Merkel cell carcinoma developing after antithymocyte globulin and cyclosporine therapy for aplastic anemia

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We report a patient who developed Merkel cell carcinoma (MCC) after treatment with antithymocyte globulin and cyclosporine for aplastic anemia. The clinical course was progressive and poor prognosis. Although MCC is relatively rare in second cancers arising after immunosuppressive therapy, patients should be closely monitored for the development of this complication as well as other second malignancies. *Anti-Cancer Drugs* 14:251–253 © 2003 Lippincott Williams & Wilkins.

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Introduction

The effectiveness of immunosuppressive therapy including antithymocyte globulin (ATG) or cyclosporine (CsA) for aplastic anemia is well established [1,2]. However, it is also reported that second malignancy occurring after treatment is one of the major complications [3]. There have been no reports of Merkel cell carcinoma (MCC) in ATG-related second cancers, but several reports of MCC arising in an immunosuppressive setting have been published [4–6]. We report a case of MCC developing in a patient who received ATG and CsA for aplastic anemia.

Case report

A 79-year-old Japanese female was admitted Fujisawa City Hospital because of pancytopenia in August 2000. She had never received anticancer drugs and had no history of exposure to genotoxic agents. Physical examination at admission revealed no skin lesions or lymphadenopathy. The findings of peripheral blood were as follows: a hemoglobin concentration of 7.0 g/dl, a reticulocyte count of 24×10^9/l, a white blood cell count of 2.7×10^9/l with 35.0% neutrophils, 11.0% monocytes and 59.0% lymphocytes, and a platelet count of 39×10^9/l. The bone marrow was severely hypoplastic and there was no dysplasia. Then, moderate aplastic anemia was diagnosed.

She was treated with ATG at a dose of 10 mg/kg per day for 5 consecutive days. Methylprednisolone, 2 mg/kg per day for 5 days, was administered concurrently. Tapering of administration of methylprednisolone was followed by oral administration of prednisolone in a gradually decreasing dosage. After discontinuation of prednisolone, she received CsA at a dose of 150 mg/day. In January 2001, she became independent of blood transfusions.

In April 2001, she developed a s.c. tumor on the forehead. Chest X-ray and computed tomography demonstrated no abnormalities at this time. The lesion was excised and histology examination showed a MCC with positive immunohistologic reactions for antibodies against chromogranin (Fig. 1), and negative reactions for TTF-1 and common lymphocyte antigen. Electron microscopic study revealed dense core granules of neurosecretory type (Fig. 2). CsA was stopped after development of MCC. As tumor cells were detected at the excision margins, she received re-excision and radiation therapy. Three months after the initial treatment, the disease progressed with metastasis to the left cervical lymph nodes. She was treated with radiation for focal relapses. Any chemotherapy for MCC was not used because of hematological dysfunction. She died of multiorgan dissemination of MCC 1 year after presentation. A post mortem was not carried out.

Discussion

MCC is a rare and highly malignant tumor, first described by Toker in 1972 as 'trabecular carcinoma of the skin' [7]. At present, MCC is considered a neuroendocrine tumor. Immunohistochemical analysis is useful for the differential diagnosis from squamous cell carcinoma and basal cell carcinoma [8]. In this case, findings of pathology including immunohistochemistry and electron microscopy were consistent with the characteristics of MCC.

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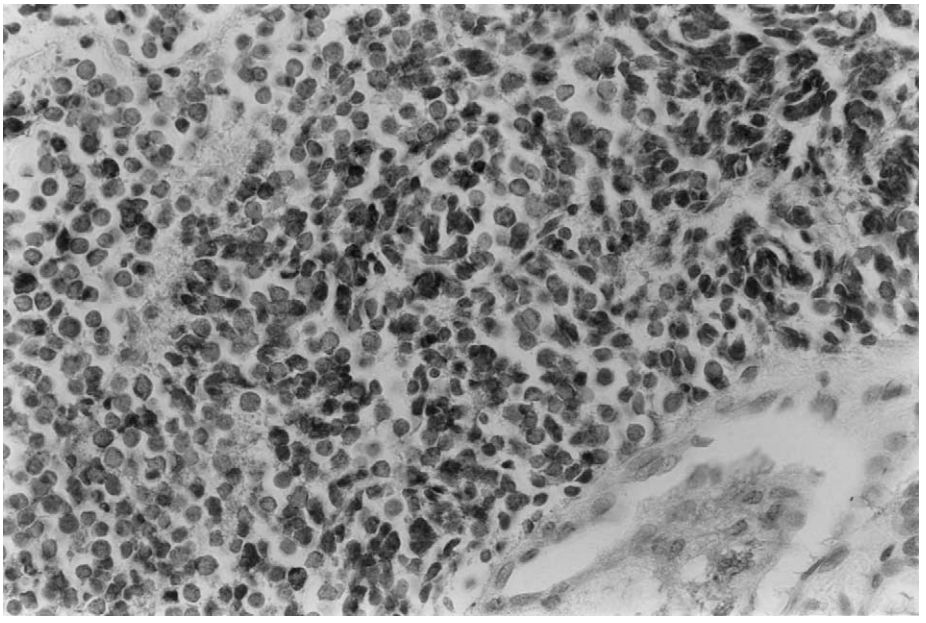
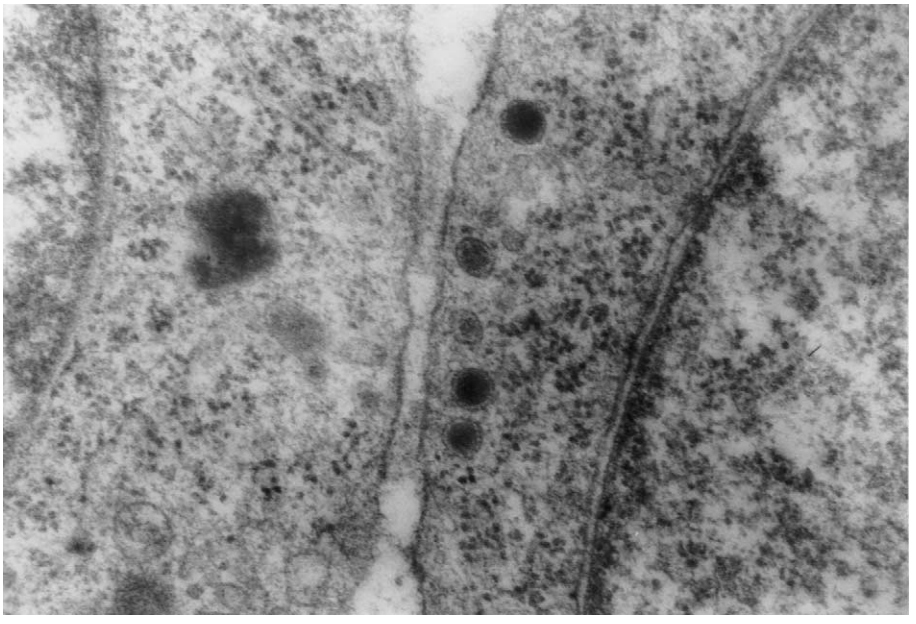
Fig. 1



A microscopic examination shows the uniform small round cells that are positive for chromogranin (original magnification × 400).

Fig. 2



Electron microscopy demonstrates several neurosecretory granules lined up along with the plasma membrane (original magnification × 6000).

It was previously described that second malignancies develop after immunosuppressive therapy or bone marrow transplantation in patients with aplastic anemia [1,3]. In particular, various malignancies such as myelodysplastic syndrome, acute leukemia or solid cancers have been observed in patients received ATG therapy. In the report by Socié *et al.*, the 10-year cumulative incidence rate of solid cancers is 2.2% in 860 patients that received

immunosuppressive therapy [3]. To our knowledge, this is the first report of MCC arising in a patient who received ATG and CsA for aplastic anemia.

It has been suggested that the duration of immunosuppressive therapy is more important than the dosage for developing second cancer [4]. In this case the duration of immunosuppressive therapy before the development of MCC was relatively short. Although the pathogenesis of MCC developing in an immunosuppressive setting is still unclear, one possibility is a disruption of immunosurveillance mechanisms by immunosuppressive agents. It is also speculated that ATG and CsA strongly contribute to the occurrence and rapid spread of MCC in the present case. Furthermore, the aggressiveness of MCC in immunocompromised patients has been confirmed in other reports [9,10].

MCC is rare tumor in secondary malignancies after immunosuppressive therapy, but it is associated with a high rate of recurrence and distant metastases in immunosuppressed or transplant patients [9,10]. Therefore, in a case presenting with skin lesions during treatment of ATG and/or CsA, the patient should be carefully followed in consideration of second malignancies.

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