

Oculomotor palsy from malignant lymphoma

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Neurologic complications of malignant lymphomas develop in 10% to 29% of all patients with lymphoma at some time during their illness.¹⁻³ Excluding opportunistic infections, therapeutic complications to the nervous system and paraneoplastic syndromes such as PML, most neurologic manifestations are the result of direct effects of lymphoma on the nervous system. Among these, compression of the spinal cord and peripheral nerves is most often encountered. Recently, diffuse lymphomatous meningitis without localized signs has been noted to be surprisingly common in patients with non-Hodgkin's lymphomas.^{4, 5} Direct invasion of the cranial nerves and the brain parenchyma remains infrequent and is associated with direct extension of lesions in the base of the skull.^{2, 3}

Neuro-ophthalmologic abnormalities are rare in patients with lymphoma and, if they occur, are mainly due to direct invasion into the orbital and ocular structures.⁶ However, lesions in the cavernous sinus producing oculovisual manifestations seem to be most unusual in patients with lymphoma.^{7, 8} We report a case of isolated right third nerve palsy as the first sign of lymphoma. Pathologic findings demonstrated localized invasion of lymphoma in the cavernous portion of the right third nerve.

Case report

A 43-year-old woman had increasing fatigue and recurrent, vague, abdominal pain for approximately one year before admission to the Cleveland Clinic Hospital. Several weeks before admission she noted the development of paresthesias and pain along the left mandible. Shortly thereafter, double vision and ptosis of the right eyelid developed without headache or pain.

Two weeks before admission, she was hospitalized at another institution because of rapidly increasing abdominal girth and a pelvic mass. At examination a partial right third palsy was noted. Exploratory laparotomy disclosed bilateral ovarian tumors that were diagnosed as malignant lymphoma. A bilateral salpingo-oophorectomy was performed. She was transferred to the Cleveland Clinic for further treatment.

Physical examination at the time of admission revealed abdominal distension, ascites, and multiple superficial ecchymoses in the skin. No lymphadenopathy was discerned. The remainder of the general physical examination was unremarkable.

Neurologic examination revealed a somnolent woman who was easily aroused. Orientation was appropriate and she answered all questions appropriately. A complete right third nerve palsy was noted. Mild ptosis was found in the left eye but no other abnormalities. Sensory testing revealed diminished pin sensation of the right half of the face, with relative preservation of light touch. Corneal responses were present. The remainder of the cranial nerve examination and the neurologic examination was normal.

Results of laboratory studies disclosed the following values: hemoglobin, 8.9 g/dl; hematocrit, 27.3%; white blood cell count (WBC), 7400/mm³ with differential count including neutrophils, 29%; band forms, 15%; eosinophils, 2%; basophils, 1%; lymphocytes, 35%; monocytes, 7%; metamyelocytes, 4%; and myelocytes 1%. There were 2% nucleated red cells, 6% atypical cells in the peripheral blood smear, and platelets 50,000/mm³. Urinalysis was unremarkable. Results of blood chemistry studies were as follows: sodium, 128 mEq/L; potassium, 5.2

mEq/L; inorganic phosphorus, 6.0 mg/dl; blood urea nitrogen (BUN) 33 mg/dl; creatinine, 2.4 mg/dl; uric acid, 20 mg/dl; and lactic dehydrogenase (LDH) 1205 mU/ml. The remainder of the blood chemistry values were within normal limits. Cerebrospinal fluid (CSF) examination disclosed no cells; CSF protein, 32 mg/dl; CSF glucose, 39 mg/dl (blood glucose, 65 mg/dl). The cytologic examination was negative for malignant cells. Various cultures were negative for bacteria, acid-fast organisms, and fungi. The bone marrow studies demonstrated diffuse infiltration of premature cells with folded nuclei.

Roentgenographic studies including skull series, sinus films, and optic foramen views were normal. Computed tomography (CT) of the head was also normal.

Chemotherapy was instituted after the patient was admitted to the hospital. At the time of the lumbar puncture, intrathecal methotrexate was given. However, progressive anuria developed and hemodialysis was ineffective. The patient rapidly deteriorated and died on the fourth hospital day.

Pathology studies

Autopsy studies showed pulmonary edema, right upper lobe atelectasis, and pleural effusion. Generalized diffuse histiocytic lymphoma (Rappaport classification) involved the kidneys, mesenteric lymph nodes, liver, spleen, and the cervix of the uterus. The bone marrow was diffusely infiltrated by the lymphoma cells.

Examination of the base of the skull showed bulging at the right anterior petroclinoid ligament along the wall of the right cavernous sinus. The cavernous sinus and part of the sphenoidal bone were removed en bloc. No gross abnormalities were found in the neighboring structures.

Coronal sections of the cavernous sinus at the level of the anterior pituitary lobe showed that the right third nerve was greatly swollen with its nor-

mal structure entirely obscured by tumor (*Fig. 1*). In high power view, this nerve was almost replaced by necrotic tumor cells (*Fig. 2*). The remainder of the nerve anterior and posterior to the site of tumor invasion revealed diffuse axonal swelling and patchy small hemorrhages. The cavernous sinus and its dura were diffusely infiltrated by tumor cells, but there was no invasion of lymphoma into the nerve parenchyma of the other cranial nerves (*Fig. 3*). The sphenoidal bone marrow was also found to have diffuse lymphoma infiltration (*Fig. 4*).

Examination of the central nervous system including the brain and the spinal cord, failed to show lymphoma invasion. There was no identifiable leptomeningeal infiltration.

Discussion

Although tumor was the most frequent cause of cavernous sinus syndrome, lymphoma did not involve the area of the cavernous sinus as reported in extensive studies by Jefferson⁹ and Huber.¹⁰ Among the various tumors, they reported nasopharyngeal cancer as the most common type of neoplasm. Thomas and Waltz¹¹ collected 108 cases of different tumors arising in the nasopharyngeal area and found five cases of

lymphoma. However, they did not discuss extension of lymphoma into the cavernous sinus.

An unusual but interesting example of lymphoma of nasopharyngeal origin extending into the cavernous sinus was reported by Lascelles and Burston.⁸ Lower cranial nerve palsies developed in a 36-year-old woman; this was followed by progressive ophthalmoplegia. Autopsy showed Hodgkin's lymphoma infiltrating the base of the skull, the cavernous sinus, and the brain parenchyma. Crocker and Lang⁷ reported a case of "cavernous sinus thrombosis" in a 44-year-old man. After death, diffuse undifferentiated malignant lymphoma was found bilaterally in the lacrimal glands, lymph nodes of the neck, and the cavernous sinus. The lesion in the cavernous sinus was thought to be an extension of orbital disease.

Our case seems to be different from the cases described.^{7, 8} No lymphoma was obvious in the adjacent structures that might invade the cavernous sinus. However, in the sphenoidal bone marrow, diffuse infiltration of malignant lymphoma was identified. Bone marrow invasion at the sphenoid appeared to be a part of generalized bone marrow infiltration of diffuse histiocytic lymphoma. Recently, it was reported that patients

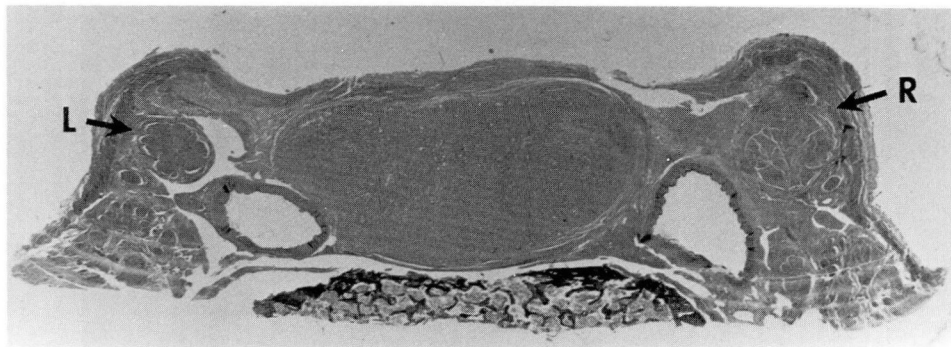


Fig. 1. Coronal section of the cavernous sinus and the sphenoidal bone. The right third nerve is greatly swollen (R); the left third nerve is normal (L). Decalcified tissue (hematoxylin and eosin stain, $\times 4.5$).

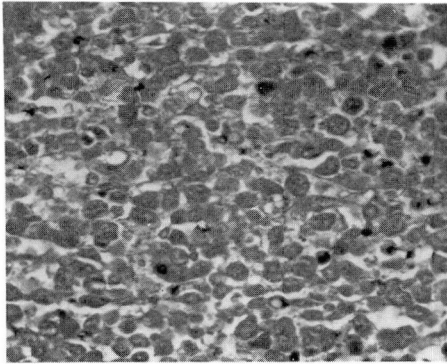


Fig. 2. The right third nerve is almost entirely replaced by necrotic tumor cells, which are poorly stained (hematoxylin and eosin stain, $\times 400$).

with non-Hodgkin's lymphoma and diffuse meningeal infiltration had a high frequency of bone marrow involvement.^{4, 5} Therefore, a close association was suspected between the bone marrow invasion and the development of the meningeal infiltration in non-Hodgkin's lymphomas. In our case the bone marrow involvement beneath the cavernous sinus may have been the source of the direct invasion into the covering dura and the cavernous sinus itself. It is also possible that circulating lymphoma cells may have metastasized at the cavernous sinus during the leukemic stage.⁵ The

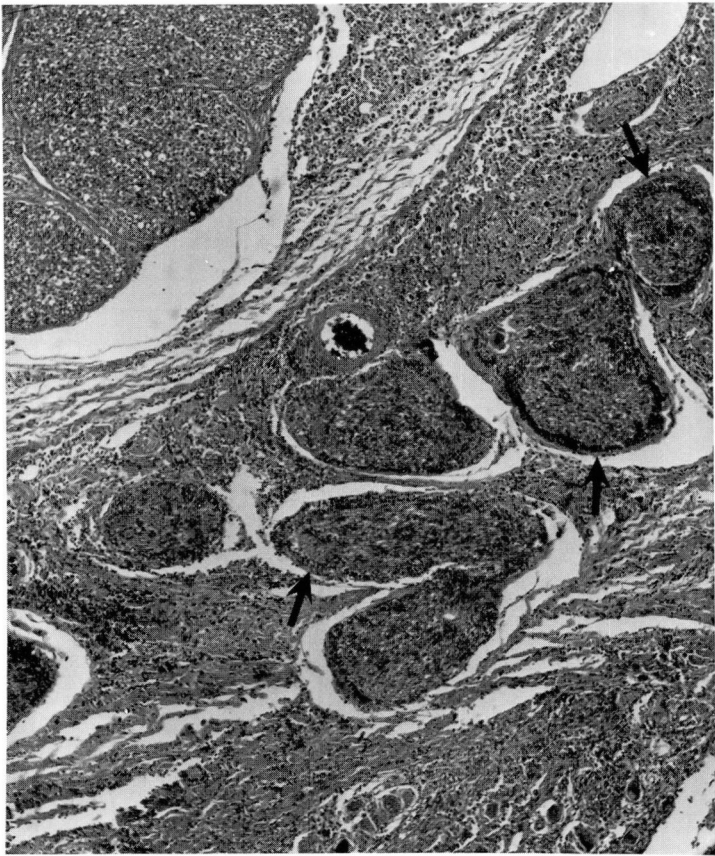


Fig. 3. The lymphoma infiltrates into the cavernous sinus and some of the other cranial nerves (trigeminal nerve) only at the epineurial tissue (arrow) (hematoxylin and eosin stain, $\times 64$).

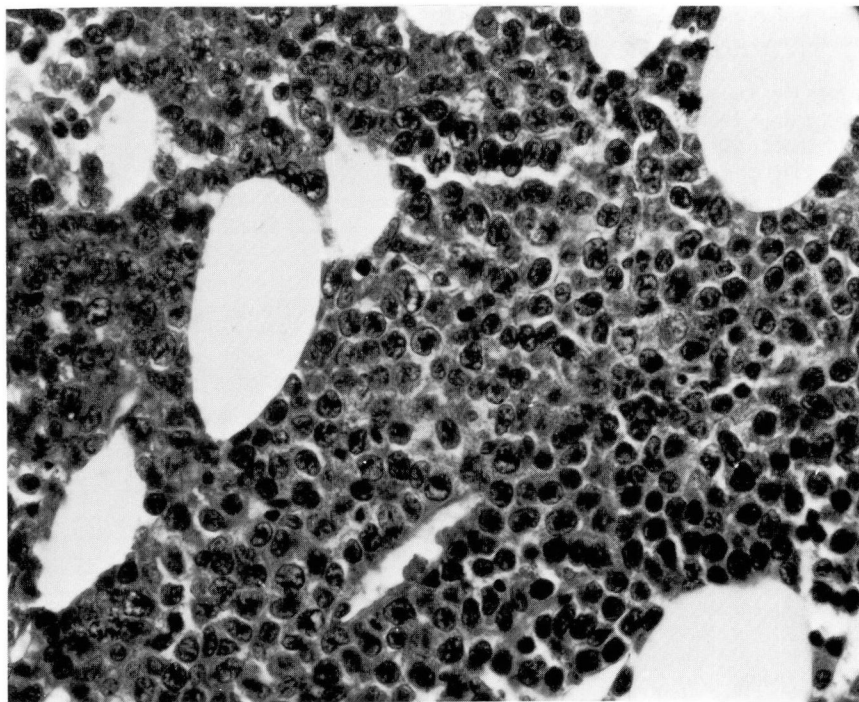


Fig. 4. Sphenoidal bone marrow is diffusely invaded by malignant histiocytic lymphoma (hematoxylin and eosin stain, $\times 400$).

dural invasion in our case may not have been limited only to the cavernous sinus area but may have been in some other area that eluded detection. However, the clinical significance of tumor invasion into the dural covering at the cavernous sinus appears to be totally different from the other part of the dura because of an extremely intricate relation to the multiple cranial nerves passing through this system.

It would be difficult for clinicians to diagnose malignant lymphoma when neuro-ophthalmologic signs and symptoms precede the signs of lymphoma elsewhere. Unfortunately, this was true in all three cases, our present case and two other cases reported in which the cavernous sinus was diffusely invaded by lymphoma.⁸

Summary

A 43-year-old woman had isolated right third nerve palsy as the first sign of the malignant lymphoma. Autopsy findings demonstrated localized invasion of lymphoma in the cavernous portion of the right third nerve. Unusual features of this condition are reviewed.

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