abstract

Vanishing bile duct syndrome (VBDS) is a rare disorder characterized by loss of interlobular bile ducts and progressive worsening cholestasis. The acute presentation of this disease is typically associated with a drug hypersensitivity and Stevens-Johnson syndrome/toxic epidermal necrolysis (TEN). The mainstay of treatment has been ursodeoxycholic acid with mixed results from immunosuppressive regimens. Anti–tumor necrosis factor-α and plasmapheresis have been speculated to be of potential benefit. It is hoped that early identification and intervention in VBDS secondary to Stevens-Johnson syndrome/TEN with continued reporting will lead to better regimens and outcomes. Our case report details the first reported use of infliximab and plasmapheresis, in addition to steroids, in a patient with VBDS secondary to TEN, as well as a literature review that supports a mechanism for why these modalities could be effective treatments. Unfortunately, our patient died, and the use of these therapies had an unclear benefit on his liver and skin disease. We hope that additional work can be published to confirm or refute their utility in the treatment of these diseases. *Pediatrics* 2014;134; e1194–e1198

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KEY WORDS
vanishing bile duct, Stephens-Johnson syndrome, toxic epidermal necrolysis, TNF-α inhibitor, plasmapheresis

ABBREVIATIONS
ALT—alanine aminotransferase
AP—alkaline phosphatase
AST—aspartate aminotransferase
GGT—γ glutamyl transferase
INR—international normalized ratio
SJS—Stevens-Johnson syndrome
TEN—toxic epidermal necrolysis
TNF—tumor necrosis factor
VBDS—vanishing bile duct syndrome

Dr White carried out initial analyses and drafted and revised the initial manuscript; Dr Appleman carried out initial analyses and reviewed and revised the manuscript; and both authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-2239
doi:10.1542/peds.2013-2239

Accepted for publication Feb 27, 2014

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).
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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.
Vanishing bile duct syndrome (VBDS) is a heterogeneous group of biliary diseases characterized by progressive loss of intrahepatic bile ducts or cholestasis.1 Diagnosis is confirmed by liver biopsy showing loss of interlobular bile ducts in >50% of sampled portal tracts.2 Adult patients typically have concurrent liver diseases.1-6 Pediatric case reports associate the development of VBDS with Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN; see Table 1). These cases led to the hypothesis that VBDS can be caused by the same hyperimmune response that causes SJS/TEN.1,3,4,7 Because of the limited cases, therapeutic interventions vary. Refractory cases have used immunosuppression, most commonly the calcineurin inhibitor tacrolimus, with mixed results.1,3,4 With increased knowledge of the pathophysiology, it has been suggested that tumor necrosis factor-α (TNF-α) inhibitors may represent an alternative therapy.4 Our patient, a 6-year-old boy, represents the first reported use of a TNF-α inhibitor and plasmapheresis for treatment of VBDS associated with TEN. We also summarized the presentation, management, and response to other therapies of patients with VBDS secondary to TEN.

**CASE REPORT**

A 6-year-old Puerto Rican/African American male, with past medical history of asthma, presented to an outside hospital 3 weeks before presentation at our institution with chief complaints of fever, rhinorrhea, and cough. He was diagnosed with pneumonia and discharged from the hospital with cefdinir. He returned a week later with no improvement, was admitted, and received intravenous ceftriaxone and methylprednisolone. Admission laboratories showed total bilirubin of 2.7 mg/dL, aspartate aminotransferase (AST) 233 U/L, alanine phosphatase (AP) 631 U/L, γ glutamyl transferase (GGT) 608 U/L, and lipase 1707 U/L.

Subsequently he developed an erythematous macular rash, conjunctivitis, chapped lips, sterile pyuria, and respiratory distress and received intravenous immunoglobulin and aspirin for presumed Kawasaki disease. His respiratory status worsened, and he was admitted to the ICU 10 days before transfer to our institution.

In the ICU, the rash evolved to scattered groupings of vesicles involving the oral mucosa, prompting a skin biopsy, which showed interface inflammation with scant lymphocytic infiltrate and epithelial cell necrosis, diagnostic of TEN. AST increased to 442 U/L, ALT to 245 U/L, GGT to 829 U/L, and total bilirubin to 7.3 mg/dL. International normalized ratio (INR) was 1.94, and ammonia was 115 umol/L. Mycoplasma immunoglobulin M levels were elevated, and azithromycin was started.

Laboratory evaluation showed a normal complete blood count and basic metabolic panel. Erythrocyte sedimentation rate was 78 mm/hour, and C-reactive protein was 6.2 mg/dL. A liver function panel showed a total protein of 5.2 g/dL, albumin of 2.7 g/dL, total bilirubin of 21.2 mg/dL, transaminases normalized (AST 366 U/L, ALT 295 U/L), and INR normalized; however, his total bilirubin rose to 18.4 mg/dL (direct 12.2 mg/dL). Hepatitis panel, Epstein-Barr virus, cytomegalovirus, HIV, herpes simplex virus 1/2 titers were all negative. Four days before transfer to our hospital, he was switched from azithromycin to levofloxacin to minimize hepatic toxicity, and vancomycin and cefepime were begun due to rising white blood cell count. No pathogens were cultured. He had worsening blisters and skin sloughing and was transferred for wound care.

Upon admission, he was afebrile and normotensive. Physical examination revealed a sedated boy with sloughing skin on his ears, trunk, bilateral arms, and legs. Eschar was noted on his eyelids and lips. Abdominal examination showed hepatomegaly, with the liver edge 2 cm below the costal margin. The remainder of his examination was unremarkable.

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mg/dL, conjugated bilirubin of 13.1 mg/dL, AST of 184 U/L, AP of 1383 U/L, GGT of 810 U/L, amylase of 75 U/L, and lipase of 80 U/L. His prothrombin time was 13.2 seconds, partial thromboplastin time was 30.8 seconds, and INR was 0.98. Ferritin was 1322 ng/mL, and soluble interleukin-2 receptor was 1747 U/mL. Admission medications included spironolactone, ursodiol, lactulose, rifampin, protonix, methylprednisolone, levofl oxacin, vancomycin, and cefepime.

Antibiotics were discontinued. Hydroxyzine, dexmedetomidine, and hydromorphone were added for sedation, pain, and pruritus. Bilirubin, AST, ALT, and AP levels began to decrease. Plastic surgery was consulted at admission for wound care and noted that although the patient still had blisters and sloughing skin involving >30% of body surface area, the newly exposed epidermis was intact. No acute therapy for TEN was recommended. On hospital day 3, he became anuric requiring hemodialysis for 3 days, with worsening respiratory status requiring intubation and mechanical ventilation. Polymerase chain reaction for hepatitis B and for cytomegalovirus, α-1 antitrypsin phenotype, antithrombin, antithrombin factor, and immunoglobulin levels were normal. C3 and C4 were 185 and 51 mg/dL, respectively.

On hospital day 4, he underwent liver and bone marrow biopsies. Bone marrow was normal. Liver biopsy demonstrated intact liver architecture with portal areas containing vascular structures; however, bile ducts were absent, confirmed by CK7 and CK19 staining. Macrophage was seen in ~85% of biopsy tissue and distributed randomly, with focal cholestasis seen within hepatocytes. There was no portal tract or lobular inflammation, no iron, copper, or Periodic acid–Schiff-diastase resistant or hyaline globules seen with special stains. Periodic acid–Schiff stained normal glycogen. Trichrome and reticulin stains revealed normal architecture. These findings were consistent with VBDS.

On hospital day 7, he became febrile and developed acute respiratory distress syndrome, requiring resumption of hemodialysis, vancomycin, gentamicin, and placement on oscillatory ventilation. A 5-day course of plasmapheresis was performed without incident. On hospital day 12, a 3-day, high-dose pulse methylprednisolone (30 mg/kg/dose) regimen was given, then resumption of daily dosing (2 mg/kg/dose). By hospital day 15, his cholestasis and transaminitis improved (Figs 1 and 2), but neomycin was added for hyperammonemia. Two doses of surfactant were given for worsened respiratory status. On hospital day 22, he was given a single 3 mg/kg infliximab dose without complication. Steroids were continued. On hospital day 24, he decompensated, requiring increased oscillatory support. On hospital day 29, he had hemopositive emesis. His steroid dose was decreased and pantoprazole, octreotide, and Carafate were started. Ursodiol...
was changed to phenobarbital. His condition worsened, requiring inotropic support and multiple blood transfusions. On hospital day 32, he suffered an acute decompensation requiring resuscitative measures, with stabilization on dopamine and norepinephrine drips. Despite interventions, he died on hospital day 51.

DISCUSSION
VBDS is an uncommon diagnosis, rare in children, with scattered cases associated with SJS/TEN. Previous case reports in which patients had both diagnoses speculated that a hyper–immune response damages the biliary system, leading to VBDS,1,3,4,7 which we believe occurred in our patient. It is possible that an infection or medication triggered the process.

VBDS can progress despite discontinuation of offending medications. Conversely, transaminase and bilirubin levels can improve despite persistent loss of bile ducts.2 We felt that our patient’s liver status was stabilizing/improving, so were hesitant to intervene aggressively for his liver disease. The decision to trial medications was based on his life-threatening multiorgan failure. Because of limited knowledge of the pathogenesis of VBDS, therapies have been chosen to blunt the immune response. Tacrolimus has had mixed results.1,3,4 We concluded that the risk/benefit ratio for tacrolimus in our patient was too high, given his kidney and lung injury. Intravenous immunoglobulin has also been used in adults that developed VBDS secondary to graft-versus-host disease and for a patient with VBDS secondary to TEN but was unable to prevent progression to liver transplant in those cases.8,9 Literature review suggested the use of TNF-α blockade.4 Okan et al did not use TNF-α blockade but hypothesized that it could be effective because case reports showed rapid resolution of skin and mucosal damage in patients with SJS/TEN after administration of infliximab,10,11 together with the theory of a common immunologic mechanism.1–7,12–14 Infliximab has been reported to increase the incidence of infections, but the majority of reports have been upper respiratory tract illnesses, < 2% of which were pneumonia.15 We chose infliximab for our patient because of its more favorable side effect profile.

Our patient also received plasmapheresis because of the shared immunologic pathway hypothesis. Reau et al noted that the cell death receptor CD95 (Fas) and its ligand (Fas-L) have been implicated in bile duct injury.2 Similarly, elevated levels of Fas-L have been found in TEN patients,16 and a case series showed resolution of the TEN mucosal damage once plasmapheresis was initiated, correlating with removal of Fas-L from the serum.17 Its use in patients with isolated VBDS is limited. A case report showed minimal improvement after plasma exchange.18 Given our patient’s critical condition, this therapy was used to attempt to blunt systemic inflammation.

We report another case of VBDS associated with TEN, but the first using both a TNF-α blocker and plasmapheresis. Because this is an uncommon condition, there is no standardized therapeutic...
approach. Despite our patient’s death, TNF-α blockade and/or plasmapheresis may still offer therapeutic alternatives for VBDS, although we acknowledge that follow-up is short, his condition was grave, and confounding therapies were used, making it difficult to know which, if any, were effective. His bilirubin levels decreased and stabilized until the days before his demise, with liver pathology from autopsy confirming VBDS. The long-term ability of infliximab to blunt further destruction and allow for biliary regeneration is undefined compared with tacrolimus because previous cases using calcineurin inhibitors followed their patients for at least 6 months from time of injury. Those cases showed mixed results, with 2 patients showing clinical resolution and 1 patient requiring liver transplant (see Table 1). Long-term follow-up will be required to evaluate infliximab’s efficacy. Our case also supports choleretic for VBDS because our patient’s bilirubin levels declined once ursodiol was started.

Although VBDS is a rare sequelae of SJS/TEN, it should remain on the clinician’s differential for conjugated hyperbilirubinemia. More clinical studies are needed to determine the optimal therapy for both disorders.

REFERENCES

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*Pediatrics* 2014;134;e1194; originally published online September 22, 2014;
DOI: 10.1542/peds.2013-2239
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