Sudden death in Whipple's disease

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Summary

Despite antibiotic therapy, some patients with uncomplicated Whipple's disease die suddenly and inexplicably. We describe one such patient who died following unexplained cardiorespiratory arrest and was found to have chronic active myocarditis related to the causative organism. We postulate myocarditis as a cause of sudden death.

Keywords: Whipple's disease, myocarditis, polyethylene glycol

Whipple's disease classically causes a multi-system disorder in middle-aged white males, comprising arthralgia, diarrhoea, abdominal pain and weight loss, often accompanied by fever, lymphadenopathy and skin pigmentation. Histologically, infection of the gastrointestinal tract is most frequently observed, although heart, lung and nervous system may also be affected. The patient reported here died as a result of cardiovascular complications of the disease.

Case report

A 60-year-old woman had a three-month history of 7 kg weight loss accompanied by abdominal discomfort, anorexia, intermittent vomiting, thirst, frequency, night sweats, mild exertional dyspnoea and dry cough. She had ocular irritation and oral ulceration for three weeks. There was no history of diarrhoea but occasional malodorous bowel motions had been noted. Arthralgia had been present for several years.

The patient was 150 cm in height, weighed 45 kg and was deeply pigmented, particularly on exposed skin. There were fine bibasal crepitations in both lungs. The left upper abdomen and epigastrium were tender to palpation. Cardiovascular and neurological examinations were normal and there was no peripheral lymphadenopathy. Blood pressure was 100/60 mmHg and temperature 36°C during the first two weeks of admission. The patient had a microcytic anaemia with normal ferritin levels. Faecal occult blood (FOB) test was negative. Both the erythrocyte sedimentation rate and C-reactive protein were raised while serum albumin and cholesterol were low. Urea and electrolytes, thyroid function tests, morning cortisol, coagulation screen, B12, folate, glucose and magnesium were all normal. Mantoux, hepatitis screen, rheumatoid factor, autoantibody screen and venous blood

culture were all negative. Chest X-ray and abdominal ultrasound were normal. Electrocardiogram (ECG) showed sinus rhythm with normal axis. Endoscopy revealed an inflamed duodenum but a CLO test (Delta West Pty Ltd, US Patent No 4784113) for *Helicobacter pylori* was negative.

The patient was commenced provisionally on omeprazole/metronidazole but these were withdrawn after two days because of nausea.

Biopsy of duodenal mucosa was typical of Whipple's disease, showing expansion of lamina propria by macrophages (CD68+) with foamy cytoplasm which was d-PAS positive and ZN-negative, consistent with *Tropheryma whippelii* infestation. Surface enterocytes were normal, as was the number of intra-epithelial lymphocytes.

Her initial symptoms persisted during the next 12 days. Colonoscopy was performed and, although FOB tests became positive during bowel preparation (with Klean-Prep, PEG 3350, Helsinn Birex), the bowel mucosa was endoscopically and histologically normal.

Five hours after colonoscopy, the patient became shocked (blood pressure 50/- mmHg), but was apyrexial. Blood pressure improved with intravenous fluids, yet three hours later profound hypotension and bradycardia recurred and were followed by cardiorespiratory arrest. The patient was resuscitated but required ventilation and inotropic support. The white cell count ($15.5 \times 10^9/l$), urea (17.6 mmol/l) and potassium (5.9 mmol/l) were elevated, with low sodium (114 mmol/l), chloride (82 mmol/l) and glucose (2.2 mmol/l). Acidosis was marked (pH 6.96). No acute changes were seen on chest X-ray or ECG, although left ventricular apical and anterior wall hypokinesia was detected on echocardiogram. The differential diagnosis included Addisonian crisis, perforation of a viscus or sepsis. Exploratory laparotomy excluded perforation.

Despite steroids, dextrose and broad-spectrum antibiotics, the patient remained persistently acidotic, inotrope-dependent and developed multi-organ failure. Candida septicaemia from a central venous cannula was found on the fourth day after collapse and treated with fluconazole. On day seven, *Streptococcus* sp was grown on blood culture. The patient died six days later.

Salient findings on autopsy included fibrinous exudates on pericardium and serosal surfaces of liver and spleen, enlarged abdominal lymph nodes, normal adrenals and scattered, small intracerebral and subarachnoid haemorrhages attributed to coagulopathy.

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Figure 1 Serosal infiltrate of histiocytes with intra- and extracytoplasmic material. (A) Low power view, (B) high power view shows organisms in histiocyte (arrowhead). Periodic acid Schiff with diastase

Figure 2 Myocardium showing infiltrate of lymphocytes associated with myocyte destruction (arrow). Haematoxylin and eosin

There was evidence of chronic venous congestion in the liver and acute tubular necrosis in the kidney. An aortic valve cusp bore a single 0.2 mm warty vegetation at the central nodule. There was no evidence of ventricular hypertrophy, coronary arteries showed only focal 20–30% atheromatous stenosis and the myocardium appeared grossly normal. Microscopically, peritoneum and pericardium were infiltrated by T-lymphocytes and histiocytes which contained PAS-positive material (figure 1). The myocardium, kidneys and soft tissues of the neck exhibited small, scattered fungal abscesses. In addition, in the myocardium, there were distinct foci of lymphohistiocytic infiltration containing *T whippelii* with adjacent myocytolysis and replacement fibrosis (figure 2). Neither fungi, *T whippelii* nor other bacteria could be identified in the aortic vegetation. There was no preferential involvement of the conducting system of the heart by inflammation.

Discussion

The causative organism of Whipple’s disease, *T whippellii*, has never been cultured and has only been identified and categorised on the

Learning points

- Whipple’s disease is caused by *Tropheryma whippelii*
- it is a multisystem disorder characterised by arthralgia, diarrhoea, abdominal pain and weight loss
- various antibiotic regimes, usually of long duration, have produced cures
- occult myocarditis may be a cause of sudden death in some cases of apparently uncomplicated disease

basis of 16S ribosomal RNA analysis.¹ The exact mechanism of infection is unknown, though impaired cellular immunity appears causally related.^{1,2} The disease was invariably fatal³ but modern antibiotic regimes have proved curative, albeit with frequent relapse post-treatment.⁴ While death from the disease is now less common, when it does occur, it is usually sudden and ‘its immediate cause is often difficult to determine’.⁵ Interestingly, although atypical presentations of the disease have attracted great attention,⁶ there is a paucity of both detail regarding *peri-mortem* events and speculation on the mechanism of death.^{3,7}

The patient described here suffered cardio-respiratory arrest after an uncomplicated and well-tolerated procedure. Addisonian crisis as a cause of this collapse can be excluded on the basis of normal cortisol level and adrenal glands, while septicaemia following biopsy of normal colonic mucosa is an exceedingly rare event. In contrast, the presence of active, chronic myocarditis, identified at autopsy, strongly suggests that collapse was due to arrhythmia. The fungal abscesses found in the myocardium were an acute phenomenon postdating the event and due to documented candida septicaemia. The foci of inflammation and fibrosis related to *T whippelii*, on the other hand, were histologically consistent with lesions of months or years duration.

While *T whippelii* myocarditis has not been identified *pre-mortem*, documentation of cardiac failure which improved with antibiotic therapy, provided circumstantial evidence of myocardial involvement in one case report,⁸ and, in another,⁷ biopsy-proven lymphocytic myocarditis was found in a patient subsequently determined to have Whipple’s disease at autopsy, with typical PAS-positive macrophages in the myocardium.

In toxicological studies, polyethylene glycol has been found to promote arrhythmias.⁹ Although systemic absorption of polyethylene glycol from colonoscopy preparation fluid is less than 1%,¹⁰ it is postulated that even this normally insignificant amount may have precipitated arrhythmia in a myocardium rendered susceptible by subclinical *T whippelii* myocarditis.

Myocardial involvement in Whipple’s disease should be considered once the diagnosis is established and all such patients should be regarded as being at risk from sudden cardiac death.

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Elevated levels of serum creatine kinase induced by hyponatraemia

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Summary
Elevated serum creatine kinase levels are one of the major criteria for the diagnosis of myocardial injury. Noncardiac causes such as muscular and brain damage may also be associated with elevated serum creatine kinase levels. Hyponatremia may induce increased serum creatine kinase in association with rhabdomyolysis or with hypothyroidism. A patient is described where three episodes of hyponatraemia not associated with rhabdomyolysis or hypothyroidism induced transient elevations of serum creatine kinase levels. The association between hyponatraemia and elevated creatine kinase levels should be emphasized to prevent erroneous diagnosis of myocardial injury.

Keywords: sodium, creatine kinase, hyponatraemia

Elevated levels of serum creatine kinase (CK) are found in conditions where damage to muscular, brain or cardiac tissue occurs.¹ An association between hyponatraemia and elevated CK levels has been previously described in psychiatric patients with water intoxication and rhabdomyolysis,^{2,3} and in hypothyroidism.^{4,5} However, elevated CK levels induced solely by hyponatraemia have not been described. We present a patient in whom three episodes of hyponatraemia not associated with skeletal muscle, myocardial or neurological injury, induced transient elevations of serum CK levels. Cardiac isoform CK-MB levels were increased on two occasions.

Case report

A 65-year-old woman was admitted to the Chaim Sheba Medical Center because of

severe headache. Her medical history was significant for hypertension treated with captopril 12.5 mg bid and verapamil SR 240 mg once daily; chronic bronchitis treated with inhalations of ipratropium and salbutamol; and peptic ulcer treated with famotidine 40 mg/day. Three days before her admission watery diarrhoea developed, followed subsequently by headache and nausea.

Physical examination revealed a generally well-appearing patient with a temperature of 37.0°C, heart rate of 67 beats/min, and blood pressure of 160/90 mmHg. Heart, lungs, abdomen, and neurological status were normal. An electrocardiogram showed normal sinus rhythm without evidence of ischaemia, and had remained without change throughout hospitalisation. Blood chemical values revealed a serum sodium level of 123 meq/l, a potassium level of 3.5 meq/l, and CK levels of 529 U/l (normal value: <150 U/l) with an MB isoenzyme fraction of 7.4%. Other chemical and haematological blood values were within normal limits. Myoglobin was not detected in the urine, and thyroid function tests were normal. Infusion of 2000 ml of NaCl 0.9%,

Table Blood levels of sodium and CK during hospitalisations

Year	Cause	Sodium (meq/l)	CK (U/l)	CK-MB (% of CK)
1990	diarrhoea	day 1: 115	233	6
		day 2: 130	97	–
1992	thiazide diuretics	day 1: 114	332	–
		day 2: 132	143	–
1995	diarrhoea	day 1: 124	529	7.4
		day 2: 123	335	8.2
		day 3: 135	142	–

Normal ranges: sodium 136–148 meq/l; CK <150 U/l; CK-MB <5% of CK

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