Leptomeningeal Melanoma Associated with Straight Sinus Thrombosis

—Case Report—

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Abstract

A 36-year-old female was admitted with leptomeningeal melanoma associated with straight sinus thrombosis manifesting as headache and vomiting. Computed tomography and magnetic resonance imaging showed the subarachnoid space was diffusely enhanced. Her consciousness rapidly deteriorated to a coma. Angiography demonstrated straight sinus thrombosis. Thrombolysis by superselective catheterization and infusion of urokinase was successfully performed. She recovered consciousness, but developed paraparesis 2 weeks later. Malignant melanoma with meningeal dissemination was diagnosed by an open biopsy of the lumbar lesion. Angiitis induced by the infiltration of tumor cells and activation of the blood coagulation cascade was probably the causative mechanism of the sinus thrombosis.

Key words: melanoma, sinus thrombosis, thrombolysis

Introduction

Sinus thrombosis is caused by oral contraceptives,¹⁴⁾ hematological disorders,^{4,18,23)} collagen disease,^{13,15)} and infection.^{5,10)} However, sinus thrombosis associated with neoplasm is rare, except for sinus compression due to the mass effect. The clinical signs and symptoms of intracranial dural sinus thrombosis are various and diagnosis is sometimes delayed. Sinus thrombosis can be treated by sinus thrombectomy,^{8,16)} simple intravenous infusion of heparin,^{3,7)} or urokinase.²⁴⁾ Thrombolysis with tissue plasminogen activator infusion was also effective in an experimental model.¹⁾ We describe a patient who presented with straight sinus thrombosis associated with leptomeningeal melanoma in the lumbar region.

Case Report

A 36-year-old female was admitted to our department with complaints of headache and vomiting. Her headache had started 6 months before admis-

sion and gradually became aggravated in association with vomiting. She came to our hospital for further examination. Generalized convulsion developed and she was referred to our department.

On admission, her consciousness was disturbed but improved within a few hours. Neurological examination found no remarkable findings. Physical examination identified no abnormal skin pigmentation. Computed tomography demonstrated enlargement of the ventricles and subarachnoid spaces. The subarachnoid spaces were enhanced by contrast medium. Magnetic resonance (MR) imaging also demonstrated diffuse enhancement of the subarachnoid space (Fig. 1). Laboratory tests found mild elevation of the white blood cell count to $10.98 \times 10^3/\mu\text{l}$, but the following were normal: red blood cell count, platelet count, prothrombin time, activated partial thromboplastin time, electrolyte level, blood urea nitrogen level, creatine content, liver enzyme, glucose level, and C-reactive protein test. Lumbar puncture showed the pressure was 30 cmH₂O. Cerebrospinal fluid (CSF) examination found xanthochromy, cell count 3/mm³, protein 166 mg/dl,

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Fig. 1 Magnetic resonance image demonstrating enlargement of the ventricles and subarachnoid space. The whole subarachnoid space was enhanced after administration of contrast medium.

glucose 42 mg/dl, and chloride 114 mg/dl. No tumor cells or bacterial growth was observed. The CSF study was repeated but the results were almost identical. She was treated with dehydrating agents, but her symptoms did not improve. Seven days after admission, her state of consciousness deteriorated to somnolence.

Angiography demonstrated a straight sinus occlusion (Fig. 2 left), and remarkable retardation of the circulation time. The deep venous flow drained to the Rosenthal vein, deep sylvian vein, and cavernous sinus. A guiding catheter (5F) was placed in the internal jugular vein, and a microcatheter was coaxially advanced into the straight sinus. The microcatheter was passed through the thrombus and reached the vein of Galen. The pressure in the straight sinus proximal to the thrombus was 50 to 60 mmHg. Urokinase (120,000 U) was infused, and the straight sinus was recanalized (Fig. 2 center, right). The sinus pressure decreased to 40 mmHg. After the thrombolysis, heparin infusion was continued for 24 hours at 500 U/hr. Her consciousness improved, but the symptoms of headache and vomiting persisted. Following the diagnosis of hydrocephalus, a ventriculoperitoneal shunt was performed. Her symptoms disappeared after surgery.

Two weeks later, she developed weakness of the right leg, which progressed to paraparesis. Myelography demonstrated a complete block at the L-3 level. MR imaging demonstrated a heterogeneously enhanced lesion at the level of the cauda equina (Fig. 3). Following the diagnosis of arachnoiditis, laminectomy was performed from L-2 to L-5. The subarachnoid space was filled with dark tumor cells. The tumor was partially resected, but her paresis did not improve. Histological examination of the resected specimen revealed necrosis and mitoses, and pigmented cells were observed (Fig. 4). Immunohistochemical staining showed the tumor cells were positive for monoclonal antibody (HNB45) to malig-

Fig. 2 left: Angiogram 7 days after admission showing the straight sinus was not visualized (arrowheads). center: Superselective angiogram of the straight sinus after thrombolysis clearly showing the recanalized straight sinus. right: Angiogram in the venous phase after thrombolysis showing the recanalized straight sinus.

Fig. 3 Magnetic resonance image demonstrating heterogeneous enhancement of the cauda equina.

Fig. 4 Photomicrograph of the resected specimen from the surface of the cauda equina revealing many pigmented cells, cellular atypism, and mitoses. HE stain, $\times 200$.

nant melanoma and S-100 protein, but negative for glial fibrillary acidic protein, epithelial membrane antigen, and vimentin, so the tumor was diagnosed as malignant melanoma. Electron microscopy demonstrated pigmented cells with abundant premelanosomes. Chemotherapy with dacarbazine was performed, but was not effective.

One month after the second surgery, the patient developed cerebral bleeding in her right frontal lobe. Craniectomy was performed and the hematoma was evacuated. Pigmentation was observed on the brain surface, and the sylvian fissure was occupied by dark tumor cells. The tumor had not adhered to the dura mater and bled easily. Histological examination of the resected specimen showed malignant melanoma. Her condition gradually deteriorated and she died 3 months later. Autopsy was not permitted.

Discussion

The diagnosis of melanoma was not easy to establish in the present case, although we suspected meningitis or tumor dissemination, because repeated cytological examinations of the CSF were negative. Cytological examination of the CSF is important,¹⁷⁾ but the findings are not always reliable. An open biopsy would have diagnosed the melanoma much earlier. Recently, increased levels of 5-S-cysteinyldopa in the CSF and urine have been reported in patients with melanoma,¹²⁾ so measurement of this marker might aid in diagnosis. Malignant melanoma is the third most common primary tumor in patients with diffuse leptomeningeal metastasis after carcinoma of the breast and bronchus.²⁵⁾ The incidence of melanoma in children with extensive cutaneous nevi is 13%.²⁰⁾ However, the diagnosis of primary leptomeningeal melanoma is difficult in patients without cutaneous nevi. The MR imaging appearance of malignant melanoma is characterized by hyperintensity on T₁-weighted imaging and hypointensity on T₂-weighted imaging. However, these findings have been recognized in only 47% of lesions.²⁶⁾

Our patient had straight sinus thrombosis causing rapid aggravation of her condition. The sinus was recanalized promptly by thrombolysis with urokinase. Only five previous cases of straight sinus thrombosis have been recanalized by selective catheterization and infusion of urokinase.^{11,22)} The results in all cases, including ours, were excellent. The cause of sinus occlusion in our patient was not obvious, as there was no compression of the sinus due to a mass lesion. Angiitis and activation of the blood coagulation system may have been the causative mechanisms. Angiitis induced by infiltration of

tumor cells to the subarachnoid layer was probably the main cause. The coagulation system is activated in the presence of neoplasia.⁶⁾ In particular, melanoma cells synthesize a tissue factor which is an initiator of the blood coagulation cascade.⁹⁾ Such activation of the coagulation system may have also contributed to the formation of thrombus in the sinus.

Anticoagulation with dose-adjusted systemic heparinization for the treatment of sinus thrombosis was evaluated in a placebo-controlled study in 20 patients.⁷⁾ Eight of 10 patients in the heparin-treated group achieved a complete clinical recovery, whereas only one patient in the placebo group recovered completely. Therefore, anticoagulation with dose-adjusted heparinization is an effective treatment.⁷⁾ However, the effect of heparin may be too slow to help some patients with rapidly progressive thrombosis. Retrospective review of 29 patients with acute dural sinus thrombosis was used to classify the disease into five stages based on clinical symptoms, imaging findings, and outcome.²²⁾ Stage I patients had mild clinical signs and symptoms, and all had good outcomes. These patients may be treated with only anticoagulant. Stage V patients had severe symptoms such as coma, and all had fatal outcomes. Our patient was in stage III based on her condition such as seizure and somnolence, and required prompt thrombolysis. Thrombosed sagittal sinus has been recanalized by infusion of urokinase through a catheter inserted via a frontal burr hole.¹⁹⁾ Recent advances in angiographic equipment and catheter technology allow superselective catheterization and local fibrinolysis of the thrombosed sinus with urokinase. The results of this treatment regimen have been excellent.^{2,21)} Recanalization succeeded in 11 of 12 patients, with the only failure occurring in a patient with symptoms of at least 2 months' duration.¹¹⁾

Controlled randomized studies for the treatment of sinus thrombosis have not been performed. However, neither systemic heparinization nor simple intravenous infusion of urokinase guarantee recanalization. Surgical thrombectomy of straight sinus thromboses is very difficult and takes time due to the location of the lesion. Therefore, we suggest that superselective catheterization and thrombolysis using urokinase is the most favorable treatment for sinus thrombosis, especially for deeply located lesions.

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