CASE REPORT

Risky behaviour: a rare complication of an uncommon disease in a returning traveller

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SUMMARY

A 49-year-old man with a history of hypertension and no known drug allergies was admitted with a 4-day history of fever, general malaise, sore throat and diarrhoea. Eleven days ago, he had returned from a 2-week adventure holiday to South Africa. On admission, he was noted to have a creatinine 392 μmol/L, alanine aminotransferase 133 IU/L, alkaline phosphatase 211 IU/L and platelets 151×10^9/L. A differential diagnosis of suspected leptospirosis or bacterial sepsis was made and he was started on ceftriaxone. Two hours later he became hypotensive, tachypnoeic with severe myalgia and a temperature of 41°C, type I respiratory failure and metabolic acidosis. There was no stridor, facial swelling or rash. A diagnosis of Jarisch-Herxheimer reaction was made. A second dose of ceftriaxone was given without any reaction. The patient thereafter completed 7 days of doxycycline. PCR confirmed leptospirosis and subsequent leptospirosis IgM was positive. He improved clinically with treatment and was discharged after 10 days of admission.

BACKGROUND

There were 44 cases of leptospirosis in England and Wales in 2011,[1] and 12 of these (27%) were acquired overseas. Leptospirosis is an important differential in a febrile returning traveller and can be fatal. Ceftriaxone is a broad spectrum antibiotic frequently used in treating bacterial sepsis associated with travel. This case is a reminder that Jarisch-Herxheimer reaction (JHR) is a rare reaction to treatment in spirochaete and rickettsial infections such as leptospirosis and is important to differentiate from a drug allergy.

CASE PRESENTATION

A 49-year-old man with a history of hypertension and traumatic kidney injury in childhood with no known allergies presented with a 4-day history of fever and general malaise.

Eleven days ago, he had returned from a 2-week trip to South Africa where he visited nature and game reserves, swam in fresh water and camped and hiked in rural areas. While away he reported no tick bites or rashes, although did have several mosquito bites. He took no malaria prophylaxis, had no sexual contacts and there were no unwell contacts while abroad. He was in the immediate vicinity of big game animals and baboons but had no direct contact with either.

Nine days after swimming in fresh water he developed coryzal symptoms, dry cough, headache, malaise and fever.

Four days later, he presented to the acute medical unit with constipation followed by diarrhoea, dark coloured urine, right upper quadrant pain, worsening myalgia and a mild headache without photophobia or neck stiffness.

His observations were as follows: blood pressure was 128/59 mm Hg, heart rate 108 bpm, temperature 36.4°C, respiratory rate 12 breaths-per-minute (BPM) and saturations were 96% on air.

On examination, there was bilateral cervical lymphadenopathy, swollen tonsils without exudate, normal heart sounds and quiet bilateral fine inspiratory crackles at the right base. No rashes, insect bites or eschars could be identified. There was abdominal pain in the right upper quadrant with 3 cm palpable hepatomegaly and mild bloating. There was no evidence of ascites or renal angle tenderness. There was no splenomegaly or ballotable kidneys.

His blood results showed creatinine 392 μmol/L (baseline 88 μmol/L) and urea 12.9 mmol/L with mildly deranged liver function (table 1) and a metabolic acidosis with lactate 1.3.

A diagnosis of suspected leptospirosis was made with a differential including rickettsial disease, malaria, bacterial sepsis, hantavirus, typhoid fever, Katayama fever and viral hepatitis infection. He was initially treated with fluid resuscitation and 1 g ceftriaxone intravenously.

Two hours later he developed vomiting and profuse diarrhoea with a blood pressure 79/50 mm Hg, heart rate 120 bpm and temperature 41°C with O_2 saturations of 93% on air. His myalgia worsened. There was no stridor, wheeze, facial swelling or rash.

An arterial blood gas showed type I respiratory failure with a compensated metabolic acidosis and lactate 5.3.

He was moved to the intensive care unit (ICU) for invasive monitoring and haemodialysis. CT of the chest/abdomen/pelvis with contrast was performed to rule out pulmonary embolus and image the urinary tract (see Investigations section). The patient tolerated a second dose of ceftriaxone without side effects.

A secondary diagnosis of JHR was made.

Medical history

He had a history of hypertension for which he had recently started perindopril 1 month prior to admission.

Surgical history

He had met with a road accident at the age of 11 that resulted in injury to his ureter at the vesicoureteral junction with temporary right-sided hydronephrosis, which was surgically repaired maintaining renal function. His ulna and radius were rebroken at the age of 16, requiring open reduction and internal fixation

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Table 1 All blood results for the duration of admission

	Minus 2 months	Minus 3 days	Day 1	Day 2	Day 2 pm	Day 3	Day 4			Day 5	Dialysed	Day 6	Day 7	Day 8	Day 10
Albumin (g/L)		43	38		28		25	24		23	23	24	25	26	34
ALP (IU/L)		65	211		247		222	198		218	263	271	262	233	213
ALT (IU/L)		56	188		139		143	134		111	104	109	174	151	131
APTT (seconds)			30.7			28.8	32.7	33.5		30.6		30.3	27.2	26.5	27.3
APTT ratio			1.1			1.03	1.17	1.2		1.09		1.08	0.97		0.98
Calcium (mmol/L)		2.21	2.28				1.99	1.89		2.06		2.38	2.23	2.19	2.14
Creatinine (μmol/L; eGFR)	83 (84)	102	392	539 (1C)	622		644	643	660	529	351	275	239	187	116
CRP (mg/L)			319	286	282	251	271	319		126		97	57	39	23
Hb (g/dL)	14.4	14.8	13.5	12	11.9	10.9		10.2		10.7		11.7	11.4		11.2
Lymphocytes	1.8	0.8	0.4	0.6	0.5			0.5		1.1		1.4	1.7		1.4
Neutrophils ($\times 10^9$/L)	4.3	4.9	8.7	7.5	3.3	7.9		11.9		10.1		5.1	2.6		5.4
Platelets ($x10^9$/L)	319	200	160	173	151	134		140		175		164	185		302
Potassium (mmol/L)	5.4	4.5	4.2	4.5	4.6		3.8	4		4.5		4.3	4.2	3.8	4.8
Prothrombin time (seconds)			12.3			12.8	13	12.3				11.5	12.2	11.9	12.2
Serum glucose (mmol/L)	5.2														
Sodium (mmol/L)	141	139	134	123	128		129	131		135		138	138	138	139
Total bilirubin (μmol/L)		9	12		14		17	16		7		7		9	10
Urea (mmol/L)	5.4	5.5	12.9	18.7	19.6		20.7	21.4	22.8	19.8	14.8	11.7	10.4	10.4	7
White cell count ($x10^9$/L)	7.1	6	9.4	8.4	3.8	8.4		13		11.9		7.4	5.4		8.3
ANA title (ref- 0–79)										Negative					
ANCA										Negative					
Antistreptolysin O (IU/mL)							Negative at 5 days								
Blood culture 1			Negative at 5 days				Negative at 5 days								
Blood culture 2			Negative at 5 days												
C3 (mg/L; 760–1870)										840					
C4 (mg/L; 100–440)										210					
Creatinine kinase (IU/L)				42				170							
Rheumatoid factor										Negative					
Electrophoresis serum										Norma					
Erythrocyte sedimentation rate (mm/L)		12													
Hantavirus serology						Negative									
Faeces culture						OCP reg'2	GDH neg			Campylobacter					
GBM Ab IU/mL									Negative						
Hepatitis A IgM			Negative												
Hepatitis B surface antigen			Negative												
Hepatitis C virus Ab EIA			Negative									Campylobacter			
Hepatitis E screen										Negative					
HIV antigen/Ab			Negative												

Continued

Table 1 Continued

	Minus 2 months	Minus 3 days	Day 1	Day 2	Day 2 pm	Day 3	Day 4			Day 5	Dialysed	Day 6	Day 7	Day 8	Day 10
IgA (g/L; ref 0.8–2.8)										1.41					
IgG (g/L; ref 6.0–16.0)										6.68					
IgM (g/L; ref. 0.5–1 9)										0.85					
Legionella urinary antigen			Negative		Negative										
Leptospira IgM ELISA				Negative				Positive 1:80							
Leptospira IgM MAT				Negative			Positive 1:160								
Leptospira PCR				Positive				Negative							
Magnesium							0.5	0.76		0.98					
Malaria		Negative	Negative	Negative											
MRSA						Negative									
Myeloperoxidase Ab (U/ml)															
Neisseria meningitidis PCR															
Phosphate							0.44	0.97	1.22	1.05	0.89	0.88	0.77	0.54	
Pneumococcal urinary antigen			Negative		Negative										
Urine protein/creatinine										0.54/2.7					
Urine PCR										200					
Schistosoma serology				Sent											
Serum electrophoresis											0.77	0.82	1.39	1.19	
Sputum culture										Flora					
Urine culture				Negative 2		Negative	No ova								

Ab, antibody; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; APTT, activated partial thromboplastin time; CRP, C reactive protein; eGFR, epidermal growth factor receptor; GBM Ab, glomerular basement membrane antibodies; GDH, glutamate dehydrogenase; Hb, haemoglobin; MAT, microscopic agglutination test; MRSA, methicillin-resistant *Staphylococcus aureus*; OCP, ova, cysts and parasites.

with plate metal work. He also underwent multiple knee arthroscopies for meniscal repair from running injuries.

Family history
There was no history of autoimmune disease, renal disease or vasculitis.

Social history
The patient never smoked, denied recreational drug use and only intermittent alcohol intake.

INVESTIGATIONS
Bloods
Two months prior to admission, creatinine was 88 μmol/L. On admission, creatinine was 102 μmol/L. Renal function progressively declined during his hospital stay to a peak creatinine of 660 μmol/L (table 1) on day 4 when haemofiltration was started. This returned to normal over 8 days.

Liver function remained deranged with an alanine aminotransferase peaking at 150 IU/L and alkaline phosphatase 250 IU/L (table 1).

Leptospirosis PCR was positive on day 2 of admission with a negative IgM microscopic agglutination test (MAT) and ELISA. By day 5, PCR had become negative with a weakly positive ELISA IgM titre 1:80 and positive MAT IgM titre 1:160.

Viral hepatitis A, B and C, HIV, schistosomal and rickettsial serology remained negative. Three malaria screens were negative.

Imaging
Abdominal ultrasonography showed a coarse liver echo texture, a slightly enlarged right kidney measuring 10.2 cm with a 1.5 cm cyst and mild dilated pelvicalyceal system and a markedly enlarged and oedematous left kidney with a normal bladder. CT of the chest/abdomen/pelvis with contrast showed bibasal pleural effusions with lower zone collapse/consolidation but no evidence of pulmonary embolus.

DIFFERENTIAL DIAGNOSIS
- Leptospirosis
- Malaria
- Typhoid
- Rickettsial disease
- Viral hepatitis
- Katayama fever
- Hantavirus

TREATMENT
The patient was initially managed with ceftriaxone 1 g once daily, and then doxycycline 100 mg twice daily for a further 7 days.

OUTCOME AND FOLLOW-UP
The patient was given a second dose of ceftriaxone in the early morning without any reaction. He continued on oral doxycycline 100 mg twice daily and improved. He was stepped down from ICU after 5 days onto the ward to complete a 7-day course of doxycycline, and then discharged from the hospital after 10 days of admission having made a total recovery.

DISCUSSION
Leptospirosis is uncommon in England and Wales with 44 cases reported in 2011, 12 of which were acquired overseas.[1] There have been few case reports and case series of JHR with leptospirosis,[2] although it is a foreseeable and treatable complication, the exact prevalence of which is hard to ascertain.[2] The underlying pathophysiology has yet to be fully elucidated but is thought to be due to a systemic response to cellular components released from dying organisms mediated by mass cytokine release, especially tumour necrosis factor (TNF) α and interleukins 6 and 8. More commonly seen with secondary syphilis in up to 45% of cases,[3] it has also been recorded in Lyme disease[4] and other rickettsial diseases. Differentiating JHR from anaphylactic reaction is important—in this case the patient has taken β-lactam-based antibiotics before, had a second dose without reaction, and did not exhibit wheezing, rashes or angio-oedema. The most common features of JHR are sudden onset of rigors, rise in temperature and hypotension.[2] It is usually mild and self-limiting but rarely can be severe. The management is supportive with fluid resuscitation, organ support if necessary and in severe cases corticosteroids, although little trial data exist.[5] Newer therapies such as premedication anti-TNF treatment have also been trialled.[6] Hantavirus has been recorded in the UK once[7] and is an important if rare differential that can mimic leptospirosis. It is found predominantly in Northern Europe, East Asia, North and South America.

Learning points
- Leptospirosis is an uncommon diagnosis in the UK but common in tropical areas and should always be considered in any returning traveller.
- Jarisch-Herxheimer reactions (JHRs) usually complicate syphilis but do occur in other spirochaete infections such as leptospirosis and can be potentially life-threatening.
- JHR should be considered in the context of clinical deterioration after treatment in secondary syphilis, other spirochaete infections, rickettsial disease and Lyme as well as leptospirosis.
- It is important to monitor patients for the first dose of antibiotics and treat supportively should JHR occur. There may be some limited benefit of premedication with corticosteroids or antitumour necrosis factor α therapies.

Contributors All authors were involved in the case, the write up and approved the final draft.

Competing interests None.

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