

A man in his sixties with severe hypotension and oedema

A man was admitted with syncope and hypotension after feeling lethargic for several days. He had an unusually pronounced need for fluid, increasing oedema and his condition became life-threatening. The diagnosis made during his stay represents a very rare condition.

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A man in his sixties was admitted to hospital late one evening after fainting in the bathroom. He had felt increasingly lethargic in the days immediately prior to hospitalisation, but had not otherwise noticed anything out of the ordinary. He had been treated for hypertension for the past 10–12 years, initially with amlodipine (Norvasc), subsequently with carvediol, irbesartan/hydrochlorothiazide (CoAprovel) and moxonidine (Physiotens). In addition he used Albyl-E 75 mg × 1. He was otherwise in good physical shape apart from sequelae in the form of bilateral drop foot following previous severe ischaemia in the lower extremities.

In Acute Admissions he had transient bradycardia and his blood pressure dropped. The lowest blood pressure reading was 64/27. At the same time he was lethargic, clammy and pale. After infusion of intravenous fluid (NaCl 0.9%), he picked up and was in such good shape that he was placed in an ordinary ward. His pulse was 70, blood pressure 109/64 and his temperature 37.9°C. He remained conscious and lucid, and the findings from his admission examination were otherwise normal.

Various causes of syncope were considered. In view of the normal ECG findings, no chest pain or laboured breathing and a dry and warm skin between falls in blood pressure, there was little likelihood of an acute cardiac or vascular cause for the syncope. He was nonetheless monitored with telemetry for arrhythmia. The cause might be a vasovagally triggered syncope in connection with a visit to the toilet or a somewhat high dose of blood-pressure medication. Because of the slight rise in temperature, we also considered the possibility of an incipient infection, but we deferred treatment start until he had been observed for somewhat longer.

Some hours after admission, the patient suffered a new fall in blood pressure when he changed position. He was again cold-sweating and unwell and was moved to the Intensive Care Department. Systolic blood pressure was around 70 mm Hg and urine

production was minimal. We therefore continued to administer fluid and started pressor therapy in the form of noradrenaline.

The low blood pressure persisted through day 2, and the situation remained unclarified. We therefore chose to start broad-spectrum antibiotics (meropenem and erythromycin supplement initially), even though CRP about 14 hours after his admission was only 6 and there was no rise in temperature.

An echocardiogram the same day showed a slightly hypertrophic left ventricle with good contractility and findings indicating significant hypovolaemia. In the course of day 2, a total of 23 litres was administered intravenously, of which 14 000 ml Ringer acetate, 7 000 ml 0.9% NaCl and 2 000 ml Glukacel 10%. Systolic blood pressure continued to fluctuate between 70 mm and 100 mm Hg (mean arterial pressure (MAP) was 50–80 mm Hg), despite the volume of fluid and two pressors (maximum dose of noradrenaline 0.5 µg/kg/min and dopamine 8 µg/kg/min, which after a while was replaced with dobutamine 10 µg/kg/min). His haemoglobin value on admission was 20.3 g/dl (13.4–17.0 g/dl). Although a large volume of intravenous fluid had been administered, his haemoglobin value had risen to 23.1 g/dl on day 2, with erythrocyte volume fraction/haematocrit measured at 0.67 l/l (0.39–0.50). In addition his blood tests showed falling albumin values, and there was increasing hyperchloremic metabolic acidosis. Table 1 shows the laboratory values. He had increasing general oedema, and despite abundant fluid he had minimal urine production (750 ml/day which fell to 112 ml/day on the third day).

On day 2 venesection was performed and 300 ml blood drawn off in an attempt to counteract the haemoconcentration. In addition, because of the high risk of thrombosis, enoxaparin (Klexane) 40 mg was administered initially as thrombosis prophylaxis. After a while his haemoglobin values fell, there was a low platelet count and disruptions in the coagulatory system in the form of falling

Table 1 Overview of selected blood samples taken during stay in hospital. Where there is more than one result, more than one sample has been taken during the day

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Haemoglobin, g/100 ml (ref. 13.4–17.0)	20.3	20.9–23, 1–19.0	12.6–9.3	11.3–8.2	9.6	9.4
Platelets, 10 ⁹ /l (ref. 145–390)	229	281	110–43	56–37	39–30	44
Albumin, g/l (ref. 36–45)	26	17	< 10–14	15	16	18
C-reactive protein, mg/l (ref. 0–6)	5	6	24	67	71	58
Creatine kinase, U/l (ref. 0–280)	51	45	–	33 309	30 743	–
Prothrombin time – INR (ref. 0.8–1.2)	1.4	1.5	3.9–1.5	1.2	1.2	1.0
D-dimer, mg/l (ref. 0.0–0.4)	–	–	0.2	–	–	–
Creatinine, µmol/l (ref. 60–100)	133	171	146	121	120	117
Lactate, mmol/l (ref. 0.7–2.1)	–	1.3–5.1	4.8–3.2	2.9–2.1	–	1.2

fibrinogen and rising activated partial thromboplastin time (APTT) and INR. D-dimer was normal throughout, in contrast to what one might expect with disseminated intravascular coagulation (DIC). The patient's condition was unstable with oligoanuria, oedema, hypotension, high chloride values and metabolic acidosis with pH value 7.17 (reference range 7.37–7.44), base excess –12.3 mmol/l (reference –2.4–2.3 mmol/l) and lactate 2.6 mmol/l (reference 0.7–2.1 mmol/l). In the afternoon of day 2 we therefore commenced continuous venovenous haemodiafiltration (CVVHDF). Citrate was used as anticoagulant.

Despite the start of continuous venovenous haemodiafiltration, arterial blood gases again showed exacerbated acidosis. He had increasing respiratory distress, probably as a result of increasing fluid leakage into the alveoli as well, and he was persistently haemodynamically unstable. He was therefore intubated and placed on a respirator in the night about 30 hours after his admission. Arterial blood gas prior to intubation showed pH 7.06, BE –18.3 mmol/l and lactate 5.1 mmol/l. He was also very cold peripherally, had mottled blue skin, increasing pain in arms and legs and needed opiates. The orthopaedists monitored him closely with high muscular pressure in mind and a possible need for fasciotomy.

Normal pressure in the interstitial spaces of the muscles is around 2–8 mm Hg. Pressure of around 30 mm Hg is often used as a threshold indication for fasciotomy, but in certain situations lower pressure may also indicate high risk of ischaemia and neuromuscular damage, and therefore make fasciotomy necessary. Prior to fasciotomy, other parameters are also assessed in addition to pres-

sure, such as increasing pain, perfusion and the patient's general condition. It was therefore decided to perform fasciotomies after intubation. Pressure was then 60 mm Hg in the dorsal compartment of his left forearm, 40 mm Hg in the right forearm dorsally and about 30 mm Hg in calves and thighs.

A few hours after intubation, in the early morning of day 3 fasciotomy was performed on all extremities (calves, thighs, forearms). During these hours, the patient's circulation was highly unstable, and following the operation there was relatively copious bleeding from both forearms. After a few hours it was decided to re-operate upon him in Intensive Care. There were many small, diffuse areas of bleeding that were stopped by means of diathermia. Disturbances were now seen in the coagulation samples, with a substantial rise in INR, low fibrinogen and high APTT, and the patient's tendency to bleed increased. In the course of the next two days he therefore received 16 units of plasma, 11 units of erythrocyte concentrate (SAG) and two units of platelets.

A similar clinical picture was seen in connection with a hospitalisation some years earlier. In that instance the haemoconcentration led to the patient developing severe ischaemia of the calf and thigh musculature. Pressure in the anterior tibial compartment was high, and he needed fasciotomy. Angiography revealed thrombosis in the femoral artery and occluded anterior tibial and fibular arteries on the left side. Hyperbaric oxygen therapy was applied and a thromboendarterectomy performed at a university hospital. He avoided amputation, but developed sequelae in the form of dropfoot bilaterally and needed braces. After the acute episode, he also had persistent colic-like abdominal pain, and was

found to have bowel damage as a result of earlier ischaemia. Six months after his stay in hospital a bowel resection and surgery to lyse adhesions were therefore performed.

We considered various kinds of angio-oedema as possible causes of the severe capillary leakage. The patient had no family history of oedema or personal history of oedema of the throat/face in particular, such as one sees with hereditary angiooedema. There was therefore little clinical suspicion of this condition. During the acute course we chose to administer icatibant (Firazyr) to dampen any bradykinin-driven capillary leakage. It was administered subcutaneously in the form of 30 mg injections from prefilled syringes as three doses at six hour intervals in the course of day 3.

After the acute course, we received test results that showed that CI inhibitor quantitation was low, while the CI inhibitor function test was normal. The low values normalised after the patient's recovery. This is consistent with a general loss of protein during the capillary leakage, and not with hereditary angiooedema.

After being connected up for continuous venovenous haemodiafiltration he was also haemodynamically monitored by means of Pulse Contour Cardiac Output Monitoring (PiCCO). When the monitoring started on the night of day 2, he had a very low cardiac index (CI) of 1.6–1.7 l/min/m² (reference 3.0–5.0 l/min/m²). On day 3 he had stroke volume variations of 11–29% (the limit for normal stroke volume variation is less than 10%, and with hypovolaemia values often over 20%). Following the fasciotomies, his cardiac index remained low during day 3, but peripheral resistance normalised. Prior to the operation this had been extremely high, and was interpreted as a consequence

of compartment syndrome. As his stroke volume variation approached normal levels of under and around 10%, his cardiac index rose towards normal levels of $>3.0\text{ l/min/m}^2$. This took place in the evening and night of day 3.

Hypotension and oedema occur in connection with a number of clinical conditions. Differential diagnoses may therefore be severe sepsis, septic shock, toxic shock syndrome, anaphylaxis or adverse reactions to drugs, as well as hereditary angiooedema. Other diagnoses that can be considered in light of this clinical picture are polycythaemia vera, adrenal cortex failure, Gleich's syndrome (episodic angiooedema with eosinophilia), mast cell disease, carcinoid syndrome, primary amyloidosis and severe heart failure.

The substantial capillary leakage was discussed at the morning meeting of the Medical Department the day after the patient was admitted. We conducted a literature search on capillary leakage, and the diagnosis idiopathic systemic capillary leak syndrome (ISCLS) emerged. The diagnosis proved to fit the findings and the patient's complex and serious history of illness.

During the acute course of his illness, we conferred with university hospitals several times. As a result of recommendations, he was given corticosteroids intravenously (Solu-Cortef) $100\text{ mg} \times 4$, and from day 2 also gamma globulins intravenously (Kiovig) 0.4 g/kg body weight for five days. Transfer was also discussed, but since the most important actions in the critical situation had been taken care of, this was not done.

During the course of his stay, a number of tests were carried out to find a possible underlying cause of the condition. Extended blood tests were taken, and various tests for viruses and bacteria (cytomegalovirus, Epstein-Barr virus, *Mycoplasma*, *Chlamydia*, *Haemophilus influenzae*, influenza A and B), immunological tests (antinuclear antibodies and antineutrophil cytoplasmic antibodies), and various other tests (S-cortisol, free thyroxine/thyroid-stimulating hormone, procalcitonin, sedimentation rate, cold agglutinins, S-protein electrophoresis, C1-inhibitor, complement factors C3 og C4, haptoglobin etc.). None of the results had a definite bearing on the condition.

In the course of day 4 the patient seemed to be less pressor-dependent and need less fluid, and his blood pressure improved. On admission the patient's weight had been around 100 kg, while on day 5 it was measured at 130 kg. He had a considerable extravascular fluid surplus, and in the course of the next few days underwent bilateral pleural fluid drainage. His diuresis gradually increased, and conti-

nuous venovenous haemodiafiltration was terminated on day 9. He was extubated on day 10, and discharged after about a month in hospital.

Since this last stay in hospital, the patient has had persistent back pain, and he has been found to have considerable degenerative spinal changes and muscular damage/muscular fibrosis. This may well have been triggered in part by hypoperfusion and ischaemic damage during the attack. The patient is being monitored with regular follow-up at the Medical Clinic. He has thus suffered attacks of idiopathic systemic capillary leak syndrome at intervals of 4–6 years, and it is now some years since his last attack. The patient is receiving prophylactic treatment consisting of terbutaline (Bricanyl) and theophylline tablets, in addition to hypertension therapy.

Discussion

Idiopathic systemic capillary leak symptom is a rare condition characterised by pronounced hypotension, hypoalbuminaemia and haemoconcentration. It was first described by Clarkson in 1960 and is therefore also known as Clarkson's syndrome (1). Only about 150 cases have been reported worldwide. Middle-aged adults are typically affected, although cases of children down to the age of 5 months have been reported (2).

In order to make a diagnosis, one or more attacks that meet the following criteria are needed (3):

- oedema with acute weight increase of more than 1 kg (< week)
- acute hypotension with systolic blood pressure $<100\text{ mm Hg}$ or average pressure $<70\text{ mm Hg}$
- haemoconcentration (an increase in haematocrit or haemoglobin to values above those normal for age and sex, and by more than 20% of the last reference value for the patient), with hypoproteinaemia or hypoalbuminaemia
- that other causes of capillary leakage or hypoproteinaemia are excluded

The fact that it was an acute attack of idiopathic systemic capillary leak syndrome could also explain the man's serious condition some years earlier. A stay in hospital about ten years earlier might also fit in. At that time he was admitted with transient elevated haemoglobin of 19.8 g/dl and a rise in creatinine. Venesection was then performed, with drainage of 600 ml blood. His blood values normalised rapidly and the workup yielded no definite findings.

What underlies and causes the attacks of hyperpermeability associated with idiopathic systemic capillary leak syndrome is still not known. Various hypotheses have been

proposed, such as transient endothelial cell apoptosis (4) or endothelial contraction (5).

In the most recent debate on pathogenesis, models have been discussed in which non-immunoglobulin humoral factors may contribute to transient endothelial contraction (for example vascular endothelial growth factor and angiotensin-2) (5). Some 80% of patients with idiopathic systemic capillary leak syndrome have monoclonal gammopathy of uncertain significance (3, 4) such as our patient has. But it is still unclear whether this pathological immunoglobulin has clinical significance or is merely an incidental finding (2).

It has been shown that vascular endothelial barrier function is maintained by intercellular contacts, largely through vascular endothelial cadherin (VE-cadherin). Apart from intravenous immunoglobulin (7), treatment with theophylline (phosphodiesterase inhibitor) and terbutaline (β -adrenoceptor agonist) (6) is the only therapy shown to be capable of reducing the number and severity of attacks. Theophylline and terbutaline promote endothelial barrier function by stabilising the VE-cadherin-mediated adhesive junctions, and they are assumed also to increase the content of intracellular cyclical adenosine monophosphate (cAMP), which counteracts capillary leakage. In the past it has been believed that the use of β_2 -agonists leads to a reduction in capillary permeability induced by histamine and bradykinin, but these inflammation mediators may be of minor significance in idiopathic systemic capillary leak syndrome (5).

At present there is no established treatment for the attacks. Successful acute treatment with high doses of intravenous immunoglobulin has been described for a few patients (7). Attacks may occur once in a lifetime, while others may suffer attacks many times a year. Clinical symptoms can be divided into three phases. In the first, prodromal phase, about 30% have an upper respiratory tract infection. Some 50% have more diffuse symptoms in the last two days before the acute attack, such as lethargy, irritability, abdominal pain, nausea, myalgia, diarrhoea, thirst, fever and rapid weight gain.

The acute phase, with substantial capillary leakage, lasts 1–3 days (2). The patient then develops a combination of hypotension, haemoconcentration, sometimes leukocytosis and thrombocytosis and hypoalbuminaemia (albumin usually $<20\text{ g/dl}$) (4). Proteins with molecular weight ≤ 200 kilodaltons, such as albumin, leak from the intravascular to the interstitial space. There is therefore often generalised oedema, with possible ascites, pleural fluid, pericardial effusion, cerebral oedema and encephalopathy. Compartment syndrome may occur,

which in turn may lead to rhabdomyolysis and kidney failure. The extent of albumin loss correlates with the risk of developing rhabdomyolysis (4). The low perfusion will usually result in acute tubular necrosis, and often ischaemic brain damage and/or ischaemic hepatitis.

After a few days, capillary leakage stops, and the third, recovery, phase starts. The transition may be rapid and be characterised by a reduction in the quantity of intravenous fluid needed to maintain the intravascular volume. During this phase, the patient is at high risk of fluid overload and pulmonary oedema (2).

The mortality associated with acute attacks of idiopathic systemic capillary leak syndrome is unknown. In two articles with 25 (4) and 28 (3) patients, five-year survival of 76% and 73%, respectively, was found. In the latter patient series, five-year survival was 85% for 23 patients who had received prophylactic treatment and 20% for five patients who had not (3). Different medicines were used in the prophylactic treatment, including terbutaline, theophylline and immunoglobulins. The cause of death is often pulmonary oedema in the reconvalescence phase, or ischaemic organ failure as a result of hypoperfusion in the acute phase.

There is also discussion as to whether there are secondary forms of idiopathic systemic capillary leak syndrome. This is because similar conditions have been reported for which the probable triggering factor is known, for example drugs such as granulocyte-colony stimulating factor (8), interferon (9), gemcitabine (10) and sirolimus (11).

We treated a critically ill patient with a very rare condition. The workup was diffi-

cult, and the diagnosis had to be based largely on exclusions. Nor is there any established treatment. Inflammation-driven capillary leakage with bradykinin as a contributory factor appears less likely in light of one of the most recent articles on the topic (5). It is therefore uncertain whether high doses of steroids and bradykinin antagonists (Firazyr) made a positive contribution. What the correct supportive treatment might be is also open to discussion. Could more use of Ringer acetate as intravenous fluid rather than NaCl 0.9% have contributed to less pronounced hyperchloremic acidosis? Might limited transfusion of fluid and more use of colloids result in less fluid retention in peripheral tissue and accordingly less risk that fasciotomies would have to be performed? Whatever the case, the acute treatment of this type of patient is complicated and requires good, broad-based cooperation across different specialities.

The patient has consented to the publication of the article.

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The author has completed the ICMJE form and reports no conflicts of interest.

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