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Case Report

A Rare Case Report: Hepatotoxicity during Fulvestrant Treatment, Is It Late-Onset Nivolumab-Induced Autoimmune Toxicity?

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Background: A limited number of post-marketing hepatotoxicity incidences are reported during Fulvestrant treatment. However, serious complications are rarely described. On the other hand, Nivolumab is associated with autoimmune hepatotoxicity that can occur during treatment or months-years after discontinuation. We report a case of hepatotoxicity followed by renal failure during Fulvestrant treatment in a breast cancer patient who received Nivolumab checkpoint inhibitor therapy, and we point out the feasibility of initiating corticosteroids in similar cases in clinical practice.

Keywords: Fulvestrant; Nivolumab; Hepatotoxicity; Breast cancer

Introduction

Fulvestrant is a selective estrogen receptor down-regulator approved by the FDA in 2002 to be prescribed in advanced breast cancer cases after previous hormonal therapy failure. [1] In 2017, the FDA approved the expanded use of Fulvestrant as initial therapy for postmenopausal patients after the phase III FALCON trial that showed a 20% reduction in disease progression compared to anastrazole. [2] Fulvestrant is associated with good tolerance and compliance. A transient asymptomatic mild elevation in hepatic enzymes was reported in 15% of patients receiving Fulvestrant, and elevation above five times was reported in 1-2% of patients. [3] A limited number of post- marketing reports suggested hepatic dysfunction and hepatitis during Fulvestrant treatment.

Nivolumab is a targeted human immunoglobulin (checkpoint inhibitor) that blocks PD-1 and promotes antitumour immunity. [4] Emerging evidence supports the beneficial outcomes of Nivolumab in managing melanoma, non-small cell lung cancer (NSCLC), and colorectal cancer. However, data supporting Nivolumab utilization in managing breast cancer are limited. Checkpoint inhibitors, including Nivolumab, are associated with reported autoimmune hepatotoxicity cases. [5] This is a rare case of hepatotoxicity followed by renal failure during Fulvestrant treatment detected in Kuwait.

Case Report

A 57 year old female patient was diagnosed with Invasive Mammary Carcinoma (IMC) of the right breast with tubular and lobular features and positive lymph node involvement. The histopathology showed overall Grade II, ER 100%, PR 100%, HER-2 negative, and Ki67 10%. Her medical history included hypothyroidism, no known drug allergies, and she never consumed alcohol. Her family history was positive for two first-degree relatives with breast cancer.

The patient underwent a right breast mastectomy abroad, followed by a PET scan showing a suspicious brain lesion. Accordingly, the patient received an adjuvant cycle of [Fulvestrant + Palbociclib], which was discontinued due to uterine bleeding. Then she received six cycles of Eribulin, Bevacizumab, and Nivolumab, even though Nivolumab is not licensed for metastatic breast cancer management by the FDA. When she returned to Kuwait, it was decided to start a dual anti-hormonal treatment [Fulvestrant + Ribociclib]. Four months later, the Liver Function Test (LFT) increased significantly; accordingly, Ribociclib was discontinued, and the patient continued with Fulvestrant

monotherapy.

Regular follow-up showed normal PET scan and satisfactory tolerance.

After 16 months of initiating Fulvestrant treatment (approximately 20 months post discontinuing Nivolumab treatment), the patient was admitted to the hospital with peritonitis and mild elevation in the LFT; she was managed accordingly. Two months later, the patient presented to the casualty with malaise, abdominal swelling, jaundice, mental confusion, nausea, and loss of appetite. Initial examination showed increased AST 158 IU/L, ALT 50 IU/L, T.Bilirubin 149 µmol/L, Alkaline phosphates 188 IU/L, and ascites. Other parameters were within normal ranges.

An abdominal ultrasound with Doppler showed hepatomegaly with Gross ascites and no evidence of thrombosis. The patient was admitted for fluid drainage and further investigations. Ultrasound and CT scans provided poor, inconsistent imaging due to fluid accumulation but were suggestive of early cirrhotic changes. A PET scan showed no evidence of metastasis. An MRCP scan was considered a suboptimal study due to abdominal ascites, degrading the image quality. However, it showed an average liver size and confirmed early cirrhotic features with no evidence of lymphadenopathy or biliary obstruction (Figure 1). Besides, The MRCP showed a normal appearance of the pancreas, spleen, adrenal, and both kidneys.

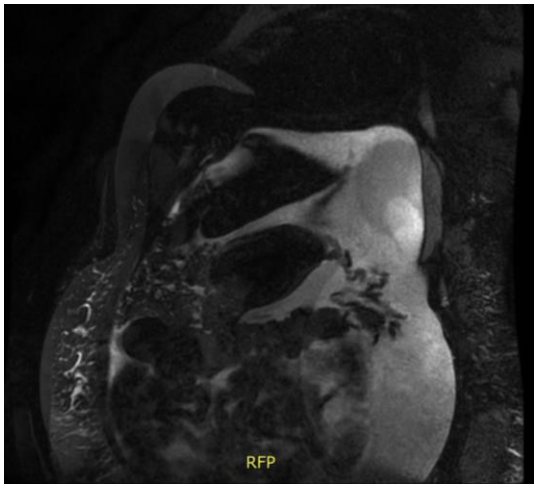

Figure 1: MRCP

During admission, repeated drainage of abdominal ascites was indicated and accompanied by a rapidly progressive increase in T.Bilirubin 235.4 µmol/L, SCr 200 µmol/L, Urea 18.8 mmol/L, and a decrease in eGFR 24 L, which was managed by IV fluids. Laboratory tests were monitored; improvement in SCr 100 µmol/L, Urea 14 mmol/L, and eGFR 45 L was observed within three days, while T. Bilirubin increased significantly up to 345 µmol/L. Fulvestrant was withheld, and further autoimmune tests were requested. Hepatitis A, B, C, and anti-liver kidney microsomal antibodies were negative. Also, anti HCV II, anti HAV IgM, and ANA tests were negative.

Within a week, the T.Bilirubin increased significantly, reaching values over 440 µmol/L. A reduced level of consciousness was noticed with a sudden deterioration in renal function [SCr 300 µmol/L, Urea 17.7 mmol/L, and eGFR 15 L], necessitating haemodialysis. Liver biopsy was not considered by the gastrointestinal specialists because the autoimmune antibodies were not detected. Accordingly, corticosteroids were not administered, and the patient was managed as a hepato-renal syndrome case. The patient remained hemodynamically unstable and passed away a few days later due to septic shock in the ICU.

Discussion

Fulvestrant can be safely administered in patients with a mild-moderate increase in the LFT. A review of the literature showed that cases of hepatic dysfunction, hepatitis, increased serum bilirubin, and creatinine levels were reported during Fulvestrant treatment. [4] The majority of cases were reported among patients receiving Fulvestrant and Palbociclib. Besides, a case of steatohepatitis with cirrhosis was reported in a patient who received Fulvestrant and tamoxifen [6]. [7] Our patient developed hepatic cirrhosis, elevated LFT, dramatic elevation in bilirubin, and repeated ascites. This was followed by a deterioration in renal function, indicating haemodialysis.

Autoimmune hepatic disease workup did not detect antibodies, excluding hepatitis. The cause of hepatic ascites was attributed to the cirrhotic changes, precipitating hepatic dysfunction followed by renal complications. The patient was symptomatic and managed as a hepato-renal case. The exact cause of the hepato-renal syndrome was unknown; however, Fulvestrant-induced hepatic cirrhosis was considered a contributing factor [8].

There is a lack of evidence about the mechanism of Fulvestrant-induced hepatotoxicity, and theories of its causation cannot be established based on this report. However, based on the timing of investigations, this case does not exclude a potential correlation between Fulvestrant and hepatic cirrhosis that was accompanied by intense ascites and progressed to a hepato-renal syndrome.

The medical team did not consider the possibility of Nivolumab (PD-1 checkpoint inhibitor) induced autoimmune hepatotoxicity that could occur either during treatment (early-onset) or months to years after discontinuation (late-onset) and occasionally contribute to cirrhosis. [9, 10] Previous case reports demonstrated that checkpoint inhibitors' autoimmune hepatotoxicity could contribute to acute hepatic dysfunction even

in the absence of increased IgG and ANA. [11] Liver biopsy was essential to exclude differential diagnosis and assess the grade and severity of hepatotoxicity, considering patients' symptoms, bilirubin, and liver enzymes levels [12].

In this case, none of the investigations carried out could exclude Fulvestrant-induced hepatotoxicity. However, the possibility of late-onset Nivolumab-induced autoimmune hepatotoxicity remains a possible cause of cirrhosis, which should be considered even in the absence of increased IgG and ANA and managed with corticosteroid administration to improve liver function and relieve the symptoms.10 Further studies are required to demonstrate the correlation between Fulvestrant/Nivolumab and hepatotoxicity patterns and establish the requirement for initiating corticosteroids in acute management to reduce morbidity and mortality.

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