Systemic vasculitis and atypical infections: report of two cases

Kuntal Chakravarty, Peter Merry

Summary

Two cases of systemic vasculitis are described; one presenting with adult Henoch-Schonlein purpura secondary to a concomitant Chlamydia infection and the other with leucocytoclastic vasculitis and mesangioproliferative glomerulonephritis secondary to a recent parvovirus B19 infection. Association of chlamydial infection has not previously been described with Henoch-Schonlein purpura and this infection should, perhaps, be added to the list of aetiologies of this disease. Parvovirus B19 causing significant urinary sediment abnormalities associated with mesangioproliferative glomerulonephritis and leucocytoclastic vasculitis has also not been described previously.

Keywords: vasculitis; Henoch-Schonlein purpura; Chlamydia infection; leucocytoclastic vasculitis; mesangial proliferative glomerulonephritis; parvovirus B19

Henoch-Schonlein purpura (HSP) is an inflammatory disease involving the skin, joints, gastrointestinal tract and kidneys.\(^1\) HSP is predominantly a disease of childhood and the clinicopathological features, as well as the long term outcome, have been studied extensively in children,\(^2,3\) although little information is available about the disease in adults. The exact aetiology of the disease is unknown, although the seasonal association suggests that there may be an infectious aetiology. Similarly, parvovirus B19 infection is predominantly a disease of childhood and its association in adults with severe systemic symptoms and concomitant skin and renal involvement has rarely been reported.

We describe two adult patients with systemic vasculitis with major organ involvement, both of whom were subsequently found to have occult systemic infection. These cases highlight the importance of looking for infection, including unusual viruses, in patients with systemic vasculitis.

Case reports

Case 1

A 28-year-old previously fit woman presented in April 1992 with general malaise, vague arthralgia and a maculopapular rash in her lower extremities. She admitted to a weight loss of 12.7 kg and recurrent abdominal pain but no diarrhoea. She had no chest symptoms apart from a recent onset of cough. She had no systemic signs of infection such as pyrexia or nocturnal sweats. She had no features of diseases such as systemic lupus erythematosus, iritis, psoriasis or colitis.

Physical examination revealed an apparently fit woman with an extensive purpuric rash on her lower extremities and abdomen. She was apyreal and her heart rate was 64 beats/minute with a supine blood pressure of 110/60 mmHg. Examination of her chest revealed fine crepitations at bases. Systemic examinations, including joints, were normal.

Investigations showed a haemoglobin concentration of 13.8 g/dl, a white cell count of 9.5 \(\times 10^9\)/l and an erythrocyte sedimentation rate of 40 mm in 1st hour. Liver and renal functions were normal as was the bone biochemistry. Microbiological investigations including blood and urine culture were negative. Immunological investigations for autoimmune and vasculitic diseases including antinuclear antibody (ANA), antineutrophil cytoplasm antibody (ANCA), antibody to double-stranded DNA, and antibody to cardiolipin, were all negative, as were viral antibodies to Epstein-Barr virus, hepatitis A, B and C, Coxsackie and parovirus. Dip-stick test of urine showed the presence of 2+ red cells and 3+ protein. Mid-stream urine for Chlamydia pneumoniae antigen by ELISA, as did immunofluorescence. An electrocardiogram and echocardiogram were normal.

A skin biopsy from the lesion revealed infiltration of the small vessels in the dermis by leukocytes with nuclear dust and extravasation of erythrocytes confirming leucocytoclastic vasculitis. Renal biopsy showed mild mesangial proliferative glomerulonephritis with granular deposits of IgA in the mesangium. No complement deposition was noted.

Treatment with antibiotics resulted in improvement in her chest X-ray but not her rash or her haematuria and proteinuria. Because of these persistent signs and symptoms, she was treated with oral prednisolone, 40 mg daily, which resulted in prompt clinical response.

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Case 1
A 67-year-old previously well man presented with an acute onset of polyarthralgia involving large joints, malaise, and a non-pruritic maculopapular skin rash for 3 days. He also described mild paraesthesia in his extremities. He admitted to no symptoms suggestive of autoimmune disease. He had no family history of any major illness. On physical examination he was apyrexial and had an extensive maculopapular eruption over her extensor aspects. Systemic examination was normal with a blood pressure of 130/80 mmHg. There was no clinical evidence of inflammatory arthritis.

Investigations that were normal or negative included: full blood count, erythrocyte sedimentation rate, C-reactive protein, ANA, antibody to double-stranded DNA, antibody to extractable nuclear antigen, complements, ANCA, urea and electrolytes, liver function test, blood culture, and viral serology for hepatitis A, B, and C. The serology for parvovirus B19 revealed raised IgM levels, indicating a recent infection. A dip-stick test of urine showed 2+ proteinuria and 24-hour urinary excretion of protein was 4.2 g. A microscopic examination of urine showed hyaline, granular and cellular casts with a few red cells and less than 10 white cells/mm³. She also had a positive rheumatoid factor of 1/40.

X-Rays of the chest, hands, and feet were normal, as was the abdominal ultrasound. Biopsies were taken of the skin lesion and the kidney to ascertain the nature of these lesions. The biopsy of the skin lesion (figure 2) showed leucocytoclastic vasculitis and the kidney biopsy (figure 3) showed mesangiproliferative glomerulonephritis. As her disease was clinically mild, no specific therapy was given and she made a spontaneous recovery. The urine abnormalities had completely resolved within 6 weeks. She has remained well for about 2 years with stable and normal renal function.

Discussion
The first patient presented with clinical features compatible with HSP. She had a typical skin rash, arthralgia, abdominal pain, haematuria, proteinuria and IgA deposition in her skin and kidneys. The only additional feature was the respiratory involvement which was found to be due to Chlamydia pneumoniae infection and which responded to antibiotics. It is possible that these were coexistent or that one triggered the other, but in someone of her age, a chlamydial chest infection is relatively unusual and the coexistence of the chest symptoms and HSP make an aetiological link very likely. The fact that her rash had recurred intermittently since the onset of illness suggests
that the chlamydia antigen acted as a trigger but may not be the entire explanation for her vasculitis.

It is well known that HSP follows infections, particularly those due to streptococcus, varicella, hepatitis and yersinia. Symptoms suggesting infection are present in over half the patients in some series. Most commonly these consist of acute bronchitis, pharyngitis and flu-like symptoms, sometimes with a distinct interval between the infection and the onset of HSP. A seasonal variation has also been reported which is compatible with infection. The association with chlamydial infection has not been previously described, however.

Renal disease is a feature of HSP and many of the other vasculitides. Renal vasculitis is most often described following viral infections, particularly hepatitis B, but has not been reported previously in association with parvovirus B19 infection. Small vessel vasculitis (leucocytoclastic vasculitis) is the most common vasculitic manifestation associated with acute or chronic infections. The most frequently affected vessels are post-capillary vessels, capillaries and, less often, arterioles. It is generally believed that viral infections, particularly those caused by RNA viruses, seem to be associated with, or to cause, vasculitides confined to relatively small vessels. Bacterial infections, on the other hand, tend to involve a spectrum of blood vessels, from small blood vessels to large arteries, while fungal infections are associated with or cause vasculitis that manifests as erythema nodosum or that seems to be associated with large arteries or the aorta. It is noteworthy that several forms of vasculitis have been reported after respiratory infections.

Treatment of systemic vasculitis usually requires systemic steroids, often in high dose. Our first patient responded to low-dose steroid but the second required no treatment. This again would suggest that infection played a significant role as our patients might have expected to have more prolonged and more severe disease if they had not been specifically associated with the infections.

We have, therefore, reported these two cases of infection-related systemic vasculitis; the first case, to our knowledge, has not been previously described in the literature and the second showed a rather unusual urinary sediment abnormality. We feel that chlamydial pneumonia should be added to the long list of microbes causing vasculitis, as misdiagnosis can have serious consequences.

Ergotism related to a single dose of ergotamine tartrate in an AIDS patient treated with ritonavir

P Blanche, A Rigolet, B Gombert, C Ginsburg, D Salmon, D Sicard

Summary

We report a rare case of ergotism related to a single dose of ergotamine tartrate in a man with AIDS being treated with ritonavir. He was treated with a prostacyclin analogue and made a complete recovery.

Keywords: ergotism; ergotamine tartrate; AIDS; ritonavir; adverse drug reaction; HIV infection

Ergotism may occur when a low dose of ergotamine or dihydroergotamine is taken in association with another drug which inhibits its hepatic metabolism. These are mostly macrolide agents, dose-dependent inhibitors of the cytochrome P450 isoenzyme CYP 3A4. Troleandomycin and erythromycin are the most potent inhibitors; azithromycin and spiramycin have not been incriminated. Ritonavir is a potent HIV protease inhibitor. Clinically significant drug interactions between ritonavir and many other medications have been predicted because of its pharmacokinetic profile.

We report a case of severe ergotism related to the concurrent administration of a single dose of ergotamine tartrate and ritonavir.

Case report

A 31-year-old HIV-1 infected homosexual man (stage C following Pneumocystis carinii pneumonia in December 1994) had been treated with stavudine (40 mg/12 h), lamivudine (150 mg/12 h) and ritonavir (600 mg/12 h) since August 1996, and with cotrimoxazole since December 1994. His CD4 cell count was 819/
and plasma HIV-1 RNA measured by reverse-transcriptase polymerase chain reaction amplification was undetectable. He had long suffered from migraines. On 5 December 1997, he complained of pain, paresthesias and cyanosis in both feet. He was admitted to Cochin Hospital on 8 December with severe pain in both legs. Loss of tibial, peroneal, but also radial and ulnar pulses was noted. Achilles deep tendon reflexes were absent. Loss of sensation, pallor and decrease in skin temperature of feet were observed. The patient denied taking any drug. An arterial Doppler test revealed the absence of flow in both tibioperoneal arteries. Echography showed a uniform reduction of diameter of the femoral (2 mm) and popliteal (1 mm) arteries. Treatment with pentoxifyllin (300 mg/8 h, intravenously), calcium nadroparin (6150 U/12 h, subcutaneously) and nicardipin (20 mg/8 h, orally) was unsuccessful. Arteriography showed a uniform reduction of flow in the popliteal arteries of both legs without images of thrombosis or vasculitis. Femoral arteries were also narrowed. Treatment with an analogue of prostacyclin (doprost, up to 50 µg/day intravenously for 7 days) was started on 12 December with immediate response.

The patient remembered taking a single dose (2 mg) of ergotamine tartrate 24 hours before symptoms appeared. Antiviral treatment including ritonavir was continued. The patient was discharged on 23 December. No recurrence occurred.

Discussion

All HIV protease inhibitors are primarily metabolised by the hepatic cytochrome P450 isoenzyme CYP 3A4. Ritonavir is also metabolised by cytochrome P450 isoenzymes CYP 2D6 and CYP 2C9/10, and is the only HIV protease inhibitor to act as an inhibitor of these three cytochrome P450 isoenzymes. Ritonavir might therefore be expected to slow the metabolism of various drugs. This mechanism explains why ritonavir increases the bioavailability of other HIV protease inhibitors, especially saquinavir, when given concomitantly, and also explains the increase of ergotamine or dihydroergotamine concentrations to toxic levels in our patient. Our case report is particularly interesting because ergotism appeared after the administration of only a single dose of ergotamine tartrate. Ritonavir was not stopped, unlike the case of Caballero-Granado,4 but the duration of symptoms was similar in both cases. The interaction with ergotamine is now described in the data sheet of ritonavir and co-prescription is contraindicated. Co-prescription with other HIV protease inhibitors is not recommended.

Learning points

- ritonavir is the only inhibitor of HIV protease to act as a cytochrome P450 inhibitor
- ergotamine and its derivatives must not be administered concomitantly with ritonavir
- ergotism due to the interaction between ritonavir and ergotamine derivatives can be treated with an analogue of prostacyclin (ritonavir can be continued)

Surgical emphysema and pneumomediastinum in a child following minor blunt injury to the neck

G W Back, G Banfield

Summary
Laryngotracheal and pharyngoesophageal tears following minor blunt trauma to the neck are uncommon. A child with such an injury is reported and the modes of diagnosis and management are discussed. Patients may initially present with minimal signs and symptoms, but their condition may deteriorate rapidly or insidiously. In the absence of respiratory compromise, conservative management is appropriate, but all patients with significant blunt neck trauma should undergo early direct laryngoscopy under a general anaesthetic.

Keywords: blunt injury; neck; emphysema; pneumomediastinum

A 4-year-old girl fell forwards onto the backrest of a wooden chair, causing minor pain to the neck and upper chest. Although initially well, 4 hours later she was taken to Mayday Hospital with neck swelling and hoarseness. On examination there was marked surgical emphysema over the neck and chest extending to the sixth rib (figure 1). There was no bruising or stridor and the trachea was central. The larynx was normal on palpation and there was no dysphagia. Oxygen saturations remained normal on air. A chest X-ray demonstrated a pneumomediastinum (figure 2).

The child was transferred to St George's Hospital where flexible fibreoptic laryngoscopy revealed moderate swelling of the supraglottis without pooling of saliva. A thoracic opinion was obtained and the clinical findings were suggested to be compatible with barotrauma to the oesophagus resulting in a pinhole perforation. The child was monitored on the paediatric ITU overnight and kept nil by mouth. The following day she remained well and apyrexial. There was some resolution of the surgical emphysema and she was commenced on clear fluids and later a soft diet. She was subsequently discharged without complication.

Discussion
Minor blunt trauma to the neck and upper chest in children is common, but significant injury to the pharynx, larynx, trachea or oesophagus is unusual. However, cases of laryngotracheal and pharyngoesophageal tears from relatively minor blunt trauma have been documented in the literature.

Children have a proportionally large mandible and short neck in comparison with adults. In addition, a child’s soft and pliable laryngeal and tracheal cartilages can probably sustain greater temporary force than the adolescent or adult airway, a child’s non-calcified larynx being more likely to recoil to its original position without fracturing. Despite protective mechanisms, however, with the neck extended, a midline blow can exert excessive force on the larynx and trachea, crushing the trachea.

Department of Otolaryngology, St George’s Hospital, Blackshaw Road, London SW17 0QT, UK
G W Back
G Banfield

Correspondence to Mr G Banfield

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against the posterior vertebral column, with tearing of the posterior membranous wall of the trachea, resulting in air being forced into the retropharynx and mediastinum.

Cervical oesophageal perforation secondary to minor blunt trauma is extremely rare. Barotrauma resulting from a compressive thoracic injury is the proposed hypothesis for this injury. The rapid rise in oesophageal pressure can exceed the tensile strength of the oesophagus leading to perforation. The mechanism for barometric perforation of the distended, hollow viscus of the oesophagus has been well documented. An anatomic weakness at the hypopharyngeal–oesophageal junction (Killian’s dehiscence) predisposes this area to perforation. With a blow or fall against the neck and upper chest, the upper airway may be sealed off at the hyoid level. Simultaneously the thoracic cavity is emptied of its inspired air. If these barometric forces exceed the bursting pressure of the hypopharyngeal–oesophageal junction, perforation results, with the compressed air from the lungs being forced through the ruptured pharynx into the fascial planes of the neck. The literature shows that most oesophageal perforations secondary to blunt trauma occur at this level.

The most common cause of acute laryngeal trauma in adults is blunt injury, especially from road traffic accidents, followed by sports injuries, falls and assaults, with victims of road traffic accidents usually presenting with the most severe trauma. In children, falls from bicycles and playground equipment-related accidents are the most common cause of blunt neck injuries. These generally insignificant injuries in children rarely result in serious harm and parents and healthcare workers sometimes discount early warning signs. Patients may present with minimal signs and symptoms, but their condition may deteriorate rapidly or insidiously. External signs of injury are usually minimal and local bruising or swelling may be absent. The child is assessed for airway compromise but often the only sign of significant upper aerodigestive tract injury will be the presence of surgical emphysema. A tear of the upper aerodigestive tract, somewhere in the larynx, trachea, hypopharynx or oesophagus, must be assumed in the presence of surgical emphysema. It should be noted that the site and extent of cervical surgical emphysema do not necessarily indicate the anatomical site of injury.

### Learning points

- minor blunt cervical trauma can lead to significant laryngotracheal and pharyngoesophageal injury, although this is uncommon
- patients need to be properly assessed and monitored for airway compromise as their condition may deteriorate after presenting with a seemingly insignificant injury
- hoarseness, stridor, dysphonia, dysphagia and odynophagia are important symptoms to look for
- surgical emphysema is often the only presenting sign
- patients presenting with a minor blunt cervical trauma should have a lateral soft-tissue neck X-ray and chest X-ray. This will disclose the presence of surgical emphysema, pneumomediastinum or pneumothorax
- conservative management is appropriate in the absence of respiratory compromise, but endoscopic assessment under a general anaesthetic needs to be undertaken if there is any suspicion of more serious injury

The most common symptoms of a laryngotracheal tear at presentation are hoarseness (including dysphonia and/or aphonia), stridor and surgical emphysema and of a pharyngoesophageal tear, dysphagia, odynophagia, dyspnoea, hoarseness and surgical emphysema. It is important to exercise a high index of suspicion and consider a laryngotracheal or pharyngoesophageal tear in any child presenting with these symptoms following a seemingly minor blunt trauma to the neck or chest. A lateral soft-tissue neck X-ray and chest X-ray will disclose the presence of free retropharyngeal and subcutaneous air, pneumomediastinum or pneumothorax. A computed tomographic scan of the neck and chest and a contrast swallow are investigations which should also be considered to further define the extent of the injury. All patients with significant blunt neck trauma should undergo early and meticulous direct laryngoscopy under a general anaesthetic. Rigid oesophagoscopy and rigid bronchoscopy should also be considered. In the absence of respiratory compromise, conservative management with close nursing observation, preferably on a paediatric intensive care unit, is appropriate.

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Extrinsic cerebral venous sinus obstruction resulting in intracranial hypertension

P Goldsmith, D J Burn, A Coulthard, A Jenkins

Summary
We report the case of a 70-year-old man reporting with headache and visual disturbances who was being treated for prostate cancer. Investigations showed him to have intracranial hypertension caused by venous sinus obstruction. Patients with metastatic disease and raised intracranial pressure in the absence of focal signs should be considered as possible cases of venous outflow obstruction.

Keywords: intracranial hypertension; venous sinus thrombosis; malignancy

A 70-year-old man presented with a 1-month history of progressive generalised headache, worse in the morning and on straining, and a 1-week history of visual obscurations. He was otherwise well, although he was taking goserelin for carcinoma of the prostate, diagnosed in 1994 on the basis of a raised prostate-specific antigen and malignant-feeling prostate. On examination visual acuity was decreased to 6/24 in the right eye and 6/36 in the left eye. Both fundi were severely papilloedematous. The remainder of the neurological and general examination was normal.

Baseline haematology and biochemistry, including calcium levels, were normal. Erythrocyte sedimentation rate was 12 mm/h. Serum immunoglobulins and electrophoresis were normal. Cranial computed tomography showed midline expansion and sclerosis of the occipital bone. Magnetic resonance imaging (MRI) confirmed midline occipital enlargement with loss of normal diploic marrow signal (figure 1). Axial images showed extrinsic compression of the superior sagittal sinus superior to the torcula (figure 2) which was confirmed on venous magnetic resonance angiography (MRA) (figure 3). A bone scan showed several metastases including the lesion in the occiput. He proceeded to have a lumbar puncture to confirm the clinical diagnosis of intracranial hypertension, to treat it by removal of cerebrospinal fluid (CSF), and to look for an underlying cause, such as malignant meningitis. The opening CSF pressure was 37 cm. The CSF was acellular with a protein content of 0.23 g/dl. He was treated with high-dose dexamethasone and repeated lumbar punctures prior to radiotherapy to his occiput. His visual acuity returned to 6/6 with resolution of his headaches. He subsequently developed further headaches and underwent surgery. The malignant deposit was peeled off the dura with visible re-expansion of the underlying venous sinus. Histology was very suggestive, but not diagnostic of a prostatic metastasis. The patient’s headaches promptly resolved.
Discussion

Idiopathic intracranial hypertension, as benign intracranial hypertension is now known, is believed to be due to a problem with CSF resorption into the arachnoid granulations which project into the venous sinuses. It may be classified as primary or secondary. The primary cases may occur in association with a variety of medical conditions, such as hyperparathyroidism, or idiopathically. Secondary cases may be due to altered CSF composition such as high protein states, or due to interference with the venous outflow. The commonest cause of venous outflow obstruction is venous sinus thrombosis. These cases may present with headache and papilloedema in the absence of focal signs. Much less well recognised is venous obstruction from extrinsic compression causing a similar syndrome.

Plant et al. presented two similar cases. In their first case a plasmacytoma was peeled off the dura at surgery resulting in visible re-expansion of the superior sagittal sinus. Their second case was of metastatic Ewing’s sarcoma compressing the torcula. Other cases reported have included neuroblastomas, breast cancer and meningiomas. Gironell et al. have recently reported midline occipital non-Hodgkin’s lymphoma causing non-thrombotic superior sagittal sinus occlusion. The vast majority of cases have compression of the terminal superior sagittal sinus and torcula. There appears to be no particular vascular anatomical reason why metastases should concentrate here but more likely reflects the fact that metastases elsewhere in the skull are less likely to become symptomatic. Presumably this is because lesions here result in raised pressure along the entire length of the superior sagittal sinus. This would therefore affect the arachnoid granulations to the maximum extent. It is important to note the absence of focal signs in these patients.

A non-contact complete knee dislocation with popliteal artery disruption, a rare martial arts injury

Y K S Viswanath, I M Rogers

Summary
Complete knee dislocation is a rare injury and an associated incidence of popliteal artery damage ranges from 16–60% of cases. It occurs commonly in road traffic accidents and in high velocity trauma where significant contact remains as the usual mode of injury. We describe a rare case of non-contact knee dislocation with popliteal artery injury sustained while practising Aikido, a type of martial art. This patient successfully underwent closed reduction of the knee with an emergency vein bypass graft. Similar injury in association with Aikido has not been described in the English literature previously. Various martial art injuries are briefly discussed and safety recommendations made.

Keywords: Aikido; knee dislocation; popliteal artery disruption; sports injury

‘Martial arts’ is a generic term encompassing a group of various fighting techniques that primarily use different body parts with or without weapons. The main projected benefits of martial arts are self-defence, and increase of fitness, flexibility and self-esteem. A few of these special techniques include karate, kendo, Tae Kwon Do, kungfu and Aikido. The term Aikido means the way (do) for the co-ordination or harmony (ai) of mental energy or spirit (ki). Morehei Uyeshiba, a Japanese master, founded Aikido nearly 50 years ago. Martial arts in general are considered as a safe sport. However, there are reports of serious injuries including several deaths in the last few years. In this article we report a case of disabling knee injury associated with vascular compromise needing emergency limb revascularisation surgery.

Case report
A 20-year-old man was brought to the emergency room with alleged history of sustaining an accidental injury to his left knee while practising Aikido. He explained that he had lost his footing while carrying someone piggyback, and fell forward with his leg bent behind the body axis. On examination he had a complete left knee dislocation with anterior displacement of tibia and fibula. His left foot was cold and cyanosed without palpable pedal pulses. Closed reduction of the dislocated knee under general anaesthesia was carried out successfully. Detailed examination of the left knee revealed complete disruption of posterior capsule, anterior cruciate ligament, and posterior cruciate ligament and varus valgus instability. An intra-operative arteriogram revealed complete blockage of the popliteal artery (figure 1) with no filling of distal vessels. He underwent end-to-side anastomosis using a reversed saphenous vein bypass graft to join the distal superficial femoral artery and tibioperoneal trunk successfully. The limb was immobilised in flexion using a cast.

Postoperatively, the limb survived and he gradually recovered. A repeat arteriogram done 4 months later confirmed a well functioning graft with a good runoff (figure 2). He received rigorous physiotherapy and rehabilitation over a period of 10 months. His proprioception improved gradually to 100%, as did his motor function. Interestingly, he never experienced a feeling of instability throughout this period. He was doing well at follow-up after 16 months.
Discussion

About 95% of the martial art injuries are minor, involving the extremities in 70% of cases. Birrer and Birrer, in their 1981 analysis of over 24,000 martial arts injuries (quoted in 1), estimated that 1 in 500 could be serious. In 1997, Wilkerson reported three deaths in association with martial art injuries, all due to anterior chest trauma.3 A few of the reported serious martial art injuries include skull fractures with or without cerebral contusion, subdural haematoma, rib fractures with haemothorax, traumatic retinopathy, hepatosplenic lacerations, and fractures involving the spine, face and hip.1, 3–4 Oler et al discussed various factors predisposing to serious injuries involving martial arts and made some important safety recommendations: the establishment of minimum standards and certification for instructors and medical practitioners who supervise these events, and the mandatory use of head gear, mouth wear, torso protection, groin protection and proper boxing gloves. They also reiterated the need for further research to study injury pathogenesis, promote better training techniques, and to design better safety equipment and rules for this sport.4

Dislocation of the knee is an uncommon injury from any trauma and the reported incidence varies from 14 in 2 million total admissions to the Mayo Clinic between 1911 and 1960 to two cases out of 140,231 in a series in Philadelphia.5, 6 The knee dislocation can be associated with popliteal artery injury in 16–60% of cases5, 6 and nerve injury in 16–43% of cases1. An inadequate initial assessment and delay of vascular repair could lead to an amputation rate of 87%.3, 5 Hence, revascularisation takes precedence over the repair of injured ligaments. The management of ligamentous injury following complete knee dislocation is unclear and controversial.3 Cumulative data suggest that primary surgical repair in general will yield better functional results than conservative treatment.5 However, of all types of knee dislocation, the anterior type is more suitable for non-operative management as it seems to spare collateral ligaments.5

Non-contact complete knee dislocation is exceedingly rare and has not been described previously in association with Aikido.4 The presented case was a complete anterior knee dislocation disrupting the popliteal artery and damaging all the ligamentous structures except both collateral ligaments. The patient was successfully revascularised and managed conservatively. This case highlights the importance of early limb revascularisation and postoperative rehabilitation in achieving a successful outcome in this disabling injury.

Proper medical supervision, supervised training by certified instructors, and adequate use of safety equipment while practising martial arts may prevent these serious injuries.

Learning points

- Initial vascular assessment is mandatory in all cases of acute limb trauma, including those caused by martial arts
- The attending surgeon must aim at limb salvage by correcting vascular injury first
- Soft tissue repair is not always necessary in an anterior knee dislocation, especially when collateral ligaments are preserved

Digoxin, hypercalcaemia, and cardiac conduction

Adrian Vella, Thomas C Gerber, David L Hayes, Guy S Reeder

Summary
The cardiac effects of hypercalcaemia are usually manifest as a shortening of the QT-interval. Hypercalcaemia is infrequently associated with a clinically manifest arrhythmia. However, concomitant therapy with digoxin or underlying cardiac disease can potentiate the arrhythmogenic effects of hypercalcaemia, leading to a symptomatic rhythm disorder. We describe a symptomatic arrhythmia, which developed in a patient with hypercalcaemia secondary to squamous cell carcinoma of the bronchus. The patient was on digoxin therapy at the time. The arrhythmia did not recur after discontinuation of digoxin therapy and correction of the hypercalcaemia. Because of its effect on cardiac conduction, hypercalcaemia should be considered in the evaluation of any patient with an unexplained bradyarrhythmia. Conversely, patients with hypercalcaemia should discontinue digoxin therapy and be evaluated for the presence of rhythm disorders while receiving appropriate treatment for hypercalcaemia.

Keywords: hypercalcaemia; bradycardia; cardiac conduction; arrhythmia

Clinical observations of conduction disturbances caused by hypercalcaemia are rare. A few case reports exist describing patients with bradyarrhythmias such as atrioventricular (AV) nodal conduction defects, sinus node dysfunction and atrial fibrillation in the setting of hypercalcaemia. Underlying disease of the conduction system or cardiomyopathy may play a role in the pathogenesis of the observed arrhythmias. We describe a patient with hypercalcaemia due to malignancy who developed a symptomatic bradyarrhythmia while on digoxin therapy and review the literature.

Case report
An 81-year-old woman had a sudden syncopal episode without premonitory symptoms while having a meal. She regained consciousness within one minute. Bystanders noted a slow radial pulse and a flushed complexion. She was admitted to a local hospital for evaluation and continuous cardiac monitoring. Over the year preceding admission, she had been evaluated repeatedly by her local physician for weakness, dyspnoea and malaise associated with an unexplained 4.5 kg weight loss.

A presumptive diagnosis of congestive heart failure was made and since that time, the patient had been treated with digoxin and loop diuretics. Over the 8 weeks prior to admission, she developed a cough productive of green sputum.

During the 12 hours following admission, the patient had several sinus pauses of 2.0 to 5.1 seconds. Laboratory evaluation on admission was remarkable for a total calcium of 3.0 mmol/l (normal 2.2–2.5). The serum digoxin level was 1.5 ng/ml (0.5–2.0). The chest X-ray showed a left upper lobe infiltrate of indeterminate nature but was otherwise unremarkable with no signs of congestive heart failure or pulmonary venous hypertension. The patient was transferred to our facility for further evaluation and treatment.

Physical examination revealed an elderly woman in no apparent distress. There was no palpable lymphadenopathy. Her pulse was regular in rate and rhythm at 74 beats/minute. There were no added heart sounds and examination of her chest and abdomen was unremarkable. She was oriented to time, place and person and there were no focal neurological deficits.

A 12-lead electrocardiogram (ECG) obtained on admission was notable for the presence of first-degree AV block. Temporary transvenous pacing was established. The hypercalcaemia resolved after intravenous hydration and diuretic therapy. Subsequently, no further sinus pauses were observed. A computed tomography scan of the thorax revealed an ill-defined, peripheral, bronchocentric lesion in the left upper lobe. Mediastinal and hilar adenopathy was also present. Transthoracic echocardiography showed a normal ejection fraction of 55%. There were no regional wall motion abnormalities. The serum parathyroid hormone was appropriately suppressed at 0.8 pmol/l (1.0–5.2). Bronchoscopy revealed an endobronchial lesion in the right main bronchus that was biopsied. The histology showed Grade 3 squamous cell carcinoma. An oncology consultation was obtained and after explanation of the therapeutic options, the patient elected not to pursue chemotherapy or radiotherapy.

Since the patient declined therapy for her malignancy, she was felt to be at risk for recurrent bradyarrhythmias and a permanent pacemaker was placed to prevent further symptoms. Digoxin was discontinued and she was discharged home after uneventful pacemaker placement. First degree AV block was still present on the ECG obtained on dismissal. Serum calcium levels were normal at that time.
**Discussion**

**CARDIAC CONDUCTION AND HYPERCALCAEMIA**

Within the range of calcium concentrations that are compatible with life, Ca\(^{2+}\) has little effect on the resting membrane potential. However, phase 2 of the action potential, the total duration of the action potential, and the duration of the effective refractory period tend to be prolonged by hypocalcaemia and shortened by hypercalcaemia.\(^3\)\(^4\)

Hypercalcaemia has been shown to decrease cardiac conduction velocity and shorten the refractory time. This facilitates re-entry mechanisms and the development of complex ventricular arrhythmias. The main ECG manifestation of hypercalcaemia is a shortened QT-interval, sometimes associated with a slight prolongation of the PR and QRS-intervals. In patients with severe hypercalcaemia (>3.4 mmol/l), second or third degree AV block can occur.\(^5\)\(^6\) The prolongation of the QTc seen in patients with hypercalcaemia is associated with a prolongation of the ventricular refractory period which may have an anti-arrhythmic action. The reverse is true of the shortened ventricular refractory period seen in hypercalcaemia (box 1). Vagal activity could play a role in the production of arrhythmia because atropine abolishes the arrhythmias created by the infusion of calcium-containing solutions.\(^7\)

Sudden death in patients with hypercalcaemia has been reported. The proposed mechanism of death in these patients is ventricular fibrillation-secondary to the underlying electrolyte disturbance.\(^2\)\(^3\)\(^6\) In a retrospective review of 47 patients with conservatively managed hyperparathyroidism, Corlew et al identified one patient whose death was attributable to a malignant ventricular arrhythmia.\(^10\) Rosenqvist et al studied cardiac conduction in 20 patients with hypercalcaemia caused by primary hyperparathyroidism.\(^11\) These patients had no clinical, radiological or ECG evidence of underlying heart disease and underwent continuous ECG monitoring in the presence of hypercalcaemia before surgery and after normalisation of serum calcium values in the post-operative period. In this series there was no difference in the prevalence of supraventricular or ventricular arrhythmias. No high-grade AV-block was observed. A postoperative prolongation of the QTc was noted in all patients.\(^11\)

A review of the records of 193 patients with surgically treated primary hyperparathyroidism identified two patients with a junctional rhythm prior to surgery. No ventricular arrhythmias were noted in this series.\(^12\) Continuous 24-hour ECG monitoring undertaken in eight patients with hypercalcaemia (2.9–4.4 mmol/l) due to metastatic breast cancer did not detect any significant arrhythmias. Extrasystoles seemed to occur more frequently in these patients than in the general population. The frequency of ventricular ectopy did not change with the correction of hypercalcaemia and was attributed to the toxic effects of the anthracycline-based chemotherapy that all of these patients received.\(^2\)

**DIGOXIN AND HYPERCALCAEMIA**

The interaction between hypercalcaemia and digoxin is often overlooked. Cardiac glycosides potentiate the effect of hypercalcaemia on cardiac conduction. Digoxin and the other glycosides inhibit the myocardial Na\(^+\)/K\(^-\)-ATPase, thereby increasing intracellular sodium which, in turn, inhibits the Ca\(^{2+}\)/Na\(^{+}\)-antiporter and increases intracellular calcium levels (figure).\(^3\)

Both digoxin and hypercalcaemia decrease the excitation threshold and shorten the effective refractory period in the ventricles and have similar effects on the automaticity of ectopic pacemakers (box 2). Symptoms and signs of digoxin toxicity may appear at normal digoxin levels in the presence of hypercalcaemia.\(^3\)\(^5\)\(^11\)

**Box 1**

<table>
<thead>
<tr>
<th>Effects of ↑Ca(^{2+}) on cardiac conduction</th>
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<tbody>
<tr>
<td>- lowering of the excitation threshold</td>
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<tr>
<td>- shortening of phase 2 of the action potential</td>
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<td>- shortening of the effective refractory period</td>
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<tr>
<td>- decreased myocardial conduction velocity</td>
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<tr>
<td>- facilitation of re-entry</td>
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<tr>
<td>- shortened QTc</td>
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<tr>
<td>- second or third-degree AV block with Ca(^{2+}) &gt;14.0 mmol/l</td>
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</table>

**Figure**

Digoxin increases intramyocardial levels of calcium by indirectly increasing the activity of the sodium/calcium antiporter; [Ca\(^{2+}\)]\(_i\) = intracellular calcium and [Ca\(^{2+}\)]\(_e\) = extracellular calcium

The patient described in this article developed a symptomatic bradyarrhythmia in the setting of hypercalcaemia and concomitant digoxin use. Other than first degree AV block, there was no other clinical or echocardiographic evidence of underlying heart disease. Since the brady-
Hypercalcaemia can have many aetiologies. Some of these aetiologies have myocardial effects other than those mediated by hypercalcaemia. The possible causes of hypercalcaemia and potential cardiac effects other than those mediated by hypercalcaemia are listed in box 3. Cardiac disease, or the underlying cause of hypercalcaemia, may increase the patient's susceptibility to the arrhythmogenic effects of hypercalcaemia.

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Systemic vasculitis and atypical infections: report of two cases

Kuntal Chakravarty and Peter Merry

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