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Acute Interstitial Nephritis Due to Tirzepatide (Mounjara)

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Abstract

Background: Tirzepatide (T) is a gastric inhibitory polypeptide (GIP) and GLP-1 receptor agonist approved by the U.S. Food and Drug Administration for the treatment of obesity and type 2 diabetes in 2022. The reported spectrum of its renal SEs was thought to be limited to volume depletion following gastrointestinal upsets. In this case report, we add an intrinsic etiology to its renal SEs. **Case:** A 43-year-old woman was referred for recent fluid overload and an increase in serum creatinine from baseline at 330 umol/L to 740 umol/L. She had type II diabetes mellitus as well as stable and chronic renal failure, which is clinically compatible with diabetic glomerulosclerosis. She did not have other previous medical illness or chronic intake of other medications. However, she admitted to taking Tirzepatide (Mounjara) for weight reduction 1 month prior to her recent admission. Her kidney biopsy showed acute interstitial nephritis on top of diffuse diabetic glomerulosclerosis. Serum complements, ANA, ANCA, protein electrophoresis, IgG4 level, hepatitis B, and C serology were within normal levels. T was discontinued, and she was treated with Mycophenolate mofetil (MMF) 1 g twice daily. To hasten the immunologic response without disturbing her diabetic management, an initial Prednisone 60 mg/day was given for 3 days. By 2 weeks, serum creatinine had improved to her previous baseline and did not require furosemide for fluid overload. By 6 weeks, MMF was discontinued, and she remained stable for 1 year. **Conclusion:** In genetically predisposed patients, acute interstitial nephritis can be triggered following T-use, yet it is amenable to drug-discontinuation and 6-week therapy with MMF.

Keywords

Genetic-Predisposition, Interstitial Nephritis, Prednisone, Tirzepatide, Moungaro, Side-Effects, Triggers

1. Introduction

Tirzepatide (T) is a gastric inhibitory polypeptide (GIP) and GLP-1 receptor agonist that was developed by Eli Lilly and Company in May 2022, as an adjuvant therapy to metformin and lifestyle modification in patients with type II diabetes mellitus (DMII) [1]. Subsequently, it was approved for weight loss in November 2023 [2]. It is more potent than selective GLP-1 receptor agonists, such as Dulaglutide (sold as Trulicity) and Semaglutide (sold as Wegovy, Ozempic, and Rybelsus) due to its: 1) greater affinity to such receptors, 2) dual action on GIP via stimulation of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, and 3) stimulation of adiponectin (adipokine involved in regulation of both glucose and lipid metabolism) [3]. Its approximate weight loss is 22.5% of their initial body weight by week 72 of treatment, at a maximum dose of 15 mg[1]. Despite its advantage, T remains a costly drug with an average wholesale price of $1080/month for its weekly injections[1]. T and all other GLP-1RAs are contraindicated in subjects with a personal or family history of medullary thyroid carcinoma or in people with multiple endocrine neoplasia type 2 [4]. Moreover, despite its widespread use and success, it is associated with short-term side effects (SEs), such as gastrointestinal upsets, pancreatitis, hair loss, anaphylaxis, angioedema, and drug interactions, as well as long-term side effects, such as gastroparesis, retinal disease, gallstones, and suicidal ideation [5]. The reported spectrum of its renal SEs was limited to volume depletion following gastrointestinal upsets [6]. In this case report, we expand such a spectrum with an intrinsic one.

2. The Case

A 43-year-old woman presented with progressive shortness of breath for 1 week. She has been known to have insulin-requiring DMII for 9 years, with chronic renal failure clinically compatible with diabetic glomerulosclerosis for 2 years. Both diseases were stable with diet, Telmisartan 40 mg daily, and insulin (glargine 20 units pm with Aspart 14, 20, and 10 units prior to respective meals). The patient's demographic data, biochemical changes, and treatment are summarized in **Table 1**. Two months prior to her recent presentation, her serum creatinine was 330 umol/L and albumin at 33 g/L with proteinuria at 1.2 g/day. She had morbid obesity, yet without previous medical illness or chronic intake of other medications except for the recent start of T at 5 mg/week 1 month ago. On her initial physical examination, she was short of breath with evident jugular venous distension, bilateral basal fine rales, and lower limbs oedema. She was afebrile and had a blood pressure of 180/120 mm Hg. She was short and had a body weight of 106 kg. Systemic examination did not show other abnormalities. She had normal peripheral leucocytic and platelet counts. Hemoglobin was 103 g/L with normal transferrin saturation% and vitamin B12. Serum urea and creatinine were elevated at 40 mmol/L and 740 umol/L, respectively. Serum sugar, electrolytes, and liver functions were

[1]Lilly Prescribing Information on Tirzepatide, January 1, 2025.

normal except for albumin at 26 g/L. Urine routine and microscopy showed 2(+) proteinuria, yet without hematuria and pyuria. Ultrasound examination of the abdomen and pelvis did not show abnormality except for fatty liver and normal-sized kidneys with increased cortical echogenicity. Since she had a recent increase in serum urea and creatinine as compared to her baseline data, a diagnosis of acute renal injury was established. Fluid overload and hypertension were controlled with high-dose furosemide, and insulin doses were adjusted to avoid hypoglycemia. T was discontinued, and Telmisartan was held. Since her clinical picture was suspicious of acute interstitial nephritis, Mycophenolate mofetil (MMF) 1 g twice daily was started, as well as Prednisone 60 mg/day. Prednisone therapy was limited to 3 days only in an attempt to: hasten the immunologic response in such a critically ill patient since MMF needs days to manifest its action, and to avoid disturbing her diabetic management with long-term high Prednisone therapy. Two days after stabilization, a kidney biopsy was done. It showed mainly diffuse and occasionally nodular glomerulosclerosis with hyalinization of afferent and efferent arterioles, confirming baseline diabetic glomerulosclerosis. Moreover, it showed diffuse interstitial infiltrate with lymphocytes, eosinophils, and plasma cells, indicating acute interstitial nephritis (Figure 1). A few days later, serological tests for autoimmune diseases, namely, serum complements (C3&C4), ANA, ANCA, protein electrophoresis, IgA level, HIV, hepatitis B surface antigen, and anti-HCV antibodies were within normal levels. Within a few days, the patients had improved clinically with a decrease in serum creatinine. By 2 weeks, serum creatinine decreased to her previous baseline and did not require Furosemide therapy. By 6 weeks, MMF was discontinued, and Telmisartan was restarted. She remained stable clinically and biochemically up to 1 year on follow-up.

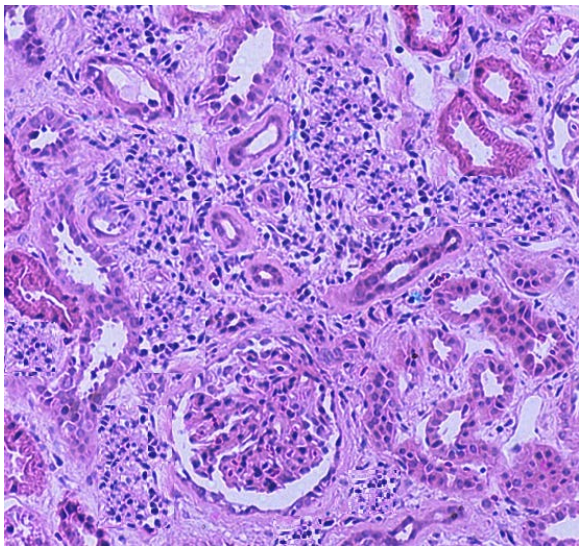

Figure 1. Photomicrograph of a kidney biopsy showing diffuse diabetic glomerulosclerosis associated with interstitial infiltration with lymphocytes, eosinophils, and plasma cells (H&E X400).

Table 1. Flow chart of demographical data, biochemical changes and treatment of a patient with acute interstitial nephritis induced by Tirzepatide (Mounjara).

	Time				
	−2 months	0	2 weeks	6 weeks	1 year
Demographical data:					
Age, gender & race: 43 years, white, female					
Clinical data:					
Main complaint: Fluid overload × 1 week					
Blood pressure: (120 - 80 mm Hg)	120/80	180/120	160/100	120/80	120/80
Body weight: (Kg)	101	106	100	101	100
Laboratory tests:					
Hemoglobin: (130 - 160 g/L)	118	103	110	110	115
Biochemistry:					
Serum urea (4 - 6 mmol/L)	21	40	29	32	39
Serum creatinine (60 - 120 umol/L)	330	740	370	350	360
Serum albumin (35 - 50 g/L)	33	26	27	31	35
Urine routine (proteinuria/hematuria): (−/−)	1(+)/(−)	3(+)/(−)	3(+)/(−)	2(+)/(−)	1(+)/(−)
24-hour urinary protein: (<150 mg)	1.2 g	2.5 g	3.5 g	2 g	1 g
Management:					
Tirzepatide					
Prednisone					
Mycophenolate mofetil					
Furosemide					
Telmisartan					

3. Discussion

Acute kidney injury has been reported with GLP-1 receptor agonists. Their gastrointestinal SEs remained a major limiting factor that can result in dehydration and subsequent pre-renal kidney injury. Discontinuation or dose-reduction of the drug in addition to symptomatic treatment of volume depletion is indicated [7]. Recently, 2 separate publications added 2 major renal SEs of the drugs, namely acute renal infarction and biopsy-proven acute interstitial nephritis [8] [9]. In the latter, management included drug discontinuation rather than dose decrement and short-course of Corticosteroids rather than plain volume expansion. The latter SE is different from the reported severe type 1 hypersensitivity reactions, such as anaphylaxis and angioedema, with T, which is associated with cross reactivity

to other GLP-1Ras [10]. Such drug-induced interstitial nephritis is a delayed T-cell-mediated hypersensitivity reaction that takes days to manifest, as in our patient. The host immunogenic response is elicited by: 1) a drug or its metabolite (hapten) with a carrier protein (haptenization) or 2) direct interaction of the drug with a specific host protein (p-i concept). Moreover, if the offending drug is not identified and discontinued in a timely manner, irreversible fibrosis and chronic kidney disease have been described [11]. Hence; management of the severe AIN in our patient dictated; a) Initial Prednisone-use for its rapid and potent action on immune-mediator cells and cytokines [12], b) limiting Prednisone-use to 3 days only to avoid its short and long-term SEs in our patient with obesity, insulin resistance and insulin-dependent DMII, and c) selection of MMF as a maintenance immunotherapy since it effectively prevents the proliferation of T and B cells, but may be less effective against already proliferating cells [13]. In our patient, the rare development of AIN following T-use, despite its worldwide use, may have been due to an idiosyncratic reaction due to genetic predisposition triggered by the drug.

4. Conclusion

T has a major role in the management of diabetes mellitus and obesity. However, healthcare providers should be aware of its short-term and long-term SEs to achieve the patient's safety and drug efficacy.

Authors' Contributions

Prof/Kamel El-Reshaid conceived the study, participated in its design, and drafted the manuscript. Dr. Shaikha Al-Bader participated in the study design, follow-up of patients, data collection, and tabulation of data.

Data Availability Statement

The data provided in the current review are available from the references.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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