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Herpes Simplex Type 2 Encephalitis Concurrent with Known Cerebral Metastases*

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Summary. A 62-year-old woman developed neurologic deficits 7 months after pulmonary lobectomy for alveolar cell carcinoma of the lung. CT scan of the head demonstrated two metastases with marked peritumoral edema. Administration of Decadron, chemotherapy and 3,000 rad cranial radiation resulted in dramatic inprovement of dysphasia and right hand paresis. Almost 2 months later, rhythmic, involuntary movements of the left hand developed. There was progression to multifocal seizures, grand mal seizures, postictal depression, status epilepticus, and coma, with death 9 days after onset of the movement disorder.

Bronchoalveolar carcinoma was widely disseminated in lungs and bones, and as three metastases in brain. Bland "ischemic" necrosis in a pseudolaminar pattern was present in the neocortex. Innumerable Cowdry type A intranuclear inclusion bodies were seen in neurons, astrocytes, and oligodendroglia. Immunofluorescence demonstrated Herpes simplex virus type 2 antigen and electron microscopy revealed virions with the morphology of the Herpes group. The case is significant for (1) the concurrence of intracranial metastases and Herpes simplex encephalitis, and (2) the causal agent, Herpes simplex virus type 2. The implication for the clinical neurocientist is the potential in a patient with systemic cancer, for the causation of neurologic complications by more than one factor or mechanism.

Key words: Herpes simplex type 2 – Herpes simplex encephalitis – Cerebral metastasis – Metastases and viral encephalitis – Immunofluorescence – Electron microscopy

Extracranial neoplasms may affect structure and function of the nervous system by several mechanisms: (1) Metastases in strategic sites may cause neurologic dysfunction or induce elevated intracranial pressure by progressive growth, edema, or block of CSF flow; (2) alterations of the reticuloendothelial, immune and granulocytic systems predispose to opportunistic infection, usually abetted by chemo-, radio-, and immunotherapy; (3) paraneoplastic syndromes may afflict the muscular, peripheral nervous, and central nervous tissues, with a multifactorial pathogenesis, including toxic, metabolic, nutritional, autoimmune, and infectious factors (Posner, 1978a, b).

The astute clinician will utilize various diagnostic tests to categorize the nature of a cancer patient's neurologic problem, because treatment for the various entities differs significantly. By the law of parsimony, symptomatology will be attributed to a known underlying, common disease process rather than to an unsuspected and uncommon complication. We wish to report the case of a 62-year-old woman with alveolar cell carcinoma of the lung who was treated for known cerebral metastases. Her terminal neurologic illness was attributed to the intracranial neoplasm. At postmortem examination, however, there was additionally disseminated Herpes simplex encephalitis.

Clinical Summary

In June 1977, this 62-year-old woman had right upper and middle lobectomy for alveolar cell carcinoma at another institution. She presented to Georgetown University Hospital in January 1978. with a three week history of clumsiness and paresis of the right hand and dysphasia. CT scan of the head demonstrated two contrast-enhancing lesions with marked peritumoral edema in the left frontal and parietal lobes. Chest-ray revealed a hilar mass and bone scan disclosed abnormalities of vertebral column and shoulder. Serum electrolytes, BUN, and calcium were normal. Oral Decadron was instituted for cerebral edema and 3,000 rad (Cobalt-60-beam) were administered to the head over two weeks, followed by standard dose chemotherapy of

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5-Fluorouracil, Adriamycin, and Methotrexate. Finger movements of the right hand and speech improved dramatically.

In early March 1978, the patient developed slow, rhythmic, involuntary movements of the left hand. Three days later a grand mal seizure prompted re-admission. Repeated focal seizures of the left extremities and adversive seizures of the head to the left were followed by status epilepticus. Postictal depression and somnolence gradually progressed to coma. During hospitalization, the leukocyte count dropped from 4,700 to 1,300/mm^3. CT scan showed improvement in size of metastases and degree of cerebral edema. The patient died in status epilepticus on the sixth hospital day.

Postmortem Examination

Disseminated intrapulmonary alveolar cell carcinoma and bronchopneumonia were the cause of death.

The brain weighed 1,260 g and its external appearance, leptomeninges, and vasculature were unremarkable. Three centrally necrotic metastases up to 1.2 cm in size were present in the cerebral hemispheres. The corticomedullary demarcation was distinct.

Sections from multiple paraffin-embedded blocks were stained with luxol-fast-blue-hematoxylin-eosin (LFB-HE); Lendrum's phloxine-tartrazine, PTAH, and PAS. Cryostat sections of formalin-fixed brain were submitted to immunofluorescent study with rabbit antisera to Herpes simplex virus types 1 and 2 (HSV1 and HSV2), Herpes zoster-varicella, and Cytomegalovirus. The bound antibodies were localized with FITC (fluorescein isothiocyanate)-labeled staphylococcal Protein A (Biberfeld et al., 1975). Blocks from appropriate areas of the formalin-fixed brain were processed for electron microscopy.

The cerebral metastases consisted of alveolar cell carcinoma with central necrosis and surrounding edema, myelin loss, and reactive astrocytosis. The neocortex of both cerebral hemispheres demonstrated patchy areas of bland, "ischemic" necrosis and vacuolation (Fig. 1). At the margins of necrotic foci, Cowdry type A intranuclear inclusions were identified in neurons, oligodendrocytes, and astrocytes (Fig. 2). Activation of microglia, glial nodules, fibrinoid necrosis or thrombosis of vessels, and hemorrhagic necrosis of cortex were not encountered. Oligodendrocytes of white matter and various cell types in basal ganglia, thalamus, and hippocampus contained viral inclusions (Fig. 3), as did neurons of substantia nigra, red nucleus, and oculomotor nucleus. Pons, medulla oblongata and cerebellum were uninvolved.

Chronic inflammatory cells were present in the perivascular spaces about a few vessels in both thalami and near the metastases and the leptomeninges disclosed slight fibrosis and macrophage activity. Endothelial cells of vessels demonstrated rare inclusions, but medial muscle cells of arterioles in the neocortex exhibited a greater number. Ependyma and choroid plexus of all four ventricles were uninvolved.

Ultrastructurally, virions with the morphology of the Herpes group were present in nuclei of neurons, astrocytes, and oligondendrocytes. They consisted of a central core and nucleocapsid, measuring 90–105 nm (Fig. 4).

Tissue architecture of cryostat sections was poorly maintained, yet small clusters of HSV2 could be demonstrated by immunofluorescence (Fig. 5), with negative reactions for other viruses and in control incubated sections. Of visceral organs, only lungs contained rare Cowdry A inclusions.

Discussion

To gain a perspective of the rarity of concurrent viral infection of the CNS and metastases from an extracranial neoplasm, the following data are provided:

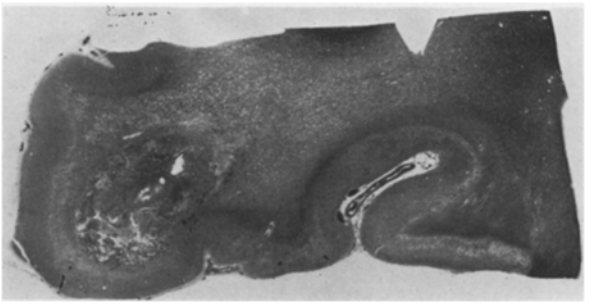

Fig. 1. Photograph of histologic section from left superior frontal gyrus illustrates metastasis with necrotic center and peritumoral edema and degeneration of white matter. Bland "ischemic" necrosis in a pseudolaminar fashion of the neocortex, particularly of the cingulate gyrus, is also evident (LFB-HE; ×1.5)

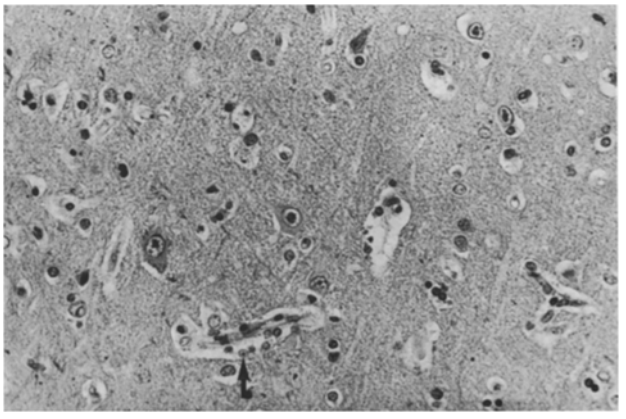

Fig. 2. Several large Cowdry-type A intranuclear inclusion bodies are present in neurons of the left superior frontal gyrus; similar viral inclusions are seen in oligodendroglia and astrocytes near the vessel (*arrow*). Note absence of necrotizing changes (LFB-HE; ×168)

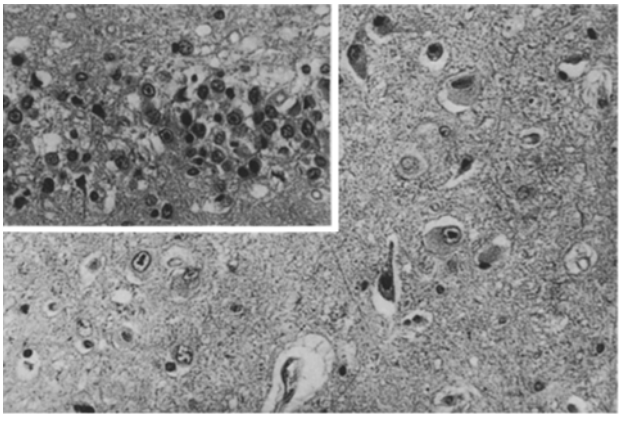

Fig. 3. Section of hippocampus illustrates intranuclear inclusion bodies in pyramidal cells and neurons of the fascia dentata (*inset*). Again, no necrosis is evident (LFB-HE; ×168)

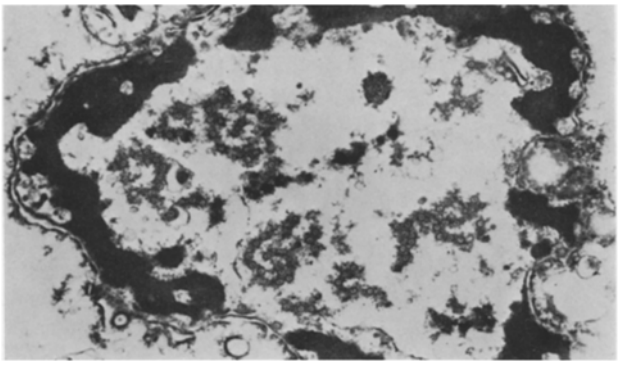

Fig. 4. An oligodendrocyte nucleus from the left superior frontal gyrus contains numerous virions of the Herpes group (uranyl acetate/lead citrate; ×11,781)

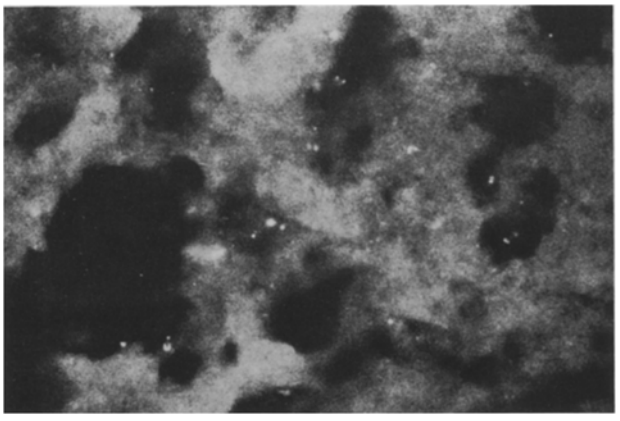

Fig. 5. Immunofluorescence photomicrograph of cortex reveals multiple clusters of Herpes simplex type II antigen (rabbit antiherpes type II IgG-FITC-labeled staphylococcal protein A; ×312)

1. From Fig. 1 of Chernik et al. (1973), an estimated 144,000 cumulative admissions to the Memorial Sloan-Kettering Cancer Center occurred between 1955–1970. Of 146 patients with CNS infections, only five were viral, including one with Herpes simplex encephalitis.

2. Subsequently, Chernik et al. (1977) reported 88 CNS infections (including five viral) among 1,416 postmortem examinations of cancer patients between 1971–1974, tabulating another Herpes simplex infection without details.

3. At postmortem examination of patients with lung carcinomas, 26% (Galluzzi and Payne, 1956) to 37% (Chason et al., 1963) had cerebral metastases. Similarly, of all cerebral metastases at necropsy 18% (Posner and Chernik, 1978) to 65% (Richards and McKissock, 1963) originated from a primary lung cancer.

4. Review of complete postmortem examinations of cancer patients at Georgetown University Hospital from January 1973 to December 1978 (Manz, 1979) discloses that:

a) 24 of 71 patients with lung cancer had intracranial metastases (34%), and

b) 13 of 382 patients with malignancy had an infection of the central nervous system: Four had purulent meningitis, three brain abscesses, three fungal infections, and three viral infections.

The patient here reported was the only one with an intracranial neoplasm, either primary or secondary, and concurrent viral encephalitis.

Viral-like particles have been demonstrated in anterior horn cells in two patients with malignant neoplasia and amyotrophy, by Walton et al. (1968) in a patient with Hodgkin's disease and Norris et al. (1970) in a patient with oat cell carcinoma. In neither case did the authors suggest a specific virus.

In our case, Cowdry type A inclusions, virions with the ultrastructural characteristics of Herpes simplex, and antigens specific for HSV2 were demonstrated. Staphylococcal protein A was used to amplify sensitivity and specificity of immunoglobulin G binding (Biberfeld et al., 1975). Because cerebral metastases were known to be present, the terminal neurologic dysfunction was attributed to them. Encephalitis was not suspected so that viral culture with fresh brain tissue was not attempted.

A fulminating clinical course and destructive hemorrhagic lesions in the limbic lobe characterize the usual sporadic case of HSE (Baringer, 1978). In contrast, in a patient anergic due to Hodgkin's disease, the neurologic course was prolonged over 7 weeks and neuropathologic features were widespread neuronal destruction, astrocytic proliferation, abundance of Cowdry A inclusions, and absence of inflammation and hemorrhagic necrosis (Price et al., 1973). They suggest that the altered host immune response accounted for the unusual clinical and morphologic features. Dayan et al. (1967) described a patient who developed HSE 8 months after radical hysterectomy for endometrial carcinoma. Again, there was randomly distributed cortical necrosis without concentration in the limbic system. Heineman and Breen (1975) isolated Herpes simplex from brain tissue at postmortem of a patient with completely resolved stage IV Hodgkin's disease with biopsy-proved HSE unresponsive to idoxuridine. A further unusual case of HSE was described by Miyake et al. (1977). A previously healthy 34-year-old male developed HSE as a primary infection. There was an inverse relationship between the severity of hemorrhagic, inflammatory, and necrotizing host responses and the intensity and distribution of immunofluorescent reaction to viral antigen. In the cases of Price et al.

(1973) and Miyake et al. (1977) the causal agent was HSV1; the virus type was not specified by Dayan et al. (1967) and Heineman and Breen (1975).

Encephalitis due to HSV2 is generally encountered only in the neonatal age group (Nahmias and Roizman, 1973; Hanshaw and Dudgeon, 1978). Of 84 cases of meningitis, meylitis, and encephalitis in patients over the age of 1 month, only one was due to HSV2, compared to 46 of 63 infections among newborn infants (Nahmias and Roizman, 1973). However, HSV2 appears to be a more common cause of "aseptic" meningitis in adults (Craig and Nahmias, 1973; Stalder et al., 1973). Whereas neonatal HSV2 encephalitis is highly necrotizing and hemorrhagic, like encephalitis due to HSV1 among adolescents and adults, the leukopenia in our patient may have precluded development of fulminant necrosis and inflammation. The malignant neoplasm and radio- and chemotherapy likely contributed to faulty immune reaction and leukopenia, thus predisposing our patient to HSE.

In summary, we wish to alert clinical neuroscientists to the coexistence of intracranial metastases and viral encephalitis with the implication that management requires accurate diagnosis of rare complications of systemic cancer. Radionuclide imaging (Karlin et al., 1978), computer tomography (Leo et al., 1978), immunofluorescent examination of cerebrospinal fluid cells (Dayan and Stokes, 1973), and the ratio of hemagglutinating antibody titers between serum and CSF (Levine et al., 1978) are of value in early diagnosis of HSE so that appropriate antiviral therapy can be administered (Whitley et al., 1977). Whether these techniques would prove useful in diagnosis or therapy of the more unusual form of HSE in a patient with cancer and/or immune deficit remains to be demonstrated. However, HSV2 is responsive to the antiviral agents used against HSV1 (Hanshaw and Dudgeon, 1978).

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