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Unexpected bleeding after Exenatide treatment: a causative relationship or a coincidence?

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Objectives. Diabetes mellitus is an endemic disease of the current era. It is important to treat it properly. All antidiabetic medications have side effects and various safety profiles.

Case report. Fifty-two years old patient with type II diabetes mellitus, who had spontaneous cutaneous and intra muscular bleeding after starting treatment with Exenatide. The patient's history did not include any kind of spontaneous bleeding. Investigations did not reveal abnormal platelets count and function or coagulation profile. The use of the Exenatide was discontinued and during one year of follow-up, the patient did not experience an additional occurrence of spontaneous bleeding.

Conclusions. To the best of our knowledge, this is the first report of spontaneous bleeding probably caused by Exenatide. The exact pathophysiology, by which the drug can cause spontaneous bleeding, is still not clear and has to be revealed.

Key words: glucagon like peptide 1, Exenatide, bleeding, complications

Diabetes mellitus (DM) is a systemic metabolic disorder, which causes microvascular and macrovascular complications. The worldwide prevalence of DM has risen dramatically over the past two decades. Based on the World Health Organization, 442 million people suffered from DM in 2014 (Mathers and Loncar 2006; Diabetes Fact Sheet, WHO, 2008). In 2012, there were 1.5 million cases of death worldwide directly caused by diabetes (Global Report on Diabetes, WHO, 2016).

Studies have conclusively determined that reducing hyperglycemia decreases the onset and progression of microvascular complications (UKPDS Group 1998; Stratton et al. 2000). The impact of glucose control on cardiovascular complications remains uncertain (Holman et al. 2008; Inzucchi et al. 2015).

Exenatide extended-release is a glucagon-like peptide-1 (GLP-1) receptor agonist, which is U.S. Food and Drug Administration (FDA) approved for treatment of Type 2 DM, not as the first line medication. Exenatide is injected subcutaneously once weekly. It lowers HbA1c in an average of 1.6% (starting at 8.5%). Each dose of Exenatide is made up of microspheres that slowly break down, gradually releasing the drug throughout a week (Syed et al. 2015; Frias et al. 2017).

Several side effects of Exenatide have been reported since marketing, affecting several body systems. Most common are gastrointestinal side effects including: nausea, vomiting, gastroesophageal reflux, abdominal discomfort, and pain (rarely obstruction). Other side effects include, pancreatitis, hypoglycemia, worsening hypertension, worsening tachycardia, kidney injury, hyperhidrosis, allergic and injection-site reactions, including serious injection-site reactions, with or without bumps (nodules), swelling, blisters, an open wound or a dark scab (Syed et al.

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2015; Frias et al. 2017; BYDUREON™, Highlights of prescribing information).

Rare hematologic side effects have been reported due to Exenatide, including increased international normalized ratio (INR) with concomitant Warfarin therapy (less than 0.1%), sometimes associated with bleeding (BYDUREON™, Highlights of prescribing information). No other hematologic side effects have been reported.

Case report

A 69 years old male patient was admitted to our internal medicine department in order to investigate new onset subcutaneous and visceral bleeding. His medical history had included diabetes mellitus diagnosed at the age of 52, hypertension, ulcerative colitis, and hyperlipidemia. The patient underwent craniotomy, because of non-secretory adenoma, 11 years before the index hospitalization. He never had major or minor bleeding before, including during or after the neurosurgery he underwent.

His regular medications include Glimepride, Verapamil, Omeprazole, Valsartan, Tamsulosin, and Pravastatin. He had also been treated with Aspirin for years without having any overt or obscure bleeding. One month before the index admission, he started treatment with Exenatide 2 mg subcutaneous once a week. After the fourth injection he was admitted to the general surgery department for abdominal pain and an abdominal hematoma. Later, he was transferred to our internal medicine department due to worsening subcutaneous bleeding. He denied any gastrointestinal or urinary bleeding.

Table 1
Laboratory results during hospitalization

Parameter	Result	Normal range
Hemoglobin (g/dL) baseline	13.5	13–17
Hemoglobin (g/dL) lowest level during hospitalization	8.9	13–17
Platelets (x10^3/μL) lowest level during hospitalization	243	130–350
PT (s)	12.2	8.5–12.5
INR	1.06	0.75–1.3
PTT (s)	26.8	22–32
Thrombin time (s)	17.4	15–20
TEG R time (min)	5.5	2–8
TEG kinetics (min)	0.8	1–3
TEG angle (degree)	80.4	55–78
TEG maximum amplitude (mm)	77.8	51–69

Abbreviations: PT – prothrombin time; INR – international normalized ratio; PTT – partial thromboplastin time; TEG – thromboelastogram

His physical examination on admission and during hospitalization included normal vital signs, with neither fever nor tachycardia. His skin exam disclosed extensive subcutaneous hematomas and ecchymosis on the right thorax, anterior abdomen, and right buttock.

Blood tests revealed a gradual hemoglobin drop of 4.6 g/dl (from 13.5 to 8.9 g/dl) (Table 1). The platelets count was normal as were prothrombin time (PT), partial thromboplastin time (PTT), thrombin time (TT), and thromboelastogram (TEG). Total bilirubin was slightly elevated up to 1.7 mg/dl with 0.48 mg/dl direct bilirubin. Kidney function tests, aspartate aminotransferase (AST), alanine transaminase (ALT), and alkaline phosphatase were all normal. A CT scan of the thorax and abdomen showed signs of hematomas in the rectus sheath, latissimus dorsi, intercostal space, and in the supra diaphragmatic fat (Figure 1and Figure 2).

During his hospitalization, Exenatide was discontinued. He was hemodynamically stable and his hemoglobin levels were stable. After his discharge, he stayed under close follow up, without treatment of Exenatide. After one year of follow-up, no recurrent source of bleeding was seen and his hemoglobin levels gradually raised back to 13.9 g/dl.

Discussion

According to the WHO-UMC system for standardized case causality assessment (WHO – Uppsala Monitoring Centre), the reasonableness that Exenatide treatment was the cause for bleeding is probable. The Naranjo Adverse Drug Reaction Probability Scale (Naranjo et al. 1981) is also probable (five points). In order to prove a definite relationship between Exenatide and the bleeding in this patient, we would have needed to re-administer the drug for a re-challenge, but this would obviously be un-ethical.

The patient never had major or minor bleeding before, not even though he had gone through a craniotomy. He also did not have any kind of bleeding during one year of follow up after the drug discontinuation. The presumed side effect of the drug appeared only after the fourth dose and ceased about one week after the drug cessation. This could have been due to the slow release of the drug after injection.

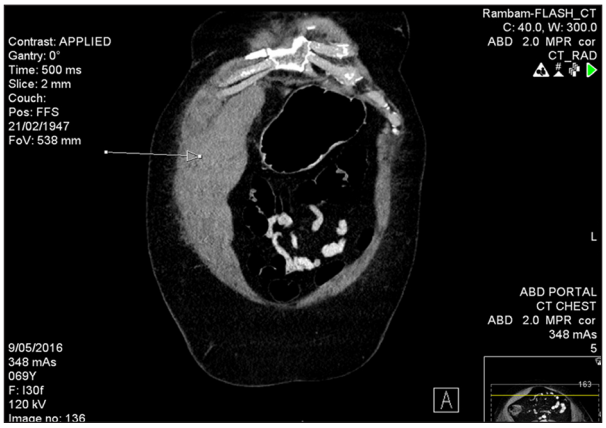

Figure 1. Abdominal CT scan, coronal view, showing a large hematoma in the right side of the abdomen.

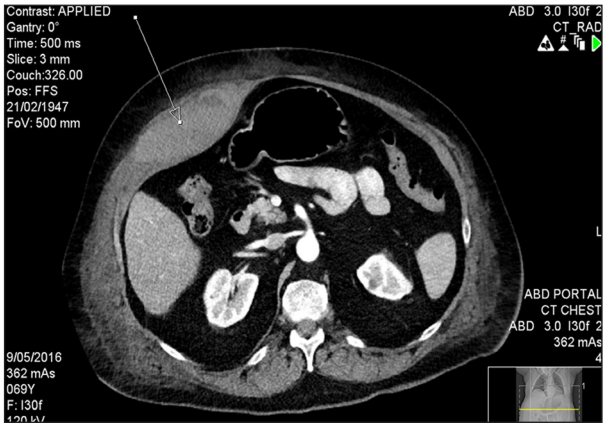

Figure 2. Abdominal CT scan, axial view, showing a hematoma in the right side of the abdomen.

A post marketing warning concerning interaction between Exenatide and Warfarin leading to INR prolongation with consequent bleeding, was previously published (BYDUREON™, Highlights of prescribing information). However, a small trial on the concomitant use of Exenatide and Warfarin did not show a prolongation in INR (Soon et al. 2006).

To the best of our knowledge, this is the first report of bleeding probably caused by Exenatide treatment without concomitant anti-coagulation treatment. The exact pathophysiology by which the drug can cause spontaneous bleeding is still not clear and has to be revealed. Our investigation did not reveal a thrombocytes or coagulation abnormality, however, the mechanism seems to be systemic, because the hematomas were not the injection sites.

In summary, we report a possible side effect of Exenatide in a case associated with an unexpected bleeding. Physicians should keep in mind such an adverse effect, especially in the patients treated with the anti-coagulation, but not only in them.

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