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CASE REPORT

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Entecavir-induced neutropenia in an adult living donor liver transplant recipient: Successful conversion to tenofovir alafenamide

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Key Clinical Message

At 22 weeks post-transplantation for HBV-related cirrhosis, an adult woman developed neutropenia which was aggravated by COVID-19 (ANC 0.4×10^9/L). Covid resolution and all "conventional" modifications were ineffective. Success within 2 weeks was achieved by switching entecavir to tenofovir alafenamide. A step-by-step judicious approach to post-transplant neutropenia is vital.

KEYWORDS

COVID-19, entecavir, liver transplantation, neutropenia, tenofovir alafenamide

1 | INTRODUCTION

Neutropenia is a well-documented adverse event among solid organ transplant (SOT) recipients. The occurrence of neutropenia within the first year of liver transplant (LT) is approximately 24%.[1] Medications commonly implicated are mycophenolate mofetil (MMF), azathioprine, antithymocyte globulin, valganciclovir, aciclovir, trimethoprim-sulfamethoxazole (TMP/SMX) and sirolimus.[1-4]

Here we present an uncommon case of entecavir (ETV)-induced neutropenia aggravated by COVID-19 infection after adult living donor liver transplantation (LDLT) for hepatitis B-related cirrhosis.

2 | CASE DESCRIPTION

A 39-year-old woman with HBV–related cirrhosis complicated by ascites infection and variceal bleeding required LT. She had no other significant medical, surgical, or family history and she neither smoked cigarettes nor consumed ethanol. Her medications were ETV 0.5 mg once daily, rifaximin 550 mg three times a day, ursodeoxycholic acid 250 mg three times a day, propranolol 40 mg every morning and 20 mg every night, sucralfate 2 g twice daily and pantoprazole 40 mg twice daily. The patient received three doses of COVID-19 vaccination, namely, Sinovac (whole inactivated COVID-19 virus vaccine)—two doses and Pfizer-BioNTech COVID-19 messenger RNA based vaccine—single dose.

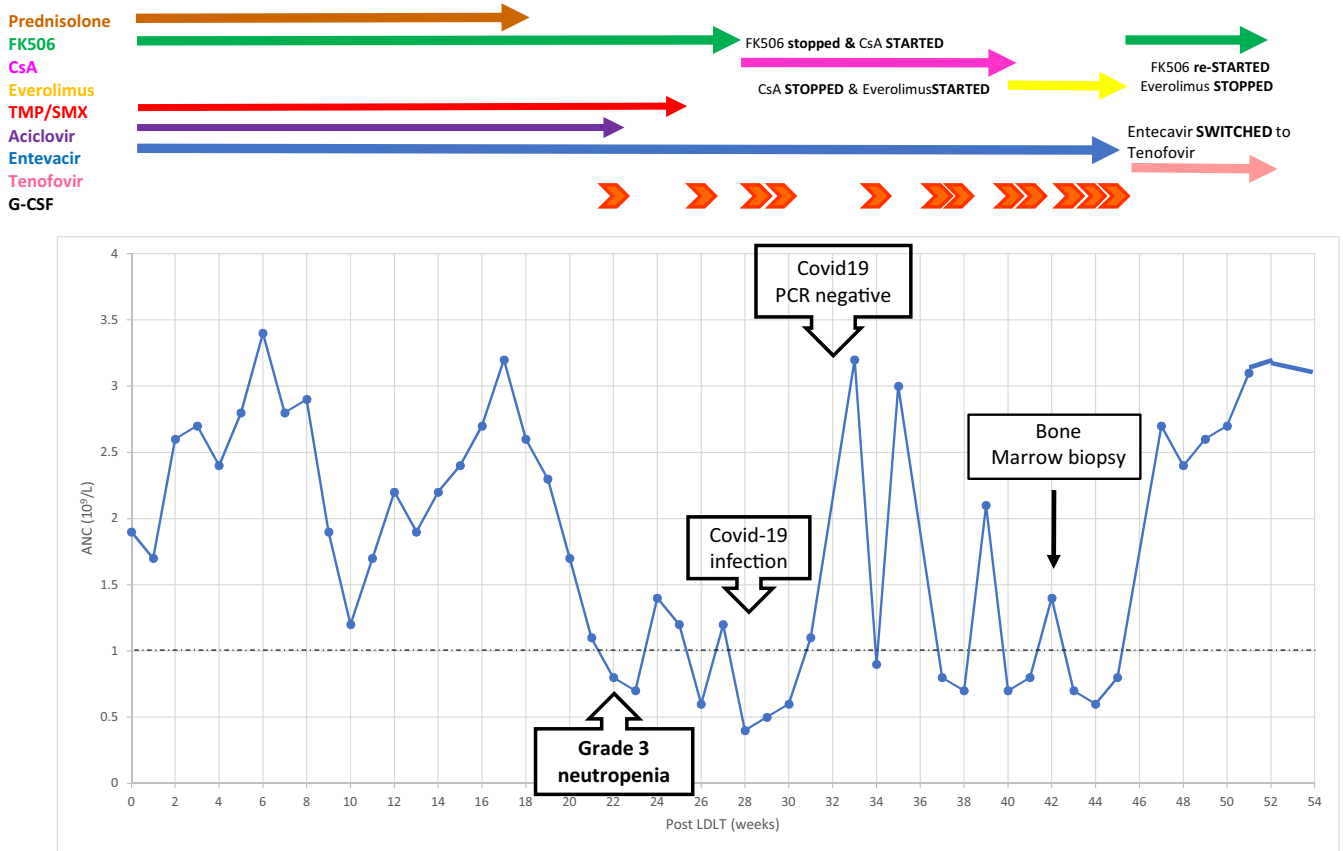
She underwent a successful right-lobe LDLT. The splenic artery was ligated at a point near its origin to prevent small-for-size syndrome. Her immunosuppressive therapy comprised prednisolone and tacrolimus (FK506), with trough whole blood levels ranging from 8 to 11 ng/mL during the early postoperative period. Her list of medications is prednisolone, FK506, ETV, TMP/SMX, aciclovir, ursodeoxycholic acid, and pantoprazole.

During the 3 months before LDLT, the leukocyte count had varied between 1.6 and 3.3×10^9/L and the absolute neutrophil count (ANC) ranged between 0.6 and 1.9×10^9/L. Between 4 and 21 weeks post-transplantation, the leukocyte count varied from 1.9 to 6.5×10^9/L and the ANC varied from 1.2 to 3.4×10^9/L.

The patient developed significant neutropenia at 22 weeks post-transplantation—the ANC was 0.8×10^9/L (Grade 3[5]). Granulocyte-colony stimulating factor (G-CSF) was administered; both aciclovir and TMP/SMX were discontinued. Nutritional deficiencies were ruled out. The PCR results for cytomegalovirus(CMV) and Ebstein-Barr virus (EBV) were negative. There was no laboratory evidence of HBV relapse. Peripheral blood smear showed marked hypochromic microcytic erythrocytes with anisocytosis and poikilocytosis. Lymphocytes were relatively increased and neutrophils decreased with no atypical cells detected. At 28 weeks post-transplantation, due to worsening neutropenia and suspicion of drug-related neutropenia; FK506, the primary choice of immunosuppression was stopped and substituted with cyclosporine (CsA). It was also at this point of time, the patient developed fever and was diagnosed with mild coronavirus infection confirmed by a positive COVID-19 reverse-transcriptase PCR test. During this period, ANC dropped to 0.4×10^9/L (Grade 4[5])—the lowest trough of her ANC trend. Within the following 2 weeks of COVID-19 diagnosis, that is, week 28–30 post-transplantation, ANC levels were between 0.4 and 0.6×10^9/L, which was the lowest range recorded throughout her clinical history (Graph 1) showing aggravation of neutropenia in relation to COVID-19 infection. Fortunately, she did not suffer from serious COVID-19 complications.

At 32 weeks post-transplantation, the patient achieved a negative COVID-19 conversion (Graph 1); however, neutrophil counts still continued to dipped intermittently below 1×10^9/L. Monocyte counts which ranged between 0.24 and 0.31×10^9/L (normal range 0.25–0.84×10^9/L) before transplantation, remained normal (0.25–0.54×10^9/L) during the neutropenic phase post-transplantation.

CsA monotherapy was maintained until 40 weeks post-transplantation but was stopped in view of hirsutism and



GRAPH 1 ANC trend and modifications in medication.

possible calcineurin inhibitor(CNI)-induced neutropenia and everolimus was started.

Bone marrow biopsy at week 42 post-transplantation revealed a reduction in neutrophils without prominent dysplasia, signs of infection, atypical, or blast cells in the myeloid array.

With time, she required increasingly frequent doses of G-CSF only to result in comparatively smaller increments in ANC demonstrating a more and more blunted ANC response to G-CSF (post-transplantation week 33–44, Graph 1).

As neutropenia persisted despite alterations of immunosuppressive therapy, immunosuppression was reverted to FK506 monotherapy at 45 weeks post-transplantation, due to the superiority of FK506 compared to everolimus as an immunosuppressant, with respect to acute/chronic rejection.

The patient's renal function, which was normal before LT, recorded a creatinine range of 0.98–1.37 mg/dL (normal range 0.5–0.9 mg/dL) in the first 2 weeks post-transplantation, after which, the renal function normalized without renal replacement therapy.

Magnetic resonance portography confirmed graft portal vein patency; the platelet count of the patient had risen from the $20–50 \times 10^9$/L range to the $50–100 \times 10^9$/L range after transplant hence excluding residual or recurrent hypersplenism as the cause of neutropenia. With all potential drug culprits discontinued, a final alteration was made, whereby ETV 0.5 mg once daily was replaced by tenofovir alafenamide 25 mg once daily (Graph 1). ANC improved within 2 weeks of cessation of ETV and has remained normal after 6 months of follow up. This implicates of ETV as the cause of neutropenia and based on the Adverse Drug Reaction Probability Scale (Naranjo) (Table 1),[6] a score 6 was attained indicating a *probable* ETV-related neutropenia in this patient.[7]

Although proton pump inhibitors (PPI) may be a cause of neutropenia, the patient was taking pantoprazole before LT and it was continued after LT. Moreover, it was after ETV cessation where neutropenia resolved, despite continuation of pantoprazole. Therefore, we deduced that neutropenia is not attributed to PPI.

3 | DISCUSSION

Neutropenia is a common occurrence in SOT recipients. Immunosuppressive therapy is frequently implicated and the complication resolves after discontinuation of the causative drug. However, identification of the cause is challenging due to multifactorial etiology, polypharmacy, and absence of specific diagnostic tests.

TMP-SMX used for Pneumocystis jirovecii prophylaxis in immunocompromised individuals, is associated with some degree of neutropenia due to inhibition of granulopoiesis in 39% of cases.[9] Antiviral agents for CMV prevention such as valganciclovir and ganciclovir may cause myelotoxicity and resultant neutropenia in up to 8.2% of cases and 3.2% of cases, respectively.[10] Isolated cases of neutropenia have been reported with acyclovir too.[11]

TABLE 1 Adverse Drug Reaction Probability Scale (Naranjo)[6]

Question	Yes	No	Do Not Know	Score
1.Are there previous conclusive reports on this reaction?	+1	0	0	+1[a]
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	+2
3. Did the adverse event 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 readministered?	+2	−1	0	0
5. Are there alternative causes that could, on their own, have caused the reaction?	−1	+2	0	0
6. Did the reaction reappear when a placebo was given?	−1	+1	0	+1[b]
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0[c]
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
	Total Score: 6			

[a]Product monograph.[8]

[b]In the strictest case, a placebo was not given. For the purpose of scoring, 1 point was given because an alternative drug did not cause reappearance of reaction.

[c]Not applicable.

Transient neutropenia also occurs in the course of viral infections such as EBV and CMV.[12-14] In the recent years, SARS-CoV-2 infection has emerged as an important disease among SOT recipients. Severe COVID-19 is a result of inappropriate and deleterious cytokine storm culminating in multiorgan failure even in healthy individuals. Lymphopenia is predominant but neutropenia has also been reported,[15,16] hence confounding this patient's existing neutropenia.

FK506, the cornerstone in immunosuppression after liver transplantation, is associated anemia, leukopenia, and thrombocytopenia.[4] Rare occurrences of isolated neutropenia have been reported although precise mechanism is unclear.[17] Pharmacokinetic interactions exist between MMF and FK506 where mycophenolic acid plasma concentration appear to be higher in the presence of FK506 increasing the risk of neutropenia in patients with MMF-FK506 therapy.[2] On the contrary, patients with MMF—CsA paired immunosuppression have been reported to have lower mycophenolic acid bioavailability.[2] This infers a lowered neutropenia risk, therefore, conversion from FK506 to CsA may be successful.[17]

Consideration of CNI-rather than tacrolimus toxicity alone[18,19] led to conversion to everolimus monotherapy. However, mammalian target of rapamycin inhibitor (mTORi) therapy alone increases organ rejection risk.[18] With neutropenia still unresolved during mTORi treatment, the patient was reverted back to FK506.

Liver transplant patients with HBV require mandatory lifelong antiviral treatment. Nucleos(t)ide analogs (NA) are essential given its strong antiviral potency, low resistance rates, high safety profile, and very low discontinuation rate of 1%. ETV, a highly selective guanosine nucleoside analog, is one of the NAs of choice for LT transplant recipients. All NAs carry an FDA "black box" warning for potential mitochondrial toxicity, albeit very rare. Manifestations include hematologic disorders—a plausible explanation for neutropenia in this patient.[20] However, mitochondrial toxicity is a "class effect" of NAs, whereas this patient had a temporal neutropenia relationship only with ETV which resolved after conversion the tenofovir alafenamide.

ETV-related neutropenia has been stated as a potential complication in pediatric patients in the monograph of the manufacturer.[8] Curiously, Pubmed and Google Scholar searches have yielded no results for both pediatric (possibly due to comparatively smaller number of treated patients) and adults. An intriguing aspect of this case is the effect of a drug, that is, ETV, that the patient had been taking for 16 years. This denotes an idiosyncratic drug-induced neutropenia (IDIN) response that is rare, unpredictable, and difficult to diagnose. There is a hypothetical immune mechanism involved with a delay in neutropenia long after initiation of the culprit drug. This delay is attributed to development of primary immune response. The onset of neutropenia varies between individuals as well as the drug involved; and may recur after rechallenging due to immunologic memory.[21] A plausible explanation is that LT and immunosuppressive therapy caused an immune-modulation process in this patient and triggered ETV-induced neutropenia which was aggravated by COVID-19.

Regular administration of G-CSF to hasten recovery of neutropenia is vital; however, the magnitude and duration of G-CSF response vary according to the underlying pathology treated. With reference to this case, the ANC levels oscillated in part due to the effects of G-CSF as well as transient bone marrow recovery. Although, suspicions of cyclic neutropenia rose, the patient's ANC trend did not conform to a regular 21 day cyclical pattern and, being a disorder of autosomal dominance inheritance, cyclic neutropenia is not present among the patient's family members. In addition, complete resolution of neutropenia was achieved after changing ETV to tenofovir.[22,23]

Analysis of drug–event occurrences in pharmacovigilance first involves clinical judgment—an individualized and subjective interpretation by the treating clinician based on experience and knowledge on the particular disease context. Secondly, the probabilistic method is applied, whereby existing epidemiologic data are examined for evidence of the probable drug–event relationship.[24] With regards to ETV-induced neutropenia, data are scarce and this event has only been recorded among pediatric patients.[8] Thirdly, algorithmic questionnaires and scores are used to analyze a drug–event pair.[24] With respect to this case, the Adverse Drug Reaction Probability Scale (Naranjo) (Table 1)[6] showed a *probable occurrence of* ETV-related neutropenia.[7] Each class of medication was altered in a systematic and sequential manner, starting from the commonest suspect to the least expected culprit drug, whilst maintaining a balance between devastating consequences of neutropenic sepsis against organ rejection; amidst the background of COVID-19 infection.

4 | CONCLUSION

Rare hematologic side effects, for example, anemia, thrombocytopenia, and neutropenia, of commonly used drugs may cause life-threatening complications in SOT recipients.[1-4,9-11,17] Drug-induced neutropenia in LT recipients require unyielding effort and time in determining

the causative drug. After modifications within one drug category, interval observations have to be made to allow recovery of ANC levels, only to make alterations in other drug categories if the latter fails because hasty deviations from standard treatment protocol may result in dire consequences in SOT recipients.

AUTHOR CONTRIBUTIONS

I Vern Lim: Data curation; resources; writing – original draft; writing – review and editing. **Nurgül Özgür Yurttaş:** Data curation; investigation; writing – review and editing. **Mesut Ayer:** Data curation; investigation; writing – review and editing. **Şule Poturoğlu:** Investigation; methodology; writing – review and editing. **Erdem Kınacı:** Investigation; methodology; supervision; writing – review and editing. **İlgin Özden:** Data curation; formal analysis; funding acquisition; investigation; methodology; resources; supervision; writing – review and editing.

FUNDING INFORMATION

None.

DATA AVAILABILITY STATEMENT

Data regarding this case report can be accessed by contacting corresponding author.

ETHICS STATEMENT

Not required by the institutional IRB due to the purely retrospective nature of the case report.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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