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A Patient With CKD Develops Cholestatic Liver Injury During a Clinical Trial

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INTRODUCTION

Patients with chronic kidney disease (CKD) develop disordered phosphate metabolism, characterized by abnormalities in phosphate and fibroblast growth factor 23 (FGF23) levels.[1] Higher serum phosphate and FGF23 levels are associated with increased risk of mortality in the CKD population.[2,3] Large clinical trials are needed to determine whether lowering phosphate and FGF23 levels will improve clinical outcomes in patients with CKD. There is growing interest in using nicotinamide (NAM) for management of hyperphosphatemia in patients with end-stage renal disease who are undergoing dialysis.[4–7] By blocking intestinal phosphate absorption through downregulation of the sodium-dependent phosphate cotransporter (NPT2b),[8] NAM is capable of reducing serum phosphate levels, and it may also reduce FGF23 levels.[9–11] Additional efficacy and safety data are needed before conducting large clinical trials of NAM for this purpose among patients with CKD.

The CKD Optimal Management with BInders and NicotinamidE (COMBINE) study is a randomized, double-blinded, placebo-controlled, parallel-group study examining the effects of NAM and lanthanum carbonate on serum phosphate and FGF23 levels in patients with stages 3 to 4 CKD.[12] Here, we report the case of a 45-year old man who developed cholestatic liver injury during participation in the COMBINE study. Initially, this adverse event was considered to be related to NAM. However, further clinical workup revealed a rare and different cause of the patient's cholestatic liver injury.

*See Appendix for the CKD Optimal Management with Binders and NicotinamidE (COMBINE) Investigators.

CASE PRESENTATION

Clinical History

A 45-year-old man with stage 4 CKD (estimated glomerular filtration rate of 34 ml/min per 1.73 m^2) was enrolled in the COMBINE study. The COMBINE study is an ongoing pilot trial testing whether NAM combined with lanthanum carbonate on a background of reduced dietary phosphate intake safely reduces serum phosphate and FGF23 levels over 12 months in 205 patients with stages 3 to 4 CKD (Figure 1). During the first month after randomization, the dose of NAM is 750 mg once daily and the dose of lanthanum carbonate is 500 mg 3 times daily with meals. After the first month, the dose of nicotinamide is increased to 750 mg twice daily and the dose of lanthanum carbonate is increased to 1000 mg 3 times daily with meals.

The patient's past medical history was significant for type 1 diabetes complicated by stage 4 CKD, diabetic retinopathy, and coronary artery disease (CAD). The patient was treated for diabetic retinopathy with vitrectomy 10 years before study participation, and for CAD with coronary artery bypass grafting 1 year before study participation. Other medical comorbidities

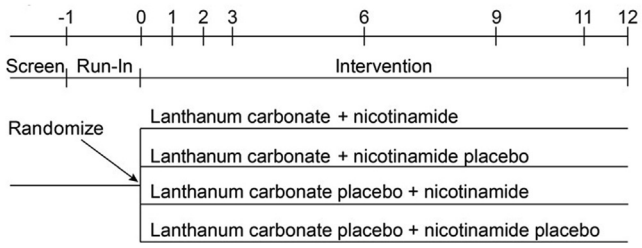

Figure 1. Schema for the CKD Optimal Management with Binders and NicotinamidE (COMBINE) study.

included obstructive sleep apnea, for which he was treated with continuous positive airway pressure. His medication regimen was as follows: atorvastatin calcium, 80 mg daily; amlodipine besylate, 2.5 mg daily; carvedilol, 12.5 mg twice daily; clopidogrel bisulfate, 75 mg daily; duloxetine HCl, 60 mg daily; losartan potassium, 100 mg daily; ropinirole HCl, 1 mg daily; levothyroxine sodium, 50 μg daily; aspirin, 81 mg daily; furosemide, 20 mg daily as needed; and omega-3 fatty acids, 1000 mg daily. The patient also had an insulin pump, which delivered regular-human insulin (RELION R) 100 unit/ml, up to 130 units daily. Except for an uncle with alcoholic liver disease, no history of liver or kidney disease had been recorded for the patient's family. The patient did not smoke or use tobacco. He denied significant alcohol intake, tattoos, or blood transfusions. The patient reported that he had had a sexual encounter with a man a few months before study participation.

Course in the Study

The patient's early course in the study was uneventful. The patient's liver function tests (LFTs) at the onset of the study were within the normal range (Table 1). The patient progressed through the baseline period and first 3-months' postrandomization visits without any problems.

At his 3-month follow up visit, which took place 13 weeks after randomization, the patient was noted to have a new anemia on the safety laboratory studies collected by the research team. He was referred to his primary care physician. Workup for anemia by the primary care physician revealed abnormal LFTs, with a cholestatic pattern. His alkaline phosphate (ALP) level was 11 times the upper limit of the local laboratory reference range. At the same time, the patient's aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin levels were also elevated; AST was $>$ 7 times the upper limit of the reference range, ALT was $>$ 9 times the upper limit of the reference range and total bilirubin was 1.5 times the upper limit of the reference range (Table 1, day 148). His study drugs were stopped, and the patient was admitted to the hospital for expedited workup of cholestatic liver injury. On the day of admission, examination demonstrated a blood pressure of 149/81 mm Hg and pulse of 85 beats/min. Skin examination revealed jaundice. Cardiovascular, respiratory, abdominal, and neurologic examinations were normal.

Table 1. Laboratory data and events

Time	AST (reference range, 0–39 IU/l)	ALT (reference range, 0–52 IU/l)	ALP (reference range, 34–104 IU/l)	Total bilirubin (reference range, 0.0–1.0 mg/dl)	Event
Screening Baseline	29	39	97	0.9	
Day 29 Week 5	17	31	83	0.9	Follow-up visit 1: NAM up to 1500 mg/d
Day 59 Week 9	25	41	83	0.9	Follow-up visit 2: NAM continued, 1500 mg/d
Day 87 Week 13	21	35	94	1.1	Follow-up visit 3: NAM continued, 1500 mg/d
Day 144 Week 21	134	246	787	1.4	NAM continued, 1500 mg/d
Day 148 Week 22	294	510	1143	1.5	NAM stopped
Day 151 Week 22	118	263	841	1.7	Off NAM
Day 169 Week 25	44	76	574	0.8	Off NAM
Day 196 Week 29	89	158	897	0.8	Off NAM
Day 205 Week 30	99	140	1006	1.0	Off NAM, PCN started
Day 212 Week 31	42	106	554	0.4	Off NAM, on PCN
Day 218 Week 32	27	40	331	0.4	Off NAM, on PCN

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NAM, nicotinamide; PCN, penicillin.

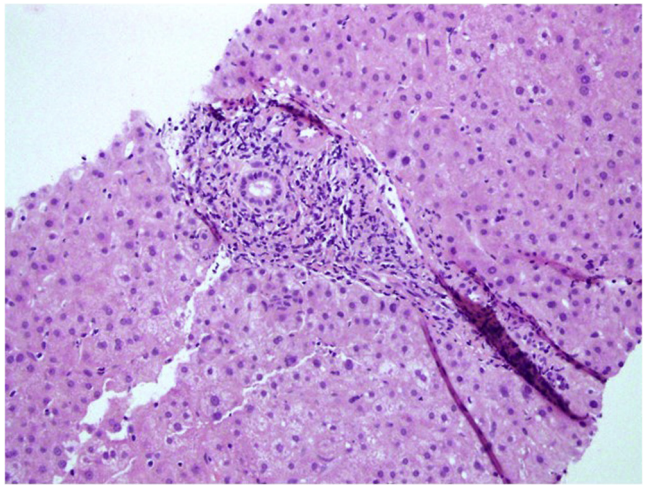

Figure 2. Portal tract showing a mild inflammatory infiltrate. The inflammation is confined to the portal tract; there is no interface hepatitis that is expected to be seen in chronic hepatitis.

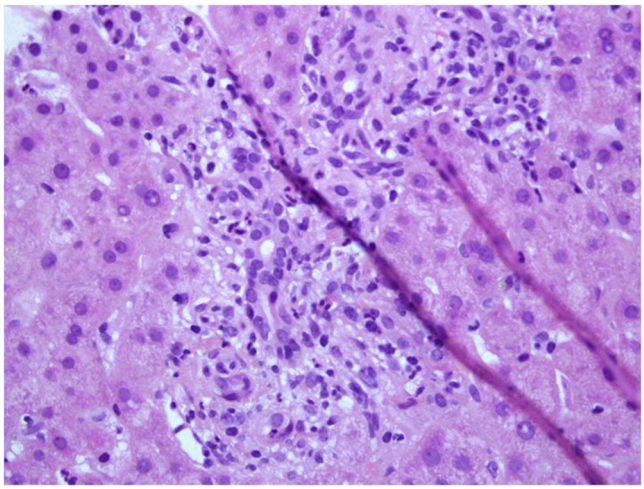

Figure 4. Portal tract with inflammatory infiltrate, consisting of lymphocytes, rare plasma cells, and scattered eosinophils. There are small proliferating ductules (ductular reaction), suggestive of some damage to the biliary system.

A magnetic resonance imaging scan without gadolinium was performed, which showed mild splenomegaly and no evidence of biliary obstruction. A liver biopsy showed mild portal inflammation, mainly composed of lymphocytes, occasional plasma cells, and eosinophils (Figures 2–4). The biopsy also revealed ductular reaction and minimal hepatocyte reactive change (Figures 4 and 5). For diagnostic evaluation of liver tissue, trichrome, reticulin, periodic acid–Schiff, and iron stains were performed, and were considered unremarkable. The morphologic findings were nonspecific, due to either an adverse drug reaction or biliary tract disease. The patient's LFTs began to improve in the weeks after stopping NAM (Table 1). Bloodwork was repeated 3 weeks after stopping NAM, and showed that bilirubin was now within normal range; ALP, AST, and ALT were also decreased. One month after stopping NAM, the patient complained of persistent fatigue, recurrent Bell's palsy, and balance and vision impairment. The LFTs increased again. At the subsequent primary care visit, the patient's doctor noted a new palmar rash (Figure 6).

Diagnosis

A rapid plasma reagin test was performed 29 weeks postrandomization, and tested positive (titer 1:128). Lumbar puncture showed pleocytosis, consistent with neurosyphilis. The patient was diagnosed with

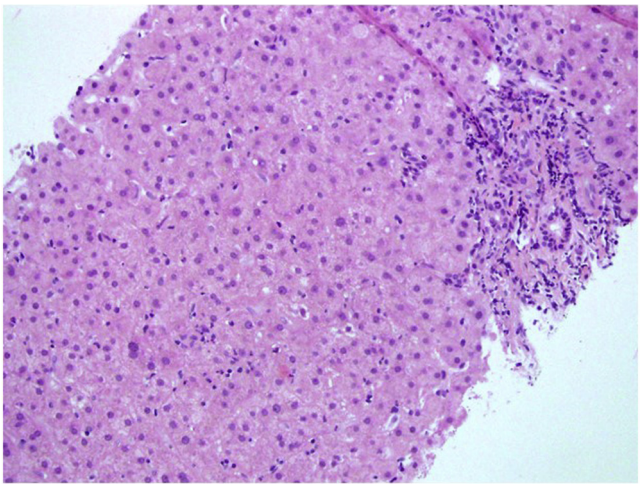

Figure 3. Portal tract showing mild inflammatory infiltrate.

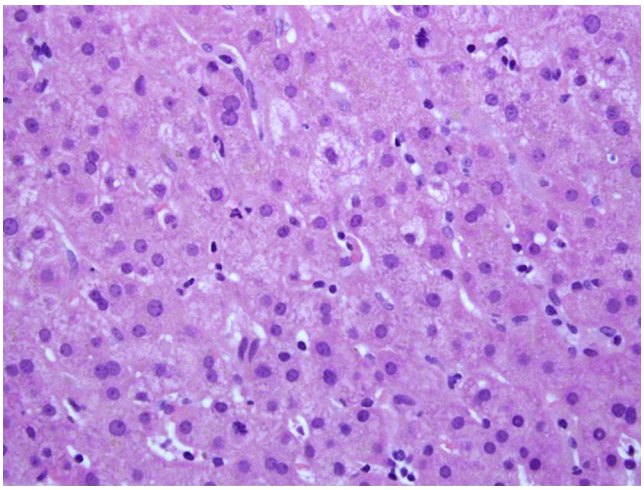

Figure 5. Hepatic parenchyma away from the portal tracts. Scattered mitoses are seen (1 o'clock and 7 o'clock), suggesting that there has been some damage to the liver, with mitotic activity representing regenerative/reparative changes as the liver heals. The findings in this biopsy are mild but would be consistent with either drug effects or biliary tract disease.

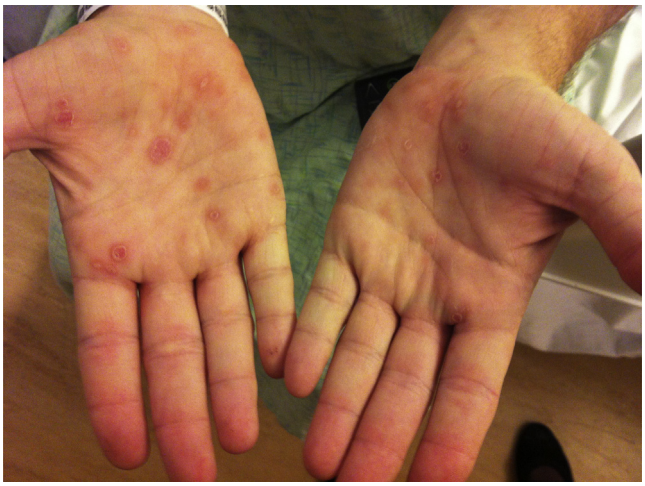

Figure 6. The patient presented with a palmar rash.

secondary syphilis. I.v. penicillin was prescribed, and the patient completed a 14-day course. The patient's LFTs improved rapidly with i.v. penicillin (Table 1), establishing the diagnosis of syphilitic hepatitis as the most likely cause of cholestatic liver injury.

DISCUSSION

Here, we report the case of a 45-year old man who developed cholestatic liver injury during participation in the COMBINE study. Initially, NAM, the study drug, was thought to be the cause of this adverse event, and was therefore stopped. A month later, the patient presented with a palmar rash that was concerning for secondary syphilis. Rapid plasma reagin testing was strongly positive, and syphilitic hepatitis was determined to be causing the liver injury based on the patient's subsequent workup and response to treatment with penicillin.

When the patient's elevated LFTs were initially discovered, his study drugs were stopped, and the study team re-examined the literature and reconsidered potential risks to participants. NAM, also known as niacinamide, is the amide form of vitamin B3.[13] Niacin, another form of vitamin B3, is used to treat pellagra, which is caused by a deficiency of niacin. Although they are structurally related, NAM has a carboxamide group on the third position of the pyridine ring where niacin has a carboxyl group (Figure 7). This consequently leads to different side effect profiles of the 2 drugs. NAM may have advantages over niacin because, unlike niacin, NAM does not cause flushing and is thought to be less likely to cause liver test abnormalities, hyperuricemia, or insulin resistance.[13] Although single case reports show that NAM may cause cholestatic jaundice,[14,15] a large randomized controlled trial examining NAM as a preventive medicine for type 1 diabetes demonstrated that treatment with this drug is

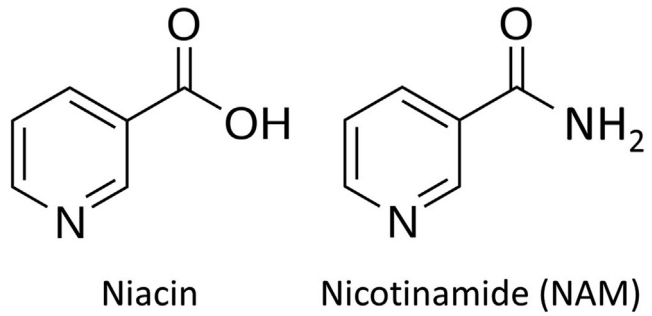

Figure 7. Structural formulas of niacin and nicotinamide (NAM).

safe and well tolerated in participants aged between 3 and 40 years, with a 5-year follow-up period.[16] Another study found NAM to be effective in reducing new nonmelanoma skin cancers and actinic keratosis in high-risk patients, and it reported no harmful adverse effects of NAM administration.[17] The doses of NAM studied in these trials were similar to those administered in the COMBINE study. However, we cannot draw conclusions about the safety of NAM in the CKD population from these earlier studies, because patients with kidney disease were excluded. An open-label study examining non-inferiority and safety of NAM when compared with sevelamer (SEV) included only hemodialysis patients.[18] Although both drugs were equally effective in lowering serum phosphate in this open-label study, NAM tolerability was inferior to that of SEV. However, liver injury was not observed in the NAM arm.[18]

In addition to considering these prior studies, we consulted the Data and Safety Monitoring Board about the development of unexpected elevated LFTs in the patient. At first, we reported the possible connection between NAM and the liver injury, based on the initial clinical course of the participant. However, our observations that LFTs did not meaningfully improve over the 2 months off NAM treatment, in conjunction with the discovery of an alternative diagnosis (syphilitic hepatitis), and the rapid improvement in LFTs and other symptoms with penicillin therapy, led us to conclude that syphilitic hepatitis, and not NAM, was the reason for this adverse event. Therefore, we assessed that the risk to other participants in the study remained unchanged. As a result, we deemed it unnecessary to change the inclusion criteria, frequency of follow-up visits, and safety stopping criteria. We modified the original informed consent to provide a more detailed description of the NAM safety profile in relation to CKD, and we left the study protocol unchanged. The study proceeded as originally planned, and to date there have been no additional incidences of liver injury.

When an unexpected adverse event occurs during a trial, the participant, the participant's treating physicians, and the research team may all be inclined to implicate the study drug. Although this is an appropriate reaction to ensure participant safety, focusing solely on the study drug as the culprit may lead to missing the actual etiology of the adverse event. In routine medical practice, physicians may also assume that a patient's new symptoms are related to a medication that they recently started. Our case highlights the importance of considering and thoroughly investigating all potential causes of adverse events, rather than assuming that they are medication related due to the temporal relationship between the initiation of the medication and the onset of symptoms.

Our patient developed liver injury with a cholestatic pattern that is indicated by his disproportionate elevation in alkaline phosphatase compared with the serum aminotransferases. Cholestasis may develop in the setting of extrahepatic or intrahepatic biliary obstruction (Table 2).[19] Extrahepatic cholestasis may be caused by choledocholithiasis, malignant biliary obstruction, and biliary strictures. Drugs, primary biliary cholangitis, primary sclerosing cholangitis, and infiltrative diseases may cause intrahepatic cholestasis. Infiltrative diseases include amyloidosis, sarcoidosis, cancer metastatic to the liver, and other granulomatous diseases, including syphilis. Therefore, syphilitic hepatitis should be included in the differential diagnosis of cholestatic liver injury.

Syphilis is most commonly transmitted through sexual activity. In 2015, the overall rate of primary and secondary syphilis in the United States among men who have sex with men was 106 times the rate among men who have sex with women only.[20] Therefore, our patient was at high risk for developing syphilis. One of the great imitators, syphilis is widely considered difficult to diagnose because of its protean manifestations. Although unsafe sexual behavior is a well-known risk factor for syphilis, and palmar rash is a widely recognized symptom of syphilis, the presentation of hepatitis is uncommonly associated with the disease.[21] Our case report demonstrates that it is important to conduct a thorough workup whenever a patient presents with cholestatic liver injury, so that syphilis can be either diagnosed or ruled out.

Table 2. Differential diagnosis for cholestatic liver injury

Extrahepatic cholestasis	Choledocholithiasis
	Malignant biliary obstruction
	Biliary stricture
Intrahepatic cholestasis	Drug induced
	Primary biliary cholangitis
	Primary sclerosing cholangitis
	Amyloidosis
	Sarcoidosis
	Metastatic cancer to liver
	Syphilis

Table 3. Take-home messages from our case

A thorough workup should be performed when a patient presents with cholestatic liver injury, and syphilitic hepatitis should be included in the differential diagnosis.
Study drugs are commonly implicated as the cause of an unexpected adverse event during a clinical trial. However, other etiologies should not be neglected. The correct diagnosis can be achieved by keeping the initial differential diagnosis broad.

In conclusion, we present a rare and interesting case involving a clinical trial participant. This case illustrates the pitfalls of implicating a study drug as the cause of an adverse event or symptom without testing for other possible etiologies (Table 3). Although it is certainly important to consider this possibility from the perspective of participant safety, researchers and clinicians must also evaluate a broad differential diagnosis before concluding that an adverse event is related to a medication. Conducting such broad, yet appropriate workups for research participants' new symptoms will not only help prevent delays in diagnosing adverse events related to study interventions, but will also lead to rapid identification of other conditions that may require urgent treatment, such as the case presented here. Future research could examine the frequency, scope, and depth of diagnostic testing after participants develop adverse events during clinical trials.

DISCLOSURE

TI has received research support from Shire. All the other authors declared no competing interests.

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APPENDIX

CKD Optimal Management with Binders and NicotinamidE (COMBINE) Investigators

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