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Luo, Yiqi Ruben
Goodnough, Robert
Menza, Rebecca
et al.

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A case of unexplained duodenal ulcer and massive gastrointestinal bleed

Yiqi Ruben Luo[a,*], **Robert Goodnough**[b], **Rebecca Menza**[c], **Adina Badea**[a], **Hubert Yiu-Wei Luu**[d], **Lucy Z. Kornblith**[d], **Kara L. Lynch**[a]

[a]Department of Laboratory Medicine, University of California San Francisco, San Francisco, CA, USA

[b]Department of Emergency Medicine, Baylor College of Medicine, Houston, TX, USA

[c]Department of Physiologic Nursing, University of California San Francisco, San Francisco, CA, USA

[d]Department of Surgery, University of California San Francisco, San Francisco, CA, USA

Abstract

A 73-year-old man was displaying symptoms of massive gastrointestinal (GI) bleed. Surgical actions were performed to control the bleed caused by an erosive duodenal ulcer with duodenal perforation. When investigating the culprit of this case, the pain medications prescribed two weeks prior by a traditional Chinese medicine doctor raised attention. The patient's admission serum sample and the pain medications from unknown sources were analyzed using a clinically validated liquid chromatography-high-resolution mass spectrometry (LC-HRMS) method. The NSAIDs diclofenac, piroxicam, and indomethacin were identified, as well as some other synthetic drugs and natural products. The patient's concurrent exposure to multiple NSAIDs significantly increased the risk of upper GI complications. It is reasonable to argue that the high-dose use of the NSAIDs was a major cause of the duodenal ulcer and GI bleed. In addition, the identified natural products such as atropine and ephedrine have well-documented toxicities. It is important to increase the visibility of unregulated medications, and the capability to perform untargeted mass spectrometry analysis provides a unique diagnostic advantage in cases where exposure to toxic substances is possible.

1. Case presentation

A 73-year-old man with no significant past medical history called emergency medical services after an episode of syncope at home. He was found alert and oriented in his bed surrounded by blood. Prior to arrival in the Emergency Department (ED), his systolic blood pressure was in the 60s mmHg and improved to the 80s mmHg following 4 units of blood transfusion. Upon arrival, he was alert, with initial vital signs: blood pressure 103/86 mmHg, heart rate 110 beats per minute, respiratory rate 13 breaths per minute, SpO2 98%, body temperature 36.8 °C (temporal artery). Physical examination was notable for pale

*Corresponding author. ruben.luo@ucsf.edu (Y.R. Luo).

conjunctiva, cool clammy skin and melena, which developed into hematochezia with bright red blood coming from his mouth and rectum during his ED course. Initial laboratory results demonstrated: RBC 1.58 mil/μl (4.40–5.90), WBC 15.3 k/μl (3.9–11.7), hemoglobin 5.1 g/dl (13.3–17.7), hematocrit 15.7% (39.8%−52.2%), platelets 198 k/μl (150–400), lactate 7.7 mmol/L (0.5–2.2), BUN 75 mg/dl (8–23), creatinine 1.34 mg/dl (0.70–1.30), INR 1.5 (< 1.2), PT 17.8 (< 14.8), PTT 30.1 (< 37.6). Computed tomography angiographic imaging demonstrated a large volume of blood in the stomach and small intestine, with active extravasation of blood into the proximal duodenum, presumed to be coming from the gastroduodenal artery. The patient was intubated for airway protection, a massive transfusion protocol was activated. The patient received an intravenous infusion of octreotide to reduce splanchnic blood flow, pantoprazole to suppress gastric acid secretion, ceftriaxone to prevent microbial infection, norepinephrine to maintain blood pressure, and tranexamic acid to improve blood clotting.

He was taken to interventional radiology for coil embolization of his gastroduodenal artery, and there he became difficult to ventilate in the setting of abdominal distension, consistent with abdominal compartment syndrome. An exploratory laparotomy was performed with on-table upper endoscopy for further localization of bleeding, which was complicated by duodenal perforation. He was noted to have a large erosive duodenal ulcer with ongoing bleeding which was controlled with suture ligation (Fig. 1). There was significant circumferential destruction of the duodenum and portal structures in this area requiring primary closure of the circumferential duodenal injury, common bile duct T-tube placement, cholecystectomy, gastric exclusion with stapled gastric transection, gastrostomy tube, duodenostomy tube, and temporary abdominal closure. The patient had multiple return operations on his open abdomen, and, three days later he underwent definitive antrectomy, jejunostomy feeding tube placement, and abdominal closure leaving him with intestinal discontinuity and plans for later reconstruction. A medication history was obtained from the patient’s family and was notable for pain medications prescribed two weeks prior by a traditional Chinese medicine doctor with unknown credentialing for knee pain.

2. Discussion

Prior to diagnostic imaging and endoscopy, the bleeding manifestations in this case which included hematemesis, melena, hematochezia, and occult blood loss were all suggestive of a duodenal and/or gastric ulcer. Laboratory findings confirmed the loss of blood and impaired blood clotting. During a gastrointestinal (GI) bleed, absorption of blood as it passes through the small bowel is impaired resulting in decreased renal perfusion and an elevated blood urea nitrogen (BUN)-to-creatinine ratio. Values > 36:1 suggest an upper GI bleed.

Gastroduodenal ulcers are a common cause of upper GI bleeds. Major risk factors include *Helicobacter pylori* infection, use of nonsteroidal anti-inflammatory drugs (NSAIDs), and physiologic stress, which are all associated with impaired mucosal permeability and back diffusion of hydrogen ions resulting in acidosis, necrosis, and ulceration. This patient tested negative for *H. pylori* IgG and had no predis-posing medical conditions. These observations raised the attention to the nature of the pain medications that the patient had been taking for his knee pain for two weeks. The pain medications were obtained from the

patient's family and were unlabeled, as shown in Fig. 1. The tablets had the appearance of compounded medications from unknown sources, and some of them resembled Asian patent medicines (herbal supplements formulated into tablets or liquids for medical purposes). It was suspected that these tablets could contain pharmaceuticals such as NSAIDs, the use of which had a high prevalence among groups at-risk for significant drug-related adverse events [1].

The patient's admission serum sample and the pain medications from unknown sources were processed and analyzed using a clinically validated liquid chromatography-high-resolution mass spectrometry (LC-HRMS) method [2,3]. Data were acquired in an untargeted manner with a high-resolution survey scan followed by information dependent acquisition of high-resolution product ion spectra. The in-house developed spectral library for data analysis contains over 1000 pharmaceuticals, including 150 small molecules from natural products responsible for their pharmacological effects. The seven tablets were extracted with methanol and the extracts were analyzed in the same manner as the serum.

Some synthetic drugs and several natural products were identified in the patient's serum and the tablets, as shown in Table 1. The NSAIDs diclofenac, piroxicam, and indomethacin were identified. The concentrations of the three NSAIDs in the patient's serum were measured using a standard curve of external calibrators prepared in drug-free serum. The quantitative results are displayed in Table 1. In the patient's serum, the concentration of piroxicam was well above previously reported toxic concentrations, while those of diclofenac and indomethacin reached therapeutic concentrations [4].

It is reasonable to argue that the high-dose use of the NSAIDs was a major cause of the duodenal ulcer and GI bleed. NSAIDs disrupt the production of prostaglandins in the stomach via inhibition of the cyclooxygenase-1 (COX-1) enzyme and are known for GI adverse effects, including erosions, ulcer, hemorrhage, and perforation [5,6]. In this case, the patient's concurrent exposure to multiple NSAIDs at high concentrations, confirmed by LC-HRMS testing of the patient's serum, significantly increased the risk of upper GI complications. A prior epidemiologic study has demonstrated that NSAIDs increase the risk of upper GI bleed or perforation, with higher risk occurring at higher doses [7]. Thus, gastroprotective strategies are recommended for certain NSAID users [8]. In addition, diclofenac has also been shown to prolong bleeding time in *peri*-operative patients, akin to what one might expect from the effect of aspirin, which may have placed the patient at increased risk of hemorrhage [9].

In this case, it was unclear if the patient understood the content of these unregulated, unlabeled, probably imported medications. Given the fact that the Yellow Tablet 2 contained both synthetic and natural substances, it is reasonable to consider it as an herbal supplement adulterated with synthetic drugs, as reported elsewhere [10–15]. One report demonstrated that 7% of 260 Asian patent medicines collected from Californian outlets contained undeclared pharmaceuticals [10]. Intentional adulteration may occur when the necessary natural substances are in short supply, expensive or in order to augment a specific pharmacologic effect [12], and NSAIDs were often found as the adulterants [12,14]. In addition, the identified natural products such as atropine and ephedrine have

well-documented toxicities. The compounding of multiple pharmaceuticals, synthetic or natural, increases the risk for significant drug-drug interactions.

The use of unregulated medications may lead to unintended adverse events and organ damage in an individual who may be unaware of the nature of the medications or even of the presence of synthetic drugs. This case highlights a particularly morbid outcome for an individual exposed to undeclared pharmaceuticals via unregulated medications. Clinicians find it challenging or impossible to accurately identify or exclude the clinical effect of unregulated medications or supplements. It is important to increase the visibility of this type of adulteration and potentially harmful polypharmacy among Asian patent medications and other unregulated pharmaceuticals in the clinical chemistry and general medicine communities. The involvement of a toxicology laboratory with the capability to perform untargeted mass spectrometry analysis, such as the LC-HRMS method used for this case, and with experience in the investigation of undifferentiated cases provides a unique diagnostic advantage in cases where exposure to toxic substances is possible.

3. Case Follow-up

The patient was hospitalized for seven months and discharged with a venting gastrostomy tube and a feeding jejunostomy tube. One year after his index operation, the patient underwent intestinal reconstruction with a Roux-en-Y gastrojejunostomy and he is now eating normally as an outpatient.

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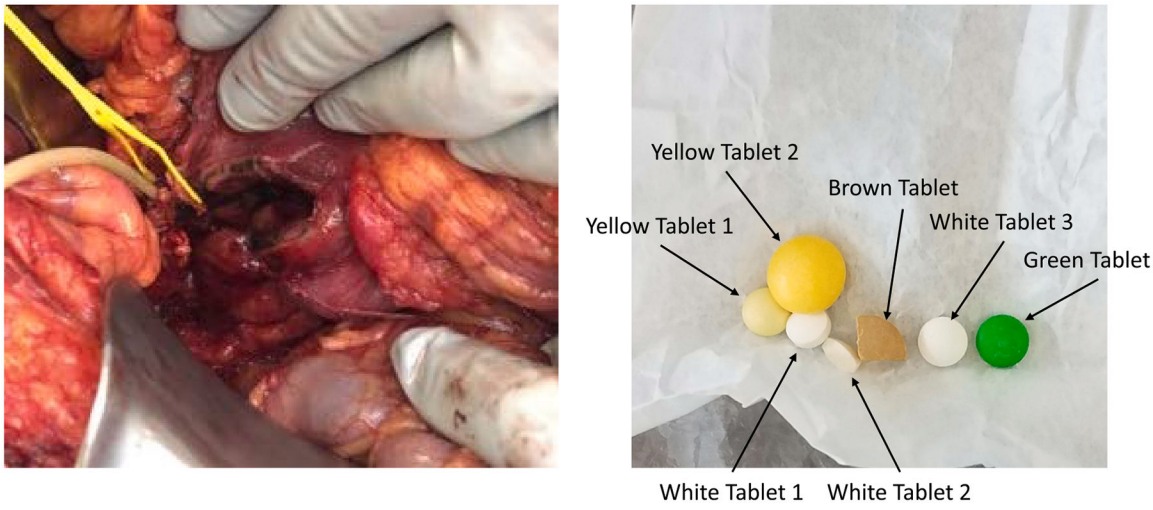

Fig. 1.
The duodenal ulcer (left) and the pain medications obtained from the patient's family (right).

Table 1

Identified compounds in the patient's serum and the seven tablets, and the concentrations of the NSAIDs in the patient's serum.

Sample	**Identified Compounds**		
Patient's Serum	Piroxicam, Cotinine, Indomethacin, Tetracycline, Diclofenac		
White Tablet 1	Piroxicam, Levamisole, Tetracycline		
White Tablet 2	Piroxicam, Levamisole, Tetracycline		
White Tablet 3	Indomethacin, Piroxicam, Tetracycline		
Yellow Tablet 1	Piroxicam, Indomethacin, Tetracycline		
Yellow Tablet 2	Corydaline, Protopine, Berberine, Palmatine, Ammoidin, Jatrorrhizine, Coptisine, Piroxicam, Tetracycline, Boldine, Cimetidine, Ephedrine / Pseudoephedrine*, Diclofenac, Atropine		
Brown Tablet	Tetracycline, Chlortetracycline, Indomethacin, Piroxicam		
Green Tablet	Diclofenac, Tetracycline, Piroxicam		
NSAIDs in Patient's Serum	Concentration in Patient's Serum (μg/ml)	Therapeutic Level in Serum (μg/ml)	Toxic Level in Serum (μg/ml)
Piroxicam	25	5–10	14
Indomethacin	0.8	0.5–3	4–6
Diclofenac	0.08	0.05–2.2	50

Note: White Tablet 1 and 2 could be identical based on the appearance. The identified compounds are listed in descending order of the peak intensity in LC-HRMS ion chromatograms. The therapeutic and toxic levels in serum are obtained from the International Association of Forensic Toxicologists (TIAFT) [3].

*Ephedrine and pseudoephedrine are stereoisomers which could not be affirmatively distinguished in the LC-HRMS method.