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Case report

Minimal change disease and subacute interstitial nephritis in association with *Edwardsiella tarda* gastroenteritis following oyster consumption

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ABSTRACT

Edwardsiella tarda (*E. tarda*) is a gram-negative, facultatively anaerobic bacillus that is associated with gastroenteritis and a host of other extra-intestinal manifestations in humans. However, its impact on the kidneys is unclear. Most literature that has explored this association involves fish, marine life in which *E. tarda* inhabits. We report a rare case of a 72-year-old female who presented with an acute kidney injury (AKI) associated with newfound minimal change disease, subacute interstitial nephritis, and a severe *E. tarda* infection. Her clinical course resolved with antibiotics and glucocorticoids.

Introduction

Edwardsiella tarda (*E. tarda*) is a gram-negative, facultatively anaerobic bacillus of the Enterobacteriaceae family, first described in 1965 [1]. Though human transmission is rare, approximately 80 % of infections arise in the form of gastroenteritis after seafood consumption [2,3]. Extra-intestinal infections include skin and soft tissue infections, intra-abdominal abscesses, myonecrosis, peritonitis, meningitis, osteomyelitis, and bacteremia [3,4]. However, the impact of *E. tarda* infections on human kidneys is poorly understood. In fish, there are reports of suppurative interstitial nephritis, renovascular congestion, renal abscesses, and an increase in acute kidney injury (AKI) associated biomarkers [5–9]. In humans, there are few reports of urosepsis and multi-organ failure requiring continuous renal replacement therapy [10,11]. Herein, we describe a case of AKI likely due to minimal change disease (MCD) with concurrent subacute interstitial nephritis in a patient with severe *E. tarda* infection.

Case report

A 72-year-old female with a past medical history of hypertension, hyperlipidemia, coronary artery disease, hypothyroidism, and liver cysts presented to our medical center as a direct hospital transfer for abnormal serum creatinine levels. Before the onset of her renal failure, she had an acute onset of severe diarrhea that lasted for three weeks after ingesting raw oysters. Associated symptoms included low-grade fever, abdominal cramping, malaise. Additionally, she had a one-week history of tea-colored urine and generalized edema extending up the chest wall. She was healthy before the oyster consumption exposure. She had no sick contacts. The diagnosis was confirmed by a stool culture that grew *E. tarda* at an outside facility. Infectious hepatitis studies were negative. A computed tomography (CT) of the chest, abdomen, and pelvis with contrast showed two hepatic cysts (measuring 4.7 cm and 5 mm respectively), splenic granulomatous changes, and diverticulosis with components of diverticulitis and tiny amounts of free fluid. The kidneys were anatomically normal with an adequate excretory function at that time. She was briefly treated with intravenous ciprofloxacin 400 mg twice daily, originally planned for a two-week course for an intra-abdominal infection. Due to intolerance, the patient only took a few doses of adjunctive metronidazole and doxycycline.

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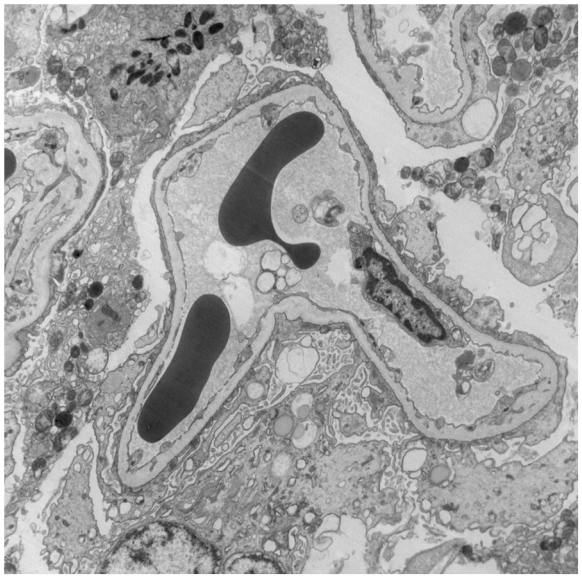

Fig. 1. Electron Microscopy- 4800X – Glomerular capillary loop with diffuse podocyte effacement.

Upon transfer to our hospital, she was hypertensive at 156/84 mmHg; other vital signs were unremarkable. Physical examination revealed 3+ bilateral pitting edema up to the level of bilateral flanks. She denied dysuria, gross hematuria, flank pain, shortness of breath, chest pain, rash or cardiac disease history. Her serum creatinine was 1.5 mg/dL (reference range: 0.59–1.04 mg/dL), an increase from her baseline of 0.9 mg/dL three days prior. Urinalysis showed 3+ protein (reference range: negative), three red blood cells per high powered field (reference range: 0–2/high powered field), and hyaline casts. Urine protein to creatinine ratio was 2.7 and fractional excretion of sodium was 0.49 %. Of note, in her prior admission at the outside hospital, she had 2.19 g of protein in the urine and an abnormally low serum C3 and C4. Serum albumin level was low at 2.3 g/dL (reference range: 3.5–5 g/dL). Due to the presence of an elevated serum Kappa/Lambda free light chain ratio, a serum protein electrophoresis with immunofixation was conducted which excluded a paraproteinemia. Other unremarkable laboratory tests include liver function tests, human immunodeficiency virus (HIV) serologies, Hepatitis B and C titers, Antistreptolysin-O titers, anti-DNase titers, anti-neutrophil cytoplasmic antibody (c-ANCA, p-ANCA), proteinase 3 (PR3), myeloperoxidase (MPO), anti-nuclear antibody (ANA), anti-double

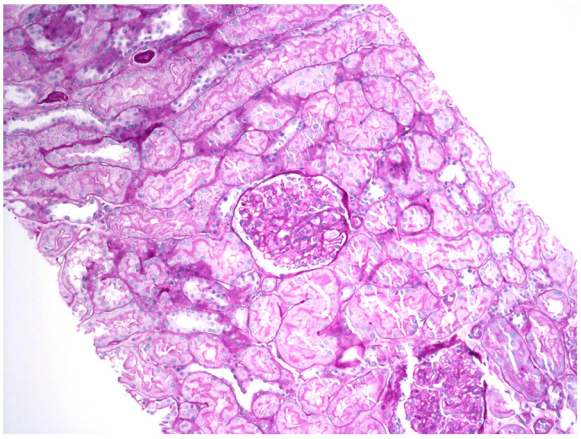

Fig. 3. Light Microscopy- Periodic Acid-Schiff stain- 20X – Normal glomerulus without significant histologic changes.

stranded DNA (anti-dsDNA) antibody, rheumatoid factor (RF), and complement levels (although a mild decrease in C4). Repeat CT abdomen and pelvis were similar to prior studies with a resolution of diverticulitis. She had not been exposed to nephrotoxic agents. The nephrology service evaluated and managed the AKI.

Within two days of her admission, the patient had a 39-pound weight gain from worsening anasarca. She was given low doses of intravenous furosemide for gentle diuresis. Additionally, she was continued on oral ciprofloxacin 500 mg twice daily for residual gastroenteritis. To definitively determine the etiology of her acute kidney injury, a kidney biopsy was pursued. Electron microscopy suggested a minimal change-like lesion with approximately 90 % visceral epithelial cell foot process effacement with villous formation (Fig. 1). Light microscopy stains showed no evidence of vasculitis, crescentic lesions, or areas of necrosis (Figs. 2 and 3). Interestingly, there were few eosinophils seen throughout the interstitium with mild edema suggestive of a possible subacute allergic interstitial nephritis (Fig. 4). Immunofluorescence staining was negative for immune complex deposition in the basement membrane. There was nonspecific vascular staining of C3. No compliment deposition in the glomeruli and no electron-dense deposits were identified elsewhere. Nephrology established a diagnosis of minimal change disease and subacute interstitial nephritis, most likely secondary to *E. tarda*.

Upon discharge, the patient had formed stools and only mild residual abdominal tenderness after completion of a two-week course of ciprofloxacin. She had excellent urine output and her

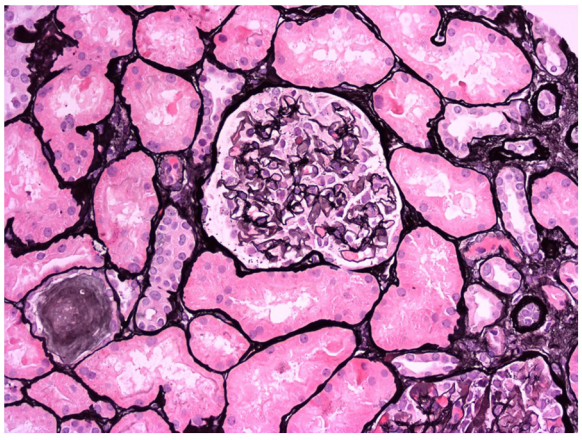

Fig. 2. Light Microscopy- Jones Methenamine Silver stain- 20X – Normal glomerulus without significant histologic changes.

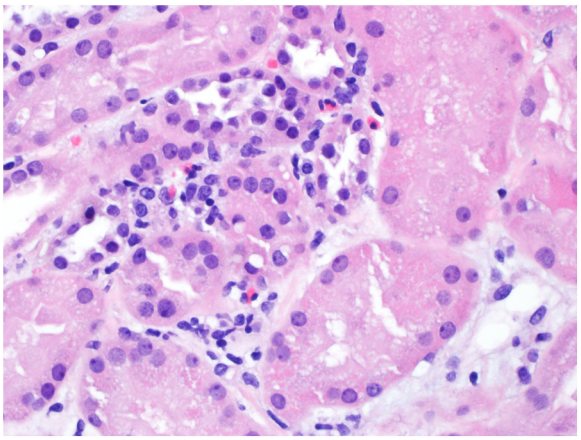

Fig. 4. Light Microscopy- Hematoxylin and Eosin stain- 40X – High power of the interstitium showing a cluster of eosinophils.

serum creatinine improved to 1.0 mg/dL. Subsequently, the patient was initiated on a 12-week course of glucocorticoids beginning with prednisone 60 mg daily, followed by a steady taper until discontinued. Upon routine outpatient follow-up, the patient demonstrated a positive clinical response. The serum creatinine normalized to 0.8 mg/dL, urine protein to creatinine ratio normalized to 0.1, serum albumin rose to 4.4 g/dL, blood pressure returned to her baseline of 90/60 mmHg, and her edema resolved.

Discussion

In summary, a 72-year-old female presented with an AKI, suspected to be from the indirect and direct effects of *E. tarda*. Although the patient's diarrhea and abdominal pain were mostly controlled by the time she presented to our hospital, there was a high possibility of residual gastroenteritis contributing to pre-renal injury as the full duration of antibiotic therapy was not yet completed. Though the exact timing of intrinsic renal injury is unknown, there was a clear demonstration of minimal change disease and subacute interstitial nephritis on kidney biopsy. MCD most commonly presents in children; however, it is responsible for 15 % of adults with idiopathic nephrotic syndrome [12]. Due to the mild nature of the patient's histopathological findings and an excellent response to glucocorticoids, a diagnosis of MCD was favored over focal segmental glomerulosclerosis (FSGS). MCD and FSGS are in the same spectrum of disease, consisting of extensive foot process effacement and functional podocytopenia [13]. If the patient was not promptly diagnosed and treated, her disease could have rapidly progressed to the collapsing variants of FSGS, which are steroid-resistant. Over time, progressive podocyte depletion can ultimately lead to end-stage renal disease. Lastly, there was a concurrent subacute interstitial nephritis that could also be associated with *E. tarda*. To the best of our knowledge, our case report is the first that describes the association between *E. tarda* and MCD, a possible extra-intestinal manifestation. *E. tarda* contains and secretes numerous virulence factors that are effective in infecting host cells [14]. Further studies are needed to better understand the pathophysiology of *E. tarda* mediated MCD [15,16].

Despite the striking observation between *E. tarda* and MCD, there is no established evidence-based treatment regimen. We treated the offending organism with the appropriate antibiotics and suppressed the inflammatory response of MCD with glucocorticoids [12,17]. Additionally, we treated the patient's anasarca with gentle diuresis. Interestingly, liver abscesses are frequently seen in patients with bacteremia secondary to *E. tarda* [4]. The patient had incidental findings of punctate calcifications in individual liver lobes and spleen. There were also multiple hepatic cysts of unknown etiology. The patient did not have a prior history of liver cirrhosis. Due to these findings, there was suspicion if the patient had developed other extra-intestinal manifestations of Edwardsiellosis.

The differential diagnoses that were ruled out in this case include contrast-induced nephropathy and post-infectious glomerulonephritis (PIGN). Contrast was administered for abdominal imaging at the outside facility; however, the time course of renal injury and contrast administration was not consistent with the diagnosis [18]. Additionally, there was no diffuse hydropic vacuolization of the tubules observed on the kidney biopsy, a finding characteristic of contrast-induced nephropathy [19]. The patient suffered an AKI approximately one week after contrast was given. PIGN was a reasonable consideration in the setting of an active gastroenteritis and positive stool cultures. However, the histological findings of the patient's kidney biopsy did not contain the typical characteristics of PIGN (diffuse endocapillary proliferation with or without crescents and C3/immunoglobulin deposits in the mesangial and basement membrane) [20].

Overall, *E. tarda* is a harmful Gram-negative bacterium that usually causes gastroenteritis, particularly after consuming raw seafood. Extra-intestinal dissemination and sequelae of this infection is a significant consideration. Clinicians should be quick to diagnose and treat potential infections as culprits of concurrent AKI and diarrhea. We highlight a rare case of minimal change disease and subacute interstitial nephritis in association with *E. tarda* gastroenteritis, which had a complete resolution following treatment with antibiotics and glucocorticoids.

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Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

IEP conceived the presented idea. AB and CC collected and interpreted the data. AB wrote the manuscript in consultation with CC, CRL, and IEP.

Declaration of Competing Interest

The authors report no declarations of interest.

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