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Severe Reversible Conjugated Hyperbilirubinemia Induced by Ribociclib: A Transporter-Mediated Toxicity with Successful Switch to Palbociclib

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Abstract **Case Report**

Ribociclib, a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, is widely used as first-line therapy for hormone receptor–positive, HER2-negative metastatic breast cancer and is generally well tolerated. Hepatic adverse events are recognized, most commonly presenting as reversible elevations in serum transaminases. However, severe isolated hyperbilirubinemia, particularly with predominance of conjugated bilirubin and without associated cytolysis, remains exceptionally rare and poorly characterized. We report the case of a 56-year-old woman with a history of right-sided hormone receptor–positive, HER2-negative breast cancer who developed a histologically confirmed right adrenal metastasis and was treated with letrozole plus ribociclib. After three months of therapy, despite radiologic disease stability and biochemical response, the patient developed clinical jaundice with grade 4 hyperbilirubinemia reaching 150 µmol/L, predominantly conjugated, while liver transaminases and cholestatic enzymes remained within normal ranges. Extensive evaluation excluded infectious, autoimmune, hemolytic, and obstructive causes, and hepatobiliary imaging was unremarkable. Ribociclib was discontinued, resulting in progressive and complete normalization of bilirubin levels within two months. Following hepatic recovery, treatment was resumed with abemaciclib in combination with endocrine therapy, without recurrence of hepatotoxicity and with sustained disease control after nine months of follow-up. This case illustrates a rare and reversible pattern of ribociclib-associated hepatotoxicity, emphasizes the importance of bilirubin monitoring even in the absence of transaminase elevation, and supports the feasibility of switching to an alternative CDK4/6 inhibitor after resolution of hepatic toxicity.

Keywords: Ribociclib, conjugated hyperbilirubinemia, CDK4/6 inhibitors, drug-induced liver injury, metastatic breast cancer, abemaciclib, hepatotoxicity, endocrine therapy.

INTRODUCTION

Cyclin-dependent kinase 4/6 inhibitors have profoundly transformed the management of hormone receptor–positive, HER2-negative metastatic breast cancer, with consistent improvements in progression-free and overall survival across multiple phase III trials [1–3]. Among these agents, ribociclib has demonstrated robust efficacy in both premenopausal and postmenopausal populations and is widely used as a first-line standard of care.

Despite its favorable benefit–risk profile, ribociclib is associated with specific hepatic adverse events that require close monitoring. Hepatotoxicity has been predominantly described as reversible elevations in serum transaminases, reflecting a hepatocellular pattern of injury [1,3]. In contrast, isolated hyperbilirubinemia without concomitant cytolysis or cholestasis is exceptionally rare and remains poorly characterized, with available data limited to sporadic case reports and pharmacovigilance observations [4–6].

Importantly, such atypical biochemical patterns may reflect mechanisms distinct from classical drug-induced liver injury and have significant implications for diagnosis, monitoring, and therapeutic sequencing. We report a rare case of severe reversible conjugated hyperbilirubinemia induced by ribociclib and provide a translational discussion focusing on transporter-mediated mechanisms and the feasibility of switching to an alternative CDK4/6 inhibitor.

We report a rare case of severe reversible conjugated hyperbilirubinemia induced by ribociclib, followed by successful switching to palbociclib, and provide an updated review of the literature focusing on hepatic toxicity and the feasibility of CDK4/6 inhibitor switching

Case Presentation

A 56-year-old woman was diagnosed ten years earlier with an invasive carcinoma of the right breast characterized by estrogen and progesterone receptor positivity and negative HER2 status. Initial treatment consisted of mastectomy followed by adjuvant chemotherapy and long-term tamoxifen therapy, with no evidence of disease recurrence for several years.

She subsequently presented with a solitary right adrenal mass. Histological examination of a biopsy specimen confirmed metastatic breast carcinoma with immunohistochemical features identical to those of the primary tumor, including hormone receptor positivity and absence of HER2 overexpression.

First-line systemic therapy for metastatic disease was initiated with letrozole combined with ribociclib at a dose of 600 mg daily administered on a 21-days-on, 7-days-off schedule. After three months of treatment, radiologic evaluation demonstrated stability of the adrenal metastasis, and serum CA 15-3 levels had decreased, indicating a favorable early oncologic response.

At the same evaluation, the patient developed clinically evident jaundice with scleral and cutaneous icterus. Laboratory investigations revealed marked isolated hyperbilirubinemia, with total bilirubin reaching 150 µmol/L, predominantly conjugated. Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase levels remained within normal ranges. The patient reported no abdominal pain, fever, pruritus, nausea, or other systemic symptoms.

A comprehensive diagnostic workup was undertaken. Viral hepatitis serologies and autoimmune markers were negative, and hemolysis was excluded through normal complete blood count, lactate dehydrogenase, and haptoglobin levels. Hepatobiliary magnetic resonance imaging showed no evidence of biliary obstruction or structural liver disease. In the absence of alternative etiologies and given the clear temporal association with ribociclib initiation, ribociclib-induced isolated conjugated hyperbilirubinemia was strongly suspected.

Ribociclib was immediately discontinued while endocrine therapy was maintained. Bilirubin levels progressively declined and returned to normal values within two months, as illustrated in Figure 1. After complete hepatic recovery, the patient was switched to abemaciclib at a dose of 150 mg twice daily in combination with endocrine therapy. She has since maintained stable disease and normal liver function tests, with no recurrence of hyperbilirubinemia during nine months of follow-up.

Serum bilirubin levels progressively declined after ribociclib discontinuation and returned to normal values within two months, as illustrated in Figure 1.

Discussion

Hepatic toxicity is a well-documented adverse effect of ribociclib, most commonly presenting as reversible elevations in serum transaminases in pivotal clinical trials [1,3]. Severe isolated conjugated hyperbilirubinemia without cytolysis, as observed in the present case, represents a rare and atypical toxicity pattern that remains poorly characterized in both clinical trials and real-world practice [4–6].

Table 1: Published studies reporting ribociclib-associated hepatotoxicity and outcomes after switching to another CDK4/6 inhibitor

Reference	Year	Study design	Hepatic toxicity under ribociclib	Switch	Outcome
Hortobagyi et al. [1]	2016	Phase III trial (MONALEESA-2)	ALT/AST elevation	No	Reversible
Im et al. [2]	2019	Phase III trial (MONALEESA-7)	Transaminase elevation	No	Reversible
Slamon et al. [3]	2020	Phase III trial (MONALEESA-3)	Grade ≥3 ALT/AST elevation	No	Reversible
Teh et al. [4]	2021	Systematic review	Predominantly cytolytic; rare isolated hyperbilirubinemia	Rare	Recovery
Leone Roberti Maggiore et al. [5]	2022	Case report	Severe isolated hyperbilirubinemia	Yes (abemaciclib)	No recurrence
El-Sheikh et al. [6]	2023	Case report	Isolated hyperbilirubinemia >100 µmol/L	Yes	Recovery
Present case [7]	2025	Case report	Conjugated hyperbilirubinemia (150 µmol/L)	Yes (abemaciclib)	Stable at 9 months

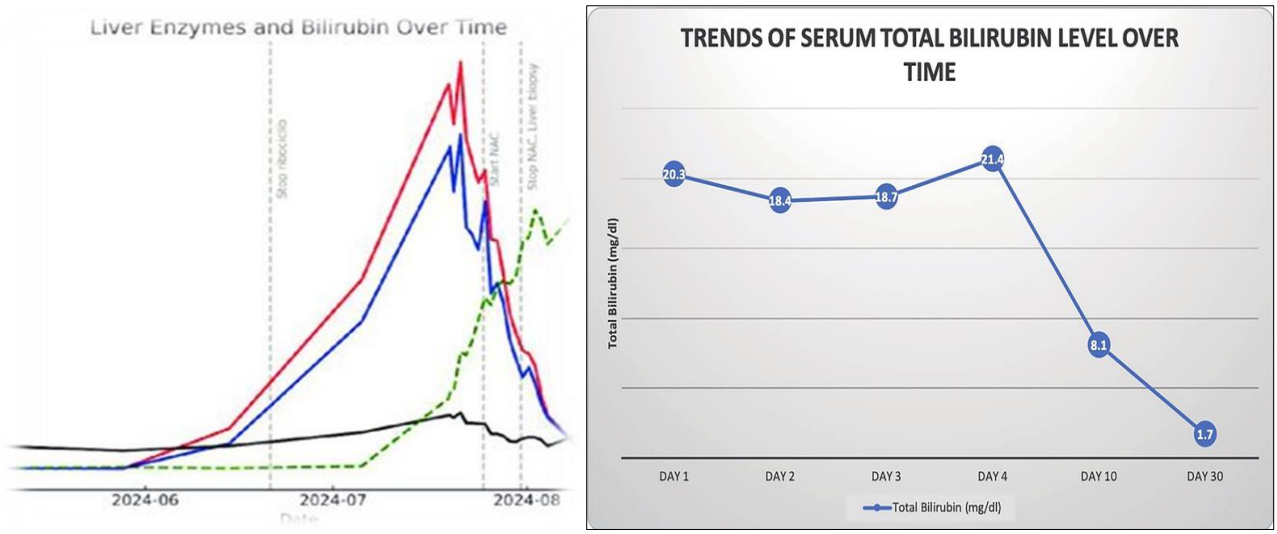

Figure 1: Time course of total serum bilirubin following ribociclib discontinuation. Total bilirubin peaked at 150 µmol/L and progressively normalized within two months.

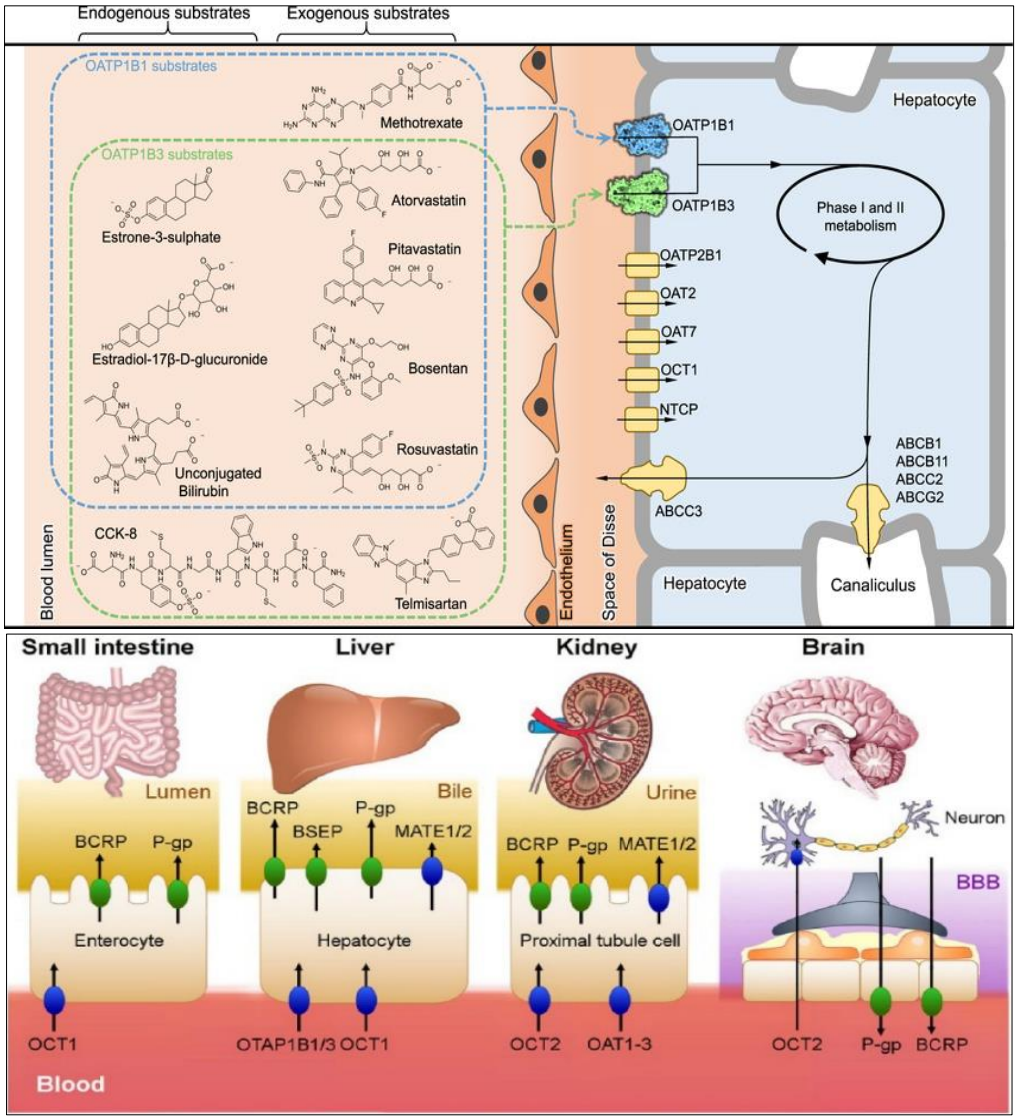

Figure 2: Proposed mechanism of ribociclib-induced isolated conjugated hyperbilirubinemia. Functional inhibition of hepatic uptake (OATP1B1/1B3) and biliary excretion pathways leads to reversible accumulation of conjugated bilirubin without hepatocellular injury.

Physiopathological considerations

The precise mechanisms underlying ribociclib-induced isolated conjugated hyperbilirubinemia remain incompletely understood. Available evidence suggests that this adverse event is predominantly related to functional disturbances in bilirubin handling rather than direct hepatocellular injury. Ribociclib has been shown to interact with hepatic membrane transporters involved in bilirubin uptake and excretion. In particular, inhibition of organic anion-transporting polypeptides OATP1B1 and OATP1B3, which mediate hepatic uptake of conjugated bilirubin, may impair clearance and lead to serum accumulation [4].

Additionally, ribociclib may interfere with canalicular transport systems responsible for biliary excretion of conjugated bilirubin, resulting in a biochemical pattern mimicking cholestasis without structural biliary obstruction [4,5]. This hypothesis is supported by the predominance of conjugated bilirubin, the absence of transaminase and cholestatic enzyme elevation, normal hepatobiliary imaging findings, and the complete reversibility observed after treatment discontinuation in the present case. A schematic representation of the proposed mechanism is provided in Figure 2.

Unlike classical drug-induced liver injury, which typically involves hepatocellular necrosis or immune-mediated inflammation, this pattern appears to reflect a reversible functional impairment of bilirubin transport. The rapid normalization of bilirubin levels following ribociclib withdrawal further supports this mechanism [5,6]. Pharmacogenomic susceptibility, including polymorphisms affecting bilirubin transporters or conjugation pathways, has also been proposed as a contributing factor, although routine genetic testing is not currently recommended [4].

The proposed pathophysiological mechanism underlying ribociclib-induced isolated conjugated hyperbilirubinemia is illustrated in Figure 2.

Clinical implications and management

Recognition of isolated conjugated hyperbilirubinemia is essential, as the absence of transaminase elevation may delay diagnosis of drug-induced liver injury and prompt unnecessary investigations. Current international guidelines recommend immediate interruption of ribociclib in cases of grade 3 or higher bilirubin elevation, irrespective of transaminase levels [7]. Rechallenge with ribociclib is generally discouraged due to the risk of recurrence.

Emerging evidence suggests that switching to another CDK4/6 inhibitor may be feasible and safe in selected patients. Several case reports and retrospective analyses have documented successful transitions to abemaciclib without recurrence of hepatotoxicity [5,6]. Abemaciclib appears to have a distinct toxicity profile, with gastrointestinal adverse events predominating over hepatic toxicity. The favorable outcome observed in the present case further supports this strategy.

Published clinical trials, systematic reviews, and case reports describing ribociclib-associated hepatotoxicity and outcomes after switching to alternative CDK4/6 inhibitors are summarized in Table 1.

CONCLUSION

Severe isolated conjugated hyperbilirubinemia is a rare but clinically meaningful manifestation of ribociclib-associated hepatotoxicity. This pattern likely reflects a reversible, transporter-mediated functional disturbance rather than classical hepatocellular injury. Early recognition and prompt treatment discontinuation allow complete recovery. Switching to an alternative CDK4/6 inhibitor, particularly palbociclib, may represent a safe and effective strategy to maintain oncologic benefit without recurrence of hepatic toxicity.

REFERENCES

1. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for hormone receptor–positive advanced breast cancer. *N Engl J Med*. 2016 ;375 :1738–1748.
2. Im SA, Lu YS, Bardia A, et al. Ribociclib plus endocrine therapy for premenopausal women with advanced breast cancer. *N Engl J Med*. 2019 ;381 :307–316.
3. Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med*. 2020 ;382 :514–524.
4. Teh J, Yang M, Lee SC. Hepatotoxicity associated with CDK4/6 inhibitors: A systematic review. *Breast Cancer Res Treat*. 2021 ;186 :1–11.
5. Leone Roberti Maggiore U, Cagnacci A, Ferrero S, et al. Ribociclib-induced liver injury: A case report and review of the literature. *Clin Breast Cancer*. 2022 ; 22 : e284–e288.
6. El-Sheikh A, Farag S, Abdel-Rahman O. Severe hyperbilirubinemia without transaminase elevation under ribociclib: An unusual toxicity. *J Oncol Pharm Pract*. 2023 ;29 :123–127.
7. Cardoso F, Senkus E, Costa A, et al. 5th ESO–ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol*. 2020;31 :1623–1649.