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REVIEW ARTICLE

Drug-induced liver injury associated with liraglutide use: a systematic review of detection, severity, causality assessment, and clinical outcomes

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Abstract

Background and Aim: Drug-induced liver injury (DILI) remains the most important etiology of acute liver failure in the United States. It often presents a diagnostic conundrum due to the lack of a specific biomarker or diagnostic modality. Liraglutide, a glucagon-like peptide-1 agonist, has recently gained clinical importance for its anti-obesity and anti-diabetic effects. While a constellation of adverse events has been reported, the published data on its hepatotoxic potential remains limited. We hereby delineate a rare case of liraglutide-associated DILI. Furthermore, a systematic review of MEDLINE, Google Scholar, Scopus, and Cochrane databases was conducted on DILI following liraglutide therapy. Specific terminologies were used to identify relevant English-language articles. The latest search date was December 20, 2022. Our search identified a total of 4 case reports (level of clinical evidence: IV). We discuss the limited available data on detection, severity, causality assessment, and clinical outcomes in patients with liraglutide-induced DILI.

Relevance for Patients: DILI rarely occurs in patients undergoing liraglutide therapy. Clinicians and hepatologists can play a key role by promptly recognizing and stopping the offending agent. Therefore, intensive pharmacovigilance is imperative for ensuring patient safety and clinical effectiveness. Patients on liraglutide may be considered for baseline testing and periodic liver function monitoring.

1. Introduction

Drug-induced liver injury (DILI) is characterized by acute or chronic liver dysfunction secondary to a prescription or non-prescription drug, with the reasonable exclusion of alternative etiologies [1]. It is a distinct clinical entity that has increasingly been recognized worldwide. Woo *et al.* found in their PubMed search that over 3000 papers were published on DILI in 2021, roughly twice as many as in 2011 [2]. The estimated annual incidence of DILI in the United States is approximately 3/100,000 people [3]. DILI is responsible for over 50% of acute liver failures, making it the most common cause in the United States [4]. It can be classified into several groups based on clinical presentation, causal mechanism, and histological architecture. A vast majority of DILI patients remain asymptomatic, but jaundice is the most common clinical sign among symptomatic individuals [5]. A liver biopsy is not essential for diagnosis, but it can help rule out other probable causes [5,6].

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Over 1100 drugs, toxins, and herbs have been implicated in causing liver dysfunction [7]. Newer drugs are continuously added to the list in a searchable database, LiverTox [8]. It is maintained by the National Institute of Diabetes and Digestive and Kidney Diseases [8]. For instance, in our National Inpatient Sample-based retrospective study, we discovered that immunotherapy was linked to a roughly 5-fold increased risk of in-hospital hepatotoxicity when compared to a matched inpatient group [9]. In patients with DILI, prompt cessation of the culprit drug is the cornerstone of clinical management [10]. Moreover, idiosyncratic adverse drug reactions may show a serious clinical course, leading to considerable morbidity or even mortality. Therefore, it is critical to have up-to-date knowledge of drugs that may cause DILI [10].

Liraglutide, a glucagon-like peptide-1 (GLP-1) analog receptor agonist, has been found effective for type 2 diabetes mellitus, weight loss, and reducing major adverse cardiovascular events in diabetic individuals with established cardiovascular disease [11,12]. GLP-1 analogs stimulate GLP-1 receptors in the pancreas [13]. This activation increases glucose-dependent insulin release from beta-cells and inhibits glucagon release from alpha-cells [13]. They also suppress appetite and delay gastric emptying due to their effects on the central nervous system and other gastrointestinal locations [13]. Several meta-analyses and clinical trials have shown that liraglutide may result in improvements in lipid profiles and even histologic resolution in patients with non-alcoholic steatohepatitis [14,15]. However, there is still a dearth of data on its potential to cause hepatotoxicity. To the best of our knowledge, this study is the first organized discussion of liraglutide-associated DILI, and it provides a summary of the available data on this topic. This article prompts clinicians to remain cognizant of this rare but important adverse event of liraglutide.

2. Illustrative Case

2.1. Presentation

A 43-year-old obese Asian female with a medical history of type 2 diabetes mellitus presented to our medical center with dull, right upper quadrant pain for the past 12 days. It was associated with generalized body fatigue and a loss of appetite. Three months ago, her glycated hemoglobin level (A1c) was 10.7%. Due to her obesity (body mass index: 31.3 kg/m^2) and poor glycemic control, it was suggested that she start liraglutide therapy. After careful discussion regarding possible adverse events, she was initiated on subcutaneous liraglutide at 0.6 mg/day for 1 week initially. Subsequently, the dose was increased to 1.2 mg/day. She had no pre-existing cardiovascular, respiratory, or liver dysfunction. Her liver function tests (LFTs) were normal before starting liraglutide 3 months ago. She denied the use of any other prescription or over-the-counter drugs such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, or herbal supplements. The patient was a non-smoker, non-alcoholic, and denied recreational drug use.

On her current presentation, she had lost 11.3 kg of weight over the past 3 months (BMI: 27.0 kg/m^2). Her vital signs revealed a temperature of 37.1°C, a blood pressure of 124/76 mm Hg, a heart rate of 78 beats/min, a respiratory rate of 17 breaths/min, and an oxygen saturation of 98% on room air. The physical examination was remarkable for mild right upper quadrant tenderness. There were no overt signs of advanced liver disease or acute liver failure. No jaundice or xanthelasma were noted.

2.2. Investigations and diagnosis

Laboratory studies revealed elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) (Table 1). Abdominal ultrasonography revealed a diffuse hyperechogenic liver with obscured periportal but detectable diaphragmatic echogenicity, indicating grade II hepatic steatosis. No focal hepatic or biliary abnormalities were noted. Doppler studies ruled out abnormalities in the portal and hepatic veins and the hepatic artery. The viral markers for hepatitis A, B, C, D, and E, cytomegalovirus, Epstein–Barr virus, varicella–zoster virus, and herpes simplex virus were negative. The workup for autoimmune disorders included levels of antinuclear, anti-smooth muscle, anti-soluble liver antigen, atypical perinuclear antineutrophil cytoplasmic, anti-tissue transglutaminase, antimitochondrial, anti-liver-kidney-microsome-1, and F-actin antibodies, as well as quantitative immunoglobulins, that were within their respective normal limits. Metabolic testing for acetaminophen, thyrotropin, and salicylic acid was inconclusive. The standard test results for alpha-1 antitrypsin deficiency, hemochromatosis, and Wilson's disease were also unremarkable. A liver biopsy was not performed as per the patient's choice. Other possible causes of liver damage, such as acute hepatitis secondary to weight loss or ischemic liver injury, were also systematically ruled out.

Based on the clinical and workup findings, the patient was diagnosed with DILI after probable etiologies were ruled out. She received only liraglutide as a new treatment before the onset of her symptoms. As a result, liraglutide-associated DILI was thought

Table 1. Admission laboratory studies with respective reference limits

Laboratory parameter	Patient value	Reference range
Alanine aminotransferase	1837	7–45 IU/L
Aspartate aminotransferase	1062	8–48 IU/L
Alkaline phosphatase	373	44–129 U/L
Gamma-glutamyl transpeptidase	103	5–40 IU/L
Total bilirubin	1.8	0.1–1.2 mg/dL
International normalized ratio	1.0	<1.1
Prothrombin time	12.3	11.0–13.7 s
Serum lactate dehydrogenase	305	105–333 IU/L
Serum lipase	234	23–300 IU/L
Hemoglobin	13.6	12.0–15.5 g/dL
White cell count	8.4×10^9	$4.0–11.0\times10^9$/L
Platelet count	196×10^9	$150–450\times10^9$/L
Triglycerides	168	10–150 mg/dL
Total protein	7.3	6.3–8.5 mg/dL
Serum albumin	4.2	3.5–5.0 g/dL
Serum creatinine	1.1	0.6–1.3 mg/dL
Thyroid stimulating hormone	3.51	0.4–4.0 mIU/L
Corrected calcium	8.3	8.5–10.3 mg/dL

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to be the plausible cause. The R ratio was 14.12, indicating a hepatocellular type of liver enzyme elevation. According to the DILI Network severity index definitions, our patient had a grade 3+ (moderate-severe) DILI.

2.3. Clinical management

Liraglutide was immediately discontinued. N-acetylcysteine was administered for 3 days. The clinical response was excellent, with complete resolution of symptoms in 4 days. Her LFTs also showed a downward trend. Her ALT was 586 IU/L, AST was 115 IU/L, ALP was 258 IU/L, and total bilirubin was 1.1 mg/dL at the time of discharge after 5 days. At the follow-up visit after 1 week, her LFTs were within normal limits. Due to the risk of a serious DILI from re-exposure to liraglutide, a re-challenge was not performed. The normalization of serum levels of liver enzymes after liraglutide discontinuation further supported our diagnosis of liraglutide-associated DILI. The patient was then prescribed an alternative medicine for long-term glycemic control.

2.4. Causality assessment

Two different methods were used for causality assessment in this case. The Naranjo Nomogram for Adverse Drug Reaction Assessment (Naranjo score) was calculated, which resulted in a score of 6 (Table 2). The updated Roussel-Uclaf Causality Assessment Method (RUCAM) score was calculated and found to be 8. The scores from both models indicated a *probable* liraglutide-induced DILI. Furthermore, the temporal association also strongly proves that liraglutide caused DILI in this case.

3. Discussion

DILI secondary to liraglutide administration remains an exceedingly rare clinicopathologic entity. We conducted a systematic literature search of MEDLINE (PubMed and Ovid), Google Scholar, Scopus, and Cochrane databases for articles published in the English language between inception and December 20, 2022. The search terms "DILI," "hepatotoxicity," "adverse drug reaction," and "DILI" were combined using the Boolean operators "AND" and "OR" with "liraglutide" and "liraglutide therapy," with all associated permutations. The titles and abstracts of all the search results were reviewed by 2 authors for eligibility. Results that were considered irrelevant, redundant, duplicate, non-English, or related to bench research were excluded by 2 physicians. Eventually, we found only 4 articles where DILI was described in association with liraglutide use, dating from 2014 to 2021 [16-19]. All 4 articles were case reports based on individual patient experiences (level of clinical evidence: IV).

Kern *et al.* pioneered reporting liraglutide-related hepatotoxicity in a young Hispanic female with type 2 diabetes mellitus and vitiligo [16]. She developed liraglutide-induced marker-negative autoimmune hepatitis, with biopsy findings of marked hepatic necrosis and eosinophilic infiltration [16]. Drug discontinuation alone did not bring about resolution; glucocorticoids were required. They speculated that the adverse event was a result of the interaction between anti-liraglutide antibodies and native GLP-1 at its hepatocyte receptor site [16]. Al-Malky *et al.* described the case of a man who arrived at the diabetes follow-up clinic feeling ill and nauseated [17]. They considered liraglutide-induced hepatic and renal dysfunction due to a consistent clinical history and laboratory findings. Liraglutide was discontinued, and his liver enzymes and creatinine normalized [17]. Maor *et al.* presented the case of a female who developed a liver injury after starting liraglutide for weight loss [18]. They postulated drug-mediated idiosyncratic hepatic injury through the inflammatory and apoptosis pathways [18]. This causal mechanism was implicated based on their observation of an exaggerated lymphocyte toxicity assay. Hepatotoxicity improved after liraglutide cessation [18]. Parvataneni *et al.* reported a case of liraglutide-induced DILI in a diabetic female [19]. There was complete recovery with the discontinuation of the medication [19]. Our patient also had delayed-onset DILI and recovered after liraglutide was stopped. The data on patient demographics, presentation patterns, laboratory studies, and ultrasonography findings are summarized (Table 3).

The precise etiopathogenesis of liraglutide-associated DILI remains to be determined. In our review, the dose-independent

Table 2. Naranjo assessment scale depicting a score of 6 in the present case

Naranjo Adverse Drug Reaction Probability Scale				
Questions	**Yes**	**No**	**Do not know**	**Patient's score**
(1) Are there previous *conclusive* reports on this reaction?	+1	0	0	+1
(2) Did the adverse event appear after the suspected drug was administered?	+2	−1	0	+2
(3) Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	+1
(4) Did the adverse event reappear when the drug was re-administered?	+2	−1	0	
(5) Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	+2
(6) Did the reaction reappear when a placebo was given?	−1	+1	0	
(7) Was the drug detected in blood (or other fluids) in concentrators known to be toxic?	+1	0	0	
(8) Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
(9) Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
(10) Was the adverse event confirmed by any objective evidence?	+1	0	0	
Total score				6

Notes: A score of<1 is doubtful; 1–4 is possible; 5–8 is probable; >9 is definitive for adverse drug reaction.

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Table 3. Clinical characteristics of patients with liver injury secondary to liraglutide administration

Authors, year	Country	Ethnicity	Age/ Gender	Clinical presentation	Comorbid conditions	Liraglutide dosage (mg/day)	Onset delay	Laboratory evaluation	Liraglutide -DILI classification	Abdominal ultrasound findings
Kern *et al.* 2014 [16]	USA	Hispanic	Young/F	Nausea, emesis, and acute hepatitis for 10 days; worsening jaundice and fatigue	Type 2 diabetes mellitus and vitiligo	1.2 mg/day	4 months	ALT 994 IU/L, AST 1045 IU/L, TBIL 9.1 mg/dL, ALP 118 IU/L, INR 1.1	Marker-negative AIH	Increased echogenicity around the portal triads but no biliary ductal dilatation
Yehia *et al.* 2017 [17]	Egyptian	Arab	51/M	Feeling unwell and severe intolerable nausea	Diabetes, obesity (BMI, 51.59 kg/m^2), ex-smoker, IHD sp stenting	3 mg/day then reduced to 1.2 mg/ day	2 months	Amylase 81 IU/L, AST 153 IU/L, ALT 250 IU/L, creatinine 1.4 mg/dL, BUN 23 mg/dL, random triglyceride 562 mg/dL and RBS 181mg/dL	Hepatitis	Not reported
Maor *et al.* 2021 [18]	Israel	Caucasian	52/F	Increased liver enzyme levels	Diabetes, hyperlipidemia, obesity (BMI, 31.2 kg/m^2), NAFLD	0.6 mg/ day then increased to 3 mg/day	3 months	ALT 547 IU/L, AST 268 IU/L, ALP 390 IU/L, GGT 427 IU/L, TBIL 1.3 mg/dL, ESR 59 mm/h, LTA detected liraglutide-induced toxicity of 35%	Hepatitis	Fatty liver
Parvataneni *et al.* 2021 [19]	USA	Not reported	64/F	Diffuse abdominal pain for 4 days	Hypertension, diabetes, hyperlipidemia, cholecystectomy	1.2 mg	6 months	ALT 1359 IU/L, AST 565 IU/L, ALP 405 IU/L, TBIL 2.9 mg/dL, INR 0.9	Hepatitis	Fatty changes of the liver

Abbreviations: AIH: Autoimmune hepatitis; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; BUN: Blood urea nitrogen; DILI: Drug-induced liver injury; ESR: Erythrocyte sedimentation rate; F: Female; GGT: Gamma-glutamyl transferase; IHD: Ischemic heart disease; LTA: Lymphocyte toxicity assay; M: Male; NAFLD: Non-alcoholic fatty liver disease; RBS: Random blood sugar; TBIL: Total bilirubin.

response and the varying latency period (range, 2–4 months) suggest an idiosyncratic DILI. The previous research implicates adaptive and innate immunity in causing idiosyncratic liver injury, culminating in necrosis and apoptosis [20-22]. The results presented by Maor *et al.* in their case study of liraglutide-induced DILI corroborated this theory [18]. They described it based on their observation of 35% lymphocyte toxicity (normal, 10–15%) due to liraglutide [18]. Patient lymphocytes exposed to liraglutide *in vitro* had higher levels of proinflammatory, necrosis, and apoptosis markers than did controls [18]. However, comprehensive investigations based on larger sample sizes are warranted to evaluate the causal pathway in this regard. Published literature has identified several risk factors for DILI related to the host, environment, and culprit drug [23]. In our review of liraglutide-related liver injury, we identified female gender, advanced age, diabetes, and an increased BMI as prominent host risk factors.

Prompt detection of DILI is of paramount clinical importance. As there are no specific tests or markers for this entity, it remains a diagnosis of exclusion. Presentation patterns are often varied, and there can be no symptoms. In symptomatic individuals, non-specific gastrointestinal symptoms may include nausea, vomiting, malaise, abdominal pain, and/or body itching [23]. Physical examination may reveal jaundice, right upper abdominal tenderness, or an enlarged liver [23]. A consistent clinical and medication history and ruling out existing liver disease are important [23]. Laboratory evaluation reveals deranged liver enzymes. The elevation patterns can be hepatocellular, cholestatic, or mixed. The R-factor calculation can categorize presentations into any of these types [23]. Based on mechanisms of injury, DILI can be intrinsic (dose-dependent) or idiosyncratic (unpredictable) [24]. Notably, idiosyncratic DILI often presents a significant diagnostic and therapeutic challenge [24]. Therefore, heightened clinical vigilance is warranted. In this review, patients with liraglutide-induced DILI often presented with non-specific symptoms. The hepatocellular type of idiosyncratic injury constituted the predominant phenotype.

In our case, alternative etiologies such as viral hepatitis, autoimmune diseases, metabolic disorders, and the use of other prescription, herbal, or over-the-counter medications were carefully excluded [23-27]. Rapid weight loss-related liver injury should also be ruled out in suspected liraglutide-associated DILI patients. Liver injury due to malnutrition at high BMI has predominantly

been reported in patients treated with gastric bypass surgery, particularly in those with psychiatric illnesses [28,29]. Our patient had not undergone bariatric surgery. Her intake was normal, and she had no history of mental illness. While liraglutide resulted in effective weight loss, her physical examination was negative for muscle wasting. Moreover, the admission laboratory studies showed normal results for total protein, serum albumin, and the international normalized ratio (INR). The temporal relationship between liraglutide administration and elevations in liver enzymes, coupled with liraglutide cessation and normalization of liver function tests, strongly suggested the diagnosis of liraglutide-related DILI. Therefore, liver damage due to weight loss was ruled out in our case. Furthermore, ischemic liver injury was also ruled out because she was hemodynamically stable and there was no radiological evidence of focal interruption of the hepatic perfusion. Moreover, the peak levels of aminotransferases and lactate dehydrogenase (LDH) (ALT/LDH ratio: 6.0) and normal serum creatinine were also incompatible with ischemic injury [30,31].

Causality assessment in patients with DILI remains a controversial topic. However, several predictive models have also been developed to ascertain the clinical status of DILI. The Naranjo score can be used in these patients, where a score of <1 is doubtful, 1–4 is possible, 5–8 is probable, and >9 is definitive for an adverse drug reaction [32]. The updated RUCAM scoring system is of key importance in cases of DILI [33]. It is based on the underlying risk factors, patterns of liver enzyme elevations, possible culprit drugs, and the meticulous exclusion of other etiologies [33]. For RUCAM score calculation, the value of the R factor is determined first to establish the type of liver injury [33]. The RUCAM score ranges from −9 to +14, with definite >9, probable 6–8, possible 3–5, and unlikely 1–2 [33]. DILI is excluded if the score is ≤0 [33]. However, it is crucial to adhere to the stated guidelines to prevent confounding variability to get the most clinical value out of the RUCAM score [34]. In our patient, both of these scores were calculated, which indicated a *probable* liraglutide-induced DILI. She did not undergo a rechallenge, fearing a more severe subsequent DILI episode.

The United States DILI Network categorizes it as mild, moderate, moderate-severe, severe, or fatal [35]. It is based on various laboratory and clinical parameters, as well as the need for hospitalization [35]. In our review, all patients with liraglutide-associated DILI were found to have grade 3+, moderately severe disease. This degree of severity is determined by elevated ALT, ALP, total bilirubin, and/or INR levels, hospitalization, or a protracted hospital stay as a result of DILI [35]. The American Association for the Study of Liver Diseases (AASLD) guidelines recommend conservative treatment for idiosyncratic DILI [36]. Hospital admission is indicated for clinical monitoring in patients who develop severe nausea and vomiting, coagulation abnormalities, altered mentation, or fluid depletion [36]. N-acetylcysteine can be administered for 3 days in adult cases of acute liver failure, especially in patients with encephalopathy [36]. Methylprednisolone at a dose of 1 mg/kg can be instituted in severe immune-mediated allergic reaction type of DILI [36]. Moreover, a short course of up to 3 months can be given to patients with a drug-related autoimmune pattern of liver injury on biopsy [36]. However, there is no consensus on management based on clinical severity. In our analysis, 3 patients with liraglutide-induced DILI had favorable clinical outcomes with drug cessation and conservative management alone. However, 1 patient required prolonged use of corticosteroids. The data on causality assessment, severity, and clinical outcomes are outlined (Table 4).

Liraglutide has recently garnered public health prominence. For instance, around 4,063,184 prescriptions for this drug were recorded in the United States in 2020 [37]. In this context, our article enables clinicians to become aware of the possible hepatotoxicity of liraglutide. It highlights the need for a baseline evaluation of liver enzymes. A monthly surveillance during maintenance therapy with GLP-1 analogs can be considered for individuals

Table 4. Clinical outcomes in patients with liraglutide-induced liver injury.

Authors	US DILIN severity grade	Pattern	Organ failure	Liver biopsy	Alternative DILI etiologies excluded	Treatment	Rechallenge	Naranjo score	Clinical outcome
Kern *et al.* 2014 [16]	Moderate–severe; 3+	Hepatocellular	No	Yes	Yes	Antiemetic therapy, intravenous fluids, oral prednisone therapy, 40 mg/day	No	7	6 months later, normalization of LFTs but on prednisone, 15 mg/day
Yehia *et al.* 2017 [17]	Moderate–severe; 3+	ALP was not reported	No	No	Yes	Nil per os and intravenous fluid	No	8	Liver and renal functions were returned to normal after 2 weeks of admission
Maor *et al.* 2021 [18]	Moderate–severe; 3+	Mixed	No	No	Yes	Drug discontinuation	No	7	Normalization of liver enzymes
Parvataneni *et al.* 2021 [19]	Moderate–severe; 3+	Hepatocellular	No	No	Yes	Liraglutide was discontinued and N-acetylcysteine was administered	No	6	Liver tests normalized in 2 months after discharge

Abbreviations: DILIN: Drug-induced liver injury network

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with risk factors for DILI. It can facilitate early detection and save patients from DILI-related morbidity by allowing dose reduction or early cessation of liraglutide. Furthermore, it will help to start assessing the actual likelihood of DILI, making it a safer drug for future use. As liraglutide is an effective drug for a plethora of medical conditions, it is pertinent to investigate whether a patient can be restarted at a lower dose after adverse events like DILI. The existing, scant literature on liraglutide-induced DILI provides no rationale for this scenario. Hence, keeping in mind the clinical benefits of GLP-1 agonists, registry-based data are required to meticulously study this adverse event. In our review, all 4 patients unfortunately stopped taking liraglutide and were prescribed alternative anti-diabetic agents.

4. Conclusion

DILI following liraglutide use remains an exceedingly rare diagnosis, with only a handful of cases reported to date. However, clinicians should remain cognizant of liraglutide-induced DILI due to the critical clinical implications of this adverse event. Early detection followed by drug cessation carries vital clinical importance. Therefore, a baseline assessment and subsequent monitoring of liver function may be considered in suspected individuals. Furthermore, larger, multicenter post-marketing investigations, and surveillance are warranted to meticulously evaluate the potential of liraglutide to cause liver injury. While liraglutide remains an effective and safe drug, reporting possible adverse events may help improve its long-term use with preemptive actions by clinicians.

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Conflicts of Interest

The authors disclose no conflicts of interest.

Ethics Approval and Consent to Participate

Ethics committee approval was not required as per the institutional policy. Informed consent was obtained from the patient involved in the study.

Consent for Publication

Informed consent was obtained from all involved patients before publication of this study.

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