Isolated tricuspid valve infective endocarditis

A report of 6 cases

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Summary

Six cases of isolated tricuspid valve endocarditis in young women are described. Preceding genital sepsis was a predisposing factor in 4 patients. Cardiac signs are unusual at presentation, rendering the diagnosis difficult. Pleuropulmonary manifestations are the predominant findings, while overt signs of tricuspid insufficiency and right heart failure occur late in the disease. *Staphylococcus aureus* is the pathogen most commonly found and requires energetic treatment for a minimum of 4 weeks. The value of echocardiography in establishing an early diagnosis is stressed. Persistent sepsis constitutes a major indication for surgery.

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Infective endocarditis localised to the tricuspid valve is uncommon. It usually occurs in intravenous drug abusers[1] and more recently has been described in patients undergoing right-heart catheterisation.[2,3] In the past 4 years we have seen 6 cases of isolated tricuspid valve endocarditis in young women, which were not related to intravenous drug abuse or right-heart catheterisation. These 6 cases serve to emphasise that the clinical presentation is frequently dominated by extracardiac manifestations and reaffirm the value of echocardiography in the early diagnosis of this condition.

Case reports

Case 1

A 25-year-old woman was referred from another hospital with a diagnosis of staphylococcal septicaemia. She complained of headache followed by right-sided pleuritic chest pain, fever and rigors for 11 days before admission to hospital. She later admitted to having had an abortion. On admission she was ill, pyrexial and pale. She had signs of right middle lobe consolidation and bilateral pleural effusions, which were confirmed on chest radiography. The liver was 3 cm enlarged and tender on palpation. Cardiovascular and pelvic examinations were normal. The haemoglobin value was 10,2 g/dl, the white cell count 13,8 x 10^9/l and the erythrocyte sedimentation rate (ESR) 87 mm/1st h. Pleural aspiration revealed a sterile blood-stained effusion. *Staphylococcus aureus* sensitive to erythromycin and cefamandole was isolated from multiple blood cultures. At this stage, the patient was treated for staphylococcal septicaemia with cloxacillin 1 g 6-hourly and cefamandole 1 g 6-hourly intravenously. After 10 days of antibiotic therapy she remained pyrexial and pale. A systolic ejection murmur audible at the left sternal border was thought to be due to anaemia (haemoglobin 8,3 g/dl). She was transfused with 2 units of packed cells and fusidic acid (580 mg 8-hourly) and erythromycin (1 g 6-hourly) were added to her antibiotic regimen. Fusidic acid was stopped after 2 weeks because of the development of jaundice. In the ensuing 2 weeks the jaundice settled, the patient became apyrexial and repeat blood cultures were negative.

On about the 40th day in hospital the patient became pyrexial again, the jaundice deepened and crepitations were again noted at the left lung base. The liver was enlarged to 4 cm and ascites was present. Chest radiography revealed lack of resolution of the left lower lobe consolidation with areas of breakdown. *S. aureus* sensitive to vancomycin, erythromycin, clindamycin and amikacin was again isolated from multiple blood cultures. Since the recurrence of bacteraemia suggested a diagnosis of infective endocarditis, the patient was referred for echocardiography, which revealed large vegetations on the tricuspid valve. Her medication was changed to vancomycin, cefamandole, rifampicin and erythromycin and a day later the patient collapsed and became seriously ill. Signs of right-heart failure with the murmur of tricuspid incompetence and a gallop rhythm were now present. She developed a pericardial friction rub, became hypotensive and died.

At autopsy vegetations were present on the tricuspid valve and there were septic infarcts in the lungs.

Case 2

A 30-year-old woman was admitted to a rural hospital with a history of cough, yellow eyes and general malaise for a month. For the preceding 2 weeks she had experienced rigors and dyspnoea. The last menstrual period was 3 months previously. Despite treatment with amoxycillin, she remained pyrexial and jaundiced and was transferred to King Edward VIII Hospital for further management.

Examination revealed a severely pale, jaundiced woman with a temperature of 38,6°C. The heart was normal. Since chest radiography showed a large right pleural effusion with several thin-walled cavities in the right lung (Figs 1 and 2), a presumptive diagnosis of tuberculosis was made.

Initial investigations were as follows: haemoglobin value 5,4 g/dl; white cell count 5,0 x 10^9/l; ESR 164 mm/1st h; serum albumin value 17 g/l, globulin 45 g/l, bilirubin 89 μmol/l, alkaline phosphatase 191 IU/l and asparate transaminase 58 U/l. Sputum and bone marrow cultures for acid-fast bacilli were negative. Blood cultures were also negative. The pleural fluid protein count was 53 g/l. In view of the long pyrexial illness and chest findings, the patient was treated for tuberculosis.

Two weeks after admission, mild pedal oedema was noted, a short systolic ejection murmur was heard at the left sternal border and the spleen was now palpable. *Fusobacterium*

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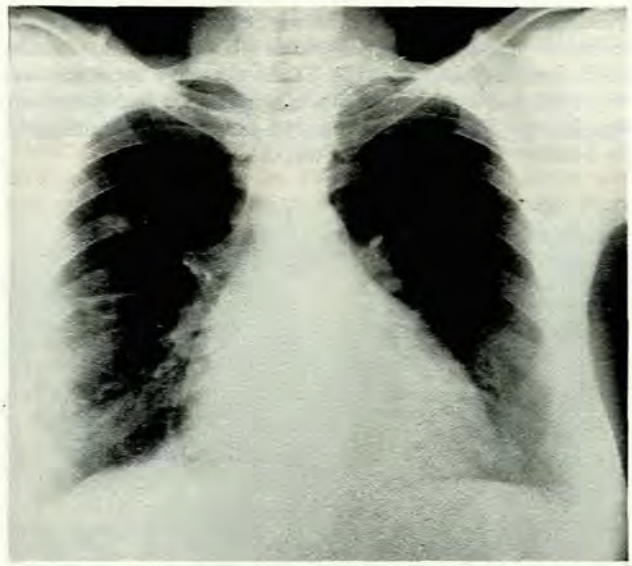

Fig. 1. Case 2. Initial chest radiograph showing rounded shadows with cavitation.

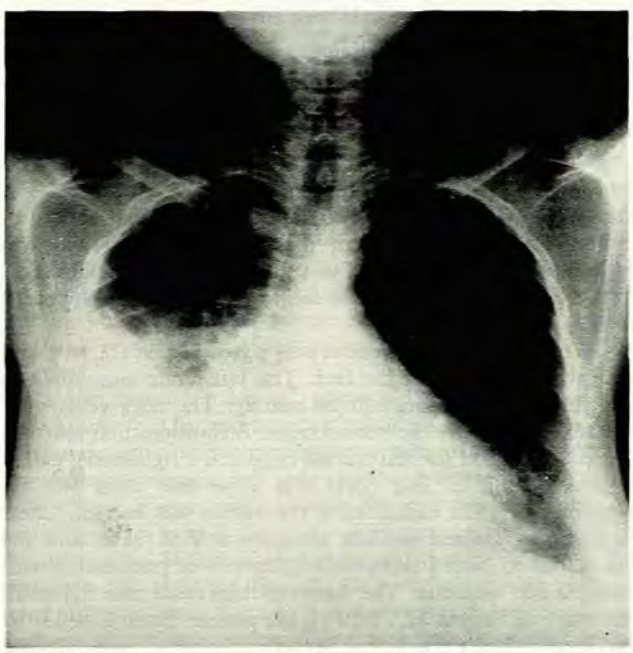

Fig. 2. Case 2. Chest radiograph showing progression to effusion.

nucleatum was isolated from repeated blood cultures. Two-dimensional echocardiography revealed vegetations on the tricuspid valve (Fig. 3). The patient was now treated for infective endocarditis with penicillin and metronidazole. Her temperature subsided and the murmur disappeared, followed by a rise in haemoglobin value to 11,7 g/dl and a fall in the ESR to 37 mm/1st h. After 6 weeks of antibiotic therapy the patient was discharged from hospital.

Case 3

A 32-year-old woman was referred with a diagnosis of mitral stenosis, tricuspid incompetence and infective endocarditis. She had presented 2 months previously with unexplained anaemia. The haemoglobin value was 6,2 g/dl; white cell count 18,5 x 10^9/l and ESR 31 mm/1st h. Despite

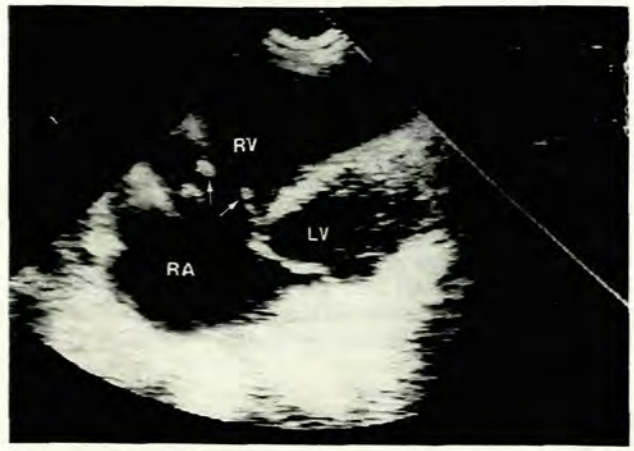

Fig. 3. Case 2. Echocardiogram showing vegetations (arrows) **attached to the tricuspid valve.**

repeated transfusions at the peripheral hospital she remained anaemic. She was treated with penicillin and gentamicin for 2 weeks and was referred for further management.

On examination the patient was pale, apyrexial and had clubbing of the fingers. The jugular venous pressure was elevated with prominent 'v' waves and there was a 6-cm pulsatile hepatomegaly. Apart from a short systolic murmur, there were no auscultatory features of mitral stenosis. Chest radiography revealed collapse with consolidation in the right upper and left lower lobes. Initial investigations were as follows: haemoglobin value 9,6 g/dl; white cell count 10,7 x 10^9/l; and ESR 81 mm/1st h. There was no evidence of deep vein thrombosis on Doppler studies. A ventilation-perfusion scan revealed wedge-shaped perfusion defects in the right upper and left lower lobes with no corresponding ventilation defects. The presumptive diagnosis at this stage was thromboembolic pulmonary hypertension. Heparin 10 000 units 6-hourly intravenously was instituted. Four days later she became pyrexial and a new systolic murmur was heard at the left sternal border. Repeat blood cultures were negative. Differential diagnosis now included right-sided infective endocarditis and right atrial myxoma. Two-dimensional echocardiography revealed vegetations on the triscuspid valve confirming a diagnosis of tricuspid valve endocarditis. The mitral valve was normal. On amoxycillin 2 g 6-hourly the ESR fell to 37 mm/1st h within 10 days and the patient made a steady recovery.

Case 4

A 20-year-old woman presented with a 1-month history of malaise, loss of appetite and loss of weight. She admitted to a yellow vaginal discharge but the menses were regular. On examination the patient was pyrexial, ill-looking and had mild pallor. A tinge of jaundice was also present. The pulse rate was 120/min and the blood pressure 100/60 mmHg. The apex beat was in the 5th intercostal space and a short ejection murmur could be heard at the left sternal border. There were reduced breath sounds at both bases with a few crepitations at the right base, and the liver was enlarged 2 cm below the costal margin. The haemoglobin value was 5,8 g/dl, the white cell count 21,5 x 10^9/l and the ESR 102 mm/1st h. Since blood cultures grew *S. aureus*, the patient was managed with intravenous cloxacillin 2 g 6-hourly and fusidic acid 500 mg 8-hourly. On this regimen she improved; the temperature settled but with partial resolution of the signs of consolidation at the right base. A chest radiograph done at this stage showed bilateral infiltrates and subsequent examination indicated that the systolic murmur increased on inspiration. A diagnosis of

right-sided endocarditis was then considered and an echocardiogram showed a tri-lobed vegetation, which prolapsed through the tricuspid orifice into the right atrium. Treatment with flucloxacillin and fusidic acid was continued. The patient remained stable until 2 weeks after admission to hospital, when she became dyspnoeic and pyrexial. The pleural effusion on the right had increased in size. Repeat blood cultures did not reveal any growth. The neck veins became distended; the murmur became pansystolic and the liver enlarged in size. Therapy with vancomycin (500 mg 8-hourly) was begun but she remained apyrexial and was referred for surgery. Upon transfer for valve replacement, she had a sudden cardiac arrest and died. An autopsy was not performed.

Case 5

A 25-year-old woman had a uterine evacuation and curettage for an incomplete abortion in April 1988. In May she was admitted to hospital with right lower lobe pneumonia, which responded to antibiotic therapy. She was re-admitted in June 1988 with a pyrexial illness. Laparotomy revealed retained products of conception but no focus of sepsis was identified. *S. aureus* sensitive to cloxacillin was isolated on repeated blood cultures. Chest radiography revealed triangular shadows and an area of consolidation in the right lower lobe. On treatment with cloxacillin and cefotaxime there was no significant improvement. On 20 June the patient's condition deteriorated suddenly and she was referred to us for further management.

On admission to this hospital the patient was noted to be ill, pyrexial (39°C) pale and jaundiced. She was tachypnoeic, coughed continuously and had bilateral basal crepitations with dullness to percussion. There was oedema of the sacrum and ankles and the neck veins were elevated to 5 cm. The liver was 6 cm enlarged but there was no splenomegaly or ascites. A right ventricular gallop was heard over the precordium. No murmurs were audible. Chest radiography showed bilateral basal consolidation, possibly with fluid. The haemoglobin value was 9,2 g/dl, white cell count 23 x 10^9/l and platelet count 82 x 10^9/l. The serum bilirubin level was 67 mmol/l, albumin 26 g/l, globulin 51 g/l, aspartate transaminase 69 U/l and lactic dehydrogenase 712 U/l.

Although no murmur was audible, the clinical features were highly suggestive of infective endocarditis. This was confirmed on echocardiogram, which showed a large mass that virtually occluded the tricuspid valve orifice but was freely mobile and prolapsed into the right atrium (Fig. 4).

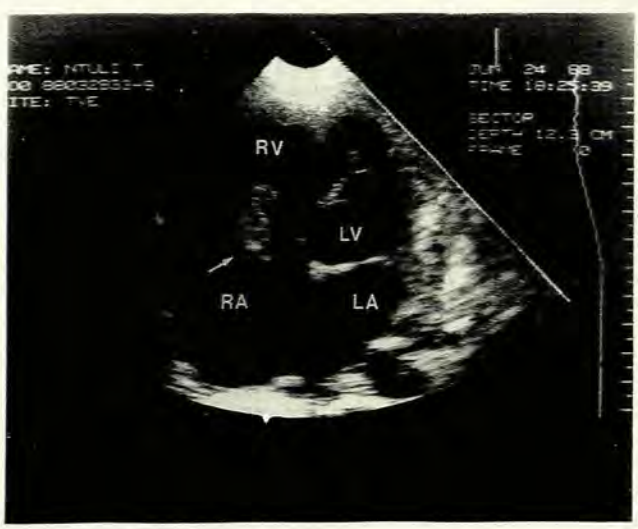

Fig. 4. Case 5. A large vegetation occupying the tricuspid valve orifice.

Emergency valve replacement was performed. A huge friable vegetation occupied the tricuspid orifice with satellite lesions on the papillary muscles (Fig. 5). As the valve apparatus was destroyed, valve replacement was performed. Postoperatively vancomycin (500 mg intravenously 6-hourly) was administered for 1-month before the patient was discharged.

Fig. 5. Case 5. Operative specimen showing destroyed tricuspid valve with a mass of vegetation.

Case 6

A 30-year-old woman was admitted to the medical ward on 26 March 1989 with a 3-week history of fever, dizziness and generalised weakness. On 1 January she had been admitted to a peripheral hospital for an incomplete abortion and was treated for anaemia with ferrous sulphate tablets. On admission to this hospital she was menstruating and the menses appeared normal.

On examination the patient was pyrexial (39°C), pale and had pitting oedema of the feet. The pulse rate was 120/min and the blood pressure 120/60 mmHg. The neck veins were elevated 5 cm above the sternal angle. A short ejection murmur could be heard at the left sternal edge and a right atrial gallop was also audible. The chest was clear and there was no hepatomegaly. On examination the vagina was normal. Chest radiography showed nodular shadows at both bases and she was admitted with a provisional diagnosis of pneumonia with unexplained anaemia. The haemoglobin value was 5,6 g/dl, the white cell count 12,5 x 10^9/l, the platelet count 218 x 10^9/l and a smear had a mircocytic hypochromic appearance. During the next 48 hours the patient remained tachypnoeic, pyrexial and developed rigors. Blood culture revealed *S. aureus* and therapy with cloxacillin (2 g intravenously 4-hourly), to which the organism was sensitive, was initiated. At this time the patient also received 2 units of packed cells. On the 7th hospital day the patient complained of pleuritic right-sided chest pain. The murmur appeared louder on inspiration and there were increasing signs of right-sided congestion. The clinical picture was thought to be consistent with right-sided endocarditis and an echocardiogram requested. The anterior leaflet of the tricuspid valve was noted to prolapse into the right atrium and it appeared to have vegetations on it.

Repeat chest radiography showed increasing nodular opacities at both bases. The ventilation perfusion scan showed areas of ventilation which were not perfused. It was elected to continue therapy with cloxacillin and fusidic acid and the patient's condition steadily improved. The tachypnoea subsided but the patient remained pyrexial and anaemic. She was again transfused with 2 units of packed cells and therapy was changed to vancomycin 500 mg 6-hourly for 2 weeks. During

this period, however, the pyrexia did not abate. Repeat blood cultures were negative and the fever was attributed to thrombophlebitis at the drip site. After 2 weeks of vancomycin therapy, flucloxacillin and fusidic acid by mouth were reinstituted. The thrombophlebitis settled and the temperature returned to normal. The haemoglobin value rose to 9,1 g/l and the ESR fell from 140 mm/1st h to 71 mm/1st h. The patient was discharged on 3 May with signs of mild tricuspid incompetence.

Discussion

Right-sided infective endocarditis is considerably less frequent than left-sided disease and accounts for 5 - 10% of all cases of infective endocarditis.[1] In most instances a predisposing cause is usually found. The most common predisposing causes are intravenous drug abuse, right-heart catheterisation, chronic alcoholism and immunosuppresive therapy. The 6 cases we have described are unusual in that the predisposing cause was genito-urinary infection in 4 patients, although at the time of presentation no overt pelvic source of sepsis was identified. In 3 cases the infection was clearly a consequence of septic abortion. The tricuspid valve is more commonly involved than the pulmonary valve and the affected valve is usually anatomically and functionally normal before the onset of infective endocarditis. Consequently, signs of pre-existing cardiac disease are often absent.[4] Indeed, pulmonary signs overshadow the cardiac findings. Nodular and segmental infiltrates on chest radiography are usually multiple and appear sequentially in different parts of the lungs with a predilection for the lower lobe.[5] Cavitation, empyema and pleural effusions are common. In 2 of our patients chest radiography demonstrated cavitation and effusion secondary to septic pulmonary infarction, a clinical picture that could be mistaken for tuberculosis. In case 3 signs of toxaemia were absent as a result of partial treatment with antibiotics, so that the clinical findings resembled thromboembolic pulmonary hypertension. Lack of radiographic resolution with reappearing infiltrates were valuable pointers to the diagnosis.

Cardiac manifestations in right-sided endocarditis are few and subtle.[6,7] The murmur of tricuspid regurgitation is a diagnostic sign that is often absent on admission to hospital or unrecognised because it is soft, short and may not increase on inspiration.[4] Hence, when present the murmur may easily be ascribed to fever and anaemia, which are usually present in this condition. Where absent it is said that pressure on the abdomen may elicit the murmur (de Cavallo's manoeuvre). As exemplified in cases 1, 3 and 4 in our report, the more typical findings of tricuspid regurgitation with large 'v' waves in the jugular venous pulse and pulsatile hepatomegaly occur late in the infection and are associated with a poorer prognosis.[4,8] Also when regurgitation is severe it is well recognised that the murmur may even disappear because the gradient between the right ventricle and the right atrium is abolished. Therefore less reliance should be placed on the presence of murmurs in making a diagnosis of tricuspid valve endocarditis.

In previous reports[9,10] the difficulty in diagnosis of tricuspid endocarditis has been stressed, especially as intravenous drug abuse was not a predisposing factor in our patients. In the absence of a murmur or sign of tricuspid regurgitation the diagnosis will remain in doubt. Patient 1 received antibiotic therapy for almost 6 weeks for unresolving pneumonia before she was referred for echocardiography. A high index of suspicion is therefore necessary. After our experience with case 1 the syndrome was easily recognisable in the cases which followed. Right-sided endocarditis should be considered in any young woman who develops a serious respiratory infection with bilateral infiltrates on chest radiography after a recent obstetric or gynaecological event with or without overt sepsis.

Clearly, early diagnosis is essential for correct management. In this respect two-dimensional echocardiography has emerged as probably the single most important investigation in confirming the diagnosis of right-sided endocarditis.[7,8] The superiority of two-dimensional over M-mode echocardiography in the detection of vegetations has now been well established[8,11-13] with a detection rate of 80 - 100%.[7,8] Vegetations appear as mobile oscillating masses involving the entire tricuspid valve or attached to one of its leaflets without interfering with leaflet motion. It is noteworthy that the diagnosis in all 6 of our patients was definitely made, albeit late, only after two-dimensional echocardiography was performed. Imaging should be performed long before signs of tricuspid regurgitation appear. In 3 cases (2,4,5) vegetations were detected even when cardiac signs were minimal.

S. aureus is isolated from 80% of cases with tricuspid valve endocarditis. Every patient in whom this organism is isolated from blood cultures should be considered to be at risk of developing infective endocarditis and treated for a minimum of 4 weeks with intravenous flucloxacillin 2 g every 4 hours in combination with either fusidic acid 500 mg orally every 8 hours or intravenous gentamicin 1,3 mg/kg body weight every 8 hours for 2 weeks.[14] In all our patients inadequate antibiotic therapy before referral permitted progression of the infection so that at presentation anaemia was a striking finding. A falling haemoglobin value despite appropriate antibiotic therapy is an indication of ongoing sepsis and an additional pointer to endocarditis as the source of sepsis. Moreover, recurrence of bacteraemia after cessation of treatment is highly suggestive of infective endocarditis. This was well illustrated in case 1, where withdrawal of fusidic acid, which was probably the most effective of the three antibiotics used, resulted in a relapse. In contrast with left-sided disease where haemodynamic decompensation dictates the need for surgery, in patients with right-sided infective endocarditis persistent sepsis constitutes the major indication for surgery. In the absence of another source of infection, pyrexia with recurrent bacteraemia should prompt consideration of surgery. Juggling with antibiotics in order to control infection may eventually preclude surgery when the patient has reached a moribund state. Neither of our two patients (1 and 4) who died had methicillin-resistant staphylococci so that therapy with cloxacillin was appropriate. The institution of vancomycin when the organism was known to be sensitive to cloxacillin and fusidic acid should have been a cue to the need for surgery.

Right-sided infective endocarditis has a better prognosis[15] with a medical failure rate of 24%[6] as opposed to 43% in patients with left-sided disease. Despite this, a delay in diagnosis can be fatal. Patients who are at high risk are those with concomitant left-sided endocarditis, those in whom the organism is unusually virulent and those in whom severe right-sided failure develops.[5,8] As indicated earlier, signs of gross tricuspid regurgitation with right ventricular failure occur late in the disease when valve destruction is severe with repeated embolisation of vegetations to the lungs. Death in these patients is related to the adult respiratory distress syndrome with respiratory failure from recurrent septic pulmonary emboli.

In conclusion, the combination of repeated pulmonary emboli together with ongoing pyrexia is highly suggestive of right-sided infective endocarditis (Table I). The murmur of tricuspid regurgitation is often absent at presentation. Signs of right-heart failure occur only late in the disease. Diagnosis is then relatively simple: cardiomegaly appearing in the pyrexial patient with a previously normal heart.

Early diagnosis, when precordial signs are minimal, is essential for effective therapy with a favourable outcome, and can easily be confirmed using two-dimensional echocardiography. Most patients will respond to aggressive antibiotic therapy,

to fly the child to King Edward VIII Hospital and for 2 U of boomslang antivenin to be flown to Durban from the SAIMR.

When the child arrived in the ICU at King Edward VIII Hospital, some 36 hours after being bitten, the only sign of bleeding was from the gums but this soon stopped. There were no other signs or symptoms, in particular no bleeding from the right foot or ankle and no tissue reaction around the clearly visible fang marks.

Haematological studies performed soon after admission to hospital and after the administration of 250 ml of freeze dried plasma confirmed a normal full blood count and classic DIC (Table I). Thrombo-elastography of native whole blood demonstrated severe hypocoagulability ('r' time 175 min; 'ma' 8 mm). At this time there was no evidence of overt haemorrhage and since the child appeared well, it was decided not to administer the antivenin. However, 12 hours later (approximately 48 hours after the bite) frank haematuria was observed. After an initial test dose, the contents of one ampoule of specific boomslang antivenin were administered slowly intravenously and there was no further haematuria or other evidence of haemorrhage. A TEG obtained 1 hour later showed a reduction of the 'r' time to 50 minutes and a 'ma' of 8 mm. The contents of the second ampoule of specific antivenin were administered 3 hours after the first ampoule without untoward effect.

Sixteen hours after the second ampoule, whole-blood coagulation, as measured by thrombo-elastography, had turned significantly towards normal although there was still evidence of procoagulant activity ('r' 11; 'k' 9; 'ma' 20; transfer test 0,5). Subsequent convalescence was uneventful.

Case 2

A 3-year-old black girl from the district of Ubombo in the north-eastern coastal region of Natal, about 300 km from Durban, was bitten on the left foot by a snake, which was subsequently killed and positively identified as a boomslang. Shortly afterwards vomiting was induced by the oral administration of a Zulu medicine; the vomitus was streaked with blood, but there was no bleeding from the site of the bite (Fig. 2). Twenty-four hours later the infant was taken to the nearest hospital with epistaxis, abdominal pain, fresh blood in the stool, a haematoma in the left groin and oozing of blood from the fang marks on the left foot. She was immediately transferred by air to the surgical ICU at King Edward VIII Hospital.

Fig. 2. Fang marks on foot of patient 2.

The results of blood tests performed some 36 hours after the bite confirmed DIC and a haemoglobin value of 7,3 g/dl (Table II). There was no obvious bleeding and vital signs were normal. Difficulty in obtaining a full cross-match due to the presence of a nonspecific auto-antibody with a positive Coombs test delayed blood transfusion.

TABLE I. LABORATORY AND TEG RESULTS, CASE 1

	Normal/control values	36 h after bite	1 h after antivenin	16 h after antivenin
Full blood count				
Haemoglobin (g/dl)	**12-14**	**11,3**		**8,5**
White cell count ($\times 10^9$/l)	**7,8**	**4,7**		**8,9**
Platelets ($\times 10^9$/l)	**130-400**	**228**		**180**
DIC screen				
Prothrombin time(s)	**13-17**	**> 60**		
Partial thromboplastin time(s)	**27-36**	**> 120**		
Thrombin time(s)	**20**	**> 60**		
Fibrinogen assay (mg/dl)	**250-500**	**< 20**		
Fibrin degradation products (μg/ml)	**< 12**	**> 48**		
Protamine sulphate	**Negative**	**4 +**		
TEG				
'r' time (min)	**8-12**	**175**	**50**	**11**
'k' time (min)	**4-8**	**—**	**—**	**9**
'ma' (mm)	**50**	**8**	**8**	**20**
Transfer test	**1,0**	**ND**	**ND**	**0,5**

ND = not done.

TABLE II. LABORATORY AND TEG RESULTS, CASE 2

	36 h after bite	3 h after antivenin	18 h after antivenin
Full blood count			
Haemoglobin (g/dl)	**7,3**	**3,7**	**8,2**
White cell count ($\times 10^9$/l)	**11,8**	**10,7**	**10,9**
Platelets ($\times 10^9$/l)	**515**	**231**	**210**
DIC screen			
Prothrombin time(s)	**> 60**	**> 60**	**15,4**
Partial thromboplastin time(s)	**> 120**	**> 120**	**27,7**
Thrombin time(s)	**> 180**	**> 180**	**22,0**
Fibrinogen assay (mg/dl)	**< 20**	**< 20**	**180**
Fibrin degradation products (μg/ml)	**> 40**	**> 40**	**> 10 < 40**
Protamine sulphate	**3+**	**3+**	**Negative**
TEG			
'r' time (min)	**> 180**	**> 120**	**8**
'k' time (min)	**—**	**—**	**6**
'ma' (mm)	**0,5**	**—**	**30**
Transfer test	**0,7**	**ND**	**1,1**

ND = not done.

Since antivenin had not yet arrived from Johannesburg, treatment overnight consisted of the administration of freeze dried plasma 250 ml and close observation for evidence of bleeding.

The following morning the haemoglobin value had fallen to 3,7 g/dl due to hidden gastro-intestinal bleeding. Approximately 48 hours after the bite a test dose of antivenin was administered subcutaneously and 15 minutes later the remainder of the contents of the vial of antivenin was injected slowly intravenously. A few minutes later an urticarial rash appeared over the infant's body, followed shortly thereafter by bradycardia and severe hypotension, i.e. anaphylactic shock. There was a rapid response to the administration of adrenalin 1 : 1 000 0,5 ml and atropine 0,2 ml intravenously. Three hours later the results of a coagulation screen test and a whole-blood TEG remained unchanged but there had been no further evidence of intestinal haemorrhage. Overnight 350 ml of packed red blood cells and 500 ml of freeze-dried plasma were infused. Eighteen hours after antivenin administration a coagulation screen and whole-blood TEG were normal apart from a slightly decreased serum fibrinogen level (180 mg/dl; 'ma' 30). There was no further evidence of intestinal bleeding and recovery was uneventful.

Discussion

The boomslang (*Dispholidus typus*) is a Columbridae belonging to the sub-family Boiginae and, although it is a tree snake, it does descend to the ground to hunt or bask. Timid by nature, it behaves aggressively only if suddenly surprised or confronted by danger. Adult snakes average 1 - 1,5 m in length with a maximum of 2 m and demonstrate a wide variety of colours according to age, sex and location. The distinguishing feature is the large pair of eyes set in a short stubby head. The fangs are set far back in the mouth. However, the hinged jaw opens to 170° thus permitting the boomslang to grip even flat surfaces, such as the region of the scapula.[4]

Evenomation is associated with virtually no local reaction or pain, and constitutional symptoms such as nausea, vomiting, drowsiness and headache may not occur. The venom is a potent procoagulant, which causes a DIC with hypofibrinogenaemia and haemorrhage. Since this process takes time to develop, the fang marks do not bleed unduly at the time of evenomation and, indeed, may have 'healed' by the time a bleeding diathesis develops. The patient's blood may become incoagulable by as little as 1 hour after evenomation but spontaneous haemorrhage is usually delayed for 12 - 48 hours.[5] The diagnosis of a bite by a snake producing haemotoxic venom is easily made when the victim either presents late with a bleeding diathesis, as was the case with patient 2, or is able to identify the snake, e.g. a snake handler.

Problems arise in making an early diagnosis after a bite by an unidentified snake. The history may provide some clues. Both children reported here were attacked while walking through the scrub, presumably while the snakes were basking in the morning sun. The older child was able to give a vivid description of the tenacity with which the snake gripped his foot, a classic description of a bite by a back-fanged snake. It is not known how he managed to identify the snake from a 'rogues gallery' of photographs but perhaps the large eyes impressed him. Another aid to diagnosis was inadvertently provided by the *inyanga's* scarifications, which produced abnormal bleeding soon after evenomation; the second child was given an emetic under similar circumstances and this provoked blood-stained vomiting. It seems, therefore, that abnormal bleeding resulting from an injury sustained shortly after evenomation, when the victim's blood is hypocoagulable is a useful clinical sign. In the absence of abnormal bleeding, local and constitutional symptoms are so insignificant that victims usually present for medical assistance only when spontaneous haemorrhage has occurred, as was the case with the second child. However, should the victim present before the onset of haemorrhage, poisoning may be confirmed by measurement of the patient's crude clotting time. Initially, this should be abnormally short due to accelerated activation of the coagulation pathway, becoming prolonged later as the coagulation factors (V, VIII and X), fibrinogen and, to a lesser extent, platelets are consumed.

The venom of *D. typus* has been analysed by Atkinson *et al.*[6] and is thought to be a serine protease capable of activating prothrombin and factor X. Since factor X is in the intrinsic and extrinsic pathways, both the activated partial thromboplastin time (PTT) and the prothrombin time (PT) become prolonged as factor X is consumed. Consumption of factors V (prolonged PT) and VIII (prolonged PTT) and especially of fibrinogen (prolonged PT, PTT and thrombin time) compound the hypocoagulable state. Severe hypofibrinogenaemia, or even

afibrinogenaemia, is probably the most significant defect contributing to the bleeding diathesis. Levels were extremely low in both cases reported here. Platelet counts, on the other hand, were within normal limits throughout.

Whereas routine laboratory tests are able to quantitate clotting factor abnormalities, thrombo-elastography identifies qualitative defects in the dynamic process of whole blood coagulation and therefore permits assessment of the clinical significance of a particular abnormality. (For example a platelet count of 40 000 x 10^9/l may be associated with a normal TEG ('ma' 50) indicating adequate platelet function.) In the cases reported here thrombo-elastography confirmed the existence of severe hypocoagulability.

The markedly prolonged 'r' and 'k' times were indicative of either intrinsic factor deficiency or the anticoagulant effect of fibrin degradation products or a combination of both.

Although the initial fibrinogen assay was reported to be less than 20 mg/dl in both patients, an 'ma' of 8 mm in case 1 indicated severe hypofibrinogenaemia and of 0,5 mm in case 2, afibrinogenaemia. Unfortunately, only in case 2 was a transfer test performed before the administration of antivenin and the value of 0,7 confirmed procoagulant (venom) activity. These thrombo-elastographic changes are compatible with the third stage of a DIC and indicate the correct approach to management.[3]

In the absence of haemorrhage there is probably little point in administering coagulation factors and fibrinogen since they will be consumed as the result of venom activity. Certainly, the administration of freeze-dried plasma to both the patients reported here failed to prevent spontaneous haemorrhage although it could be argued that not enough was given. However, the definitive treatment is afforded by specific boomslang antivenin, which neutralises the procoagulant effect of the venom. The administration of only one ampoule of antivenin to patient 1 resulted in the immediate cessation of haematuria with reduction of the TEG 'r' time to 50 minutes. Interestingly, despite the administration of the contents of a second ampoule there was still evidence of venom activity (transfer test 0,5) 16 hours later although the TEG had turned significantly towards normal. No blood products had been administered. In patient 2 the administration of specific antivenin was followed by the transfusion of packed red blood cells and freeze-dried plasma. Eighteen hours later there was no evidence of venom activity (transfer test 1,1) and a 'ma' of 30 mm reflected a serum fibrinogen level of 180 mg/dl.

Ideally, specific boomslang antivenin should be administered before the onset of spontaneous haemorrhage. In practice, it is unlikely to be immediately available. Should serious haemorrhage occur before the arrival of specific antivenin, the administration of heparin should be considered, although this is controversial.[5,6]

Heparin is generally effective in the treatment of DIC if the triggering mechanism activates factor X and prothrombin via the extrinsic pathway, as is the case with boomslang venom. Further evidence to support the use of heparin is provided by thrombo-elastography, i.e. a TEG compatible with one of the stages of DIC and a transfer test < 1. Thrombo-elastography is especially useful in determining the dose of heparin, the rate of infusion being titrated against repeated transfer tests. A transfer test of 1,0 - 1,2 indicates adequate heparinisation, which is usually achieved by 400 - 1 000 IU/h.[3]

Although specific boomslang antivenin proved to be very effective in reversing DIC and stopping haemorrhage, its use in patient 2 demonstrated its propensity to cause shock. This is not an uncommon complication of all antivenin preparations available in South Africa (personal experience) and may be a true anaphylactic phenomenon or more usually a reaction to preservative agents.

Sensitivity testing and the administration of test doses of antivenin are unreliable methods of predicting potentially fatal reactions. These may, however, be prevented by the prophylactic systemic administration of hydrocortisone and an antihistamine. This has now become routine in our unit.

The rapid cessation of bleeding seen in both cases after the administration of specific boomslang antivenin is characteristic, as is the persistence for several hours of a severe hypocoagulable state.[4,5] It may be possible to encourage a more rapid return to normality by administering more antivenin but this preparation is in short supply and is very expensive. Attempts to correct coagulation factor deficiencies by the infusion of freeze-dried or fresh-frozen plasma may precipitate fluid overload. Platelet counts and function remain within normal limits until the onset of bleeding and need replacement only with persisting haemorrhage. It may therefore be reasonable to adopt a wait-and-see policy when treating the victim of a boomslang bite and to reserve blood product transfusions for those patients who bleed either before or (rarely) after the administration of specific antivenin.

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