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Spinal subarachnoid hermorrhage associated with leptomeningeal metastases

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Summary

Retrospective evaluation of 120 patients treated for leptomeningeal metastases at the Hadassah Hebrew University Hospital disclosed 3 patients with spontaneous spinal subarachnoid hemorrhage (SAH) occurring in the absence of bleeding tendency. These patients are described in detail. A search of the English literature revealed only 2 additional cases. The primary neoplasm originated in the central nervous system in 4 of these 5 patients; a resection of an intraparenchymal posterior fossa tumor antedated the development of subarachnoid seeding in 3 of the 5 patients; SAH occurred in face of a negative CSF cytology and in the presence of macroscopic subarachnoid deposits that were diagnosed with the aid of neuroimaging techniques. It is suggested that spontaneous spinal SAH in a patient with a history of primary or secondary brain tumor and with no bleeding tendency indicates probable presence of macroscopic leptomeningeal deposits.

Introduction

Subarachnoid hemorrhage (SAH) complicating spinal intradural tumor is rare, and is most frequently reported in association with ependymomas [1]. Occasionally the bleeding is related to neurofibromas, meningiomas, astrocytomas or other locally arising neoplasms [1–5]. Metastatic intradural extramedullary tumors associated with SAH have been previously described in only 2 case reports [6, 7]. We present 3 additional patients whose manifestations of spinal leptomeningeal metastases were associated with SAH in the absence of bleeding tendency. They were encountered during a retrospective evaluation of 120 patients with leptomeningeal metastases treated in the Neuro-Oncology Clinic of the Hadassah Hebrew University Hospital between 1980 and 1989.

Case reports

Case 1

A 16 year-old girl was admitted on October 1981 for investigation of headaches, vomiting and nystagmus. Computed tomographic (CT) scan demonstrated an enhancing midline cerebellar mass which was completely resected and diagnosed as medulloblastoma. A postoperative staging myelogram disclosed irregular thickening of the cauda equina nerve roots, suggestive of malignant infiltration. The cerebrospinal fluid (CSF) was clear and colorless with elevated protein level and negative cytology.

After completion of radiotherapy (whole brain: 4000 cGy, posterior fossa boost: 1500 cGy, spinal cord: 3950 cGy), repeated myelogram and CSF analysis were interpreted as normal. Six months later she developed diplopia, low back pain and a bilateral positive straight leg raising sign. CSF evaluation revealed an increased opening pressure and

an acellular fluid with a high protein level. She was treated with intrathecal and intraventricular methotrexate for a presumed symptomatic leptomeningeal seeding. Repeated CSF analyses showed no malignant cells, the level of protein gradually returned to normal, and the patient's symptomatology subsided.

In August 1982, over several days, she developed a severe headache, neck pain and pain radiating into both upper extremities. On examination neck stiffness was prominent and hypoesthesia of the right C6-C8 segments was noted. CSF analysis was repeated twice and showed high opening pressure, xanthochromic fluid containing 1×10^4–2×10^4 RBC/mm^3, 724 mg/l total protein (normal 200–600 mg/l), 12 WBC/mm^3 and negative cytology. Head CT scan revealed no evidence of tumor recurrence, nor contrast enhancement or blood in the subarachnoid space. The blood coagulation profile was normal. Myelogram demonstrated an intradural extramedullary mass at C3-C6 vertebral levels, encasing the cervical nerve roots. Additional radiotherapy to the cervical area was given (2000 cGy) with rapid clinical improvement. The lumbar puncture, performed at completion of radiotherapy, did not contain erythrocytes. Eight months later she developed a progressive quadriparesis due to a massive spinal seeding and died after failing to respond to cisplatin chemotherapy.

Case 2

A 49 year-old woman had undergone an abdominoperineal resection of a rectal adenocarcinoma in 1984. There was no evidence of an active disease until August 1988, when she presented with headaches and left cerebellar syndrome. CT scan demonstrated a single enhancing left cerebellar mass. The mass was resected and diagnosed as a metastatic adenocarcinoma. Following a postoperative radiotherapy course (whole brain: 5000 cGy, posterior fossa: 1260 cGy), a repeated CT study showed no evidence of residual tumor. Six months later a right Horner syndrome was noted and subsequent investigation revealed a right lung mass, liver metastases and pericardial effusion. Radiotherapy to the mediastinum, followed by 5-Fluorouracil chemotherapy resulted in marked clinical response.

In April 1989 she was admitted because of severe low back pain, incontinence and paraparesis of several days duration. On examination, percussion over the lower thoracic vertebrae caused severe pain, the straight leg raising sign was positive bilaterally and there were no antigravity muscle movements. Hyporeflexia of the lower extremities was evident with equivocal plantar reflexes. A sensory deficit was present up to the level of T10. A CT-myelogram study revealed a complete subarachnoid block at T10 and T11 levels secondary to an intradural extramedullary mass. The CSF was xanthochromic with 1820 mg/l total protein, 8×10^3 RBC/mm^3, 25 WBC/mm^3 and negative cytology. The blood coagulation profile was normal. Following the first dose of spinal irradiation (200 cGy), she became paraplegic and underwent an urgent decompressive surgery. The intradural tumor mass was located at the vertebral level of T10-T11. It measured 2.5×1.0 cm, penetrated the arachnoid and was surrounded by a blood clot that trailed cephalad. A complete macroscopic resection was followed by the rest of radiotherapy course. The tumor was diagnosed as a metastatic adenocarcinoma. The patient completed our treatment protocol for intraventricular chemotherapy [8], her CSF cytology has been consistently negative and she is maintained on systemic chemotherapy. Her neurological status is gradually improving, she regained sphincteric control and is ambulatory with a walker (last follow up – January 1991).

Case 3

(partially described in reference 9). A 17-year old girl was hospitalized in August 1984 with a two months history of headaches and vomiting. Physical examination revealed bilateral papilloedema and a minimal left hemiparesis. CT scan showed an enhancing intraaxial lesion at the cranio-cervical junction. A suboccipital craniotomy and laminectomy of C1 were performed and a complete macroscopic removal of an intramedullary tumor was accomplished. The tumor was diagnosed as a low grade fibrosarcoma. No radiotherapy was given in light of this diagnosis.

Eleven months later, over several days, she developed increasing headaches and vomiting. On examination neck stiffness and paresis of the left sixth and third cranial nerves were found. CT scan showed diffuse contrast enhancement of the basal subarachnoid space and a midline subarachnoid enhancing nodule at the level of C1. Lumbar puncture revealed an increased opening pressure and a xanthochromic fluid that contained 3×10^4 RBC/mm^3, 21 WBC/mm^3, 850 mg/l total protein and no malignant cells. The blood coagulation profile was normal. Cerebral angiography showed only a prominent vasospasm of the basilar artery. During the following days her neurological status stabilized with some improvement in the cranial nerves function. At that stage, a repeated CT scan showed no meningeal enhancement but the cervical subarachnoid nodule persisted. CSF studies continued to reveal bloody fluid with negative cytology. A cisternal puncture was then performed. The CSF contained 1×10^4 RBC/mm^3, 18 WBC/mm^3, 580 mg/l total protein (normal 100–250) and a few malignant cells. She was treated with total neuroaxis irradiation (whole brain: 4050 cGy, posterior fossa boost: 1350 cGy, spinal: 4000 cGy) after which no erythrocytes were found in the CSF. Following completion of cranial irradiation an Ommaya device was inserted and a therapy with methotrexate according to a standard protocol [8] was started. She responded to treatment with partial neurological improvement and an incomplete pain relief. Her ventricular CSF persistently revealed high protein levels and an intermittent positive cytology. Twenty months following the initial diagnosis, she developed increasing pain and neurological deficit. Intraventricular therapy was resumed with combined injections of thiotepa and methotrexate. Neurological stabilization followed and was maintained for 10 months. Then she developed an extensive macroscopic seeding in the thoracic and lumbar subarachnoid space, responded transiently to ifosfamide chemotherapy, and died nearly 4 years after the initial diagnosis.

Discussion

Spontaneous SAH of spinal origin is rare, mostly related to spinal arteriovenous malfomations [2, 10] and only infrequently to spinal tumors [1–5]. The bleeding tumors arise locally and are of neuroaxial or nerve sheath origin. Among these tumors ependymoma is the most common source of bleeding [1]. An acute onset of either back or radicular pain followed by signs of spinal cord or nerve roots dysfunction characterize spinal bleeding but sometimes symptoms and signs may not be distinguished from intracranial SAH [3, 4].

The association of spinal SAH with leptomeningeal metastases has been previously reported in only 2 patients [6, 7] and was also mentioned in our former report [9] of case 3 in this series. Papo *et al.* [6] described a patient who presented with signs of SAH followed by spinal cord compression at the level of T9. At autopsy nodular metastases were widespread over the cord and cauda equina and the primary neoplasm was identified as a cerebral ependymoma. Tarlov *et al.* [7] reported an infant with sudden onset of quadriparesis accompanied by findings of meningeal irritation signs, bloody CSF and a myelographic block at the level of T2. Autopsy revealed an infiltrating dural sarcoma that penetrated the leptomeninges and formed discrete subarachnoid deposits.

Table 1 summarizes clinical features and laboratory findings in the previously described and the present patients with symptomatic spontaneous spinal SAH associated with leptomeningeal seeding. Four of the 5 tumors were primary central nervous system neoplasms, 2 of which, of the rare entity of meningeal or intramedullary sarcoma [9]. In 4 of the 5 patients SAH was the 1st clue of leptomeningeal seeding, and in 1 patient it signified a subarachnoid relapse. An abrupt onset of symptoms is described in the previous reports [6, 7] but our 3 patients presented a subacutely evolving clinical picture that may occur in spinal SAH [4]. The progressive development of spinal symptoms and signs indicated a spinal pathology. Headaches, neck stiffness and the straight leg raising sign could be related to the presence of spinal tumor or to SAH. After bleeding from a spinal tumor or a

spinal arteriovenous malformation cranial symptoms and signs may develop [3, 4, 11, 12], more often with a rostral localization of the bleeding [11, 12]. Two of our patients (case 1 and 3) presented with headaches, and patient 3 with vomiting and multiple cranial nerves signs following bleeding from cervical metastatic nodules.

The diagnosis of SAH secondary to neoplastic seeding is based on CSF studies and on neuroimaging evaluation. CSF findings proved initially misleading, since repetitive CSF cytological evalulations were negative in face of macroscopic subarachnoid neoplastic deposits.

Symptomatic leptomeningeal metastases may derive from primary neuroaxial neoplasms or may spread from a systemic tumor [13–18]. The incidence of subarachnoid metastases is probably higher, for both primary and secondary brain tumors, if the parenchymal neoplasm is located in the posterior fossa [14, 15]. All our patients presented with such a posterior fossa tumor prior to the development of symptomatic leptomeningeal seeding.

In an experimental animal model it was demonstrated that leptomeningeal metastases can form neovascularization [19]. These newly formed blood vessels probably account for the remarkable reponse to systemic chemotherapy sometimes observed in face of macroscopic leptomeningeal deposits [17]. It is likely that these blood vessels are also the source of the observed subarachnoid bleeding. It has been previously observed that in spinal SAH due to spinal tumors radiotherapy resulted in cessation of bleeding [4]. In 2 of our patients (patient 1 and 3) radiotherapy was initiated soon after diagnosis of SAH and a similar effect of irradiation was noted.

A spontaneous spinal SAH in a patient with a history of a primary or secondary brain tumor and no bleeding tendency may indicate macroscopic leptomeningeal deposits, even if the CSF cytology

Table 1. Clinical and laboratory features of spinal subarachnoid hemorrhage associated with leptomeningeal metastases

Author (ref no)	Age/sex (yr)	Primary tumor	Previous CSF seeding	Clinical features				Laboratory findings		
				Onset of symptoms	Neck stiffness/ SLR	spinal symptoms/ signs	Cranial symptoms/ signs	Bloody CSF	Lumbar CSF cytology	Neuro-imaging
Papo [6]	35/M	cerebral ependymoma	–	acute	+	back pain, progressive paraparesis	headaches, dizziness	+	nr	T9 block (autopsy-intradural mass)
Tarlov [7]	0.4/F	spinal dural sarcoma	–	acute	+	progressivee quadriparesis	anisocoria	+	nr	T2 block (autopsy-intradural mass)
Lossos case 1	16/F	medullo-blastoma	+	subacute	+	neck pain, cervical radicular signs	headaches	+	neg.	C3-C6 block intradural-extramedullary mass
Lossos case 2	49/F	rectal adeno-carcinoma	–	subacute	+	back pain, paraparesis, incontinence, sensory deficit	none	+	neg.	T10-T11 block intradural-extramedullary mass
Lossos case 3	17/F	cervico-medullary fibrosacoma	–	subacute	+	none	headaches vomiting cranial n. palsy	+	neg.	C1 intradural extramedullary mass

nr = not reported; neg. = negative; cranial n. = cranial nerves; slr = straight leg raising sign.

is negative. Myelogram or a gadolinium-enhanced magnetic resonance imaging may serve as the diagnostic procedures of choice [20–22].

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