

Ichthyotoxic ARF After Fish Gallbladder Ingestion: A Large Case Series From Vietnam

Bich Huyen Nguyen Xuan, MD, Tan Xuan Nguyen Thi, MD, Su Tan Nguyen, MD,
David S. Goldfarb, MD, M. Barry Stokes, MD, and Rahmin A. Rabenou, MD

● Fish gallbladders are consumed in rural areas of Asia as a traditional medicine to improve symptoms of arthritis, decreased visual acuity, and impotence. Consumption of large amounts of this traditional medicine can result in systemic toxicities; in particular, acute renal failure. We reviewed records of all admissions to Cho Ray Hospital (Ho Chi Minh City, Vietnam) between January 1995 and December 2000 after this ingestion. Clinical courses and outcomes were similar in 16 of 17 patients. Within hours, patients experienced profuse vomiting ($n = 16$) and diarrhea ($n = 15$). All developed acute renal failure, with a mean serum creatinine concentration of 14.7 ± 3.9 mg/dL ($1,299.5 \pm 344.8$ μ mol/L). Four patients administered intravenous fluid (IVF) developed extracellular fluid volume overload, as did 1 patient not administered IVF. Time to peak creatinine concentration was 8.6 ± 3.0 days, which was accompanied by decreased urine volume (174.7 ± 161.6 mL/24 h). Blood pressure remained normal, with a mean arterial pressure of 91 ± 12 mm Hg. Twelve patients required renal replacement therapy. A mean of 1.9 ± 1.1 hemodialysis sessions was performed per patient. Sixteen patients recovered renal function; 1 patient died of fulminant hepatic failure. Kidney biopsies showed features of acute tubular injury. Acute renal failure after fish gallbladder ingestion is characterized by a failure to respond to IVF, an 8.6-day interval to peak creatinine level, frequent need for dialysis therapy, and findings on renal biopsy consistent with acute tubular necrosis. Acute renal failure after fish gallbladder ingestion has an excellent prognosis. However, death from fulminant hepatic failure can occur. *Am J Kidney Dis* 41:220-224.

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INDEX WORDS: Gallbladder; acute renal failure (ARF); acute tubular necrosis; dialysis; traditional medicine; Vietnam.

THROUGHOUT rural Asia, people consume gallbladders from various fish species for the treatment of various disorders, including arthritis and decreased visual acuity.¹ The most common fish species from which gallbladders are eaten is carp, ostariophysan family Cyprinidae. When associated with toxic effects, it represents a form of ichthyotoxism resulting in acute renal failure. The toxin is believed to be cyprinol sulfate or cyprinol, a C27 bile acid.² Fish poison-

ing, ichthyotoxism, occurs in three forms: toxins in visceral organs (ichthyosarcotoxic), reproductive organs (ichthyootoxic), or blood (ichthyohemotoxic).³ Gallbladders of certain freshwater fish are increasingly recognized as an important source of ichthyosarcotoxism in Asian populations. We present a large case series describing a cause of fish poisoning from gallbladder ingestion with resultant gastrointestinal, renal, hepatic, cardiac, and neurological toxicities.

PATIENTS

Between January 1995 and December 2000, a total of 17 patients presented to Cho Ray Hospital (Ho Chi Minh City, Vietnam) after consuming gallbladders from four fish species. Patients were from eight different rural provinces in South Vietnam. All were farmers, except for one student. Symptoms of arthritis were the most common reason for ingestion. Other reasons included urticaria and eczema and to enhance sexual vitality and improve vision.

On entry, vital signs and serum chemistries (expressed as mean \pm SD) were measured and followed up (Table 1). Mean age was 40.5 ± 14.8 years (range, 16 to 68 years). Patients consumed 3.7 ± 5.4 gallbladders. All patients identified the consumed fish. Most commonly identified were the grass carp (*Ctenopharyngodon idellus*), by nine patients, and the black shark (minnow) fish (*Morulus chrysophekadion*), by seven patients (Fig 1). One patient ate the gallbladder from the bony-lipped barb fish (*Osteichilus mela-*

From the Nephrology Section, Cho Ray Hospital; Department of Pathology, Nhan Dan Hospital; Ho Chi Minh City, Vietnam; Department of Medicine, Nephrology Division, New York Harbor Veterans Affairs Medical Center; Department of Pathology, New York University Medical Center; and Center for Global Health, New York University School of Medicine, New York, NY.

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Patients were cared for and data were collected at Cho Ray Hospital, Ho Chi Minh City, Vietnam.

Address reprint requests to Rahmin A. Rabenou, MD, NYU School of Medicine, 545 1st Ave, #8K, New York, NY 10016. E-mail: rahmin.rabenou@med.nyu.edu

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Table 1. Patient Characteristics

Patient No.	Age (y)	No. of Gall Bladders	Mean Arterial Pressure (mm Hg)	Heart Rate (beats/min)	Urine Output (mL/24 h)	Blood Urea Nitrogen (mg/dL)	Peak Creatinine (mg/dL)
1	32	1	97	54	200	108	18
2	27	1	93	68	10	142	14.4
3	31	1	90	80	20	128	17.3
4	42	1	77	72	50	72	9.5
5	43	1	83	72	30	78	14.4
6	53	1	88	56	250	65	9.4
7	17	1	73	54	10	74	11.5
8	48	2	97	56	100	88	14.5
9	64	2	100	100	600	185	17.1
10	27	2	103	80	50	98	24.4
11	68	2	103	76	200	NA	NA
12	40	2	63	40	250	69	19
13	53	2	87	76	100	64	11.3
14	50	3	107	65	200	45	14.4
15	35	6	100	80	450	66	10.6
16	16	15	93	90	200	163	14.9
17	42	20	93	60	250	113	14.5
Mean	40	3.7	91	69	175	97.4	14.7

NOTE: For SI conversions, multiply by 88.4 for creatinine ($\mu\text{mol/L}$) and 0.357 for urea nitrogen (mmol/L).
Abbreviation: NA, not available.

*Patient was started on peritoneal dialysis therapy at a provincial hospital.

nopi). We are unable to identify one of the fish consumed by a single patient except by its Vietnamese name, ca hoi.

RESULTS

Renal Function

Fifteen patients for whom data are available sought medical care 3 ± 1.7 days after the ingestion of raw gallbladders. Renal failure was present in all patients who presented initially to Cho Ray Hospital or were transferred from a provincial hospital. It is possible that patients from provincial hospitals with nonoliguric renal failure were not transferred. Intravenous fluid

(IVF) administered to 15 patients did not improve renal function and contributed to peripheral or pulmonary edema in 4 patients. One patient presented with pulmonary edema without being administered IVF. Mean arterial pressure on presentation was 91 ± 12 mm Hg. Most patients were either anuric ($n = 5$) or oliguric ($n = 10$). Serum creatinine concentrations increased to 14.7 ± 3.9 mg/dL ($1,299.5 \pm 344.8 \mu\text{mol/L}$), excluding 1 patient who underwent early peritoneal dialysis in the provinces for whom no peak creatinine concentration is available.

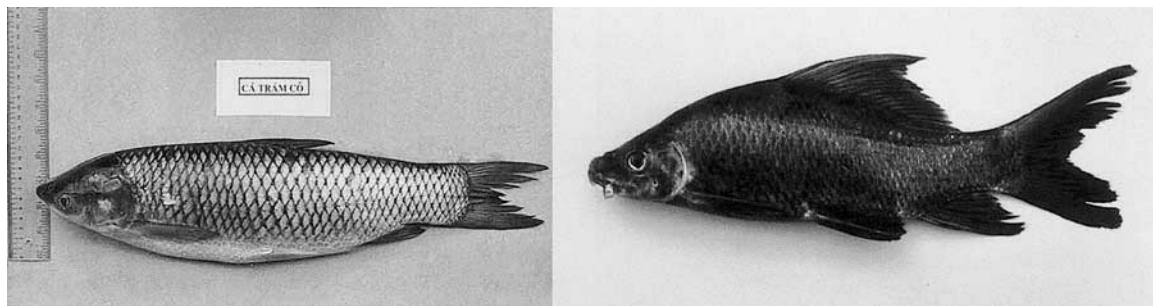


Fig 1. (Left) *C idellus* and (right) *M chrysophekadion*, also known as *Labeo chrysophekadion*. (Photo on right courtesy of Ian Baird.)

Eleven patients underwent hemodialysis at Cho Ray Hospital, most with anuria or continued oliguria despite fluids and diuretics. Six patients underwent a single hemodialysis treatment, three patients underwent two treatments, and two patients required four treatments. Five patients did not undergo any form of dialysis. Mean peak creatinine level in this group was 15.6 mg/dL (1,379.0 $\mu\text{mol/L}$).

One of these patients had the highest peak creatinine level in this series; 24.4 mg/dL (2,157.0 $\mu\text{mol/L}$). On admission, he had urine output of only 50 mL/24 h and a serum creatinine level of 7.3 mg/dL (645.3 $\mu\text{mol/L}$). Despite a rapidly increasing creatinine level, his urine output increased daily with furosemide therapy, and hemodialysis was not performed.

Renal function recovered over a course of days to weeks in all patients, except for one patient who died. Depending on the rate of recovery, serum creatinine concentrations were tracked for a mean of 9.1 ± 3.4 days after attainment of the peak creatinine level. During this period, creatinine levels decreased to 3.2 ± 0.94 mg/dL (282.9 ± 83.1 $\mu\text{mol/L}$). Patients were discharged while still recovering.

Urine protein concentrations are available for 11 patients. Concentrations ranged from 0 to 100 mg/dL in six patients, 370 to 700 mg/dL in four patients, and 1,800 mg/dL in a single patient. Thirteen patients had hematuria, with 25 to 50 red blood cells/ μL . White blood cells were seen

in three patients (100 to 500 white blood cells/ μL).

Pathological Examination

Four patients agreed to undergo kidney biopsy. These were performed approximately 1 week after recovery from oligo-anuria. Light microscopic analysis showed features of acute tubular injury, including simplification of tubular epithelium and focal karyorrhexis (Fig 2). Intra-tubular sloughed epithelium was present. Acute interstitial nephritis was unlikely to account for the severe impairment in renal function in the absence of significant interstitial inflammatory cells. Glomeruli and arterial vessels were unremarkable. Immunofluorescence and electron microscopy were not performed.

Extrarenal Manifestations

Extrarenal manifestations were common and persisted for several days. Within minutes to hours of ingestion, all except 1 patient began vomiting and 10 patients had diarrhea. Laboratory analysis showed elevated transaminase levels in all patients (Table 2). Excluding the patient who died of fulminant hepatic failure with a total bilirubin level of 43.5 mg/dL (743.0 $\mu\text{mol/L}$), alanine aminotransferase (ALT) levels were elevated out of proportion to aspartate aminotransferase (AST) levels (851 ± 560 and 262 ± 255 U/L, respectively) in all except 1 patient, in whom concentrations were nearly equal. This was associated with elevated serum bilirubin

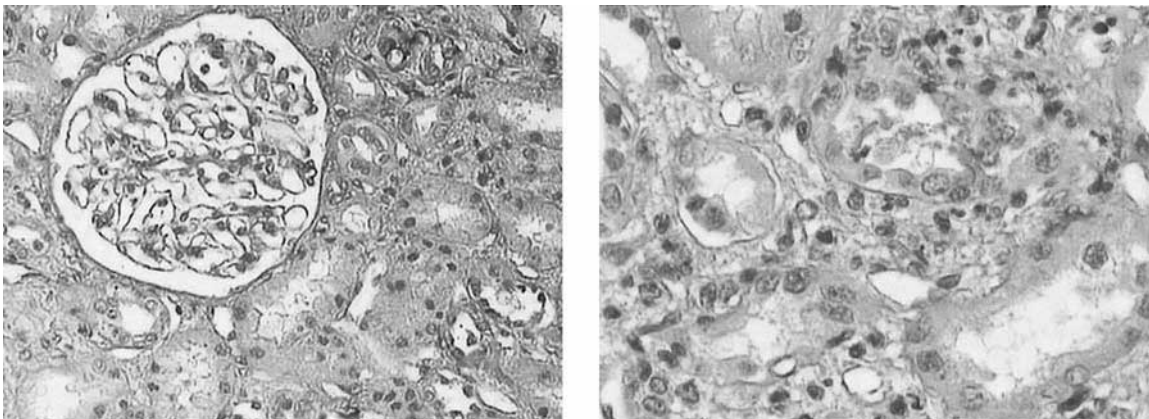


Fig 2. (Left) Light microscopic analysis of kidney biopsy sections from patient 5 shows a normal-appearing glomerulus. (Right) Tubules show focal karyorrhexis with sloughed epithelium. This specimen shows a mild interstitial infiltrate not seen in the other sections examined.

Table 2. Peak Liver Transaminase and Bilirubin Levels

Patient No.	AST (U/L)	ALT (U/L)	Total Bilirubin (mg/dL)	Direct Bilirubin (mg/dL)
1	134	1,099	4.1	2.7
2	1,900	305	43.5	28.5
3	82	653	3.5	1.9
4	121	207	5.7	3.8
5	37	110	2.8	1.2
6	78	692	2.5	1.7
7	461	1,681	2.4	1.6
8	41	538	4.3	2.7
9	878	837	2.3	1.4
10	124	1,080	NA	NA
11	124	178	NA	NA
12	152	267	NA	NA
13	333	1,385	4.8	3.4
14	40	302	2.6	2.1
15	393	1,469	5.9	1.9
16	543	1,521	4.2	2.7
17	651	1,597	4.6	3.7
Mean	358	819	6.7	4.3

NOTE: For SI conversions, multiply by 17.1 for bilirubin ($\mu\text{mol/L}$).

Abbreviation: NA, data not available.

levels (total bilirubin, 3.8 ± 1.2 mg/dL [65.0 ± 20.5 $\mu\text{mol/L}$]; direct bilirubin, 2.4 ± 0.8 mg/dL [41.0 ± 13.7 $\mu\text{mol/L}$]). We do not know if the patient who died had underlying liver disease before the intoxication; hepatitis B surface antigen was not present in his serum, and he was not tested for hepatitis C virus.

Five patients (29%) had sinus bradycardia. For all patients, mean heart rate was 69 ± 15 beats/min. For the group with bradycardia, heart rate was 52 ± 6.8 beats/min; they presented 4 hours to 5 days after ingestion. Tonic-clonic seizures occurred in three patients, including the patient who died of hepatic failure. Generalized seizures occurred within 1 day of ingestion in one patient.

DISCUSSION

Freshwater fish gallbladder consumption is a traditional medicine, primarily in rural areas of Asia. Cases have been reported in Taiwan, Korea, Hong Kong, India, and Japan.^{1,4-8} This is the first report of cases in Vietnam and represents one of the largest series to date. We report on 17 patients at Cho Ray Hospital who had a similar constellation of signs, symptoms, and laboratory

test result abnormalities that define this intoxication. This report expands the number of freshwater fish associated with this intoxication to include the shark (minnow) fish (*M chrysopheka-dion*) and the bony-lipped barb fish (*O melanopi*). We are the third group to report death associated with this ingestion. However, in the other reports, deaths were attributed to sepsis or late gastrointestinal bleeding, rather than a direct effect of the ingestion.^{7,8}

All our patients developed renal failure. Extracellular fluid volume depletion likely occurs from the vomiting and diarrhea that follow ingestion. However, the slow resolution over several days to weeks despite IVF, normal blood pressure, evidence of extracellular fluid volume overload in five patients, and biopsy results are consistent with acute tubular necrosis. Most of our patients had oligo-anuria requiring dialysis therapy.

After ingestion, gastrointestinal symptoms were seen in all patients: nausea, vomiting, and/or diarrhea. Onset typically occurred within hours and likely represents the direct effect of a toxin.

Another prominent feature of this intoxication is seizure activity, which resulted in no permanent neurological deficits in the two patients who survived. Because one patient developed seizures within a day of ingestion, we believe this is a direct effect of a toxin. The other patient experienced seizures several days after hemodialysis. Therefore, it was unlikely to be related to postdialysis disequilibrium. In the third patient, seizure activity may have been secondary to fulminant hepatic failure.

Although most patients developed elevations in serum transaminase and bilirubin levels, irreversible hepatic manifestations occurred only in the patient who died. A common pattern is for ALT levels to be greater than AST levels. Cardiac toxicity was limited to sinus bradycardia in five patients. With appropriate supportive therapy, including dialysis, patients typically recover. Because patients are discharged before normalization of serum creatinine levels, we cannot definitively state that there is full recovery. Death appears to be infrequent and occurred in only one patient with fulminant hepatic failure.

We do not know whether people with underlying liver disease are at greater risk for this outcome. In a report of three cases from Japan, one patient with known underlying liver disease

of unreported cause also had a large increase in AST levels to 12,270 U/L, with a relatively smaller increase in ALT levels to 4,100 U/L, a reverse of the typical pattern.⁸

Although toxicity has been observed after ingestion of gallbladders from different fish species, the similar clinical effects are consistent with a common toxin. One study examined the incidence of death after feeding extraction components of bile from *C idellus* to mice. Dissolving the bile in ether or precipitation with ethanol did not alter toxicity, indicating it is neither a protein nor a lipid. It also was heat stable, consistent with reports of toxicity caused by ingestion of cooked bile.⁹ Cyprinol sulfate or its desalted form, cyprinol, a C27 alcohol, has been proposed to be responsible for the effects of freshwater carp gallbladder ingestion.² In this series, all patients consumed uncooked gallbladders or bile.

Toxic effects from gallbladder ingestion from these fish are not known to always occur. Ingesting either numerous or one or two large gallbladders, as occurred in our patients, may be responsible for the toxicity. Consumption of gallbladders from smaller fish is common in rural Vietnam and is not known to result in severe acute renal disease. Patients are referred to Ho Chi Minh City only in the event of severe renal toxicity. Subclinical nephrotoxicity may occur with smaller ingestions. In addition, effects of chronic ingestion are not known and are worth investigating. Because our patients presented during 9 different months and two cases have been reported among Asian immigrants in the United States, seasonal and environmental factors do not appear important.¹⁰

The current list of fish known to possess nephrotoxic gall bladders includes grass carp (*C idellus*), common carp (*Cyprinus carpio*), silver carp (*Hypophthalmichthys molitrix*), *Mylopharyngodon piceus*, *Labeo rohita*, and *Aristichthys nobilis*.⁵ Our report expands this list to include the black shark (minnow) fish (*M chrysophekadion*) and the bony lipped barb fish (*O melanopi*). Most of these belong to the family Cyprinidae, also known as the minnow, which is the largest family of freshwater fish and distributed worldwide. Some are grown for human consumption, and others, such as the koi, for decorative

aquariums. Most minnow species are small, but a few can grow to more than 1 m.¹¹ Fish gallbladder intoxication in this series and others typically occurred with the larger species. The largest number of species is present in southeast Asia and Asia. In North America, 251 species are known. *M chrysophekadion* now populates Florida waters, likely released from pet aquariums. *C idellus* and *C carpio* can be found throughout the continental United States and Hawaii.¹¹ With large Asian immigrant populations in the United States, this form of intoxication could become evident.

In conclusion, consumption of bile from certain freshwater fish is associated with toxin-induced acute tubular necrosis, which is associated with only a few commonly ingested medications or toxins.

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