Discussion

Our present report is of the youngest child, to the best of our knowledge, to be newly diagnosed with T2DM and presenting with HHS. Although the incidence of HHS in children is increasing, it is still considerably less frequent than diabetic ketoacidosis (DKA) [1]. Fourtner et al. [6] reported that 3.7% of adolescents with T2DM also presented with HHS. Rosenbloom [4] compared 26 cases of HHS reported during 1966–2000 with 65 reported and six unreported cases during 2001–2008, and found that all patients in the more recent group were aged > 9 years, with a male-to-female ratio of 3.5:1, and 75% of them were obese, whereas 73% of patients in the earlier reports were < 9 years of age and showed an equal gender distribution, with no reported cases of obesity [4].

Underlying infection represents the most common precipitating cause of HHS [7]. However, delayed diagnosis of new-onset T2DM with an insidious presentation could lead to the development of HHS as well, as in the case of our present patient, whose clinical presentation was similar to those of previously reported cases of children with HHS [4,7], except that she is one of the youngest so far and the index of suspicion was too low for such a diagnosis. Yafi and Collins [8] reported a case of Texan toddler with T2DM, but no HHS. This was thought to be the youngest child ever diagnosed with T2DM, although other causes of diabetes were not ruled out by the necessary genetic tests.

Most current case reports of HHS in T2DM are of adolescent patients, although other atypical presentations of HHS had been previously reported. Tsai et al. [9] reported on an obese 15-year-old African American boy newly diagnosed with T2DM who presented with HHS, but with a mixed picture of DKA, whereas Moued et al. [5] reported on a 7-year-old boy who presented with HHS with newly diagnosed type 1 diabetes mellitus complicated by hypernatraemic dehydration.

As an increasing prevalence of T2DM in children and adolescents of all ethnicities has recently been reported around the world [10], regular screening for diabetes in patients with risk factors, regardless the age, should be reemphasized to avoid diagnostic delays and to minimize the risk of life-threatening complications like HHS.

Conclusion

T2DM should be anticipated in children of any age as long as they show the typical phenotype and risk factors. Delaying the diagnosis could lead to more serious, and sometimes life-threatening, complications.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

The authors wish to extend their gratitude to the parent of the patient in this case report for giving permission to have this case published for academic purposes.

References

[1] Wolfsdorf JI, Allgrove J, Craig ME, Edge J, Glaser N, Jain V, et al. ISPAD Clinical Practice Consensus Guidelines 2014 Compendium. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. Pediatric Diabetes 2014;15:154–79.
[2] Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. Diabetes Care 2006;29:2739–48.
[3] Maletkovic J, Drexler A. Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State. Endocrinol Metab Clin N Am 2013;42:677–95.
[4] Rosenbloom AL. Hyperglycemic hyperosmolar state: an emerging pediatric problem. J Pediat 2010;156:180–4.
[5] Moued M, Al-Agha AE, Ahmad IA. Hyperosmolar hyperglycemic state (HHS) in newly diagnosed child with type 1 diabetes mellitus: a case report. Turk Jem 2013;17:19–21.
[6] Fourtner SH, Weinzimer SA, Levitt Katz LE. Hyperglycemic hyperosmolar non-ketotic syndrome in children with type 2 diabetes. Pediatr Diabet 2005;6:129–35.
[7] Pasquel FJ, Umpierrez GE. Hyperosmolar hyperglycemic state: a historic review of the clinical presentation, diagnosis, and treatment. Diabetes Care 2014;37:3124–31.
[8] Yafi M, Collins K. A toddler with type 2 diabetes. In: EASD 2015; 2015.
[9] Tsai SL, Hadjiyannakis S, Nakhla M. Hyperglycemic hyperosmolar syndrome at the onset of type 2 diabetes mellitus in an adolescent male. Paediatr Child Health 2012;17:24–6.
[10] Reinehr T. Type 2 diabetes mellitus in children and adolescents. World J Diabetes 2013;4:270–81.

N. Al Hassani*, W. Kaplan
Division of Diabetes and Endocrinology, Department of Pediatrics, Tawam Hospital, P O Box 15258, Khalifa-Ibn-Zayed street, Al Ain, United Arab Emirates

*Corresponding author
E-mail address: nohassani@seha.ae (N. Al Hassani).

Received 26 October 2017
Received in revised form 6 November 2017
Accepted 12 November 2017
Available online 25 November 2017

https://doi.org/10.1016/j.diabet.2017.11.004

GLP-1 agonist associated acute kidney injury: A case report and review

Introduction

Glucagon-like-peptides (GLP)-1 agonists have gained popularity over the last decade and are being increasingly used in the management of obese diabetes type-2 patients, owing to their much desired weight loss benefits in addition to effective glycemic control. However, since the FDA approval of Byetta® (exenatide) in 2005, there have been cases of acute kidney injury (AKI) reported to the agency [1] and 11 such published cases [2–8], leading to FDA's revision of the drug label in 2008, to highlight that Byetta should not be used in patients with severe renal impairment or end stage renal disease.

All these cases of AKI have occurred in patients taking Byetta®, which needs twice daily dosing. However, in 2012, a new extended release (ER) preparation of exenatide, requiring once weekly dosing (Bydureon) was approved by the FDA. Ours is the first case of acute kidney injury (AKI) caused by the extended release formulation in a patient who had normal baseline renal function before commencing the drug. The patient had a distinctive clinical presentation that included a peculiar skin rash appearing just before the kidney injury and improvement with treatment of the same. Also included are the detailed renal biopsy report as the only two published biopsy reports of exenatide induced AKI, have

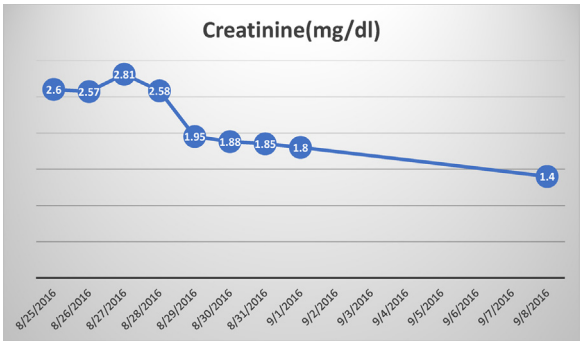

Fig. 1. Creatinine levels at diagnosis of AKI and trending over 2 weeks.

reported different pathologies for renal failure in these patients: acute tubular necrosis and tubulointerstital nephritis [5,8].

Additionally, we also review the 13 [2–9] so far published cases of exenatide (11 cases) & liraglutide (2 cases) induced ATN to analyze and understand the patient characteristics, clinical symptoms and prognosis associated with this serious complication which will help physicians anticipate and prevent AKI in these patients.

Case report

A 52-year-old severely obese female with BMI 36, hypertension and 2 year history of diabetes mellitus presented to the emergency department with complaints of nausea, vomiting, abdominal pain and an expanding abdominal rash for 1 week. She was found to have acute kidney injury (AKI).

Exenatide (Bydureon®) 2 mg ER subcutaneous injection was added to metformin 1 mg BD, 6 weeks before presentation. At the time, her kidney function was normal with a creatinine of 0.82 mg/dL (72.5 umol/L), GFR 80.1 mL/min/1.73 m^2 and a baseline Hb1Ac of 7.2% (55 mmol/mol). Her medical conditions included migraine, asthma, celiac disease and hypothyroidism and she was being treated with Triamterene-Hydrochlorothiazide 37.5–25 mg, Losartan 100 mg, Exemestane 25 mg, Amlodipine 10 mg, Levothyroxine 50 mcg, Ezetimibe 10 mg, Cholecalciferol 50,000 IU biweekly, Beclomethasone, Albuterol inhalers and Epinephrine. Patient had known allergies to fish oil, Iodine, Mango, Penicillin, Tirosin and Azithromycin.

After the very first dose of exenatide patient had itching and lump formation at injection sites which was attributed to local atopy considering her multiple allergies and as a common side effect of the drug, but after the fifth (last) dose she developed a large erythematous lesion on her abdomen which was followed by progressive nausea leading to multiple vomiting episodes and diarrhea in the following week. She had no fever, abdominal or flank pain, no urinary symptoms and no history of NSAID intake. The rash resolved over the next few weeks.

Her vitals at presentation were BP 154/74, HR 104, RR 16 and Temp 37.1 °C (98.7 °F). Lab tests revealed Glucose 116, BUN 32, Creatinine 2.6 mg/dL (229.89 umol/L), GFR 20.5 mL/min/1.73 m^2, Na 140, Potasssium3.7, Chloride 96, Albumin 4.8 and a Calcium 11.4. Her Hb1Ac had improved to 5.9% (41 mmol/mol) from 7.2% (55 mmol/mol) with Exenatide and she had lost over 10 lbs in 5 weeks of treatment. Abdominal USG showed no urinary tract obstruction. Urinalysis reported clear straw colored urine, specific gravity of 1.004, leukocytes 3+, WBC > 25, bacteria 3+ and few squamous epithelial cells. Eosinophil smear was negative. Urine chemistry revealed albumin creatinine ratio of 35 indicating increased risk for diabetic nephropathy.

The differential diagnosis included non-oliguric acute kidney injury secondary to volume depletion (caused by diarrhea, vomiting, diuretics) versus direct kidney injury due to Exenatide. Intravenous fluids were started and Losartan/HCTZ/Triamtrene were withdrawn. Patient was also treated with ciprofloxacin for potential UTI based on urinalysis. In addition to fluids and antibiotic for UTI, in-hospital medications included amlodipine 10 mg, levothyroxine 50 mcg, ondansetron, exemestane, ezetimibe, insulin lispro and heparin.

Over the next 3 days, her renal function did not improve despite volume repletion and continued to worsen with creatinine increasing from 2.6 mg/dL to 2.81 mg/dL (229.89 to 248.46 umol/L) (Fig. 1). However, hypercalcemia and leukocytosis resolved with intravenous fluids. With continued IVFs, patient showed delayed response when her renal function began to recover on the fourth day of admission. However, it did not reach baseline levels over next 2 weeks, when we obtained renal biopsy. The kidney biopsy pathology revealed evidence of acute tubular injury, tubular atrophy, mild interstitial fibrosis and moderate arterio- and arteriolosclerosis (Fig. 2). Negative immunofluorescence findings provided evidence against active immune complex mediated glomerular disease.

Electron microscopy revealed normal texture, thickness and contour of glomerular basement membranes. Podocyte foot process effacement was minimal, involving 10% of the capillary surface area. No immune type electron dense deposits were seen. Tubules displayed mild degenerative changes including prominent autophagolysosomes. Hence, both ischemic and toxic forms of ATN were in the differential diagnosis. Light microscopy also reported prospect for significant renal recovery, given the lack of significant renal scarring.

Our patient continued to show recovery of renal function over the next week with her creatinine dropping to 1.25 mg/dL (110.53 umol/L) 3 weeks after the event. She did not require steroids or hemodialysis anytime during hospital stay.

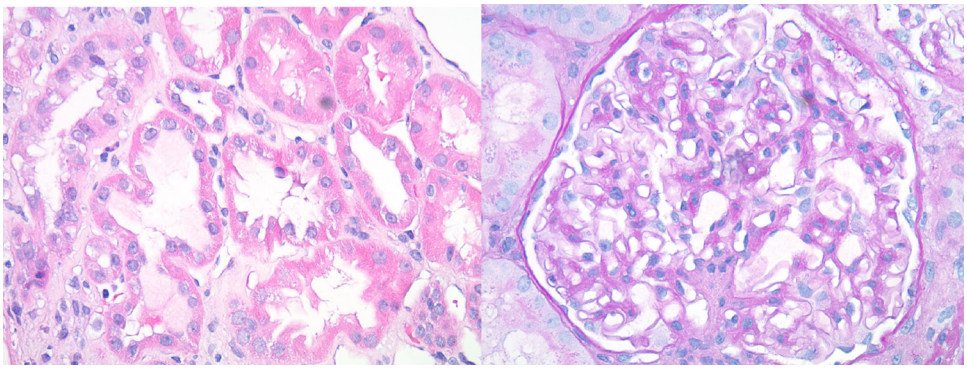

Fig. 2. Renal biopsy revealing evidence of acute tubular injury, tubular atrophy, mild interstitial fibrosis and moderate arterio- and arteriolosclerosis.

Analysis of published cases

On analyzing the 13 published cases of acute renal failure attributed to GLP-1 agonists, both liraglutide (2 cases) and exenatide (11 cases) [2–9], we found the mean age to be 63, however one case was reported in a 20 year old. The patients had a baseline mean Hb1Ac of 10.1 (87.1 mmol/mol) and a BMI ranging from 35 to 47. The renal function was normal (< 1.2 mg/dL or 106.1 umol/L) in the majority (70%) of patients at the time of commencing the drug. The other 30% had creatinine between 1.2 to 2 mg/dL (106.1 to 176.84 umol/L). The dose of Byetta® was 5 mcg BID in 50% of patients and 10 mcg BD in the other 50%. Dose of liraglutide was 1.2 mg/day in one and 1.8 mg/day in the other. Patients had responded well initially with Hb1Ac improving by an average of 1.5% (17 mmol/mol) and patients experiencing a mean weight reduction of 7.7 kilograms before renal failure. Patients either reported initial good GI tolerance to the drug or easing of these symptoms after first few weeks. However, patients either had sudden recurrence or new-onset of GI symptoms just prior to presentation, the incidence of which seemed to peak at 11 weeks of treatment (ranging from 5 days to 9 months). The symptoms were reported for an average of 5 days before presentation and included nausea (85%), vomiting (70%), skin rash, diarrhea, drowsiness, decrease urination and flank discomfort in few. None of the patients reported abdominal pain or symptoms suggestive of pancreatitis. Fifty percent of the patients needed hospitalization. Majority of the patients (85%) had no overt hypotension at presentation. Creatinine level at diagnosis was below 5.0 mg/dL (442 umol/L) in the majority (60%) and ranged from 2.09 to 22.8 mg/dL (184.8 to 2015.98 umol/L). None of the patients was taking NSAIDs. However, all of the patients were taking stable doses of ACEi/ARBs and diuretics. Renal USG was negative for obstruction in 100% of patients. Tests for antinuclear antibodies (ANA) and anti-neutrophil cytoplasmic antibodies (ANCA), and cryoglobulinemia were negative in all. GLP-1 agonists were discontinued permanently in all except 1 patient. Majority of the patients (9.64%) responded to IV fluids and discontinuation of nephrotoxic drugs, 2 needed dialysis (13%), 2 needed steroids (13%) and 1 needed both steroids and dialysis (5%).

With regards to pathology of AKI in these patients, exenatide induced to acute tubular necrosis (ATN) was identified in 2 reports (including ours) and tubulointerstital nephritis in one. In the single available biopsy report of Liraglutide induced AKI, tubulointerstital nephritis was identified. Renal function recovered partially (57% patients) or completely (43% patients) over an average of 5 weeks.

Conclusion

The review of published cases suggests the following considerations: GLP-1 agonists may cause AKI via two mechanisms: acute interstitial nephritis (AIN) as well as acute tubular necrosis (ATN). Majority of cases developed in patients with normal baseline renal function with no age or gender predilection, emphasizing caution with every patient. Renal failure may occur despite patients originally experiencing encouraging responses to the drug: significant drop in Hb1Ac and loss of weight. Mean duration of treatment before AKI was 11 weeks, but may occur as early as 5 days to several months. Regular adequate fluid intake should be encouraged in all patients on GLP-1 agonists, as majority of cases were attributed to volume depletion and responded well to fluids. Physicians should exercise caution and monitor renal function/discontinue drug, if patient experiences sudden recurrence of nausea or vomiting after a symptom-free period following drug initiation. Skin rash, anorexia, fatigue, malaise, drowsiness, and flank discomfort should also draw attention. Both Byetta® and the extended release form Bydureon® of exenatide may cause this event. Similar incidence of AKI was noted in patients taking starting dose (5 mcg BD) or escalated dose (10 mcg BD) of Byetta®.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm188656.htm.
[2] Dubois-Laforgue D, Boutboul D, Levy DJ, Joly D, Timsit J. Severe acute renal failure in patients treated with glucagon-like peptide-1 receptor agonists. Diabetes Res Clin Pract 2014;103:e53–5.
[3] Bhatti R. Exenatide-associated renal failure. Pract Diabetes Int 2010;27:232–4.
[4] Johansen OE, Whitfield R. Exenatide may aggravate moderate diabetic renal impairment: a case report. Br J Clin Pharmacol 2008;66:568–9.
[5] Weise WJ, Sivanandy MS, Block CA, Comi RJ. Exenatide-associated ischemic renal failure. Diabetes Care 2009;32:e22–3.
[6] Lopez-Ruiz A, del Peso-Gilsanz C, Meoro-Aviles A, Soriano-Palao J, Andreu A, Cabezuelo J, et al. Acute renal failure when exenatide is co-administered with diuretics and angiotensin II blockers. Pharm World Sci 2010;32:559–61.
[7] Ferrer-Garcia JC, Martinez-Chanza N, Tolosa-Torrens M, Sanchez-Juan C. Exenatide and renal failure. Diabet Med 2010;27:728–9.
[8] Nandakoban H, Furlong TJ, Flack JR. Acute tubulointerstitial nephritis following treatment with exenatide. Diabet Med 2013;30:123–5.
[9] Linnebjerg H, Kothare PA, Park S, Mace K, Reddy S, Mitchell M, et al. Effect of renal impairment on the pharmacokinetics of exenatide. Br J Clin Pharmacol 2007;64:317–27.

T. Sharma*, R. Paixao, C. Villabona

Department of Internal Medicine, University of Connecticut, 262, Farmington Avenue, Farmington, CT 06030, USA

*Corresponding author
E-mail address: sharmatoishi@gmail.com (T. Sharma).

Received 29 October 2017
Received in revised form 25 November 2017
Accepted 3 December 2017
Available online 09 December 2017

https://doi.org/10.1016/j.diabet.2017.12.002
1262-3636/Published by Elsevier Masson SAS.

Patients with diabetes and foot ulcer present cognitive dysfunction and express fewer needs in terms of educational support

Introduction

Despite global improvement in the care of diabetes patients (DPs), the frequency of diabetic foot ulcer (DFU) is expected to increase because of ageing of the population [1]. Patient education on self-care is recommended for the prevention of foot ulceration and amputation [2]. However, despite better screening of patients at high risk of DFU and specific structured podiatric care, healing failure, DFU recurrence and amputation still affected > 50% of patients over a 5-year observation period [3]. To improve individualized foot care management, a proof-of-concept study explored patients' needs in terms of therapeutic patient education