Symptomatic Acute-on-Chronic Subdural Hematoma

A Clinicopathological Study

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Abstract: The pathophysiology of acute-on-chronic subdural hematoma (ACSDH) is complex and incompletely understood. Evidence to date indicates that the overall process is initiated by rotational force with movement of the brain inside the skull, which exerts tensile strain and rupture of bridging veins, leading in turn to acute hemorrhage in the subdural potential space. This is followed by the proliferation of mesenchymal elements with angiogenesis and inflammation, which in turn becomes a substrate for repeated hemorrhage and expansion of the lesion. Given the prevalence of traumatic subdural processes in the forensic setting and the importance of proper assessment of timing, etiology, risk factors, and clinicopathological correlation, we studied 47 patients presenting to the University of Maryland Shock Trauma Center, all of whom underwent craniotomy with resection of the outer membrane due to symptomatic ACSDH. The surgically resected tissue was examined for histopathologic features in all cases. Our findings highlight that ACSDH is a condition precipitated by trauma that affects middle-aged and older adults, is relatively indolent, is unilateral or asymmetric, and has a low in-hospital mortality rate. Pathological analysis demonstrates a substantial outer membrane in all cases with varying degrees of inflammation and organization that cannot be precisely dated as a function of clinical presentation. The extrapolation of adult ACSDH to mixed acute and chronic subdural hemorrhage in the pediatric setting is problematic due to substantial differences in clinical presentation, severity of underlying brain injury, gross and microscopic findings, and outcome.

Key Words: acute-on-chronic subdural hematoma, neomembrane, Glasgow Coma Scale, burr hole, craniotomy, subdural drain

(*Am J Forensic Med Pathol* 2017;38: 126–130)

The pathogenesis of chronic subdural hematomas has been controversial since their first description in 1835 as "serous cysts of the arachnoid."[1] The early recognition by Hewett that subdural collections and associated pathological lesions were secondary to hemorrhage[2] was countered by Heschl, who suggested a primary inflammatory process of the dura. Virchow (1857), Cruveilhier (1865), and Kremiansky (1868) embraced this concept, although it was Virchow who lent the weight of his authority to the term *pachymeningitis interna hemorrhagica*, or internal pachymeningitis, thus embedding a primary inflammatory etiology to subdural collections for decades thereafter, effectively obscuring the role of trauma and primary hemorrhage (review in Friede[3]).

Wigglesworth was among the first to call into question Virchow's internal pachymeningitis concept,[2] although it was still decades before a traumatic etiology would predominate over the primary inflammatory hypothesis. A number of investigators supported the role of pachymeningitis or inflammatory thickening of the dura.[3] Trotter[4] represented one of the exceptions, suggesting that subdural hemorrhages were "quite invariably" due to tearing of the large veins. Still, others accepted both hypotheses as equally valid.[5]

In rare instances, subdural collections may appear "spontaneously." Such collections may alternatively be associated with leukemia,[6] venous sinus thrombosis,[7] vascular malformations,[8] ruptured aneurysms,[9] or meningiomas.[10] However, the current view held by most clinicians and researchers maintains that subdural hematomas typically result from head trauma of varying degrees of severity. With the presence of blood in the subdural compartment and the disruption of the dural border cells at the interface between the dura and the arachnoid, a putative cascade is initiated with the proliferation of fibroblastlike dural border cells,[11] new capillary in-growth or angiogenesis,[12–15] and a host inflammatory reaction.[16,17] This results in the formation of the outer neomembrane (a membrane between the arachnoid and the subdural blood). The vascularity of the neomembrane, along with limited stromal support, renders the neomembrane vulnerable to repeated hemorrhages and expansion of the hematoma between the outer membrane and the dura. An inner neomembrane also forms (lining the dura on its subdural aspect), although the inner neomembrane is relatively avascular, and may be less relevant with respect to the expansion of subdural collections.[11,15,18] For the sake of clarity, this study refers to the outer neomembrane between the arachnoid and the subdural collection.

Although the previously mentioned construct may be useful as an operational paradigm, it is important to emphasize that the pathogenesis of chronic subdural hematomas, and acute-on-chronic subdural hematomas (ACSDHs), is incompletely understood and in need of further research. In the forensic pathology setting, an oversimplified view of the paradigm risks assigning an erroneous time course based on gross or histopathological findings.[19–21] Moreover, similarly appearing lesions may have quite different causes, presentations, and clinical courses in adult versus pediatric patients.

In adults, an ACSDH often presents with mild changes in mental status and/or focal neurological deficits and has an indolent clinical course, whereas similar pathological findings in infants and toddlers are often hallmarks of acute, nonaccidental, and sometimes lethal head trauma.[22] We therefore examined consecutive cases of adults with symptomatic ACSDH presenting to a level 1 trauma center, all of whom underwent craniotomy with excision of the outer neomembrane, to define the clinical and pathological substrates for acute-on-chronic subdural collections.

METHODS

Approval from the University of Maryland, Baltimore, Institutional Review Board was obtained. Medical records for all patients older than 18 years who presented with an ACSDH and underwent craniotomy and membranectomy between January 2005 and May 2016 were reviewed. Data collected included demographics, history of anticoagulation or antiplatelet medication use, history of bleeding diathesis (eg, alcoholic liver disease,

Manuscript received November 28, 2016; accepted January 22, 2017.
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ISSN: 0195-7910/17/3802–0126
DOI: 10.1097/PAF.0000000000000300

systemic cancer, thrombocytopenia), injury characteristics, presenting symptoms, radiographic findings, surgical treatments, and clinical outcomes.

Pathological specimens of resected outer neomembranes from 46 patients were examined. All specimens were fixed in formalin, followed by sectioning, processing for histology, and paraffin embedding of the neomembrane on edge. Postfixed tissue was dehydrated in graded ethanol and xylene solutions, embedded in paraffin, sectioned at a thickness of 5 μm, and stained with hematoxylin and eosin. Neomembrane histopathological characteristics were recorded, and the mean on-edge thickness of each neomembrane was measured using Aperio ImageScope (Leica Biosystems Inc, Buffalo Grove, Ill). In each case, only the proliferation of fibrovascular elements was measured; the varying degrees of attached blood clot were not included in the measurement.

Histopathological parameters were compared with 3 clinical variables: Glasgow Coma Scale (GCS) at presentation, symptom duration before presentation, and the interval between injury (when known) and membranectomy. The Mann-Whitney *U* test was used to compare the previously mentioned nonnormally distributed clinical quantities as a function of binary pathological parameters (proliferating/neovascularized vs hyalinized neomembrane, mild vs marked chronic inflammation, mild vs marked eosinophilic infiltrate, presence vs absence of extramedullary hematopoiesis, and >1 vs <1 mm of neomembrane thickness). χ^2 Analysis was used to compare pathological parameters with the presence or absence of a focal neurological deficit at presentation.

RESULTS

Patient Population

The demographics and clinical features of the 46 patients included in this study are summarized in Table 1. The mean age at presentation was 70 years (range, 40–92 years). Thirty-nine patients were men, and 7 were women. Thirty-four patients (73.9%) were determined to have risk factors for coagulopathy. Of these, 28 patients (60.9%) were using anticoagulation or antiplatelet agents—including warfarin, apixaban, aspirin, clopidogrel, and aspirin/extended-release dipyridamole—at the time of presentation. In addition, 16 patients (34.8%) were potentially coagulopathic secondary to chronic liver disease, systemic carcinoma, leukemia, and/or thrombocytopenia. Eleven patients (23.9%) both were taking an anticoagulation or antiplatelet agent and were at risk for intrinsic coagulopathy.

Injury Characteristics

A history of trauma was recorded in 37 (80.4%) of 46 cases. Of the 10 cases in which a trauma history was not apparent, trauma was specifically denied by 4 patients, 2 of whom had possible dementia. Thus, the specific absence of a trauma history was rare. Falls from standing were the most common mechanism, occurring in 29 cases (63.0%). Striking of the head by/against a blunt object occurred in 5 cases (10.9%). Two patients (4.3%) were assaulted, and 1 patient (2.2%) was involved in a motor vehicle collision.

Presentation, Treatment, and Clinical Course

The mean GCS score on arrival was 13.5 (range, 3–15). Five patients (10.9%) had a GCS of 3 to 8, whereas 2 patients (4.3%) had a GCS of 9 to 12, and 40 patients (87.0%) had a GCS of 13 to 15. In addition, 23 patients (50.0%) had a focal neurological deficit on arrival. Of the 22 subjects with a GCS less than 15, 1 patient was intubated but followed commands, 3 had baseline dementia, 1 was intoxicated, 1 was postictal, and 1 was leukemic and febrile. The remaining patients likely experienced mental status decline secondary to mass effect exerted by the subdural hematoma. Furthermore, of the 5 patients with a GCS of 8 or less, 2 patients were taking warfarin, 1 was septic, 1 had disseminated cancer, and 1 had chronic liver disease secondary to alcohol use. It therefore seems that, among those patients with significant alterations in consciousness, premorbid conditions and/or anticoagulation may have exacerbated the deterioration.

The mean duration of symptoms before presentation was 11.6 days (range, 1–90 days). The mean duration from initial injury to craniotomy was 42 days (range, 1–304 days). Thirty-one patients (67.4%) underwent treatment before craniotomy, consisting of bedside craniostomy and subdural drain placement in 21 patients (45.7%), burr hole washout in 7 patients (15.2%), and both procedures in 2 patients (4.3%). Nine patients (19.6%) experienced reaccumulation of the subdural hematoma postcraniotomy, requiring an additional surgical procedure.

TABLE 1. Demographic and Clinical Features of Patients With Resected Outer Neomembranes (N = 46)

Mean (range) age, y	70.6 (40–92)
Male, n (%)	39 (84.8)
Laterality, n (%)	
Unilateral left	23 (50.0)
Unilateral right	13 (28.2)
Bilateral	10 (21.8)
Bilateral, symmetric	0 (0)
Mechanism of injury, n (%)	
Fall from standing	29 (63.0)
Struck by/against	5 (10.9)
Assault	2 (4.3)
MVC	1 (2.2)
No trauma history	9 (19.6)
Oral anticoagulation and/or antiplatelet agents	28 (60.9)
Mean (range) GCS on arrival	13.5 (3–15)
Focal deficit	23 (50.0%)
Mean (range) duration of symptoms before presentation, d	11.9 (<1–90)
Mean (range) duration from initial injury to craniotomy, d	42.0 (<1–304)
Treatment before craniotomy, n (%)	
Craniostomy/subdural drain	21 (45.6)
Burr hole washout	7 (15.2)
Both	2 (4.3)
Acute subdural caused by drain	1 (2.2%)
Reaccumulation of subdural hematoma postcraniotomy*	9 (19.6%)
Mortality during acute hospitalization	0 (0.0%)

*Defined as a reaccumulation that required repeat evacuation in the operating room.

MVC indicates motor vehicle collision.

Pathological Findings

Previous studies have suggested 4 subcategories for neomembranes: type I, noninflammatory membrane; type II, inflammatory membrane; type III, hemorrhagic inflammatory membrane; and type IV, scar-inflammatory membrane.[18] Histopathological examination of the specimens in this study revealed that all cases included hemorrhagic and inflammatory components

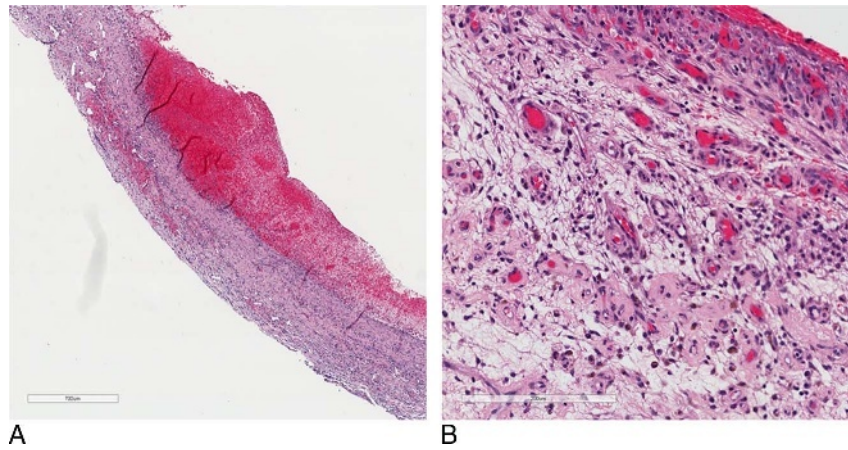

FIGURE 1. Low-magnification photomicrograph of a neomembrane (A) after membranectomy. The specimen consists of neomembrane and blood clot, without dura mater. Scale bar, 700 μm. Higher magnification (B) shows extensive neovascularization within the neomembrane. Figure 1 can be viewed online in color at www.amjforensicmedicine.com.

(Figs. 1, 2). Although each component varied in extent, the overlap among the previously reported subcategories precluded an objective and discrete classification. We therefore examined the case material with respect to basic pathological alterations, including (1) predominantly active mesenchymal proliferation (n = 30) versus predominantly, densely hyalinized, collagenous neomembrane (n = 16); (2) extent of chronic inflammation, semiquantified as none to sparse (n = 32) versus marked (n = 14); (3) extent of eosinophils, semiquantified as absent or sparse (n = 34) versus abundant (n = 12); (4) presence of extramedullary hematopoiesis (n = 9); and (5) presence of hemosiderin (n = 46).

The mean on-edge thickness of the neomembrane was 918 μm (range, 276–2050 μm). All neomembranes were easily identifiable and distinguishable from purely acute subdural

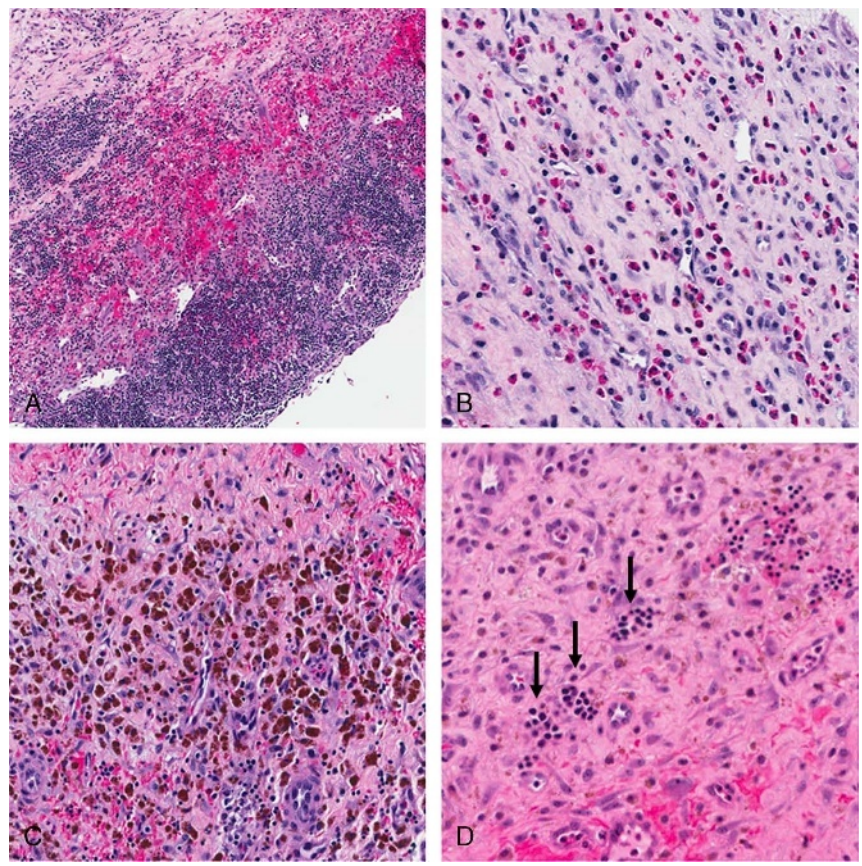

FIGURE 2. Histopathological examination showed varying amounts of lymphoid aggregates (A), eosinophilic infiltrates (B), hemosiderin (C), and extramedullary hematopoiesis (D). Figure 2 can be viewed online in color at www.amjforensicmedicine.com.

hemorrhage by gross examination. Acute hemorrhage was present external to the neomembrane (between the neomembrane and the dura) in all cases, as evidenced by adherent arachnoidal tissue opposite to the attached blood clot. Although the state of organization of the neomembrane (subacute proliferative vs hyalinized), the type of inflammation (eosinophils, lymphoid aggregates), neomembrane thickness, and other features such as extramedullary hematopoiesis may broadly suggest chronicity, we found no relationship between any of the pathological findings and GCS at presentation, duration of symptoms before presentation, time interval between injury and surgery, or presence of focal neurological signs at presentation. There was a trend toward an association between the presence of abundant eosinophils and a prolonged interval between injury and surgery ($P = 0.06$), suggesting overall that some length of time may be required for a robust eosinophilic neomembrane infiltrate, although short intervals were noted in rare cases that had abundant eosinophils within the neomembrane.

DISCUSSION

A number of features of symptomatic ACSDH are apparent from this study. First, ACSDH is a disease of middle-aged to older adults, often with preexisting risk factors for hemorrhage, and is typically related to a traumatic etiology. Trauma was specifically denied in only a small minority of cases, and of those, the patient's condition casted some doubt on the ability to recall a traumatic event. Furthermore, this series included only a single patient without any history of trauma and without a preexisting bleeding diathesis. Therefore, the prototypical patient seems to be an older adult with a bleeding diathesis (either due to medication or intrinsic causes) and a history of falling from a standing position.

The duration of symptoms before the initial presentation ranged from the day of the injury to several months. Approximately half of the patients in this series presented within a few days of the injury. However, the presence of chronic blood suggests that the patients likely experienced a previous injury that went unnoticed, whereas the more recent, recorded injury may have been responsible for the acute component of the collection. Importantly, the rarity of abrupt decompensation differs from other acute hemorrhagic events such as ruptured aneurysms or arteriovenous malformations, hypertensive bleeds, or acute subdural hematomas. In the case of ACSDH, rebleeding typically involves the capillaries embedded in a relatively loose stromal tissue and often occurs in patients with preexisting cerebral atrophy, thus accounting for the ability to compensate for the gradual increase in mass effect.[23]

Acute-on-chronic subdural hematoma is associated with a distinct clinical course. Importantly, the "lucid interval" is not a feature of ACSDH. Although sometimes invoked in infants and toddlers with mixed acute and chronic subdural hemorrhage, in adults, the lucid interval is a characteristic of severe acute trauma and is typically associated with epidural hematomas, which require close monitoring of neurologic function and are often treated by emergent surgical evacuation. In addition, it is noteworthy that, in this series, there were no in-hospital deaths, despite the mean age of 70 years. This is comparable with a previous study of 303 consecutive patients, in which 1.65% of in-hospital mortality was noted, most of whom died of postoperative acute bleeding.[24] In the more elderly population (mean age > 80 years), mortality as high as 16.7% has been noted.[25] In either case, this is in contrast to head trauma accompanied by the lucid interval phenomenon, which is more commonly lethal regardless of age or comorbid medical conditions.[26,27]

We noted a mean GCS score of 13.5 in this series, which may be an underestimate given that some patients with low GCS scores often had factors other than mass effect, which contributed to an alteration in consciousness. This is consistent with the finding that neomembrane rebleeding is a slowly progressive process, for which age-related brain atrophy and spatial compensation may delay clinical presentation, thus contributing to an indolent clinical progression. As a result, ACSDH is often diagnosed only in response to mild alterations in consciousness and/or focal neurological deficits. A minority of patients in this series, however, decompensated relatively rapidly. Significantly, among those with the lowest GCS scores at presentation, all had risk factors for hemorrhage. Overall, these data suggest that ACSDH typically becomes symptomatic for a period of days or longer, and moderate to severe alterations in consciousness are the exception rather than the rule.

In addition, symptomatic ACSDH tends to be an asymmetric process, despite that bilateral blood products are often identified radiographically. Of the 47 patients, 37 (79%) had unilateral findings, with acute hemorrhage limited to the side of the neomembrane. Of the 21% that had bilateral blood products, all were asymmetric and accompanied by midline shift. Only 1 patient in this series required bilateral treatment. Furthermore, all neomembranes that were surgically excised demonstrated acute and organizing hemorrhage, which was contained by the neomembrane. Clinical decompensation in the setting of ACSDH therefore seems to result from lateralized repeated hemorrhages between the neomembrane and the dura and subsequent midline shift. This contrasts with mixed density hemorrhages in the infant and toddler population, in which hemorrhage apart from the neomembrane is often encountered.[22]

Pathological findings in this series were variable. The defining features of the resected specimens were the presence of an outer neomembrane and acute and organizing hemorrhage. Among the finer histopathological details that were assessed—degree of organization, extent and type of associated inflammation, neomembrane thickness, presence of a hyalinized component, and presence or absence of extramedullary hematopoiesis, we could discern no relationship between these findings and GCS at presentation, duration of symptoms, interval between injury and surgery, or presence or absence of focal neurological deficits. This suggests that pathological analysis by itself offers little, if any, independent information about the chronicity of the clinical disease process apart from the fact that it represents an ongoing disease characterized by repeated hemorrhages. Nevertheless, all patients in this series had an obvious, macroscopically identifiable neomembrane. Symptomatic ACSDH therefore seems to occur most likely in the presence of a substantial neomembrane, perhaps with extensive neovascularization vulnerable to repeated hemorrhage.

CONCLUSIONS

In summary, we present a series of patients with symptomatic ACSDH who underwent craniotomy and membranectomy. Our results confirm that ACSDH is typically caused by trauma, often a fall from a standing position, and tends to occur in older adults with bleeding diatheses. Although symptomatic ACSDH is invariably a lateralized processed with midline shift, intact consciousness at presentation is the rule rather than the exception. Histopathological analysis indicates that a substantial neomembrane is present in all cases and that the accumulating blood causes mass effect by accumulating between the neomembrane and the dura. The histopathological features of the neomembrane, including the degree of organization and extent/type of inflammation, were not related to any of the clinical parameters. Our findings emphasize important differences between symptomatic ACSDH in adults and mixed acute/chronic subdural hemorrhages in children, suggesting that ACSDH terminology be reserved for the adult patient only, who demonstrates the characteristic clinicopathological presentation described in this study.

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