Subarachnoid hemorrhage following chymopapain chemonucleolysis

Case report

JOSEPH F. CUSICK, M.D., KHANG-CHENG HO, PH.D., M.D., AND JAY F. SCHAMBERG, M.D.

Departments of Neurosurgery and Pathology, Medical College of Wisconsin, Milwaukee, and Department of Pathology, West Allis Memorial Hospital, West Allis, Wisconsin

Subarachnoid hemorrhage is a frequent finding in patients who have incurred neurological complications following chymopapain chemonucleolysis, but the basis for this occurrence remains controversial. The authors report the clinical and postmortem findings in a 42-year-old man who died 5 days after chemonucleolysis at the L4-5 and L5-S1 disc spaces. The predominant histological abnormality was a severe inflammatory arteritis of a medium-sized artery at the upper cervical level with disruption of the vessel wall. The potential causative role of chymopapain in this situation and the correlation of a vascular basis for many of the complications found after inadvertent intrathecal chymopapain injection are discussed.

KEY WORDS • chymopapain • subarachnoid hemorrhage • chemonucleolysis

SINCE chymopapain was released for clinical use in 1982, a large number of intradiscal injections of this proteolytic enzyme have been made in the treatment of lumbar disc disease. The two main commercial suppliers of chymopapain estimated that through July, 1984, approximately 122,000 procedures, termed "chemonucleolysis," have been performed. A major factor in this widespread acceptance has been the purported safety of chemonucleolysis, and clinical trials completed before 1982 indicate that anaphylaxis was the most serious anticipated complication. Recent information, however, has implicated a greater than expected incidence of serious neurological complications. Although few case studies have detailed the possible relationship between chymopapain and central nervous system (CNS) injury, the major fund of information has been tabulated in surveillance reports by the commercial distributors of chymopapain and is limited by its anecdotal and nonreferential character. Preliminary animal investigations evaluating the toxicity of chymopapain predicted the potential for serious CNS injury associated with the intrathecal injection of chymopapain. Subarachnoid hemorrhage (SAH) was a common finding in these studies and was attributed to disruption of the vascular wall of capillaries and veins. Although the clinical risk of serious CNS injury after the inadvertent intrathecal injection of chymopapain in man has been generally recognized, the definition of the causal role of chymopapain requires clarification of two major factors. First, the CNS toxicity of coexisting intrathecal injections of positive contrast agents used during the discography portion of the procedure has frequently made the allotment of responsibility for the CNS injury controversial. Second, surveillance reports imply that the SAH noted in certain individuals who manifested CNS abnormalities following chemonucleolysis may be the result of rupture of a coexisting intracranial aneurysm or arteriovenous malformation. The details of these reported coexisting vascular lesions which have a close temporal association with the chemonucleolysis, however, are not available for review.

The following case report details the neuropathological effects of intrathecal injections of chymopapain un-associated with any coexisting discography or with the presence of a preexisting vascular anomaly. This report offers insight into the vulnerability of the CNS and supportive structures.

Case Report

This 42-year-old man was admitted to the hospital for treatment of low-back pain and right lower-extrem-
ity pain. Five years previously, he had undergone a unilateral laminotomy and disc excision at the L4–5 level with complete and sustained recovery until the original symptomatology recurred 3 months prior to hospitalization. Two days before admission, an outpatient metrizamide discogram at the L5–S1 level demonstrated evidence of probable disc degeneration; the procedure was tolerated without incident. The patient had a long history of essential hypertension which was treated daily with hydrochlorothiazide, 50 mg, and Inderal (propranolol), 40 mg, and had suffered a single episode of ureterolithiasis 10 years before admission. No other chronic medical problems were noted. Family history is significant in that the patient's father and two brothers had reportedly died of complications due to hypertension.

Examination. On admission, examination revealed the following pertinent findings: blood pressure 132/90 mm Hg, straight-leg raising limited on the right, and mild decrease of the right ankle jerk. Corresponding laboratory studies were normal except for a nonfasting blood glucose level of 205 mg/dl. Benadryl (diphenhydramine), 50 mg, and cimetidine, 300 mg, were given every 6 hours, and the following day chemonucleolysis was performed at the L4–5 and L5–S1 levels.

Course. The procedure was carried out with the patient under general endotracheal anesthesia and in the right lateral decubitus position. The operating surgeon stated that the needles were inserted 9 cm lateral to the midline and were positioned in the central portion of the respective disc spaces. Needle position was verified by biplane fluoroscopy. After a test dose was delivered, 1.5 cc of chymopapain (3000 units of Chymodyramine), 50 mg, and cimetidine, 300 mg, were given every 6 hours, and the following day chemonucleolysis was performed at the L4–5 and L5–S1 levels.

The severe headache persisted and a noncontrast-enhanced computerized tomography (CT) scan obtained approximately 24 hours after chemonucleolysis was normal. During the next 24 hours, the patient noted progressive relief of headache and lumbar pain. This improvement, however, ceased approximately 72 hours after the chymopapain injection when he developed a sudden recurrence of severe headache associated with diaphoresis and progressive obtundency. A repeat CT scan showed blood in the third and fourth ventricles with extension into the basilar cisterns. The patient was intubated but rapidly deteriorated neurologically over the subsequent few hours to a status demonstrating no clinical evidence of cerebral or brain-stem function. Over the next 2 days, clinical examination remained unchanged and radioisotope blood flow studies 24 hours apart showed no evidence of intracranial blood flow. Respirator support was discontinued 5 days after the chemonucleolysis.

Autopsy Findings. The general autopsy findings were unremarkable except for the liver which demonstrated centrilobular fatty changes and the kidneys which showed nonspecific lymphocytic infiltrate without any evidence of vasculitis. Gross examination of the brain confirmed the CT finding of SAH which was most extensive in the posterior fossa. Brain edema and moderate bilateral uncal herniation with midbrain compression were present. The cerebral arteries showed mild to moderate arteriosclerosis, and careful search failed to demonstrate any aneurysm. Coronal sections of the brain revealed softening of choroid plexus in the third and fourth ventricles, and punctate hemorrhages in the midbrain. Gross examination of the spinal cord showed SAH which was most prominent at the upper cervical level. Coronal sections of the spinal cord showed focal grayish discoloration in the posterior and lateral columns of the upper thoracic and cervical segments of the spinal cord as well as a dark reddish discoloration of the anterior horns in the cervical and lumbar spinal segments.

Microscopic examination revealed the following principal neuropathological findings: massive recent SAH around the brain stem and within the fourth ventricle; hemorrhage and rupture of the choroid plexus of the fourth ventricle; axonal swelling in the lateral columns of the upper thoracic cord as well as the lateral and posterior columns of the middle cervical cord segments; loss of myelin in the posterior columns of the upper cervical spinal segments; and small, recent focal hemorrhages in the anterior horns of the upper cervical spinal segments. Slight lymphocytic and leukocytic infiltration of the adventitia was present in the intrathecal blood vessels in the lumbosacral region. Similar but equivocal changes in the blood vessels were noted in the thoracic and lower cervical regions. In the upper cervical level near the cervicomedullary junction, severe acute inflammation of the adventitia with necrosis of the median wall and endothelium of the artery was observed. Serial sections of this artery showed disruption of the wall with massive hemorrhages in the nearby area (Fig. 1). Focal thrombosis of the artery was found adjacent to the area of necrosis.

Discussion

The prominent feature of the autopsy was intense arteritis associated with lysis of the vessel wall of a medium-sized artery located on the ventrolateral aspect of the upper cervical spinal cord. Although the arteritis resulted in rupture of the vessel with resultant SAH, the temporal sequence of events leading to the patient's death is similar to other clinical patterns of suspected reactions to intrathecal chymopapain. The onset of nausea, headache, neck stiffness, and hypertension 6
SAH following chymopapain chemonucleolysis

Fig. 1. Left: Photomicrograph of a cross section of the artery with arteritis and eventual rupture. R = site of rupture; A = inflammation of adventitia; N = necrosis of the media. H & E, × 22. Right: Higher-power view of the area within the square shown left, showing necrosis and inflammation of the wall of the artery (N) and inflammation of the adventitia (A). H & E, × 110.

hours after the chymopapain injection were indicative of the CNS and meningeal response to the chymopapain as it diffused through the cerebrospinal fluid spaces. At 24 to 36 hours after the onset of symptoms, a significant resolution of the patient's complaints suggested that the CNS problems were abating. This process, however, was ended abruptly 72 hours after the injection of chymopapain by a catastrophic SAH.

Other authors have noted the onset of sudden or vacillating neurological abnormalities many hours or days after a suspected intrathecal chymopapain injection.1,16 Occlusion or vessel rupture, as noted in the present case, could result in sudden and permanent neurological damage, whereas a less intense toxic reaction could cause variable degrees of long-term vessel wall alterations with resultant intermittent or partial ischemic problems. The consensus of opinion in laboratory studies is that SAH is the predominant complication of intrathecal injection of chymopapain. Many of these early investigations, which essentially ceased after 1967 and mainly used dog and rabbit preparations, indicated that the basis for the hemorrhage was injury to capillaries and veins of the pia arachnoid.2,7-10 Recent studies have indicated that chymopapain can cause lysis of the media and adventitia of small and medium-sized arteries.14,18 This process could potentially lead to rupture of an artery or reactive thickening of arterial walls resulting in compromise of the lumen. This latter pattern of vascular change, causing varying levels of ischemia to regions of the CNS, could explain the suspected occurrence of delayed or recurrent neurological deficits after the intrathecal injection of chymopapain.

The present patient did have a history of essential hypertension and mild hyperglycemia on admission screening, but autopsy did not demonstrate any serious corresponding vascular or cardiac abnormalities. The autopsy study also showed no evidence of vasculitis in any organ system other than the CNS, nor did it reveal the presence of an aneurysm or arteriovenous malformation. Certain reports have proposed that these intracranial vascular lesions may frequently be the causative factor of SAH noted following chemonucleolysis.1 This contention, however, fails to recognize the almost consistent pattern of SAH documented by lumbar puncture studies in patients developing neurological complications after chymopapain injection and the relatively few cases of proposed and undocumented coexistence of intracranial aneurysms or arteriovenous malformations. The pathological findings in this case not only demonstrated the toxic vascular effects of chymopapain but also illustrated intramedullary spinal cord alterations of axonal swelling and early focal demyelination away from the puncture site.

Until July, 1984, discography was recommended as a component of the chemonucleolysis procedure. One commercial supplier of chymopapain noted that 28 of 30 patients incurring serious neurological complications following chemonucleolysis had undergone discography as a component of the procedure.3 Many positive contrast agents used in the discography, either alone or in combination with chymopapain, were the principal neurotoxic agents and, therefore, should not be continued as a recommended portion of the procedure.3 Many positive contrast agents used in the discography were known to have certain neurotoxic qualities, but, in the present case study, a discogram with a water-soluble contrast agent which is widely accepted for intrathecal use was performed more than 2 days before the chemonucleolysis. The bulletin recommending avoidance of discography noted no incidence of neurological complications when the discogram was performed days before the chemonucleolysis, which agrees with the expected almost total clearance in the present case of the water-
soluble contrast material within a 24-hour period. Regardless of the potential contributing neurotoxicity of the positive contrast agent, discography remains the definitive method for visualization of positive contrast extravasation into the subarachnoid space verifying the probable subsequent intrathecal injection of chymopapain. The careful biplane fluoroscopic confirmation of needle positioning within the central portion of the disc using the lateral technique for needle placement has been offered as a method to avoid the potential for violation of the intrathecal space. Wiltse, et al., emphasized, however, that irrespective of technique there is a leakage of chymopapain into the extradural space at the time of injection in about one in four humans. McCulloch and Waddell reported 20 cases of dural puncture occurring in 1500 discograms which indicates that violation of the dura mater even with the lateral approach is not a rare event. The outflow of cerebrospinal fluid following needle insertion would certainly be verification of dural puncture, but the absence of this occurrence unfortunately does not exclude the potential for intrathecal injection of chymopapain. None of these precautions, therefore, preclude the possible intrathecal injection of chymopapain.

Although product surveillance reports indicate that the number of serious neurological sequelae following chemonucleolysis is small, the present case report emphasizes the risk for catastrophic neurological injury, including death, following the inadvertent intrathecal injection of chymopapain. This problem of CNS toxicity to chymopapain is compounded by the present inability to formulate a definitive treatment plan for patients incurring these complications. Additionally, the observation in the present case of severe inflammatory arteritis distant from the site of intrathecal injection as one of the major sequelae to relatively small amounts of chymopapain offers insight into the pathogenesis of certain neurological abnormalities that have been noted following this procedure.

References


Manuscript received September 17, 1986.
Address for Dr. Schamberg: Department of Pathology, West Allis Memorial Hospital, West Allis, Wisconsin.
Address reprint requests to: Joseph F. Cusick, M.D., Department of Neurosurgery, 8700 West Wisconsin Avenue, Milwaukee, Wisconsin 53226.