Central Nervous System Angioendotheliosis

A Treatable Multiple Infarct Dementia

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SUMMARY CNS neoplastic angioendotheliosis is a treatable primary proliferative disorder of the endothelial cells of blood vessels characterized by a clinical neurological picture of multiple infarct dementia and an inordinate amount of local cerebral edema, so striking that it may simulate primary or metastatic central nervous system tumor. The malignant cells remain within the lumen of the vessels and rarely if ever metastasize or occur in peripheral blood. There is remarkable improvement in symptoms by treating with high dose steroids. Antimetabolites and irradiation are suggested means of additional treatment.

NEOPLASTIC ANGIOENDOTHELIOSIS is a rare disorder of blood vessels characterized by a bizarre array of neurological symptoms associated with dementia, stroke-like syndrome, and dermatological involvement. There is widespread vascular endothelial cell proliferation contained within the blood vessels throughout the body. This condition has been referred to under various designations as "angioendotheliolemmatosis proliferans, systemistra" and "diffuse malignant proliferation of the vascular endothelium." 9

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References

ing apraxia, decreased spontaneity of speech, and left-sided weakness followed.

Her initial examination at the Indiana University Medical Center revealed an abnormal mental status exam and moderate anomic aphasia. There was left-right disorientation and marked constructional dyspraxia. She was lethargic, and her speech was delivered slowly. There was a mild left-sided hemiparesis with increased tone and right central facial paresis. Blood pressure remained normal throughout her hospitalization.

Initial brain scan showed a localized uptake in the right parietal area. The EEG revealed bilateral high amplitude slow activity with some emphasis to the right. Arch and cerebral angiography were normal, including observations for small vessel disease. Pneumoencephalography revealed a minimal right to left shift of the third ventricle.

Increased stupor and hemiparesis occurred. An echoencephalogram showed a 4-mm right to left shift, and repeat cerebral angiography showed a 5-mm right to left shift with a suspected mass effect of the right parietal area. The patient was begun on dexamethasone, 4 mg every six hours. Over the next few days her sensorium cleared markedly, and the left hemiparesis subsided. Echoencephalogram showed no shift. She became responsive, and her orientation was almost appropriate. A repeat EEG performed during this period was greatly improved, with no lateralization of the slow activity. Decision was made to taper the steroids. Thereafter, the patient developed a skin rash, thought to represent a drug reaction. When the prednisone was reduced to 7.5 mg daily, the patient developed increased lethargy, left hemiparesis, fever, and obtundation. A repeat EEG showed marked deterioration with reappearance of lateralized slow activity over the right hemisphere. Prednisone was reinstated at 15 mg daily, and within 24 hours she became alert and demonstrated increased strength on the left side. Steroids were again decreased and then stopped. An ACTH stimulation test demonstrated adequate adrenal function. Within 24 hours the patient developed fever, tachycardia, increasing stupor, and return of the left hemiparesis. The patient was given intravenous dexamethasone, as above, and begun on 15 mg prednisone daily. Blood, urine, and sputum cultures showed no growth. Twelve hours after instituting steroids, the patient became increasingly alert and demonstrated no drift of the left arm. Isoniazide, broad-spectrum antibiotic coverage, and steroids were maintained.

Because of the perplexing clinical course and response to steroids, it was felt that a brain biopsy was necessary. The patient was taken to surgery but suffered a cardiac arrest immediately after the induction of anesthesia.

Laboratory Data

The patient had numerous creatinine determinations during her hospitalization, and the results varied from 1.2 to 1.9. BUN varied from 20 to 68 mg %. The SGOT and SGPT determinations were normal. Neither the liver nor the renal function tests showed any correlation with steroid administration. Serum triglycerides varied from 390 to 540 mg %. Serum electrolytes remained essentially normal throughout the hospitalization. Cholesterol, LDH, CPK, aldolase, glucose metabolism, heavy metal screens, and serum protein electrophoresis were all within normal limits. Urinalysis on several occasions showed evidence of bacterial infection. White blood cell counts were within normal limits prior to steroid administration. An occasional atypical lymphocyte or macrocyte was reported in the WBC differential. Except for these findings, there was never any indication of abnormal cells in the blood. Blood gases were all normal except for a minor decrease in PO2. Spinal fluid revealed three white cells, four red cells, and one mononuclear cell. Cerebrospinal fluid cytomorphology revealed no tumor cells, plasma cells, or glia cells. Total protein was 54 mg %. There was a relative increase in the concentration of the beta globulins with a reversed gamma to beta globulin ratio. Total alpha globulins were 12 mg % and total beta 16 mg %. The total gamma globulin was 18 mg %. ECG indicated left anterior hemiblock.

Brain Scans

The initial brain scan demonstrated a localized peripheral area of increased activity on the right (figs. 1 and 2). There was a slightly delayed arterial phase in the filling on the corresponding area. Three weeks later, there was increased flow on the dynamic study and decreased activity on the static study. When the steroids were discontinued, the dynamic study showed persistent decrease of flow to the right hemisphere.

Other X-rays

Excretory urogram indicated somewhat large kidneys with poor visualization, suggesting the possibility of acute glomerular or acute pyelonephritis. Pulmonary angiography showed slightly prominent vascular structure, suggesting increased interstitial edema. Abdominal films were normal.

Autopsy Findings

General autopsy revealed neoplastic proliferation of the endothelial cells of the heart, liver, pancreas, adrenals, kidneys, bladder, ovaries, uterus, lungs, and gastrointestinal tract. The skin showed no change.

Microscopic examination demonstrated many small arterioles, capillaries, and venules packed with malignant pleomorphic cells with hyperchromatic nuclei, prominent nucleoli, and numerous mitoses. Multiple small foci of re-

![Figure 1. Dynamic and static cerebral scintigraphy. Serial two-second images in the anterior projection show decreased localization of activity in the right cerebral hemisphere during the arterial phase with homogenous localization during the venous phase between both hemispheres.](image-url)
FIGURE 2. Static brain images performed two hours after injection in the usual projections show peripheral localization of activity in the right cerebral cortex, primarily in the parietal region. The pattern of uptake is somewhat amorphous but primarily within the vascular supply of the middle cerebral artery. In the lateral projections two small, questionable areas of abnormal uptake of activity are noted.

FIGURE 3. Small patchy areas of grayish discolorations on the cortical surface.

FIGURE 4. In lumen of vessel are abnormal cells with large pleomorphic nuclei, some closely attached to vessel wall (hematoxylin-eosin, ×500).

cent semiorganized thrombi with hemorrhage secondary to the vascular lesions explain the few areas of infiltration of perivascular tissue. The lymph nodes were completely free of invasion. Some of the malignant cells were attached to the vessel wall by cytoplasmic strands, and there appeared to be transitional forms between the neoplastic cells and the normal endothelial cells.

The brain weight after removal was 1,230 gm. Gross examination revealed a slight change in consistency over the right parietal region with a peculiar grayish color on the surface (fig. 3). Similar changes were noted in patchy areas along other regions of the cortex of both hemispheres. Sections of the brain showed many areas of necrosis of a few millimeters. Many of the vessels were filled with neoplastic cells; others contained recent thrombi, similar to those in other viscera, sometimes attached to the wall of the vessel (fig. 4). There were no swellings, tumors, sheets, or clusters of cells forming new vascular channels. The only clearly extravascular cells appeared to be leukocytes and red blood cells in areas where organizing or recent thrombi occurred.

Discussion

Two previous patients with neoplastic angioendotheliosis of the central nervous system were reported by Strouth et al. Neither of these patients received steroids during the course of their disease.

Their first patient, a 42-year-old white man, became sud-
the vessel lumens of the brain, lungs, kidney, and heart. There were multiple foci of ischemic necrosis throughout the central nervous system.

Pfleger et al. reported a 31-year-old woman with recurrent skin lesions accompanied by intermittent hyperpyrexia. This patient recovered after an illness of eight years. Multiple skin biopsies during her illness revealed proliferating endothelial cells within the blood vessels. The patient did receive treatment with steroids. There was no central nervous system involvement, however.

Braverman et al. described a woman with extensive skin lesions, loss of vision, deafness, and muscle weakness. At autopsy there was involvement of the uveal tract, skin, heart, thyroid gland, petrous portion of the temporal bones, and vasculature of the brain. This patient, in addition, had abnormal cells within the lymphatics of many organs of the body and in the petrous portion of the temporal bones. In our case, as well as in those described above, there was no involvement of abnormal cells outside the blood vessels. This patient was treated with steroids, but the course of her disease remained progressive and resulted in death.

Angioendotheliosis can be differentiated from angiosarcoma because there are no sheets or cell clusters and no new vascular channels or tumor swellings. Histochemical studies in Strouth's cases revealed decreased activity for dehydrogenases in the abnormal endothelial cells compared with controls. Oxidative enzymes were only weakly demonstrated, suggesting a low metabolic rate of these cells. These observations plus the beneficial effects of steroids suggest that irradiation and antimetabolite therapy may be potent means of treating neoplastic angioendotheliosis.

The antemortem diagnosis rests upon recognition of this protein disease characterized by a picture consistent with a semiacute multiple infarct dementia often associated with skin manifestations, fever, and renal involvement. BUN and creatinine may be elevated. Microscopic urinalysis shows no neoplastic cells. The degree of cerebral edema may be so striking as to simulate primary or metastatic tumor. It differs from the edema of vascular occlusive disease in its protracted course and remarkable sensitivity to steroids. Angiography before and after steroid administration demonstrates significant change in midline displacement of the anterior cerebral vessels and no signs of vasculopathy. Midline echoencephalograms reveal an inverse relationship between steroid dose and midline shift. Renal and pulmonary angiography may be suggestive of glomerulonephritis and/or small vessel disease. Peripheral blood smears are surprisingly unrevealing.

Gross inspection of the brain may show only subtle grayish discoloration, and the neoplastic proliferation of the endothelial cells must be examined microscopically since on gross inspection the blood vessels usually appear normal unless infarction occurs. Only a clinical awareness and an index of suspicion will reveal the true incidence of this thus far rare, potentially treatable multiple infarct dementia.

References

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