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Case report

Massive spinal cord necrosis associated with adult T-cell leukaemia caused by *Aspergillus*

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Abstract. A man with adult T-cell leukaemia (ATL) underwent massive spinal cord necrosis caused by *Aspergillus* infection. Leukopaenia due to anti-cancer chemotherapy resulted in pulmonary *Aspergillus* infection. The aspergilloma was reduced in size by anti-fungal chemotherapy, but paraplegia occurred. At autopsy, the pulmonary aspergilloma was encapsulated and showed no contiguous extension of the infection to the epidural or subdural spaces or spinal cord. However, at the T5 level of the spinal cord, there was marked necrosis with haemorrhage caused by *Aspergillus* infection, but without leukaemic cell infiltration of the spinal cord. Dichotomously branching *Aspergillus* hyphae filled the blood vessels of the T5 level of the spinal cord.

Key words: Paraplegia – Spinal cord necrosis – *Aspergillus* infection – Adult T-cell leukaemia

Introduction

Acute onset of paraplegia in adults is usually traumatic, or due to vascular accident or metastatic neoplasms in the spinal cord. Acute paraplegia resulting from massive necrosis caused by *Aspergillus* infection is extremely rare (Sheth et al. 1985). There have been several reports of *Aspergillus* infection of the spinal cord, some of which were associated with immunosuppression, in, for example, renal transplant patients (Ingwer et al. 1978; White et al. 1988; Woods and Goldsmith 1990). Others were caused by *Aspergillus* epidural abscess resulting from contiguous extension from a pulmonary focus (Byrid et al. 1982; Sheth et al. 1985; Wagner et al. 1985). Disseminated *Aspergillus* infection including infection of the central nervous system has also been reported in the acquired immunodeficiency syndrome (AIDS, Woods and Goldsmith 1990) and in patients receiving antibiotics or steroid treatment (Grcevic and Matthews 1959), but localized involvement of the spinal cord is rarely seen.

The incidence of subcutaneous fungus infection in autopsy cases in Japan as a whole is about 2.5%, whereas in subtropical Okinawa it is 19.1% (Iwamasa et al. 1990). The warm, wet climate of Okinawa may influence the incidence of the infection. Additionally, in Okinawa the presence of adult T-cell leukaemia (ATL), which causes immunosuppression, may also be an influential factor.

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Case report

A 45-year-old man was admitted to Ryukyu University Hospital in January 1991 with general fatigue, weight-loss and lymphadenopathy. Laboratory examinations revealed hypercalcaemia (11.6 mg/dl) and elevation of serum antibody titre to human T-lymphocyte virus type 1 (HTLV-1) ($\times$ 4096, passive agglutination method). T-cell leukaemia cells (CD4+) having cerebriform nuclei proliferated in the bone marrow and were demonstrated in the peripheral blood. The white blood cell count was 8800/mm^3 with a differential count of 1% basophils, 7% eosinophils, 59% neutrophils, 23% lymphocytes (3%, normal and 20% leukaemic cells) and 10% monocytes. The lymphocyte subclass analysis showed 72.4% CD4, 6.5% CD8, 3.8% CD24 and CD4/8 ratio 11.1. The diagnosis was ATL. As anti-cancer therapy, daily doses of 1.5 mg vincristine, 60 mg epirubicin, 150 mg etoposide, 60 mg prednisone, and 4.5 mg 2′-deoxycoformycin, were administered from March 12 to April 9, 1991 (VEPA-DCF therapy). From April 14 to 29, 1991 LSG (Japanese lymphoma study group) protocol 11 salvage therapy was carried out (3.6 mg vindesine, 60 mg carboplatin, 525 mg cyclophosphamide, 52.5 mg methotrexate and 60 mg prednisone daily). On August 5, 1991, ATL-CSF therapy of 560 mg cyclophosphamide, 56 mg coxorubicin, 11 mg mitoxantrone, 2 mg vincristine, 45 mg prednisone, 14 mg bleomycin, 140 mg etoposide and 75 μg DCSF (colony stimulating factor) daily was initiated. However, on August 26, 1991, this was discontinued because of unexpected side effects (mainly leukopaenia). In spite of anti-cancer chemotherapy, there was repeated regression and recurrence of the disease. As a side effect of the anti-cancer chemotherapy the number of leukocytes decreased. The peripheral white and red blood cell counts were 1,900/mm^3 and 216×10^4/mm^3 respectively

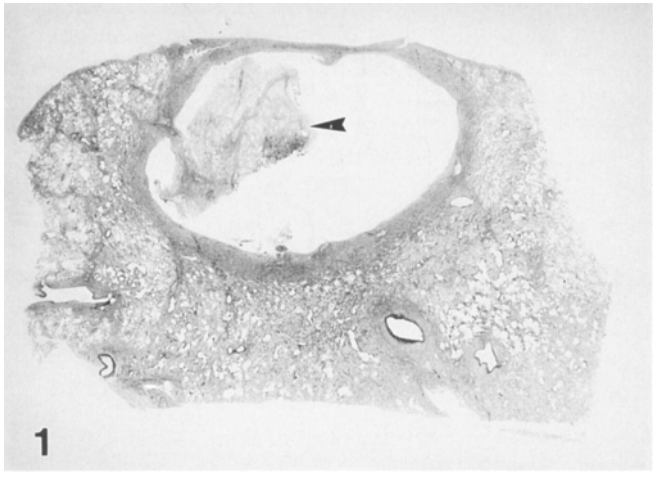

Fig. 1. A cavity, 1.7 cm in diameter, in the right upper lobe of the lung with thick fibrous capsule. In the cavity, there is fungus ball (*arrowhead*). Gomori's silver impregnation. ×2.8

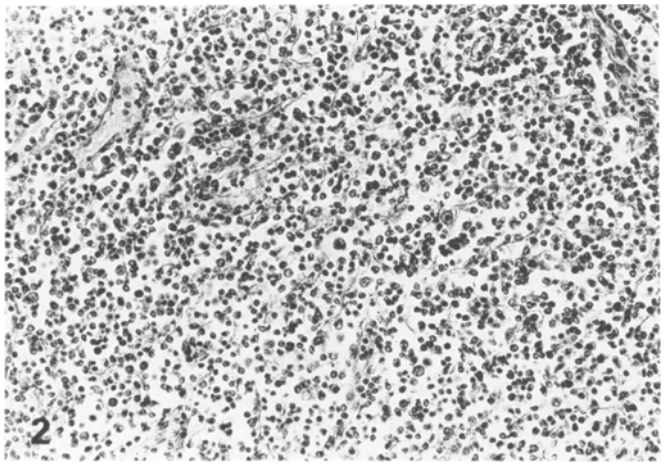

Fig. 2. Profusion of leukaemia cells in the bone marrow. There are numerous leukaemia cells with characteristic large nuclei. H&E. ×240

on July 1, 1991, 5,400 and 265×10^4 on September and 1,200 and 195×10^4 on October 10, 1991.

On September 12, 1991, chest radiographs showed a pulmonary aspergilloma on the right upper lobe. An anti-fungal regimen (44 mg amphotericin B and 7.5 mg flucytosine daily) decreased the size of the aspergilloma. However, on October 5, 1991, acute paraplegia was observed. On October 10, bilateral pleural effusion and elevation of serum BUN (92 mg/dl) were noted. On October 13, 1991, the patient died of respiratory and renal failure. *Aspergillus fumigatus* was demonstrated in the aspergilloma at autopsy.

Materials and methods

Necropsy including the spinal cord was performed, but permission for brain examination was not obtained. After formalin fixation, the samples from all organs were examined routinely. H&E, Gomori's and Grocott's silver impregnations, phosphotungustic acid haematoxylin (PTAH) and PAS stainings were carried out using 4 μm sections, and 6 μm frozen sections were prepared for Sudan III staining. The spinal cord was cut in the horizontal plane. Sections of thickness 4 μm and 10 μm were stained with H&E, PTAH, Klüver-Barrera, Bodian and Gomori's silver impregnations and Enarson's Nissel.

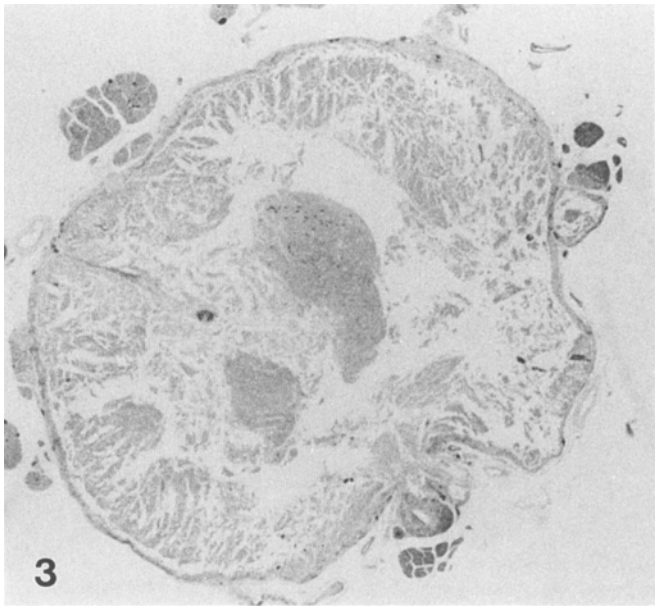

Fig. 3. Transverse section of the spinal cord at the T5 level showing massive necrosis with haemorrhage. Klüver-Barrera stain. ×11

Immunohistochemical examinations for cytomegalovirus (CMV), herpes simplex virus types 1 and 2 (HSV 1 and 2) and *Candida albicans* were performed on deparaffinized sections of the spinal cord. The polyclonal antibodies were all obtained from DAKO Kyoto, Japan. The T-cell markers, OKT4 and OKT8, were stained immunohistochemically using frozen sections of lymph nodes. These mouse monoclonal antibodies were obtained from Ortho Diagnostic (Tokyo, Japan).

Both lungs were markedly congested and atelectatic at necropsy. In the right upper lobe (S3) a cavity 1.7 cm in diameter with thick fibrous capsule was found (Fig. 1). There was no communication between the cavity and the bronchiole. The cavity contained a fungus ball of greenish-brown, soft friable material. Numerous *Aspergillus* hyphae were observed in the cavity by light microscopy. A moderate number of lymphocytes and small number of macrophages and polymorphonuclear leukocytes had infiltrated into the fibrous capsule.

Intranuclear inclusion bodies (Cowdry type A inclusions) of CMV were demonstrated in the alveolar epithelial cells in both lungs, which had been positively stained immunohistochemically using anti-CMV antibody. *Pneumocystis carinii* was also demonstrated by Grocott's silver impregnation method. Leukaemic cells had proliferated in the bone marrow (Fig. 2) and had infiltrated the liver, spleen, lung, small and large intestines and lymph nodes (mediastinal, lung hilum, para-aortic and mesenteric). These leukaemic cells stained positively for OKT4 but not for OKT8. In the spleen, CMV inclusions were also observed. Both kidneys showed tubular necrosis which might have been caused by anticancer and anti-fungal chemotherapy.

At level T5 of the spinal cord, there was marked necrosis with haemorrhage (Fig. 3). The subdural vessels, branches of anterior and peripheral arteries, were filled with dichotomously branching *Aspergillus* hyphae, resembling thrombi (Fig. 4). In the necrotic area, small numbers of *Aspergillus* hyphae were also found outside the blood vessels (Fig. 5). There was very little inflammatory infiltration; only a few macrophages and lymphocytes were observed. The massive necrosis seemed to have occurred following thrombic occlusion by *Aspergillus*. No fibrin thrombi were detected on PTAH and Gomori's silver impregnation methods. Immunohisto-

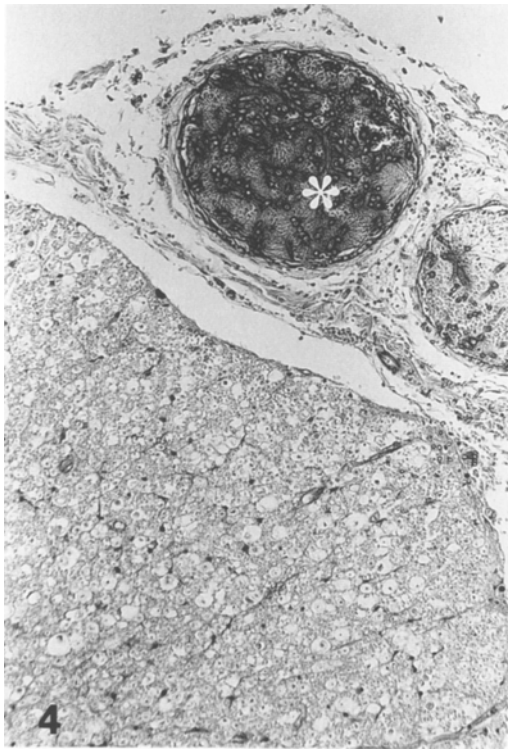

Fig. 4. Intravascular proliferation of *Aspergillus* at the T5 level of the spinal cord (anterior – lateral funiculus). The blood vessel is filled with *Aspergillus* hyphae (*). PAS. ×200

chemical reactions for *Candida albicans*, HSV 1 and 2 and CMV in the necrotic area were all negative. At T6–12, there were small foci of haemorrhage, but no *Aspergillus* was detected. Other parts of the spinal cord were free from *Aspergillus*, and no other organs also showed evidence of *Aspergillus* infection.

Discussion

There has been no previous report of the combination of cord infarction by aspergillosis in ATL. The right upper lobe aspergilloma was encapsulated by thick fibrous tissue, with no contiguous extension of the infection to the epidural or subdural spaces or the spinal cord. In the latter, the blood vessels were filled with *Aspergillus* hyphae and massive necrosis with haemorrhage was observed. The infection of the spinal cord might well have resulted from its dissemination from the lung focus. However, at autopsy *Aspergillus* was demonstrated mainly in the blood vessels in the spinal cord. *Aspergillus* in other organs was not detected and had presumably been cleared by anti-fungal chemotherapy. Blood vessels at T5 of the spinal cord were filled with *Aspergillus* with a thrombus-like appearance. In the necrotic area, there was only a mild inflammatory infiltrate, and very few macrophages and lymphocytes. The necrosis resembled infarction with haemorrhage. However, no fibrin thrombi were detected on PTAH staining and Gomori's silver impregnation method.

The blood circulation at the T5 (T4–6) level of the spinal cord is known to be slightly lower than other areas (Hirano 1992); it is called a watershed region for this reason. This physiological condition may influence the course of necrosis and haemorrhage.

In the present case, CMV and *Pneumocystis carinii* infections were also observed in addition to the *Aspergillus* infection, due to the immunosuppressive effects of the ATL and anti-cancer treatment.

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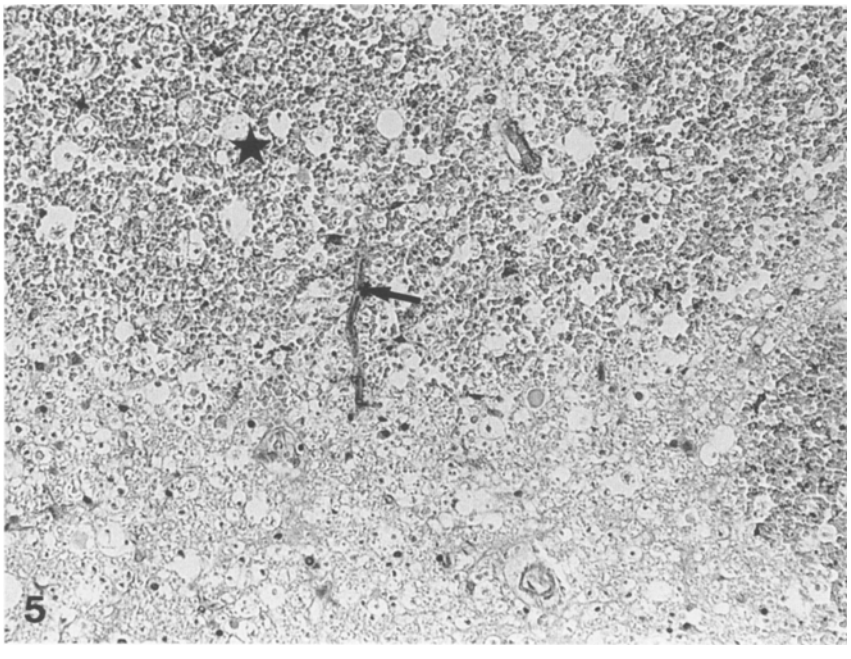

Fig. 5. Massive necrosis with haemorrhage at the T5 level of the spinal cord (lateral funiculus). *Aspergillus* hyphae (*arrow*) can be seen outside the blood vessels. However, there are very few inflammatory infiltrates, macrophages and lymphocytes. *: haemorrhage. PAS stain. ×250

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