Turk J Gastroenterol 2008; 19 (2): 125-128

A case of angiographically verified non-occlusive mesentery ischemia induced by digitalis

Digitalisin neden olduğu, anjiografik olarak kanıtlanan non oklusiv mezenterik iskemili bir olgu

Hasan KAYAHAN[1], Ömer TOPALAK[1], Yiğit GÖKTAY[2], Müjde SOYTÜRK[1], Murat MERAL[1], Karaca BAŞARAN[3], Özgür DAĞLAR[4]

Department of [1]Internal Medicine, Divisions of Gastroenterology, [2]Radiology, [3]Internal Medicine, and [4]Cardiology, Dokuz Eylul University, School of Medicine, İzmir

Here we present a case of non-occlusive mesentery ischemia induced by digitalis, which was verified angiographically. Non-occlusive mesentery ischemia, a subgroup of "acute mesentery ischemia", is known as a period of intestinal ischemic hypoperfusion without a demonstrable vascular occlusion in the mesentery bed. It can be caused by factors leading to splanchnic hypoperfusion, which can be of cardiac, renal or hepatic origin. In addition, it can be induced by certain drugs such as digitalis, ergotamines and vasoactive agents. In clinical practice, digitalis toxicity is commonly seen. In contrast, non-occlusive mesentery ischemia secondary to digitalis is quite rare. However, non-occlusive mesentery ischemia should be included in the differential diagnosis for patients who develop sudden and diffuse abdominal pain while on digitalis therapy.

Key words: Nonocclusive mesenteric ischemia, acute mesenteric ischemia, digitalis

Anjiografik olarak kanıtlanan digitalisin neden olduğu non okluziv mezenterik iskemi olgusunu sunuyoruz. Akut mezenterik iskeminin bir alt grubu olan non oklusiv mezenterik iskemi, mezenterik yatakta gösterilebilir vasküler okluzyon olmaksızın intestinal iskemik hipoperfüzyon süreci olarak bilinir. Splaknik hipoperfüzyona ilerleyen kardiyak, renal ve hepatik nedenli faktörler neden olmaktadır. İlave olarak digitalis, ergotaminler ve vasoaktif ajanlar gibi bazı ilaçlarla indüklenmektedir. Klinik pratikte digitalis toksitesi sıklıkla görülmekle birlikte digitalise ikincil non okluziv mezenterik iskemi oldukça nadirdir. Bununla birlikte, digitalis tedavisi almakta iken ani ve yaygın karın ağrısı gelişen hastaların ayırıcı tanısında non okluziv mesenterik iskemi bulunmalıdır.

Anahtar kelimeler: Non okluziv mezenterik iskemi, akut mezenterik iskemi, digitalis, toksikasyon

INTRODUCTION

Non-occlusive mesentery ischemia (NOMI) is an entity defined under the heading of "acute mesentery ischemia" and is simply known as an intestinal ischemic hypoperfusion caused by an ongoing splanchnic vasoconstriction without a demonstrable occlusion in the mesenteric vasculature. Although infrequently seen during clinical practice, it has a high mortality.

Splanchnic hypoperfusion has many causes such as myocardial infarction, congestive heart failure, valvular heart diseases, various arrhythmias, hemorrhage, shock secondary to sepsis, and end-stage renal failure that especially requires hemodialysis. All these events eventually lead to a decrease in cardiac output. Patients who have undergone a major cardiac or abdominal surgery previously are also prone to NOMI. Infrequently, NOMI can be induced by various drugs like ergotamines, digitalis and vasoactive agents.

The diagnostic angiographic criteria for NOMI include narrowing of the origins of multiple branches of the superior mesenteric artery (SMA), irregularities in the intestinal branches, spasm of arcades, impaired filling of the intramural vessels, and a slow flow with increased reflux of contrast into the aorta during selective SMA injection (1, 2).

Here we present a case of a patient who died of an angiographically proven NOMI caused by digitalis toxicity.

Address for correspondence: Hasan KAYAHAN
Dokuz Eylül Üniversitesi Tıp Fakültesi
Gastroenteroloji Bilim Dalı
İnciralti, İzmir, 35340, Turkey
Tel: +90 232 412 37 01 • Fax: +90 232 259 97 23
E-mail: hasan.kayahan@deu.edu.tr

Manuscript received: 14.05.2007 **Accepted:** 10.01.2008

CASE REPORT

A 76-year-old woman was admitted to the emergency department due to a three-day history of nausea and mild abdominal pain. She was known to be on digitalis therapy and after evaluation, her symptoms were thought to be secondary to digitalis overdose because of the high digoxin level of 6.04 ng/ml (normal range 0.8-2 ng/ml). The history of the patient revealed hypertension, mild congestive heart failure and chronic atrial fibrillation. She did not have diabetes mellitus, renal or hepatic diseases or hypotension. She did not smoke or drink alcohol previously. She was on fosinopril sodium and digitalis therapy.

On admittance, her physical examination revealed blood pressure: 140/80 mmHg, heart rate (HR): 76/min and a body temperature of 37.1°C. She had an ejection fraction of 51% and mild aortic and mitral regurgitations during echocardiography. Electrocardiography demonstrated atrial fibrillation with a normal ventricular response (HR: 86/min), an incomplete left bundle branch block, presence of a U wave and left ventricular concentric hypertrophy. Lateral deviations, particularly at V4-V6 and D1-aVL, revealed a depression of ST segment compatible with the digoxin effect.

Three days later, the patient developed a sudden hematochezia accompanying a severe periumbilical abdominal pain. In physical examination, she had a blood pressure of 130/80 mmHg and an arrhythmic pulse with a rate of 80 beats per minute, tenderness on left lower quadrant and periumbilical regions and decreased bowel sounds. Hematochezia was found in digital rectal examination. Upright abdominal X-ray did not show obstruction or perforation. Abdominopelvic ultrasonography (USG) was reported as an increased bowel gas and minimal fluid in pelvic region. Laboratory values were as follows: Hgb: 13.5 g/dl, Htc: 40.3%, WBC: 6200 µL, platelets: 221000 µL, glucose: 118 mg/dl, BUN: 26 mg/dl, creatinine: 1.5 mg/dl, AST: 19 U/L, ALT: 14 U/L, ALP: 201 U/L, GGT: 19 U/L, Na: 144 mmol/L, K: 3.6 mmol/L, Cl: 104 mmol/L, amylase: 41 U/L, albumin: 4.6 g/dl and globulin: 2.3 g/dl. Nothing was seen on chest X-ray except a minimally increased cardiothoracic ratio. Colonoscopy was performed, which revealed hyperemia throughout the entire colon with generalized edema. Superficial ulcers and hemorrhagic areas mainly localized in the sigmoid region were also noted. Doppler USG revealed that portal vein and main branch of mesenteric venous system were patent. Thrombus and collateralization were not detected. At the same time, an abdominal computerized tomography (CT) scan was done and thickening with irregularity was observed throughout the entire colonic wall (Figure 1). Abdominal CT findings supported the Doppler USG findings with patent inferior mesenteric vein.

After all these procedures and colonoscopic findings compatible with acute mesenteric ischemia, a mesenteric angiography was performed. Angiography revealed that SMA and inferior mesenteric artery (IMA) were intact with their main branches. However, distal narrowings and irregularities were observed in segmental and subsegmental branches with diminished intestinal mural perfusion (Figure 2A), and significant delay in capillary filling phase was observed during selective SMA injections (Figure 2B). Selective IMA images showed diminished contrast enhancement especially in the rectosigmoid region with distal narrowings and irregularities (Figure 2C). During the angiographic examination, indirect portographic study with late phase imaging was performed but diagnostic images could not be obtained because distal branches of the SMA could not be visualized by standard angiographic injections of the contrast material and parenchymal intestinal wall perfusion could not be obtained.

The case was accepted as NOMI and papaverine HCl infusion was started during angiography. After approximately 30 minutes, the patient develo-

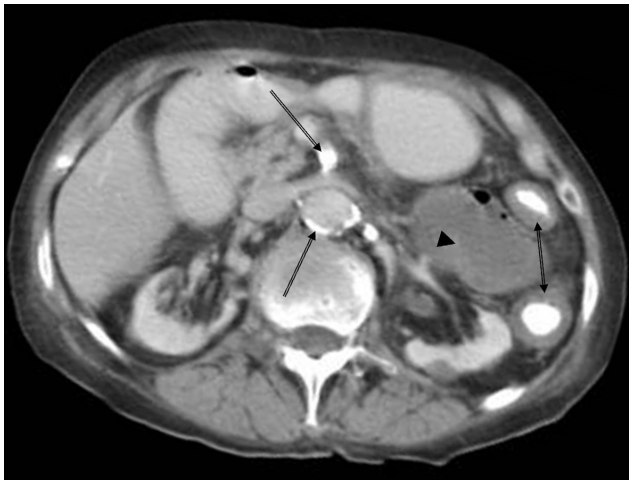

Figure 1. Abdominal CT examination: Diffuse concentric thickening observed in the descending colonic wall. Contrast filling cannot be seen in the wall (double head arrow). Intestinal distention with fluid observed nearby (arrow head). Calcified plaques in abdominal aorta and SMA are visualized (arrow).

ped a severe hypotension and infusion was discontinued. Nothing other than digitalis intoxication was suggested as an etiologic factor causing splanchnic vasoconstriction as a cause of NOMI. In the follow-up, the patient progressively deteriorated. Sepsis developed with shock, high fever and leukocytosis. Her blood pressure was 90/60 mmHg, HR 108/min, and body temperature 38.8°C. Laboratory values were Hgb: 9.9 g/dl, Htc: 29.9%, WBC: 17000 µL, and platelets: 308000 µL. Intravenous fluid replacement and broad spectrum antibiotic therapy were immediately started. However, the patient was unresponsive to the measures undertaken and eventually died.

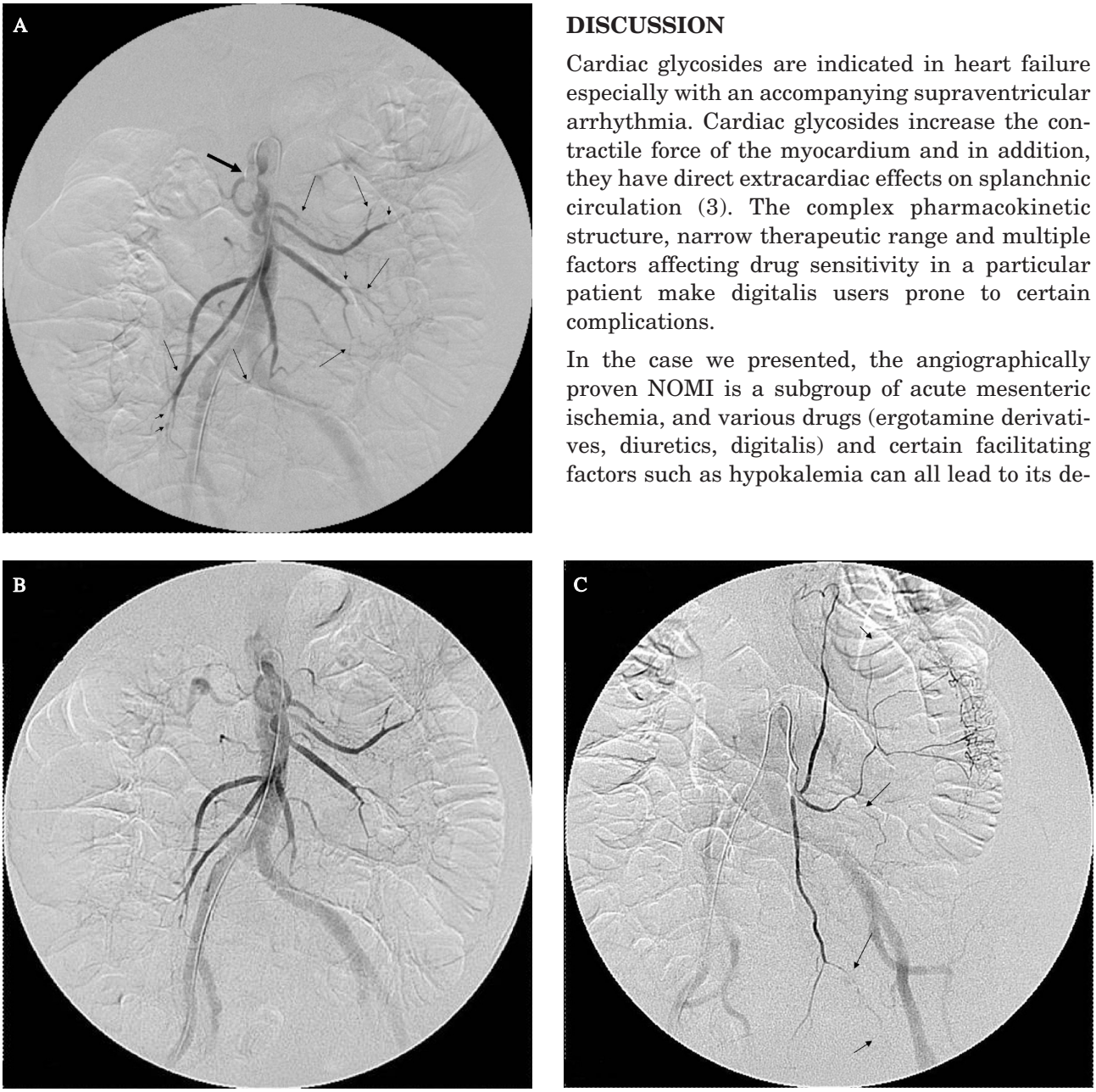

Figure 2. *Selective SMA and IMA angiograms:*
A) Main trunk of SMA and its major intestinal branches are observed to be patent and normal in calibration. The narrowing due to atherosclerotic calcified plaque at the SMA origin is visible on the anterior wall as a filling defect near the ostium of SMA (thick arrow). Distal narrowings (long arrow) and irregularities (short arrows) are observed in segmental and subsegmental branches with diminished intestinal mural perfusion. **B)** A significant delay in capillary filling phase is observed during selective SMA injections. Selective IMA angiogram showing diminished contrast enhancement especially in the rectosigmoid region with distal narrowings and irregularities (arrows).

DISCUSSION

Cardiac glycosides are indicated in heart failure especially with an accompanying supraventricular arrhythmia. Cardiac glycosides increase the contractile force of the myocardium and in addition, they have direct extracardiac effects on splanchnic circulation (3). The complex pharmacokinetic structure, narrow therapeutic range and multiple factors affecting drug sensitivity in a particular patient make digitalis users prone to certain complications.

In the case we presented, the angiographically proven NOMI is a subgroup of acute mesenteric ischemia, and various drugs (ergotamine derivatives, diuretics, digitalis) and certain facilitating factors such as hypokalemia can all lead to its de-

velopment (4). Cases focusing on these factors have been rarely reported in the literature previously (5, 6).

Digitalis intoxication is commonly encountered, but NOMI is actually a rare complication with digitalis use. Glycosides are proven to cause vasoconstriction in vascular smooth muscles *in vivo* and *in vitro* and can play a potentiating role in ischemia directly by increasing peripheral splanchnic resistance or indirectly via worsening the underlying ischemic factor (1, 2). Vasoconstriction in splanchnic beds have been demonstrated by intravenous digitalis application in normal patients and in those with heart failure (3). Digitalis causes mesentery bed vasoconstriction both directly and indirectly by the alpha adrenergic pathway, and this seems to be responsible for the cause of NOMI with digitalis use (7). However, the reason for digitalis causing mostly arteriolar vasoconstriction in the splanchnic region is still unclear. Cessation of digitalis therapy does not improve the clinical outcome, as observed in our case. This can be explained by the long elimination time of digitalis due to its long plasma half-life (7 days), and vague symptoms during the initial splanchnic bed hypoperfusion, which lead to a late or an incorrect diagnosis. NOMI is a clinical state in which clinical symptoms and signs are usually unclear initially. Therefore, this difficulty frequently leads to a late and inaccurate diagnosis, which can be fatal for the patient.

Generally, NOMI is diagnosed by mesentery angiography. Papaverine HCl infusion to the SMA frequently corrects the hypoperfusion (8), but in our patient this could not be achieved because of the development of hypotension as previously mentioned. Although at present there is no known specific agent for reversing the vasoconstriction effect of digitalis on the mesenteric vasculature, glucagon has been shown to normalize the increased mesenteric resistance caused by digitalis in animal models (9).

Glycosides have also been shown to have side effects on the heart, brain and intestines with different rates. Intestinal infarction secondary to NOMI caused by digitalis therapy leads to high mortality. For this reason, it should be kept in mind that patients on digitalis therapy who develop sudden and diffuse abdominal pain with or without tenderness and rigidity can have a non-occlusive mesentery ischemia.

REFERENCES

1. Trompeter M, Brazda T, Remy CT, et al. Non-occlusive mesenteric ischemia: etiology, diagnosis, and interventional therapy. Eur Radiol 2002; 12: 1179-87.
2. Lock G. Acute intestinal ischaemia. Best Pract Res Clin Gastroenterol 2001; 15: 83-98.
3. Bynum TE, Hanley HG. Effect of digitalis on estimated splanchnic blood flow. J Lab Clin Med 1982; 99: 84-91.
4. Weil J, Sen Gupta R, Herfarth H. Nonocclusive mesenteric ischemia induced by digitalis. Int J Colorectal Dis 2004; 19: 277-80.
5. Bareiss P, Desbrosses D, Christmann D, et al. Acute fatal non-occlusive intestinal ischemia during treatment with a cardiotonic glucoside. Ann Cardiol Angeiol (Paris) 1984; 33: 169-73.
6. Guglielminotti J, Tremey B, Maury E, et al. Fatal non-occlusive mesenteric infarction following digoxin intoxication. Intensive Care Med 2000; 26: 829.
7. Longhurst JC, Ross J Jr. Extracardiac and coronary vascular effects of digitalis. J Am Coll Cardiol 1985; 5: 99A-105A.
8. Brandt LJ, Boley SJ. AGA technical review on intestinal ischemia. American Gastrointestinal Association. Gastroenterology 2000; 118: 954-68.
9. Levinsky RA, Lewis RM, Bynum TE, Hanley HG. Digoxin induced intestinal vasoconstriction. The effects of proximal arterial stenosis and glucagon administration. Circulation 1975; 52: 130-6.