Disseminated aspergillosis in a patient with ocular reticulum cell sarcoma

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SUMMARY A 75-year-old healthy woman developed uveitis and chorioretinal infiltrates OD compatible with reticulum cell sarcoma. She was admitted to hospital 18 months later with somnolence and confusion. Examination revealed diffuse white matter hypodensity on computed tomography and a persistent cerebrospinal fluid pleocytosis. At necropsy reticulum cell sarcoma was found in the right globe and *Aspergillus fumigatus* was present in almost every other organ, including the brain.

Disseminated aspergillosis occurs most commonly in immunocompromised patients.^{1,2} We report a case of disseminated aspergillosis in a patient with reticulum cell sarcoma (RCS) restricted to one globe.

Case report

A 75-year-old woman was in good health until June 1982, when she developed "floaters" OD and was found to have bilateral posterior uveitis with a fundus appearance thought most compatible with birdshot choroidopathy (Fig. 1). Examination revealed a positive purified protein derivative (PPD) test, negative syphilis serology, and normal toxoplasma and histoplasmosis titres. Her visual acuity declined to 20/200 OD by July 1983 despite topical steroids and one periocular injection of Depo-Medrol (methylprednisolone acetate) 60 mg. The patient refused diagnostic vitrectomy. She became confused and had difficulty ambulating in December, 1983, and was admitted to hospital for evaluation.

She was somnolent and disorientated to time and place with a temperature of 101° F (38.3°C). On general physical examination she was otherwise normal. Her visual acuity was no light perception OD and light perception OS. Neurological examination showed moderately depressed level of consciousness and symmetrically increased flexor tone. Chest x-ray,

complete blood count, biochemical profiles, arterial blood gasses, erythrocyte sedimentation rate, anti-nuclear antibody, complement levels, VDRL, cryptococcal antigen, and toxoplasma antibody titres were normal. Fever resolved with hydration. Brain CT showed diffused deep white matter hypodensity and a lucent area in the left thalamus thought to be a lacunar infarct (Figs. 2A, B). The lumbar puncture opening pressure was normal, and the cerebrospinal

Fig. 1 Fundus photograph OD of multiple small, yellow lesions in the posterior pole and retinal periphery involving the inner choroid and retina.

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Fig. 2 CT scan of brain without contrast: (a) at level of thalami showing hypodense area in left thalamus (open arrow) without mass effect (thought initially to be a lacunar infarct) and frontal white matter hypodensity (small arrows); and (b) at level of lateral ventricles showing diffuse white matter hypodensity without other focal lesions. Patient's left is on right.

fluid was normal except for 13 leucocytes, predominantly lymphocytes. Cytological examination showed only reactive lymphocytes. CT scans of the retroperitoneum and bone marrow biopsy were normal. Two additional lumbar punctures revealed a persistent lymphocytic pleocytosis with normal protein and glucose and no evidence of malignant cytology.

Decadron (dexamethasone) 6 mg intravenously six hourly and isoniazid 300 mg were started after 10 days in hospital because of progressive obtundation. Pars plana vitrectomy and chorioretinal biopsy OD two days later showed reticulum cell sarcoma (Figs. 3A, B), and whole brain irradiation was begun with the presumptive diagnosis of lymphomatous meningitis. After three weeks in hospital she developed a fever and a large left pyopneumothorax. The pleural fluid leucocyte count was in excess of 100,000, mostly polymorphonuclear leucocytes, and cultures grew *Staphylococcus aureus*. The patient died one week later despite antibiotic treatment.

Pleural fluid cultures grew *Aspergillus fumigatus*

one week after death. Post-mortem examination revealed invasive aspergillus in lungs, adrenals, oesophagus, colon, heart, kidneys, lymph nodes, skeletal muscles, pancreas, thyroid, parathyroids, and spleen. There was diffuse invasion of the cerebral white matter by aspergillus, and a large left thalamic abscess cavity was filled with branching septate hyphae (Figs. 4A, B). No primary source of aspergillus was found in the lungs or paranasal sinuses. The globes showed necrotic reticulum cell sarcoma cells OD and invasion of the choroid and retina by fungus OS with microabscesses but without evidence of tumour. The remainder of the necropsy, including mediastinal and retroperitoneal dissection, failed to reveal systemic lymphoma. An incidental thyroid carcinoma was restricted to one thyroid nodule.

Discussion

Disseminated aspergillosis occurs most commonly in immunocompromised hosts, although it can occur

Fig. 3 Eye wall biopsy: (a) tumour infiltrating retina, choroid, and sclera; and (b) malignant cells with abundant cytoplasm and large, irregular, convoluted nuclei with prominent nucleoli. Immunohistochemistry (T200) was positive for lymphocyte antigen; kappa, lambda, and S-100 were negative.

rarely in patients thought to be otherwise normal.^{3,5} It is notoriously difficult to diagnose, because cultures are frequently unreliable⁶ and serological testing is not yet widely available.^{7,8} *Aspergillus* typically invades cerebral blood vessels, causing ischaemic lesions and abscesses. Aspergillosis of the central nervous system may be suspected clinically after the apoplectic onset of focal neurological deficits in a febrile, immunocompromised patient with pulmonary infiltrates.⁹ CT findings usually consist of low absorption areas with minimal mass effect and slight contrast enhancement. The cerebrospinal fluid (CSF) is frequently normal but may contain a modest lymphocytic pleocytosis or raised protein concentration.

Ocular reticulum cell sarcoma usually presents in patients middle-aged or older as a chronic uveitis involving the posterior segment more than the anterior segment and is variably responsive to steroids. The disease involves both eyes in 80%¹⁰ and the central nervous system (CNS) in more than 50% of

reported cases.¹¹ CNS symptoms include personality changes, changes in level of consciousness, and focal neurological deficits. Brain CT in patients with ocular and CNS reticulum cell sarcoma usually shows contrast enhancing parenchymal masses with surrounding oedema. The CSF cytology was positive in 25% to 50% of these patients.¹¹

This patient with ocular reticulum cell sarcoma was presumed to have lymphoma involving the CNS. In fact, the sarcoma was limited to the right globe while aspergillus was found in almost every other organ, including the left globe. The site of aspergillus entry is uncertain, because the initial chest x-ray was normal and the patient had no sinus disease at post-mortem examination. Chest x-rays are normal in 15% to 20% of patients with invasive pulmonary aspergillosis,^{1,12} and terminal pulmonary involvement by aspergillus implies that our patient probably had radiologically inapparent pulmonary disease at the time of admission. Patients with impaired granulocyte function due to hereditary disorders, myeloprolifer-

Fig. 4 (a) Coronal sections of gross brain (patient's left on right) with abscess cavity in left thalamus and multiple smaller areas of ischaemic damage located throughout deep white matter.

Fig. 4 (b) Section stained with Grocott fungal stain showing white matter tissue necrosis and branching hyphae penetrating blood vessel walls into surrounding brain.

ative disease, or immunosuppressant therapy are most at risk for aspergillus infections.^{13,14} Granulocyte function was not specifically tested in our patient, but she was not granulocytopenic in hospital, she had no history of recurrent bacterial infections, she had a normal bone marrow examination, and she had never received chronic immunosuppressant or antibiotic therapy. A defect in cell mediated immunity associated with focal lymphoma should not have affected resistance to ubiquitous fungi. One previous case of ocular reticulum cell sarcoma died with disseminated

nocardiasis, but this patient was probably immunosuppressed after receiving six months' oral prednisone therapy in modest doses.¹⁵

It is unlikely that this patient had these two very uncommon diseases by chance, and it may be that patients with ocular reticulum cell sarcoma are at increased risk of local or disseminated infections with aspergillus or other opportunistic organisms. The therapeutically important distinction between CNS lymphoma and CNS aspergillosis may be difficult when other clinical clues are absent, for both processes can cause obtundation, focal neurological deficits, and CSF lymphocytic pleocytosis. The onset of neurological symptoms is most commonly sudden in CNS aspergillosis and gradual in CNS lymphoma, although this distinction was not helpful with the patient reported here. Brain CT showed hypodense areas corresponding to aspergillus invasion and abscess and may have been the best premorbid indication of disseminated aspergillosis.

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