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Case Report

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Spontaneous bleeding and curcumin: Case report

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Abstract

Background: Supplemental over-the-counter high-dose curcumin preparations are in widespread use for inflammatory conditions.

Case summary: We describe a case of a 74-years old male that presented to the emergency department complaining on left thigh pain and spontaneous large hematoma. His medical history was notable for hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, ischemic heart disease, status post renal transplantation, and benign prostatic hyperplasia. A week before admission he began taking 1 gram curcumin/day. A diagnosis of left-thigh large hematoma was confirmed by CT scan. Anemia and secondary ischemic changes resolved following packed-red-cells administration but local pain and disability persisted in a follow-up examination, weeks later. In vitro studies have demonstrated inhibition of platelet aggregation by curcumin. In addition, in a rat model, curcumin caused an increase in AUC and Cmax of oral clopidogrel by 1.61 fold and 1.81 fold, respectively.

Conclusion: Further research is warranted to study the potential interactions between antiaggregants, anticoagulants and curcumin, and the resultant major risk.

Keywords: Hemorrhage; Bleeding; Curcumin; Turmeric; Antiaggregants; Anticoagulants; Clopidogrel; Apixaban; Anemia; Polypharmacy.

Case report

A Seventy-four years old male presented to the Emergency Department (ED) with three days pain and large skin hematoma in the medial aspect of his left thigh, started when he stepped out of his car and felt sharp pain in his left groin.

An orthopedic surgent in the ED saw him three days before current admission. The patient was limping but bearing weight. There was limited range of motion in active movement of the hip, and pain produced upon touching the medial thigh, but no neurovascular deficiency, and no fracture on X-ray. The patient was discharged home with recommendations for a pain reliever and a follow up orthopedic examination.

His medical history was notable for hypertension, diabetes mellitus, hyperlipidemia, chronic atrial fibrillation, ischemic heart disease, status post coronary-artery-bypass-graft surgery and multiple coronary angioplasties, status post renal transplantation due to end stage renal failure, and benign prostatic hyperplasia.

Abdominal CT had been performed few months before current admission, as part of an investigation into chronic abdomi-

nal pain the patient was suffering of, and had shown signs compatible with mild inflammation surrounding the pancreatic tail and around the transplanted kidney.

His chronic medications list included: bisoprolol (3.75 mg/day), doxazosin (1 mg/day), lercanidipine (10 mg/day), basal insulin (8 units/day), repaglinide (1 mg/day), clopidogrel (75 mg/day), eliquis (5 mg BID), atorvastatin with ezetimibe (80/10 mg/day), furosemide (40 mg/day), prednisone (5 mg/day), mycophenolic acid (180 mg BID), tacrolimus (11.5 mg/day), omeprazole (20 mg/day), tamsulosin with dutasteride (0.4/0.5 mg/day), and dipyrone (500 mg/day). He had suffered from Penicillin allergy.

A week before his current admission he began consuming 1-gram curcumin/day that he bought over-the-counter following a pharmacist recommendation "for the abdominal inflammation". He stopped taking the curcumin two days before current admission.

Upon physical examination, the patient looked pale, but had normal vital signs, and no dyspnea. There were normal heart sounds, normal lung auscultation, and no pain evoked on abdominal palpation. The left thigh was swollen and a large hematoma was spreading through his medial thigh, with no clinical signs of infection/compartment syndrome/ neurovascular compromise.

Laboratory tests on admission showed serum Hemoglobin (Hb) 8.2 g/dL (normal: 13.5-17.5), (while his last serum Hb level from fifty days before current admission was 12.7 g/dL); white blood cells count 8.19 x 10^3/ microliter (normal: 4.5-11), with lymphopenia (0.49 x 10^3/ microliter) (normal: 1.0-4.8) but normal neutrophil count; mild thrombocytopenia: platelet count 113 x 10^3/ microliter (normal: 130-400); PT-INR 1.24 (normal: 0.80-1.30); APTT ratio 0.97 (normal: 0.8-1.2); Na 129 nEq/L (normal: 135-145); K 4.1 mEq/L (normal: 3.5-5.1); urea 57 mg/dL (normal: 17-43); creatinine 1.39 mg/dL (normal: 0.67-1.17); glucose 228 mg/dL (normal: 70-100); calcium 8.8 mg/dL (normal: 8.8-10.6); bilirubin total 0.46 mg/dL (normal: 0.30-1.20); troponin 52.6 ng/L (normal: 0-14); C-reactive protein 7.06 mg/dL (normal: 0-0.50).

CT scan was performed and demonstrated large hematoma in the muscles and subcutaneous soft tissues of the left thigh. ECG diagram performed on ED admission showed normal sinus rhythm, with no ischemic changes. Recurrent ECG performed a few hours later, while complaining of chest pain showed marked ST segment depression on the lateral chest leads.

A diagnosis of left thigh large hematoma was confirmed, with anemia and secondary ischemic changes. A unit of packed red cells was administered in the ED, and the patient was admitted to an internal medicine ward. Upon admission to the internal medicine ward, his serum Hb level was 9.6 g/dL. Liver function tests were normal, as well as folic acid, B12, and TSH levels. Apixaban was withheld. There were no clinical signs for continued bleeding and serum Hb level was stable during 14 days of hospitalization. CRP and serum creatinine gradually decreased to normal values. Recurrent ECG did not show ST segment depression, and there was no further troponin elevation.

Cardiac dipyridamole isotope scan was performed and showed mild decrease in perfusion in the anterior and inferior walls. The patient was transferred to the cardiology unit. A few events of rapid atrial fibrillation were accompanied with mild chest pain but no signs of myocardial ischemia on ECG. Amiodarone treatment was initiated.

The patient was discharged home with recommendation for onset of amiodarone, micropirin, continuing apixaban, withholding of clpidogrel and continuation of the rest of the drugs administered before his admission.

Two weeks following his discharge, the patient was visiting an outpatient clinic for difficulty walking due to pain in the left thigh. Twenty days later he was seen by his nephrologist. His serum Hb was 13.2 gr/dL. He reported feeling well, but had still prominent difficulties in walking and he asked for a letter to help him get permanent rights as handicapped.

Supplemental over-the-counter high-dose curcumin preparations are recently marketed. Curcumin is the main active ingredient of the spice turmeric, extracted from the rhizomes of the plant Curcuma longa. It was used in indigenous medicine to treat common ailments such as stomach upset, flatulence, dysentery, ulcers, arthritis, sprains, wounds, acnes, and skin and eye infections. It is attributed with numerous pharmacological activities including anti-inflammatory, antioxidant, antimicrobial, anti-proliferative and antiaggregant properties [1]. Due to its pleotropic effect, curcumin has been recently suggested as a new adjuvant therapy for the treatment of COVID-19 [2].

Curcumin is a hydrophobic molecule and have been shown to change cell membranes properties by increasing membrane permeability and inducing membrane thinning. Membrane proteins might be influenced [3]. Oral bioavailability of Curcuma oil, as assessed by monitoring of its metabolites was 7-13%, indicating relatively low bioavailability [1].

Only minor interactions alerts between turmeric and antiaggregants/anticoagulants are listed in online software (for example https://www.drugs.com/interactions-check.php?drug_list=2682-0, 3438-0,705-0). However, pharmacodynamics interactions might exist between curcumin and antiaggregants/anticoagulants. In vitro studies have shown that curcumin inhibits platelet aggregation [4]. In addition, a PTT and PT were significantly prolonged by curcumin in vitro. Bleeding time prolongation by inhibiting Factor Xa and the generation of thrombin was exhibited in vivo in a murine tail assay [5]. On the other hand, in a rat model, although Curcuma oil caused reversal of ADP-induced platelet aggregation, there was only mild effect on the bleeding time, and there was no effect on coagulation parameters [1].

Pharmacokinetic interactions might also exist between curcumin preparations and antiaggregants/anticoagulants. Curcumin is a competitive inhibitor of the metabolizing enzymes: CYP1A2, CYP2B6, CYP2C19, CYP3A4; a non-competitive inhibitor of CYP2C9, and CYP2D6; inhibitor of the efflux transporter Multidrug Resistance Protein 1 (MRP1), and of the influx transporter Organic Anion Transporting Polypeptides (OATP). Inhibition as well as increasing activity of the efflux pump P-gp had been demonstrated following a single curcumin dose. Phase II metabolizing enzymes were affected by curcumin in vitro: inhibition of glucoronidation performed by Uridine Dinucleotide

Phosphate Glucuronosyl transferases (UDPG); inhibition of sulfation by sulfotransferase; and inhibition of Glutathione-S-Transferase (GST) have been described [6].

Curcumin caused an increase in AUC and Cmax of oral clopidogrel by 1.61 fold and 1.81 fold, respectively, in a rat model [7]. Clopidogrel clearance was also significantly reduced by 58%. Inhibition of P-gp by curcumin may be one of the mechanisms by which the pharmacokinetics of clopidogrel is altered. However, in the rat model, the above mentioned alterations were only observable with 100 mg/kg of curcumin while lower doses did not show significant changes [6]. There are no data on possible interactions between curcumin and apixaban.

Limited data from human studies make it difficult to judge the clinical importance of these alterations. However, an increase in Cmax and AUC of drugs such as warfarin [7], and losartan [8] have been established. Conversely, it seems that dietary turmeric does not influence significantly the pharmacokinetics of conventional drugs [6].

Conclusion

In summary, we describe a major-hemorrhage event that resulted in prolonged hospitalization and continuing pain and disability, in a patient receiving multiple drugs, including an antiaggregant and an anticoagulant, as well as over-the-counter high dose curcumin preparation, that might have been associated with increased effects of the antiaggregant/anticoagulant effects.

Further research and follow up is warranted on potential interactions between curcumin and antiaggregants/anticoagulants. Cautious is recommended when administering curcumin to patients with polypharmacy and particularly to patients receiving narrow therapeutic-index drugs, due to potential pharmacokinetic and pharmacodynamics interactions.

Declarations

Ethics: No conflict of interest reported for all authors.

There was no funding for the study.

The patient signed an informed consent to publish his case.

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Author contribution: NG, HH, IW, SH interpreted the patient data. NG drafted the manuscript. All authors made substantial contributions to the paper, revised it critically for important intellectual content, approved the version to be published, and agreed to be accountable for the paper.

Essentials

- Supplemental over-the-counter high-dose curcumin preparations are recently marketed.
- We describe a case of a 74-years old male, receiving chronic treatment with an antiaggregant and an anticoagulant that presented to the emergency department with left thigh spontaneous hematoma accompanied with local pain, difficulty walking, and chest pain.A week before admission he began taking 1-gram curcumin/day.
- In a rat model, curcumin caused an increase in AUC and Cmax of oral clopidogrel by 1.61 fold and 1.81 fold, respectively. Clopidogrel clearance was also significantly reduced.

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