurrence is common, but there are also case reports describing the occurrence in reverse order, with MCC developing before CLL.[10,11] In addition, while there is substantial variation in the timing of diagnosis of CLL and MCC, it seems that MCC usually occurs within 3 years after CLL diagnosis.[14] As in most other reported cases, our patient had Rai stage 0 CLL, which was stable and required no specific or supporting therapy.[10]

MCC usually metastasizes to the lymph nodes, skin, and liver, but all organ systems, including the central nervous system, may be potentially affected.[3] As MCC has a high probability of lymphatic spread, it is extremely important to evaluate lymph nodes after confirmation of primary MCC. It is currently recommended to perform sonography of the draining lymph nodes and abdomen, in addition to performing chest radiography.[3] Moreover, it is advised to carry out a sentinel lymph node biopsy (SLNB) in all patients with MCC regardless of whether they have lymphadenopathy or not. These recommendations resulted from the apprehension of many researchers who agree that there is no primary tumor size that can reliably predict nodal involvement.[3,13,22] This can be particularly important for patients with concomitant CLL and MCC. As an SLNB was not performed in our patient at the time of MCC diagnosis, we cannot exclude the possibility of pre-existing MCC metastases. If an SLNB had been done at the time of MCC confirmation, radiotherapy of the regional lymph nodes might have prolonged the course of the disease in our patient. In addition, an SLNB would have potentially reduced the diagnostic dilemma concerning the etiology of lymphadenopathy as well as hasten the initiation of treatment.

Several favorable prognostic factors for MCC have been identified, including a primary tumor size of 2 cm or less, local disease, female sex, and primary tumor localization on the upper limb.[3] Of these factors, our patient had only one—localized disease. Although MCC in our patient at the time of diagnosis was not macroscopically disseminated, relapse occurred only 6 months after surgical treatment. When MCC is a solitary neoplasm, it usually relapses within the first 2 years in up to 50% of patients.[5] However, it has been proved that patients with CLL who subsequently develop MCC have substantially lower overall survival, which could be a consequence of more aggressive forms of MCC that these patients are prone to develop.[14]

As MCC is a radiosensitive tumor, it has been shown that adjuvant radiotherapy delivered to the primary tumor site and regional lymph nodes reduces recurrence, increases the 5-year survival rate, and is the only significant predictive factor for relapse-free survival.[3,5,23] Although there are currently no prospective studies addressing this issue, it is advised to consider radiation therapy as the major prophylactic management after initial surgical treatment of MCC.[3,13] If our patient had received prophylactic radiotherapy, the time to recurrence of his MCC might possibly have been prolonged.

Eventually, our patient received radiotherapy (a total dose of 36 Gy) when his disease relapsed. His condition at that time did not permit a higher radiation dose, but it should be noted that a previous study showed that doses of 55 Gy and higher provided the best disease control when large tumor masses were present.[24] This could be another reason for treatment failure in our patient.

Conclusion

This report presents a case of concomitant CLL and MCC. Due to the association between these malignancies, skin lesions in CLL patients should be examined and evaluated. As lymphadenopathy can result from the spread of either neoplasm, lymphadenopathy seen in patients with both CLL and MCC should be carefully evaluated. We highlight the importance of lymph node biopsy and prompt treatment of MCC, not only because MCC is a highly aggressive neoplasm, but also because MCC on the background of CLL has a worse prognosis.

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