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Unusual Cervical Spinal Cord Toxicity Associated with Intra-arterial Carboplatin, Intra-arterial or Intravenous Etoposide Phosphate, and Intravenous Cyclophosphamide in Conjunction with Osmotic Blood Brain–Barrier Disruption in the Vertebral Artery

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BACKGROUND AND PURPOSE: **When the clinical and radiologic characteristics of an unusual cervical spinal cord complication of intra-arterial (IA) chemotherapy with blood brain–barrier (BBB) disruption in the vertebral circulation are documented. Seven cases are reported and analyzed in search of a pathophysiologic explanation.**

METHODS: **We retrospectively identified 94 patients who received a total of 380 standardized regimens of IA carboplatin, IA or IV etoposide phosphate, and IV cyclophosphamide infusion in conjunction with osmotic BBB disruption of the vertebral artery. We describe seven of those patients in whom unexpected neck pain developed followed by neurologic symptoms primarily in the upper extremities.**

RESULTS: **The symptoms correlated with MR abnormalities (T1 hypointensity, T2 hyperintensity, and unusual contrast enhancement) in the cervical spinal cord, usually involving the gray matter. The neurologic deficits and MR changes were generally transient. One patient who received a flu vaccination 48 hours before the chemotherapy incurred progressive myelitis and expired.**

CONCLUSION: **The pathophysiology of this complication is probably multifactorial but may be related to vascular streaming and an atypical inflammatory toxic reaction to carboplatin and etoposide. The complication has not recurred during a 6-month period following modification of the protocol.**

Primary parenchymal brain tumors are infiltrative lesions without a clear margin between tumor and normal brain, therefore precluding complete resection at surgery or successful local treatment (1). Moreover, some studies have established, on the basis of findings obtained from the most sensitive imaging technique available (T2-weighted MR sequences), the presence of neoplastic cells at a distance from the abnormal signal. A recent study has even reported the presence of neoplastic glial cells grown from cultures of samples that were considered normal at formal histologic examination (2).

When considering a broad approach to the treatment of these tumors, the blood brain–barrier (BBB) is usually identified as an important obstacle to the delivery of antineoplastic agents. It is with that understanding that the osmotic BBB disruption technique was developed (1). This technique has been performed in conjunction with chemotherapy infusion at the Oregon Health Sciences University since 1981, and preclinical and clinical studies have clearly established that this approach significantly increases the delivery of antineoplastic agents to the tumor, to the brain around the tumor, and to the brain distant from tumor (1, 3).

The carboplatin tridrug regimen administered in conjunction with BBB disruption is the most commonly used regimen in the consortium (five centers) for the treatment of glial tumor, primitive neuroectodermal tumor (PNET), germ cell tumor, and

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metastatic lesions involving the CNS. This regimen consists of intra-arterial (IA) carboplatin, IA or IV etoposide phosphate, and IV cyclophosphamide, and has shown activity in glial lesions, PNET, and metastatic disease (small cell, ovarian, and breast). The major toxic effects observed in patients treated with multiple courses of this regimen were reversible myelosuppression and high-frequency irreversible hearing loss. Recently, sodium thiosulfate (STS) has been shown to be effective in reducing this hearing loss (4–6), and its use is now integral to the protocol.

We report seven cases of unusual and unexpected cervical spinal cord complications following vertebral artery BBB disruption and administration of chemotherapy with the carboplatin regimen. The clinical and radiologic characteristics of the seven patients are detailed and discussed relative to our principal pathogenetic hypothesis regarding this complication.

Methods

Between 1994 and 1998, a total of 1135 BBB disruption procedures were performed in conjunction with the carboplatin tridrug regimen in the BBB disruption consortium. The procedure is considered standard across the consortium and involves the following steps (1, 11): 1) Selective catheterization via percutaneous transfemoral puncture of the left internal carotid artery, right internal carotid artery, and left or right vertebral artery. 2) Determination of rate of infusion of mannitol by iodinated contrast injection and fluoroscopy as the lowest infusion rate in which there is retrograde flow from the arterial catheter. The volume of mannitol infused is determined in milliliters per second $\times$ 30 seconds (usually between 4 and 12 mL/s in the carotid circulation, and between 4 and 10 mL/s in the vertebral circulation). 3) Osmotic disruption of the BBB by infusing 25% mannitol in the previously catheterized artery at the defined rate. 4) Contrast infusion to confirm catheter position and rule out arterial injury after disruption. 5) IA infusion of antineoplastic agent in the disrupted circulation. 6) Termination of procedure and documentation of the degree of disruption by CT scan. Iodinated contrast agent is administered 5 minutes after the disruption for that purpose.

In this group of 1135 BBB disruptions performed in conjunction with the carboplatin tridrug regimen, 380 procedures in 94 patients involved chemotherapy infusion after osmotic disruption in the vertebral artery. Over a period of 18 months, seven patients incurred neck ache or upper extremity symptoms or both 1 to 5 days after treatment in three of the five institutions that form the consortium. Table 1 summarizes the carboplatin tridrug regimen with regard to the drugs involved, the timing and rate of administration, and the doses. All patients shared similar findings on cervical spinal cord MR studies, suggesting a common pathogenesis. This complication was not seen in 253 patients who underwent 1151 vertebral artery osmotic disruption procedures in conjunction with the methotrexate tridrug regimen, nor in 405 patients who underwent 3498 procedures in the internal carotid artery in conjunction with either the methotrexate or carboplatin regimen.

All seven patients had MR imaging of the brain and cervical spine with and without contrast material at symptom onset (Figs 1–3). With the exception of one patient (case 4) who had an insidious onset of symptoms, all MR images were obtained 1 to 5 days after treatment involving the vertebral artery. The patients were followed up clinically on a weekly basis. Routine imaging examinations were obtained at 4 weeks. Additional studies were requested when the patients' clinical status was deteriorating or when a plateau was reached before complete recovery.

TABLE 1: Carboplatin tridrug regimen: agents, doses, timing, and rate of administration

Agent	Dose and Rate
Mannitol 25% IA (osmotic disruption vertebral circulation	3 to 10 mL/s for 30 s (total dose, 90–300 mL)
Carboplatin IA	200 mg/m^2 diluted in 100 mL NS after disruption over 10 min
Etoposide phosphate IA or IV	200 mg/m^2 diluted in 150 mL NS before/during disruption
Cyclophosphamide IV	330 mg/m^2 diluted in 150 mL NS before disruption
Sodium thiosulfate IV	Patients with normal hearing; 20 g/m^2 at 2 hr after disruption over 15 minutes: patients with abnormal hearing; 20 g/m^2 at 2 hr, and 16–20 g/m^2 at 4 hr after disruption.

Note.—IA indicates intra-arterial; IV, intravenous; NS, normal saline.

Results

Clinical Findings

Table 2 summarizes relevant pretreatment clinical information. The age and sex of the patients, as well as the histologic characteristics and locations of the tumors, are widely different and unlikely to have contributed to the pathogenesis of this syndrome. As mentioned earlier, the only established common features in the seven patients were the chemotherapy regimen used (carboplatin based) and the osmotically disrupted vascular territory (vertebral artery). One patient (case 6) had an influenza vaccination 48 hours before treatment. This patient had the most severe reaction, with a related respiratory arrest and rapid progression of quadriparesis on day 3 after treatment. The patient remained quadraparetic and ventilator-dependent, and died 75 days after treatment. Six patients had a similar onset of symptoms, with neck pain as the initial complaint 1 to 5 days after treatment. This was followed by neurologic signs and symptoms, invariably involving the upper extremities (Table 3). One patient (case 4) had neck paresthesia as an isolated symptom. In this patient, no neurologic signs were found, and the symptoms gradually resolved as insidiously as they had appeared. This patient's symptoms were so subtle that it was only because of a high index of suspicion from previous, more symptomatic, cases (detailed in this report) that she underwent an MR examination. Unexpectedly, the MR study depicted significant changes in the cervical spinal cord, similar to those found in the more symptomatic patients. Other patients treated under this protocol in the vertebral territory also reported neck pain but had no neurologic abnormalities and did not undergo MR examination. Specific parameters regarding the treatment course that preceded the

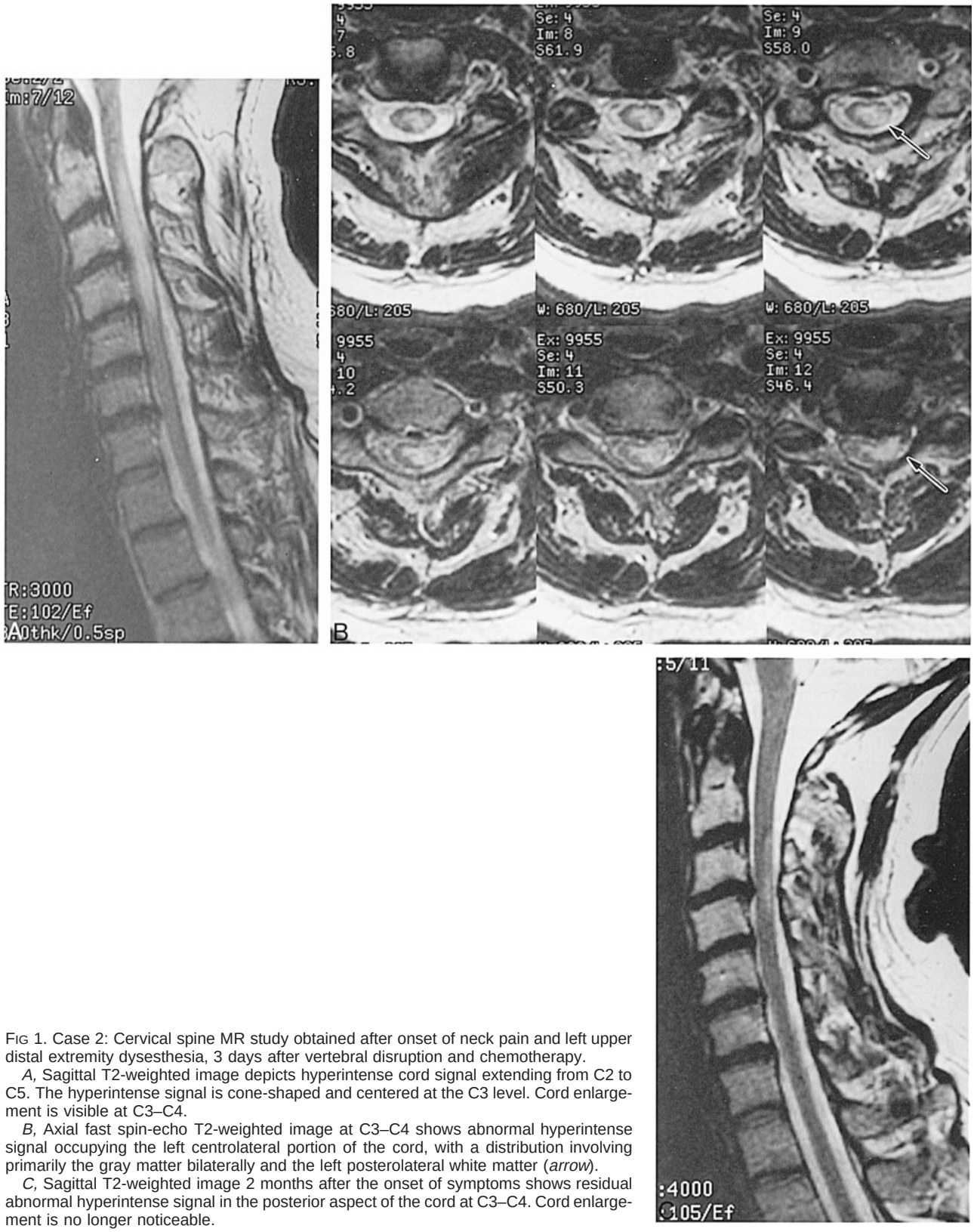

FIG 1. Case 2: Cervical spine MR study obtained after onset of neck pain and left upper distal extremity dysesthesia, 3 days after vertebral disruption and chemotherapy.

A, Sagittal T2-weighted image depicts hyperintense cord signal extending from C2 to C5. The hyperintense signal is cone-shaped and centered at the C3 level. Cord enlargement is visible at C3–C4.

B, Axial fast spin-echo T2-weighted image at C3–C4 shows abnormal hyperintense signal occupying the left centrolateral portion of the cord, with a distribution involving primarily the gray matter bilaterally and the left posterolateral white matter (*arrow*).

C, Sagittal T2-weighted image 2 months after the onset of symptoms shows residual abnormal hyperintense signal in the posterior aspect of the cord at C3–C4. Cord enlargement is no longer noticeable.

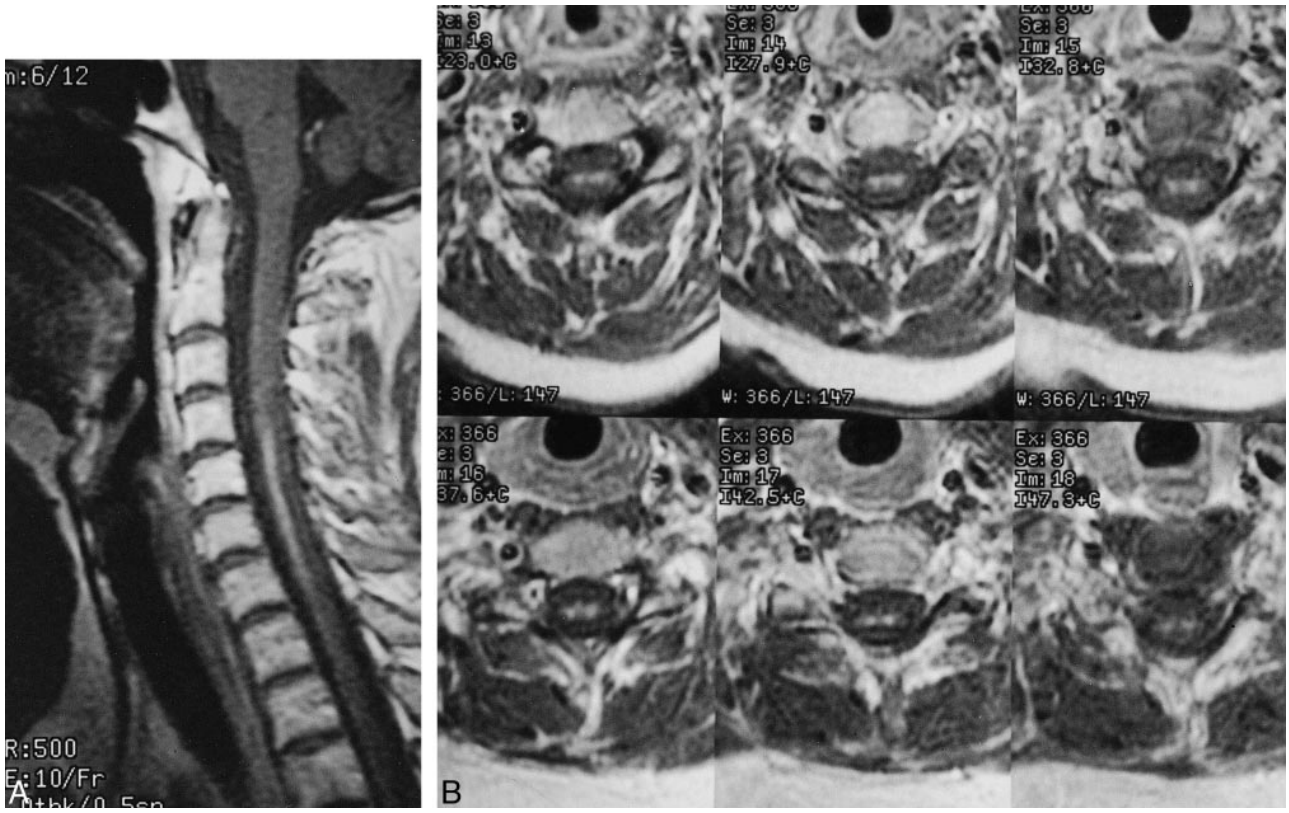

FIG 2. Case 3: Cervical spine MR imaging performed 2 months after onset of neck pain, left upper distal extremity dysesthesia and paresis in patient 3. Symptom onset occurred 4 days after a vertebral disruption and chemotherapy. The patient's initial MR study showed findings similar to those in Figure 1 (case 2).

A, Sagittal contrast-enhanced T1-weighted image shows linear anterior cord enhancement extending from C4 to C7.

B, Axial T1-weighted contrast-enhanced image at C5–C6 shows an enhancing signal occupying the anterior central portion of the cord. The distribution of this signal is symmetrical and involves mostly the gray matter, seeming to spare the peripheral white matter. There was no significant enhancement on the initial study.

complex of cervical spinal cord symptoms for each patient are summarized in Table 2.

Radiologic Findings

Table 4 depicts the MR changes in the seven patients. Interestingly, they share several common features, again pointing toward a single pathogenetic process, which is potentially multifactorial.

T2 hyperintense signal abnormalities were identified on all images, primarily involving the central portion of the spinal cord and the gray matter. The T2 changes were noticeable over three to six cervical segments between the C1 and C7 vertebrae. The spinal cord was also noted to be mildly enlarged in the same regions as the T2 hyperintense signal abnormalities in all cases. T1 changes were less consistent, as only two patients had subtle T1 hypointensity corresponding to the T2 abnormality. Of five patients in whom contrast material was administered in the initial study, all had abnormal enhancement. The degree of enhancement was mild in three patients and prominent in two. The pattern of contrast enhancement was unusual, with a faint bilobate ring in two patients, and patchy and diffuse enhancement in three patients. No abnormalities were seen in the brain stem, in the cerebellum, or in the vascular distribution of the posterior cerebral arteries in the cerebrum.

Outcome

All patients but one (case 4) were treated empirically with steroids. Four patients showed improvement, which was clearly associated with steroid therapy in at least one of them. The patient with neck paresthesia (case 4) made a gradual spontaneous recovery.

Two patients had severe adverse outcomes after the onset of the syndrome. As previously stated, the patient who had received flu immunization 48 hours before the treatment rapidly progressed to quadriparesis and respiratory failure. The second patient (case 3) reported progression of a left-sided parietal oligodendroglioma at the onset of this complication, after having been stable for 12 years. She experienced sudden neck pain and rapid onset of left-sided weakness involving mainly the distal aspect of the left upper extremity. She never improved, developed severe muscle wasting of the left arm, and later died as a result of tumor progression. Unfortunately, pathologic specimens were not obtained in either of

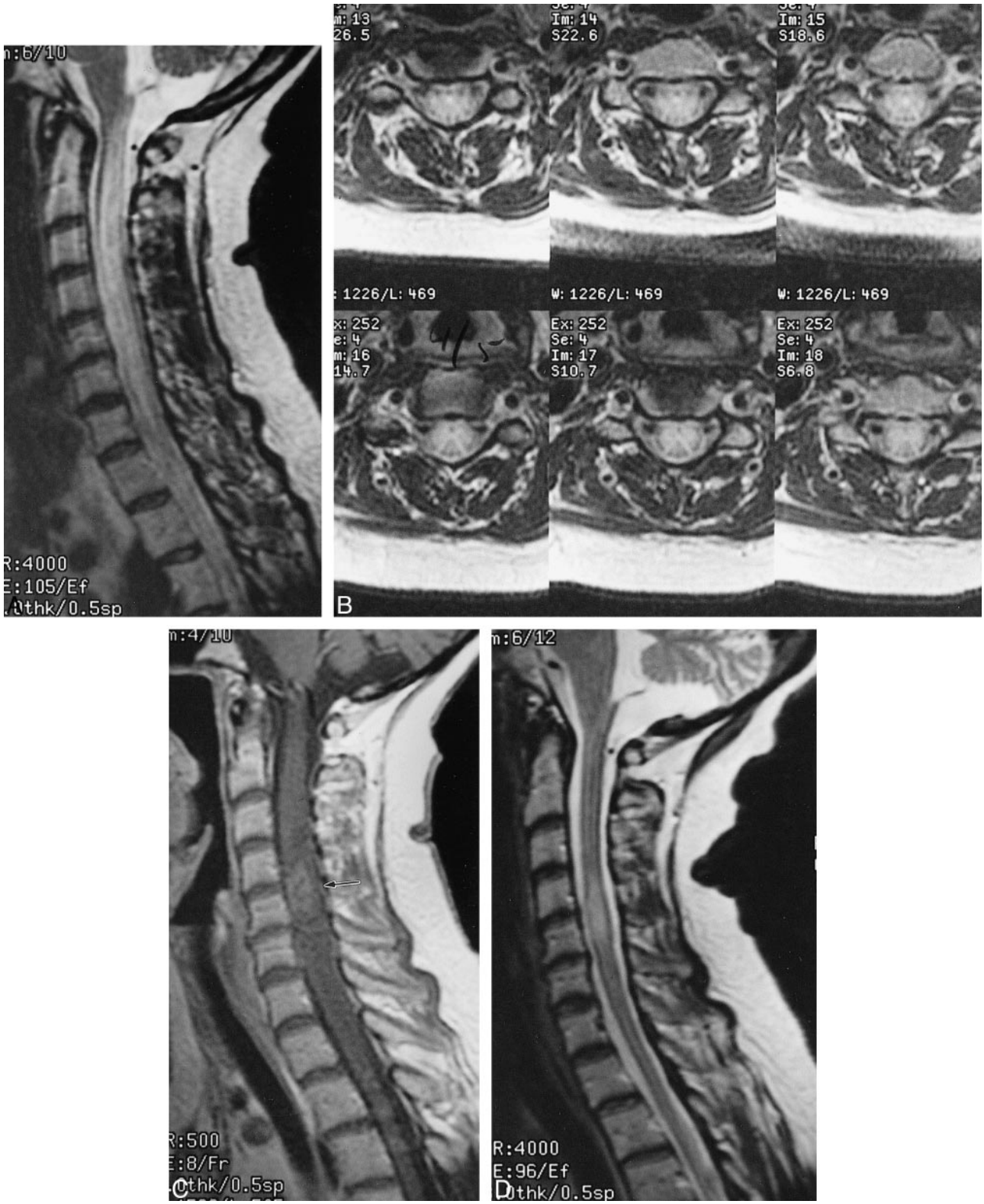

FIG 3. Case 7: Cervical spine MR study obtained after onset of neck pain and dysesthesia and paresthesia in upper distal extremities, 3 days after vertebral disruption and chemotherapy.

A, Sagittal T2-weighted image displays extensive abnormal diffuse hyperintense signal extending from the medulla down to the C7 level. Also note mild cervical spinal cord enlargement.

B, Axial fast spin-echo T2-weighted image at C4–C5 depicts abnormal diffuse hyperintense signal involving the cord, sparing only the peripheral white matter.

C, Sagittal contrast-enhanced T1-weighted image shows an area of abnormal faint and diffuse enhancement at the level of C5, over a 2-cm longitudinal segment (*arrow*). Also note the increase in cord diameter with obliteration of the subarachnoid spaces at that level.

D, T2-weighted sagittal image obtained 1 month after the initial study shows hyperintense signal now limited to the C4 and C5 vertebral segments. Also note the decrease in cord enlargement, as evidenced by the clear delineation of the anterior and posterior subarachnoid spaces.

TABLE 2: Patient characteristics and treatment summary (data presented for treatment course that immediately preceded C-spine complication)

Case	Age/Sex	Diagnosis	Tumor Location	Cranial Radiation	Commorbidities /Comments	No. of Treatment	Degree of Disruption	Steroids	Vessel Treated	Catheter Level
1	16/F	PNET	Pineal with negative staging	No	Tetralogy fallot, single kidney	3	Good	No	L vertebral	C5–C6
2	42/M	Oligoastrocytoma	L parietal, corpus callosum	Yes	· · ·	1	Moderate	12 mg/day	L vertebral	C3–C4
3	42/F	Oligodendroglioma	L. parietal	Yes	· · ·	20	Excellent	No	R vertebral	C5–C6
4	28/F	Oligoastrocytoma	L parietal	No	Scanned while asymptomatic	18	None	No	L vertebral	C7
5	33/F	GBM	R tempparietooccipital	Yes	· · ·	12	Excellent	No	R vertebral	N.A.
6	44/M	GBM	L occipital	No	Influenza vaccine 48 h previously	3	Good	16 mg/day	L vertebral	C5
7	52/F	PCNSL	L parietooccipital, CSF, ocular	No	· · ·	19	Good	No	L vertebral	C5–C6

Note.—PNET indicates primitive neuroectodermal tumor; GBM, glioblastoma multiforme; PCNSL, primary central nervous lymphoma; L, left; R, right; N.A., not available.

TABLE 3: Clinical presentation

Case	Symptoms Onset after Treatment (days)	Symptoms	Outcome
1	5	Neck pain, paresthesias in hands, distal paresis 4/5 upper extremities bilaterally	Symptoms resolved at 3 mo, MR normal at 3 months
2	4	Neck pain, L upper extremity pain (diffuse)	Improved at 3 months
3	4	Neck pain, L sided paresis 3+/5	Never improved; died of disease progression
4	N.A.	Neck pain	Neck pain gradually resolved
5	1	Neck pain	Improved; stopped treatment; disease progression
	4	R upper extremity sensory deficit	
	5	L upper extremity sensory deficit	
6	3	Respiratory arrest; quadriparesis; C3 sensory level	Remained quadraparetic and respirator-dependent; died
7	3	Neck pain, L upper extremity distal paresis 3−/5, R upper extremity distal paresis 4/5	Improved at 3 months

TABLE 4: MR characteristics

Case	T1 Signal	T2 Signal	Contrast Enhancement	Cord Enlargement	Gray/White Matter Topography of T2 Signal
1	↓ C4–C5	↑ C1–C6	↑ C4–C5	↑ C3–C6	Gray matter predominance
2	Normal	↑ C2–C5	↑ C2–C5	↑ C2–C5	Gray matter predominance
3	Normal	↑ C2–C6	↑ C2–C6	↑ C2–C6	Gray matter predominance
4	Normal	↑ C1–C3	Not administered	↑ C2 minimally	Gray matter predominance
5	Normal	↑ C2–C5	↑ C2–C5	↑ C2–C5	· · ·
6	↓ C4–C5	↑ C1–C7	Not administered	↑ C1–C7	· · ·
7	Normal	↑ C1–T1	↑ C4–C5	↑ C1–T1	Gray matter predominance

these patients; however, after an analysis of the findings, the chemotherapy protocol was modified. These modifications are detailed and discussed below.

Discussion

Pathogenesis: Common Factors

Table 5 summarizes the common factors identified in the seven reported patients. In our view, a common pathogenesis is likely, given the similarities in most aspects of the cases. There are obviously some isolated factors that may or may not be related to the syndrome, and case 6 (the patient who had the worst reaction with a fatal outcome) represents one such consideration. This patient had an influenza immunization 48 hours before treatment. Was the immunization somehow related to the reaction and to its severity? This could be the case if the immunogen incited a postvaccine mye-

TABLE 5: Common factors

Treatment variables	Vertebral circulation disruption
	Carboplatin tridrug regimen
	Sodium thiosulfate
Symptoms	Neck pain
	Neurologic deficit upper extremities
Chronology of symptoms after treatment	1 to 5 days
MR findings	T2 hyperintense signal
	Gray matter distribution (central cordlike)
	Cord enlargement
	Contrast enhancement

litis. The osmotic disruption of the cervical circulation would have then opened the tight endothelial junctions and enhanced the local immune process.

Interestingly, the patient (case 4) who experienced the mildest form of the syndrome (with vague neck pain as the sole complaint—continuing treatment without complication and undergoing only IA chemotherapy infusion without disruption in the vertebral distribution) had an anaphylactic reaction nearly a year later during an IA infusion of chemotherapy in the vertebral distribution (without osmotic disruption). This reaction was clearly established as being related to carboplatin by an immunologist at our institution.

Remsen et al (7), while studying long-term toxicity and neuropathology associated with sequencing of cranial irradiation and enhanced chemotherapy (carboplatin/etoposide versus methotrexate) delivery in a rodent model, found an unusual and unexpected complication associated with the combination of IA carboplatin (200 mg/m^2) and IV etoposide (200 mg/m^2). An experimental, allergic, neuritic syndrome with hind-limb paralysis occurred in 11 animals who received radiation and chemotherapy. Ten of these animals received the combination of carboplatin and etoposide, which was strongly associated with the complication ($P = .0006$), more so than any other factor. Most of the symptoms in these animals were observed approximately 120 days after their first treatment, indicating that this may have been a delayed response to the combination of radiation and chemotherapy. Although this lengthy latency period is different from the short period of onset our patients experienced, the pathophysiology could be related if there is an amnestic immune response, with surgery or prior chemotherapy causing the primary sensitization. The relationship to radiation therapy was, however, not as consistent with our patients, since only three of the seven had been previously irradiated.

Table 1 details the agents, doses, and infusion parameters used in our regimen. Obviously, a single causal agent is unlikely to be implicated. All the agents have been used in different combinations (as part of the methotrexate regimen, for example), or in the carotid circulations, without producing this type of complication. The disruption is important in the pathogenesis, because IA chemotherapy with the same agents but without disruption in the vertebral circulation (used in patients with borderline functional status or excessive mass effect) has never produced this syndrome.

The quality of disruption obtained, as assessed on a postdisruption CT scan, is detailed in Table 2. It is readily apparent that the intensity of disruption is not accountable for the syndrome, nor is the total number of treatments administered at the time of the syndrome's occurrence.

Etoposide has been shown to induce BBB disruption when infused intra-arterially (8). In rats, it has produced an increase in the permeability of the BBB for less than 24 hours when doses of 3 mg/kg were used, and for up to 4 days at doses of 22.5 mg/kg. Although histologic studies did not reveal evidence of parenchymal damage, mild perivascular lymphocytic infiltration was found in the infused hemisphere (9). Etoposide has also been found to be cytotoxic to neurons by inducing apoptosis in neurons cultured from the fetal rat CNS (10).

Carboplatin is a second-generation platinum analogue displaying the same spectrum and level of activity as cisplatin but with fewer toxic side effects (11). Preclinical studies of IA carboplatin have depicted a safety profile at doses below 400 mg/m^2 (12, 13). In our protocol, we currently use doses of 200 mg/m^2 per circulation. At therapeutic doses, however, carboplatin and etoposide are synergistic (3, 14).

Although carboplatin is less toxic than cisplatin (4, 6, 15, 16), it has retained some toxicity, especially ototoxicity. To reduce this effect, our laboratory investigated the use of STS as an otoprotectant (17, 18). STS was found to be effective in preventing hearing loss when administered up to 8 hours after carboplatin in a guinea pig model (19). In our preclinical rat studies, STS was found to be neurotoxic (induced seizures) when slowly infused in a carotid artery immediately after osmotic disruption, or, to a lesser extent, when infused IV immediately after disruption. When administered intravenously 30 to 60 minutes after the osmotic disruption, when the BBB is presumed to be closed, no signs of toxicity were detected (5). Other animal studies report a similar safety profile.

Although our preclinical data suggest that the barrier is closed when the first bolus of STS is administered at 2 hours, extended opening of the barrier by etoposide may increase brain parenchyma exposure to STS to nonphysiologic levels. Zylber-Katz et al (20) demonstrated some degree of BBB opening for up to 3 hours. Currently, STS administration has been delayed to 4 hours after disruption.

Intravascular Streaming

Intravascular streaming is caused by poor mixing of the drug at the infusion site, resulting in hetero-

geneous delivery to the brain. Although this phenomenon has been well studied and characterized, investigations have focused primarily on intracarotid infusion (21). By following the distribution of the tracer $^{2}H^{15}O$ by positron-emission tomography, a highly heterogeneous distribution was found, most likely because of intravascular streaming, when supraophthalmic but not infraophthalmic infusion was used (22). Rate of infusion has been identified as one of the major factors involved in the production of streaming, bearing an inverse relationship; that is, streaming would be favored by decreasing the rate of infusion (22, 23).

Early experience with IA chemotherapy infusion in the vertebral circulation has clearly established that vascular distribution has a narrower toxicity index than the carotid circulation, and this was thought to be attributable to the lower blood flow (24). This, combined with the fact that high-grade glial lesions in adults are mostly supratentorial, probably accounts for the paucity of reports of vertebral chemotherapy infusion (3, 25).

The Reynolds number (22), a crucial parameter in fluid dynamics, predicts the transition from streamlined to turbulent flow. It is calculated from the following equation:

$$\text{Reynolds number} = \frac{(\text{density of fluid})(\text{lumen diameter})(\text{velocity of flow})}{(\text{viscosity of fluid})}$$

As the Reynolds number increases, flow turbulence increases and so does the mixing of agent infused with blood, therefore decreasing the phenomenon of streaming. In this equation, because density and viscosity of fluid are not expected to change significantly, regardless of the vessel used and the rate of infusion (unless a very high administration rate is used, which is not typically the case in a clinical setting), lumen diameter and velocity of flow become the most significant variables. Therefore, on the basis of this concept, if the vessel diameter decreases, the likelihood of streaming increases. Infusion in the vertebral artery is therefore much more likely to produce streaming than is infusion in the carotid artery.

Disrupted Circulation and Vascular Anatomy

Osmotic disruption is expected to open the tight endothelial junctions of the entire vascular tree through which the mannitol is infused. We therefore assume that all vascular structures in the vertebral circulation distal to the catheter position will be disrupted.

The anterior spinal artery arises cranially, typically as two branches (one from each vertebral artery) that fuse at the level of the medulla and run caudally in the anterior spinal sulcus. Although fairly constant in 85% of patients (approximated from cadaveric studies), the anatomy of these tributaries can be somewhat variable in at least 15% of patients (26). The anterior spinal artery can arise from only one vertebral artery, at different levels. It is supplied at the lower cervical level by two to four radicular arteries arising from the vertebral, deep cervical, superior intercostal, and ascending cervical arteries. The vertebral arteries feed directly into the anterior spinal artery through small collateral branches at various cervical levels. One such feeder is frequently identified at the C5 level.

Catheter placement level is likely to be relevant to the genesis of this complication. With the anatomic variation of the vertebral feeders of the anterior spinal artery system, the catheter tip positioned near the origin of one such tributary, combined with streaming (while infusing IA carboplatin after the osmotic disruption) could account for the abnormally high delivery ratio of mannitol or carboplatin or both in the tributary itself. It is worthy of mention that in this series, the catheter's tip was positioned near C5 in four of the seven patients. If the catheter is placed higher (C1–C2), this risk is less likely, as it bypasses the vertebral feeders. Nevertheless, infusion near the origin of one of the anterior spinal arteries combined with the phenomenon of streaming could then be involved in the genesis of this syndrome. This is especially true if the catheter is in a vertebral artery from which arises a unique origin or branch to the anterior spinal artery, as might be the case in up to 15% of patients (26). An attempt to bypass the origin of the anterior spinal arteries would imply a catheter placement distal to the posteroinferior cerebellar artery, and therefore no coverage of this territory by treatment. On the other hand, opting for a more proximal catheter placement (near C7) decreases the risk of streaming by allowing better blood flow at the tip of the catheter and enabling the tip of the catheter to be farther from the vertebral feeders to the anterior spinal artery. The risk of streaming is also decreased by the fact that the drug is delivered in a more proximal segment of the vessel, most likely with a larger diameter.

In light of this anatomic information, we may draw the following conclusions concerning the clinical and radiologic findings in our series of patients: 1) The pathologic process seems to involve mainly the anterior spinal vascular circulation. 2) The axial extent of the pathophysiologic process does not involve the whole anterior spinal circulation distribution but seems limited to the terminal branches of this circulation in the central spinal cord. 3) The pathophysiology is limited longitudinally to three or four levels, and is frequently centered on the C4–C5 spinal level (T1 hypointense signal and T1 contrast enhancement). 4) The T2 hyperintense signal is more extensive than the T1 hypointense signal and the contrast enhancement, which supports the contention that a zone of reactive edema surrounds the primary injury. Although the zone of hyperintense signal is extensive in most cases, the clinical symptoms suggest only limited involvement, with one or two spinal levels incrim-

inated, similar in many ways to a traumatic central cord syndrome.

As a result of this syndrome, we have implemented the following changes to our protocol: 1) the catheter position is kept low, near C6–C7; 2) the carboplatin is diluted in 200 mL of normal saline, instead of 100 mL; 3) the rate of infusion has been increased from 10 to 20 mL/min; and 4) the first bolus of STS is administered 4 hours after disruption.

Conclusion

Anatomic variants in the vertebral circulation may be responsible for cervical spinal cord complications associated with IA chemotherapy with BBB disruption in a limited subset of patients. The phenomenon of streaming is likely to be involved in the pathogenesis and is probably partially responsible. In addition, although etoposide has been shown to open the BBB when infused intra-arterially, four patients in this series received IV etoposide phosphate. The combination of carboplatin and etoposide is synergistic. It is yet unknown if IV etoposide phosphate has any effect on the BBB. If the barrier remains open for a prolonged time, STS could also play a role in the pathogenesis.

The exact circumstances of this atypical central cord syndrome are most likely multifactorial. We can therefore only elaborate a hypothesis implicating the drug combination and infusion parameters that incited an inflammatory/toxic central cervical cord reaction. Since instituting changes to the protocol, no further cases have been identified.

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