Letters to the Editor are welcomed. They may report new clinical or laboratory observations and new developments in medical care or may contain comments on recent contents of the Journal. They will be published, if found suitable, as space permits. Like other material submitted for publication, letters must be typewritten, double-spaced, and must not exceed two typewritten pages in length. No more than five references and one figure or table may be used. See “Information for Authors” for format of references, tables, and figures. Editing, possible abridgment, and acceptance remain the prerogative of the Editors.

Implications of Occult Cranial Injuries for Perpetrator Identification in Cases of Alleged Abusive Head Trauma

To the Editor: After reading the recent article in the Southern Medical Journal, “Occult Cranial Injuries Found with Neuroimaging in Clinically Asymptomatic Young Children Due to Abusive Compared to Accidental Head Trauma” by Fickenscher et al. and the accompanying editorial comments by Dr. Block and Drs. Waseem and Zipin, I agree that this article is significant. However, for me one major implication of this work was not addressed by the article or the accompanying commentaries – its impact on our understanding of the determination of the timing of injury. Given that these cases often lead to family court hearings and criminal prosecutions, it is vital to not only identify abuse, but to accurately identify the perpetrator of abuse.

While the current policy statement from the American Academy of Pediatrics (AAP) on Diagnostic Imaging in child abuse now recognizes that “abused infants may not demonstrate neurologic signs and symptoms despite significant central nervous system injury,” previously published and oft-cited articles in the field have generated the common belief that the symptoms of abusive head injury are immediate and thus, the caregiver with the infant after the infant was last known to be acting normally was the perpetrator of the abuse.

Common examples:

“On the basis of these data, it can be discerned that there is no evidence of a prolonged interval of lucidity between the injury and the onset of symptoms in children with acute subdural hematoma and brain swelling – the injuries also seen in severe cases of the shaking-impact syndrome (ie, those associated with coma or death). Thus, an alert, well-appearing child has not already sustained a devastating acute injury that will become clinically obvious hours to days later.”

“These clinical signs of shaken baby syndrome are immediate and identifiable as problematic, even to parents who are not medically knowledgeable.”

“Studies in children with nonaccidental head injuries also indicate that they show an immediate decrease in their level of consciousness at injury.”

“Individuals sustaining diffuse brain injury of moderate to severe degree become symptomatic immediately.”

While it may be argued that I have taken quotes somewhat out of context, the line of reasoning expressed by these quotations has been regularly asserted in courts of law – ie, the “last man standing” is the perpetrator.

However, Fickenscher now reports that over a 2-year period, they had 58 patients <20 months of age who had neuroimaging in the setting of a question of mechanical trauma (both accidental and abusive), where 23/58 (40%) were neurologically asymptomatic at presentation, and 19/23 (80%) of these asymptomatic patients had abnormal neuroimaging studies. That is 30% of all their patients! Then when one looks at their Table 5, one realizes that these abnormal findings were not confined to scalp swelling or skull fractures or even to extra-axial fluid collections (epidural hemorrhage [EDH], subarachnoid hemorrhage [SAH], or subdural hemorrhage [SDH]), but included cases with real brain injury. There were 5 cases with brain atrophy, 3 with brain contusion, and 1 with brain edema. While it has been recognized that extra-axial fluid collections can present after a lucid interval, Fickenscher has shown us that even infants with injury to the brain tissue itself can be neurologically asymptomatic on first medical evaluation, and that such presentations occur with surprisingly high frequency.

To me, the real take-away message from this article is:

1. The “last man standing” criteria for identifying a perpetrator of infant abuse has been discredited. It should no longer be asserted; and cases where guilt was assigned on the basis of “last man standing” should be open for review and possible appeal based on new evidence.

2. Since it is now established that there can be significant intracranial injury and no immediate symptoms, the assertion of “delay in seeking medical attention” as an indicator of abusive injury or negligence must now be suspect. If an infant can be neurologically asymptomatic on evaluation by medical personnel, even when brain contusion/atrophy/edema is present, then one must be very cautious in alleging that a caregiver was negligent in not recognizing intracranial injury and seeking medical attention earlier.

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Southern Medical Journal • Volume 103, Number 6, June 2010
Ankle-Brachial Index Measurement in the Primary Care Setting

To the Editor: In their articles, Pearson et al,1 Salameh and Federman2 and Aslam et al3 (November 2009 issue) emphasize the important role of the ankle-brachial index (ABI) as a consistent and significant predictor of cardiovascular events. However, ABI is rarely performed in primary care office settings due to time and training requirements and the interobserver variability. Pearson et al1 suggests that with proper scheduling and training, the ABI can be completed in a timely manner. We alternatively propose that ABI measurement by the oscillometric method (OsM) is quick and easy and does not require specialized training.5,6 We have compared the ability of nonspecialist physicians to perform these methods using arteriography as the gold standard.7 To this end, 158 legs of 85 patients with intermittent claudication were analyzed by DoM and OsM with an Omron M4-I automatic oscillometer. An ABI <0.9 was considered a positive test when at least 50% of the artery was occluded. Pressure was not detected in 35% of the patient’s legs by DoM vs 44% by OsM. Diagnostic accuracies of the ABI <0.9 by DoM or OsM are (%) sensitivity: 97/95, specificity: 89/56, positive predictive value: 98/91, and negative predictive value: 86/68. Thus, the ABI was more accurately determined by nonspecialist physicians utilizing the easy and quick oscillometer method than with the classic DoM.

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Fig. A, Glioblastoma with sarcomatoid features. B, Glioblastoma with primitive neuroectodermal tumor features.
Lymphocytic Colitis in Satoyoshi Syndrome

To the Editor: Satoyoshi syndrome characterized by progressive, intermittent, and painful muscle spasms, alopecia, and severe watery diarrhea is a rare disease of unknown pathogenesis. It may include a malabsorption state that can cause abnormal childhood development, such as epiphysial destruction and growth retardation, and must be treated effectively.

A 25-year-old Japanese man presented with painful muscle cramps, alopecia, and watery diarrhea. He had noted recurrent painful muscle cramps in his legs after exercise since he was 13 years old, with gradual worsening. Soon after onset he experienced diarrhea and noted mild alopecia. At 24 years, severe watery diarrhea had caused malnutrition and weight loss. Neurological examination showed no abnormality except for intermittent muscle cramps in all limb and truncal muscles. These cramps were easily provoked by muscle contraction or exercise and continued for a few minutes. Extension of the affected muscle provided the only relief. Percussion- or gripping-induced myotonia was not seen. A forearm ischemia test did not provoke continuous contractions. Skeletal deformities and dysplasia were absent.

Blood test results, including electrolytes, glucose, and immunoglobulins, were normal. All hormones assayed in the blood were in the normal range. Autoantibodies, including antinuclear, antDNA, and antiglutamic acid decarboxylase (GAD) antibodies were negative, but anti-acetylcholine receptor (AChR) antibodies were elevated at 10.2 nmol/L without any symptoms of myasthenia gravis. Electromyography and nerve conduction studies including repetitive stimulation showed no abnormality. Scintigraphy using 99mTc-high solid anaerobic digestion pool showed accumulation of isotopes in the colon and small intestine, suggesting leakage of albumin. Stool studies indicated the diarrhea to be secretory, and no eosinocyte increase or the presence of parasites or their eggs were found in the stool.

Although inspection by colonoscopy documented no abnormality, a histological study of a biopsy specimen disclosed intraepithelial lymphocytes with more than 15 lymphocytes per 100 epithelial cells and lymphocytic infiltration in the submucosal layer without increased subepithelial collagen, leading to a diagnosis of lymphocytic colitis.

We diagnosed the patient with Satoyoshi syndrome, including lymphocytic colitis. The syndrome presents with chronic watery diarrhea, normal endoscopic findings and characteristic inflammatory histological changes, including those of lymphocytic colitis. Though the patient was taking dantrolene sodium hydrate to treat muscle cramps, there is no report indicating that this triggers lymphocytic colitis. In other cases lymphocytic infiltration was seen in pearly regions of anagen follicles in scalp biopsy specimens. Some reports have included complication with systemic lupus erythematosus or myasthenia gravis. An autoimmune mechanism possibly impaired function of natural killer cells or lymphokine-activated killer cells and is believed to mediate this disorder in each target organ. Steroid therapy recently has shown effectiveness.

We began a 3-day course of intravenous methylprednisolone (1 g/day), followed by oral prednisolone (30 mg/day), together with oral dantrolene sodium. Later, low-dose steroid (10 mg/day) successfully controlled all his symptoms to achieve complete remission for 3 years.

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Splatter-Free Compression Cryotherapy for Skin Lesions

To the Editor: Cryotherapy using liquid nitrogen spray is a mainstay of office skin care. It is used by both dermatologists and primary care physicians to eradicate select skin lesions with minimal to no scarring. The spray is trigger released from a pressurized canister. Since the spray is released from varying (unmeasured) distances from the target; and since a variety of (unmeasured) canister trigger-release pressures are used; and since a variety of (usually undocumented) nozzle tips are selected, there is no way to tally the total dose administered. There is no dosing measuring tool. There is only the operator’s experience to guide dosing. The best alternative for guidance is the counted number of seconds of spray administered after the white freeze ball or halo appears. Time to the moment of freeze appearance is expected to vary with skin condition.

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Letters to the Editor
thickness, with vascularity and with inherent qualities of the lesion type. Continued seconds of spraying after freeze ball appearance is presumed similar for all lesions of the same histology. Thus 10 seconds for warts, 5 seconds for skin tags, etc.¹

As liquid nitrogen is sprayed, the target lesion and encompassed adjacent tissues form a white halo or turn into a white ball called the freeze ball. The freeze ball is associated with a detectable therapeutic effect down 4 mm from the skin surface. For most benign skin lesions, it is deemed that effective destruction begins at −22 °C. Interestingly, although lesions of the epidermis are quite vulnerable to destruction at that temperature, the dermis is immune and remains sturdy intact. Thus, while liquid nitrogen spray destroys unwanted epidermal lesions, the underlying dermis remains safely preserved. Of further interest is the fact that cellular destruction takes place during the thawing phase, not the freezing phase. Therefore, prolonged freezing may indeed lower the attained temperature and even extend the depth of penetration, but it is often less effective than a short freeze/thaw followed by a second freeze/thaw several minutes later. A repeat procedure rather than simply a protracted initial freeze phase seems the more effective.¹²

Most liquid nitrogen is used for annoying skin tags, warts, actinic keratoses, some seborrheic keratoses, prurigo nodularis, etc. Patients are alerted that the treated area may blister and to let the blister break on its own (so underlying tissues are more mature when the blister does break). Most treated lesions turn brown and fall away in 10 to 14 days. Occasionally, a lesion only gets smaller and a second dosing is then appropriate and effective. Some larger and more vascular lesions, however, may simply not respond at all.

The customary spray may unexpectedly extend beyond the intended target of a diagnosed lesion and its narrow margin of normal skin, ie, 1 mm margin for benign lesions, 5 mm for malignancies and 2.5 mm for premalignant ones. Unplanned intrusion of the spray onto normal contiguous tissues risks unintended blistering and unintended scarring.

Otoscope speculums are available in various sizes, from 2.5 mm, 3.0, 4.0, 5.0, 6.0, to 9 mm. Selecting a speculum whose tip matches the target lesion plus a narrow margin of normal tissue and then boldly thrusting the speculum tip into the skin provides an effective protective barrier. Adjacent normal tissues remain untouched beyond the freeze.

Holding the speculum with one’s hand is uncomfortably cold for the operator. A grasper was devised (Fig. 1) from two wooden spring-loaded clothespins. The initial clothespin was unaltered. Parts of the second clothespin were glued onto the initial one to make the final clothespin longer and its mouth wider to accept the speculum. All six speculums have different-sized tips, but their tops are all one size. This permits the grasper to hold and push the speculum into the patient’s skin to better provide a spray barrier (Fig. 2). The canister spout is also pushed into the speculum to reinforce the skin’s circular compression. On withdrawing the speculum, canister, and grasper, there is a visible, temporary circular depression. The area beyond is

Fig. 1 Top, One clothespin remains intact with other disassembled sections. Bottom, Assembled clothespin with handle and mouth both enlarged to better hold cold speculum.

Fig. 2 Clothespin grasper in left hand, speculum compressed tightly against the skin, and pressurized canister in right hand.
protected, thus providing splatter-free cryotherapy. The circular compression also seems to enhance effectiveness and it is conjectured that this compression transiently diminishes the target’s blood supply, making the target lesion more vulnerable to cryotherapy freeze/thaw destruction.1

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Standing at the Crossroads—Will the Increments in Resident Clinic Sessions Help?

To the Editor: Recent years have witnessed an increasing trend towards reforming and redesigning the configuration of internal medicine residency training to prepare the residents for future clinical practice.1,2 This has meant a step-by-step increase in the number of resident clinic sessions and the percentage of time spent in outpatient settings for meeting accreditation requirements. Increased exposure without a well thought out infrastructure may, however, prove counterproductive.

A major bulk of preventive and diagnostic medicine is practiced in the outpatient clinics, which lends an ideal educational model for residents to provide high-quality, cost-effective patient care under the supervision of faculty members. However, residency programs are more often than not designed around the needs and requirements of recruiting institutions. Resident clinics are frequently understaffed with limited access to information technology. Coexisting inpatient responsibilities add to the burden, which limits the excitement that a well-rounded outpatient exposure is supposed to provide.

In a study exploring ambulatory care experience at the Johns Hopkins School of Medicine,3 resident ratings were highest on diversity of illness seen, medical record systems used, and contact with preceptors who were receptive to questions. On multivariate analysis, high ratings of preceptors as role models were most strongly associated with valuing clinic (corrected relative risk 3.44). Another study4 demonstrated that patients with extremes of age, female sex, less education, Medicare and Medicaid insurance, increased number of chronic conditions and medications, number of visits to the practice, and worse self-reported health status placed higher value on continuity of care.

Conflicting arguments on the significance of continuity of care can stem from variability in its importance to different patient subsets. A substantial percentage of patients seen in university outpatient clinics have multiple, complex, inter-related medical and psychological problems that are compounded by the social and financial burdens that they face. These patients may need urgent appointments and more frequent follow-ups, suggesting a need for patient-stratification and improved coverage while the resident physician is not available. Inability to secure a much-needed appointment and/or inability to get a prescription refill in time are some examples of how patient satisfaction can suffer in such an environment. A solution could be the use of hospitalists and midlevel practitioners in the healthcare team including resident clinics. However, in the era of tumbling economy and plunging revenues, resources available for primary care clinics may be scarce and implementation of such policies may prove difficult. Time spent in such a chaotic, disorganized environment of an outpatient clinic could be a major deterrent, preventing residents from pursuing a career in internal medicine.

These are hefty challenges and present themselves with plenty of questions for administrators and program directors; however, there are no easy answers. It would be a great beginning if a subgroup of clinical faculty could be provided protected time and incentives to develop learning tools and to evaluate, supervise, and teach residents. This should be accompanied by the presence of ‘core faculty’ members who work with residents longitudinally and a well-balanced curriculum addressing clinical and nonclinical topics related to patient care. Incorporation of these changes could be the first major step towards enhanced ambulatory training.

A 21st century internal medicine resident should be well prepared to care for patients who may have complex needs, by practicing evidence-based medicine, equipped with the latest in information technology.

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Swallowed Dental Bridge Perforating the Terminal Ileum

To the Editor: A 53-year-old male presented to the emergency department complaining of right iliac fossa pain 24
hours after swallowing his dental plate. On examination his abdomen displayed signs of right iliac fossa peritonism. He was taken to the theatre and, during the operation, a tooth was seen protruding from his terminal ileum. The dental plate was extracted through a small enterotomy which was closed primarily.

Ingestion of foreign bodies is common, whether deliberately or not. Favorably, most pass harmlessly through the gastrointestinal (GI) tract. Usually, if the foreign body passes through the three anatomical narrowings in the esophagus to arrive at the stomach, there is a high chance of passing out through the anal canal without complications. Foreign bodies may become dislodged anywhere in the GI tract and may have serious consequences. A literature review shows that an estimated 1500 deaths occur annually in the United States following foreign body ingestion.1

Clinicians, particularly emergency department physicians, gastroenterologists, and surgeons ought to be familiar with the prognosis and management of foreign body ingestion.

A diagnostic laparoscopy was performed and identified a tooth protruding from the terminal ileum. The procedure was converted to open through a Lanz incision. The small bowel with the tooth protruding was exteriorizing, before an examination and enterotomy was performed. The dental plate was extracted and the enterotomy closed with 2–0 polydioxanone (Ethicon, UK). The abdomen was irrigated and the wound was closed in the standard way.

The patient made an excellent recovery and was discharged home on day 2 postoperatively.

Foreign body ingestion is not uncommon. Children account for 75–80% of the patients in this cohort. The remainder are usually psychiatric patients, prisoners, and edentulous adults.

Serious morbidity and mortality may result from foreign body ingestion. A literature review reports tracheoesophageal fistula, perforation, and obstruction requiring surgery.2 Hence, such cases must always be assessed adequately and appropriate referral made.

The management depends upon diagnosis once the patient is stable. Imaging modalities vary in sensitivity, yet patients ought to have plain radiographs. In this patient, given local peritonism, further imaging was not necessary.

Objects in the stomach with dimensions of less than 5 × 2 cm (length by width) are highly likely to pass through the pylorus unaided,3 but they may lodge at the ileocecal valve. For small objects, which are likely to pass, a watch-and-wait approach is appropriate.4 If there is any evidence of perforation, then surgery is almost inevitable. There are many other options, most of which are based on anecdotal evidence.

Once the foreign body passes, an underlying pathology that may have contributed to the obstruction should be ruled out.

Ingestion of foreign bodies is not uncommon and relevant health care professionals ought to be aware of the management, complications, and pitfalls. Though usually managed conservatively, a small number of patients will require surgery. Appropriate follow up looking for potentially underlying lesions is occasionally necessary.

Acknowledgment

The patient kindly gave full written permission for this report to be made.

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Secondary Aortoenteric Fistula Presenting with Recurrent Episodes of Sepsis

To the Editor: A 78-year-old female with an aortobifemoral bypass graft two years previously was seen in consultation for a 3-month history of recurrent episodes of sepsis with Enterobacter cloacae. Each episode was treated with antibiotics; however, following a brief regression, the symptoms recurred each time. Extensive workup, including computed tomography (CT) of the chest, abdomen, and pelvis, and indium scans were unremarkable. Laboratory tests at the current admission revealed a white blood count of 33.1 K/mm³ (3.8–10.8 K/mm³); hemoglobin of 9.7 g/dL (13.8–17.2 g/dL), and a hematocrit of 28.6% (44–51%). A repeat CT scan of the abdomen showed a patent aortobifemoral bypass graft with limited retroperitoneal emphysema in the periaortic region. Upper endoscopy revealed the prosthetic graft with erosion of the distal duodenum. Surgery was offered but the patient refused. She was then continued on antibiotics and died in hospice care one month later.

Secondary aortoenteric fistula is a rare, life-threatening complication of aortic revascularization surgery. The most frequent forms of presentation are gastrointestinal hemorrhage, abdominal pain, shock, or other symptoms associated with compression of adjacent structures. However, symptoms of systemic infection may be the only manifestation when other local signs are absent, as in this case. There is no single diagnostic modality that has a high sensitivity and specificity, including CT scan, angiography, endoscopy, or indium scan.1,2 A secondary aortoenteric fistula presenting as recurrent episodes of sepsis is highly unusual but should be considered in patients with aortic re-
Can a Normal Colonic Mucosa Harbor an Aggressive Underlying Lymphoma?

To the Editor: Chronic diarrhea is a common gastrointestinal (GI) complaint with an overall prevalence of 3–5% in the United States. Common causes include irritable bowel syndrome, inflammatory bowel disease, microscopic colitis, malabsorption syndromes, chronic infections, and medications. The laboratory tools available for evaluation are often expensive and invasive. As such, the diagnostic evaluation must be rationally directed by a careful history and physical examination.¹

A 66-year-old male presented to our hospital with recurrent episodes of profuse, nonbloody, watery stools of 6 months’ duration. The patient denied any consumption of unpasteurized dairy products/undercooked meat or seafood. He denied any travel history, antibiotics/NSAID use, or exposure to sick contacts. There was a history of significant weight loss of 30 pounds during this time period. His other medical problems included coronary artery disease, hypertension, chronic obstructive pulmonary disease (COPD), and gastroesophageal reflux disease (GERD). There was no change in his medication antecedent to the onset of diarrhea. Physical examination was unremarkable with no evidence of dehydration, lymphadenopathy, cardiac murmurs, wheeze, abdominal tenderness, or organomegaly.

His labs showed normal basal metabolic profile and cell counts. Serum thyroid stimulating hormone and tissue transglutaminase antibody were within normal limits. Stool studies were negative for infectious etiology, including *Clostridium difficile* and the stool osmolar gap was within normal limits. Colonoscopy revealed normal colonic mucosa and random colonic biopsies were obtained to rule out microscopic colitis. Colonic biopsy revealed atypical lymphoid infiltrate comprised mostly of expanded mantle zones and a few areas of identifiable residual germinal centers consistent with mantle cell lymphoma. A majority of the lymphoid infiltrate was positive for CD20, bcl-2, CD5, and cyclin D1. Flow cytometry showed clonal proliferation of B-cells consistent with the diagnosis of mantle cell lymphoma. Thus, the patient was diagnosed with mantle cell lymphoma involving the colon. Imaging study of the thorax, abdomen, and pelvis did not show any lymphadenopathy or organomegaly. A positron emission tomography scan revealed multiple metabolically active lymph nodes in the axillary, external iliac, and inguinal regions. The patient was initiated on chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab with resolution of his diarrhea and steady weight gain over the next few months.

Primary gastrointestinal lymphomas are rare conditions. Mantle cell lymphoma (MCL) comprises about 7 percent of adult non-Hodgkin lymphomas, and the GI tract is involved in about 20% of cases. It is characterized by a monotonous proliferation of small-to medium-sized lymphocytes with co-expression of CD5, CD20, and Cyclin D1. Median age at diagnosis is 68 years. Colon and rectum were affected in about 90% of GI lymphomas, followed by the small bowel (69%), stomach (57%), and duodenum, (52%).²

Mantle cell lymphomas (MCLs) behave as aggressive neoplasms. The most frequent endoscopic finding is multiple lymphomatous polyposes. It is characterized by multiple polypoid lesions involving long segments of the gastrointestinal tract. Abdominal pain, diarrhea, hematochezia, and palpable mass are the most common presenting manifestations of MCL. The prognosis is poor, with a mean survival time of less than three years. Response to chemotherapy is seen in up to half of the patients.³ Cyclophosphamide, doxorubicin, and prednisolone and cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) are used as conventional chemotherapies for MCL.⁴ Infiltrating lymphoma cells express CD20 molecules on their surfaces. Using this as the cellular target, rituximab (a chimeric monoclonal antibody to CD20) is now used in chemotherapy regimens. Single agent rituximab has produced response rates of about 30%, and, when combined with CHOP, response rates increase to above 90%.⁵

Of interest, our patient presented with chronic diarrhea and weight loss, and colonoscopy did not reveal any polypoid lesions. The underlying malignancy was diagnosed by histopathological analysis of random biopsies of normal-appearing colon. A combination chemotherapy with CHOP-rituximab resulted in complete resolution of his diarrhea, along with steady weight gain over the next four months.

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Letters to the Editor

Acute Profound Thrombocytopenia Following Eptifibatide Administration

To the Editor: An 84-year-old female with a history of diabetes mellitus, hypertension, ulcerative colitis, and dyslipidemia presented to the emergency room with acutely worsening shortness of breath (SOB). Home medications included aspirin, glimepiride, insulin, furosemide, metoprolol, mesalamine, ibesartan, simvastatin, and vitamins. Examination showed bibasilar fine crackles with 1+ pitting pedal edema. She denied history of upper gastrointestinal bleed, and stool guaiac was negative. Complete blood count (CBC) was normal except leukocytosis (15,900/mm³). Her blood urea nitrogen and creatinine were 53 and 1.6 mg/dL. Chest x-ray showed bilateral hilar infiltrates. Cardiac biomarkers were only significant for brain natriuretic peptide (BNP) of 472 pg/mL. She was admitted with a history of diabetes mellitus, hypertension, ulcerative colitis, and dyslipidemia.

On day 2 while in the telemetry unit, the patient developed worsening SOB and chest pain which was relieved with sublingual nitroglycerin. Electrocardiograph showed sinus rhythm with new 1 mm ST elevation in lead V1. Cardiac biomarkers showed elevated creatinine phosphokinasase, creatinine kinase (CK)-MB and troponin-I. The patient was started on beta blocker, IV heparin, and IV eptifibatide (dose based for creatinine clearance and weight) for acute non-ST elevation myocardial infarction. Aspirin was continued. Considering her tachypnea and respiratory distress, she was endotracheally intubated and mechanical ventilation was started. CBC showed leukocytosis, hemoglobin of 11.2 g/dL with normal platelets (255,000 cells/mm³). On day 3 (20 hours after starting eptifibatide and 48 hours after starting heparin), CBC showed platelets/hemoglobin of 3,000/mm³/9.1 g/dL. Pro-thrombin time (PT)/international normalized ratio was 13.9 sec/1.2. On examination she had scattered petechiae, mild bloody secretions in nasogastric suction and positive stool guaiac.

Differential diagnosis included drug-induced thrombocytopenia including heparin-induced thrombocytopenia (HIT), disseminated intravascular coagulation (DIC), thrombocytopenia secondary to sepsis, and autoimmune thrombocytopenia. Eptifibatide, aspirin, and heparin were stopped, and two units of red blood cells and super packed platelets were transfused, respectively. Repeat CBC six hours later showed platelets/hemoglobin of 3,000/mm³/8.4 g/dL. Hematology evaluation was done and 50 gms of IV gamma-globulin were given empirically for possible autoimmune thrombocytopenia, given the clinical state of sepsis. On day 4 platelets/hemoglobin were 4000/mm³/7.9 g/dL. Another transfusion of 2 units of super packed platelets was given, raising the platelets to 23,000/mm³.

On day 5 platelets were 20,000/mm³ and showed progressive improvement without transfusion. Six days after stopping eptifibatide, platelets were 159,000/mm³. Heparin induced platelet antibody and serotonin release assay (HIT panel) came back negative and subcutaneous heparin was restarted for deep vein thrombosis (DVT) prophylaxis. Anti-platelet antibody assay by optic density was negative. Work up for disseminated intravascular coagulation showed fibrinogen levels of 659 mg/dL (normal 250 – 500 mg/dL), fibrinogen degradation products were >10 <40 microgram/mL (normal <10 microgram/mL), PT/INR were 13.9 sec/1.2; peripheral smear was only significant for anisocytosis. Because of elevated D-dimers at admission, they were not rechecked. Subsequent platelet counts were 210,000/mm³ and 249,000/mm³. Considering all the clinical and laboratory evidence, this case represents eptifibatide-induced acute profound thrombocytopenia. No platelet drop was noticed despite reintroducing heparin, which further supports HIT as unlikely.

Eptifibatide is a glycoprotein IIb/IIIa receptor antagonist inhibiting platelet binding to fibrinogen and is currently being used in patients with acute coronary syndrome. Within a few hours of administration, it has been associated with acute profound thrombocytopenia defined as a platelet count of <20,000/mm³ within 24 hours of starting the drug, and the exact prevalence of this adverse drug reaction (ADR) is not known but estimated to be 1%. Thrombocytopenia has not only been reported in patients with prior exposure to eptifibatide but in eptifibatide-naïve patients as well. In our patient, no history of prior eptifibatide exposure was present and the Naranjo ADR scale score was 6, consistent with probable ADR. Drug dependent anti-platelet antibodies, either eptifibatide induced or ‘naturally occurring,’ have been implicated in the pathogenesis.

Treatment involves discontinuation of eptifibatide and supportive treatment. No antidote is available and immunoglobulins have no proven benefit. This case reinforces the importance of monitoring platelet count. It has been proposed to monitor platelet count within 2–4 hours of starting medica-
tion,2 or within 24 hours.5 Given the easy availability of CBC, platelet count should preferably be monitored every 6 hours for the first 24 hours after the initiation of therapy for early recognition of eptifibatide-induced thrombocytopenia.

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