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CLINICAL LISTERIOSIS IN RENAL ALLOTRANSPLANTATION

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Abstract. Two cases of Listeria monocytogenes meningitis among 212 kidney transplanted patients (total of 339 patient years of observation) under immunosuppression with azathioprine and prednisone are presented. Both cases developed shortly after an increase of the immunosuppression. The first case appeared in a 27-year-old man 5 days after a minor increase of the azathioprine dose from 75 to 100 mg/day. The course was relatively mild, and the patient was cured by tetracycline. The second case appeared in a 52-year-old woman 5 days after a massive increment of the steroid dose and administration of a moderate azathioprine dose, carried out to revert a rejection of the graft. This case had a fulminant course and was complicated by Listeria sepsis with hemolysis, pronounced oliguria and *thrombocytopenia* leading to fatal internal bleedings, primarily in the brain. Considering the poor prognosis of this complication it is suggested that cytotoxic drugs are temporarily discontinued and the steroid dose reduced at the height of the infection.

The rather common infection with Listeria monocytogenes is generally asymptomatic in healthy, untreated individuals (1).

Clinical listeriosis is usually found in individuals with lowered resistance relating to malignancy (leucaemia, lymphoma, Hodgkin's disease), diabetes mellitus, cirrhosis of the liver and/or medication with cytotoxic drugs or steroid hormones (1, 2, 4, 5, 11, 12, 13). A few cases have, moreover, been reported in immunosuppressed patients after renal allotransplantation (6, 7, 11).

This paper describes 2 cases of Listeria meningitis among 212 immunosuppressed kidney transplanted persons, who have lived on an average 1.6 years after grafting.

CASE REPORTS

Case 1

A 27-year-old man with chronic glomerulonephritis received a kidney transplant from his father (HL-A mismatch in one locus). Immunosuppression with prednisone and azathioprine was started and after 2 ½ months the patient was discharged with a 24 hour creatinine clearance of 60–70 ml/min, no proteinuria and normal BP. At this time he received prednisone, 30 mg/day, and azathioprine, 75 mg/day.

Five months after the transplantation the patient was readmitted on Jan. 13, 1969 after 2 days of intense, diffuse headache, pains in the back and the neck, slight dysuria, but no diarrhea. On Jan. 9 the azathioprine dose had been increased from 75 to 100 mg/day. On admission the patient was relatively unaffected. Physical examination revealed only a temperature of 38.7°C, and slight tenderness, but no stiffness of the neck. Hb 15.1 g/100 ml; WBC 15 000/mm³ with 89% polymorphonuclear leucocytes, 7% lymphocytes, 2% monocytes and 2% neutrophil myelocytes; thrombocytes 97 000/mm³. Blood cultures were negative. Urinalysis revealed 5–8 leucocytes, 5–7 erythrocytes and bacteria. As urine cultures, performed on Jan. 9 in the Outpatient Service, had grown more than 10^5 Klebsiella pneumonia per ml, treatment with tetracycline was started. However, during the day the temperature rose to 40.1°C.

On Jan. 14 stiffness of the neck and nystagmus to the left was noted. Lumbar puncture was unsuccessful due to artificial bleeding. On Jan. 15 a new lumbar puncture revealed clear cerebrospinal fluid under normal pressure. Analysis gave a WBC of 118/mm³ with 70% mononuclear and 30% polynuclear cells. Protein was 90 mg/100 ml and glucose 54 mg/100 ml (blood glucose 132 mg/100 ml). Microscopy and culture of the spinal fluid revealed no microorganisms. EEG was normal. Urine culture from the day of admission had now revealed significant growth of Klebsiella pneumonia resistant to tetracycline, which therefore was discontinued after administration of a total dose of 1.75 g within 36 hours. Treatment with colistin 4 mill. U/day and cephalothin 4 g/day was started.

On January 16 the temperature decreased, but a paresis of the left abducens nerve had developed. On the next day the temperature rose again, but blood cultures remained negative. EEG was normal.

On January 18 a new lumbar puncture revealed slightly cloudy spinal fluid under a pressure of 450 mm H_2O. The WBC was 2 400/mm³ with 70% mononuclear and 30% polynuclear cells. Protein was 99 mg/100 ml and glucose 42 mg/100 ml (blood glucose 118 mg/100 ml). Microscopy and cultures of the spinal fluid revealed no microorganisms.

On Jan. 20 the EEG was markedly abnormal with

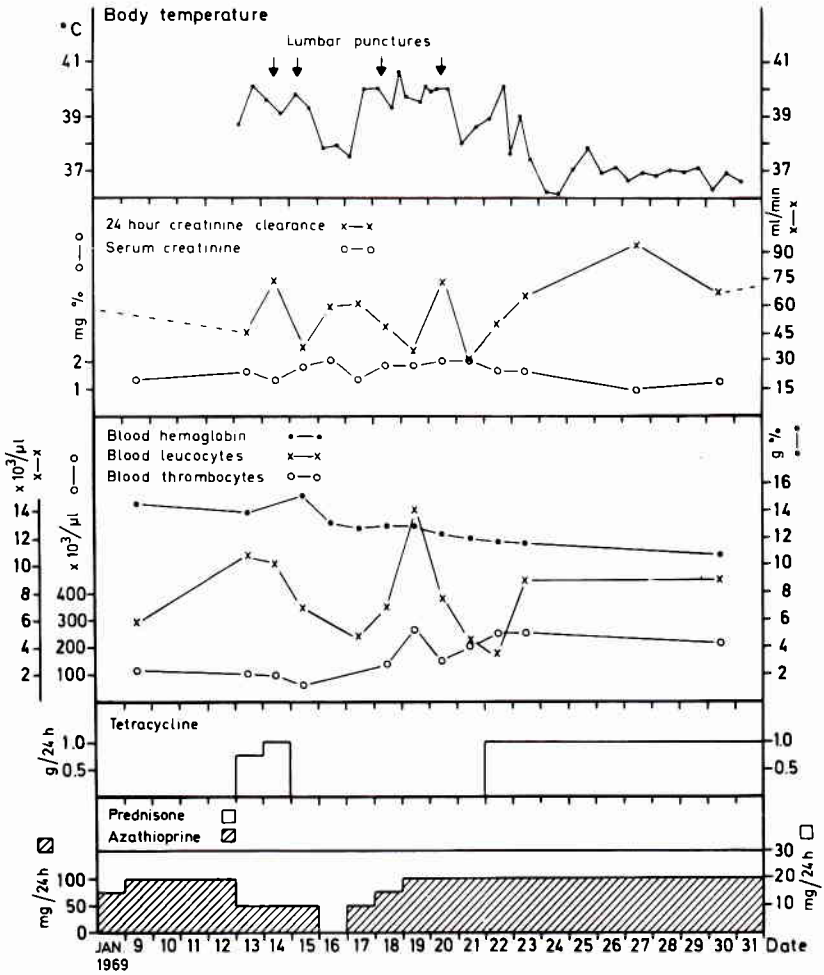

Fig. 1. Temperature, kidney function, Hb, leucocytes, thrombocytes, antibiotic treatment and immunosuppression in case 1.

depression of α-activity on the right side and a focus of 2–3 Hz activity of low amplitude in the right temporal region. A new lumbar puncture revealed slightly xantochromatic spinal fluid under a pressure of 200 mm H_2O. WBC was 577/mm³ with 50% mononuclear and 50% polynuclear cells. Protein was 124 mg/100 ml and glucose 49 mg/100 ml (blood glucose 130 mg/100 ml). Microscopy revealed no microorganisms.

On Jan. 22 the cultures of the last spinal fluid had grown Listeria monocytogenes, and treatment with tetracycline, 1 g daily, was resumed. The urine had been sterile for 4 days and colistin and cephalothin were discontinued. Now the temperature fell, the condition improved, and the nystagmus and the abducens paresis disappeared. The EEG normalized, and after 4 weeks of treatment with tetracycline the patient was discharged in well-being without sequelae.

During the febrile period the kidney function was temporarily decreased and also fluctuated from day to day, probably due to variations in the hydration of the patient.

Today, 5 1/2 years after the transplantation, the patient is still alive. The kidney function is good, and there are no sequelae after the meningitis.

Case 2

A 52-year-old woman with chronic pyelonephritis received a necrokidney transplant (HL-A mismatch in one locus). Bilateral nephrectomy was performed at the same time, and immunosuppression with prednisone and azathioprine was started. After a minor myocardial infarction the patient was discharged from the hospital in well-being 6 weeks after the transplantation with a 24-hour creatinine clearance of 35 ml/min, a proteinuria less than 0.5 g/24 h, normal BP and sterile urine. At this time she received prednisone, 30 mg/day, and azathioprine, 100 mg/day.

Over the next 5 months the 24 hour creatinine clearance gradually decreased, the proteinuria and the BP increased and edema developed. Methyldopa, spironolactone and furosemide were given in gradually increasing doses with some effect. Seven months after the transplantation the decrease in the kidney function accelerated. As an increase of the prednisone dose to 60 mg/day had no effect, the patient was readmitted to the hospital.

On admission June 14, 1973 the patient had no complaints apart from fatigue; she had had no diarrhoea. Except for BP of 170/115 mmHg the physical examination was normal. 24-hour creatinine clearance was 19 ml/min and

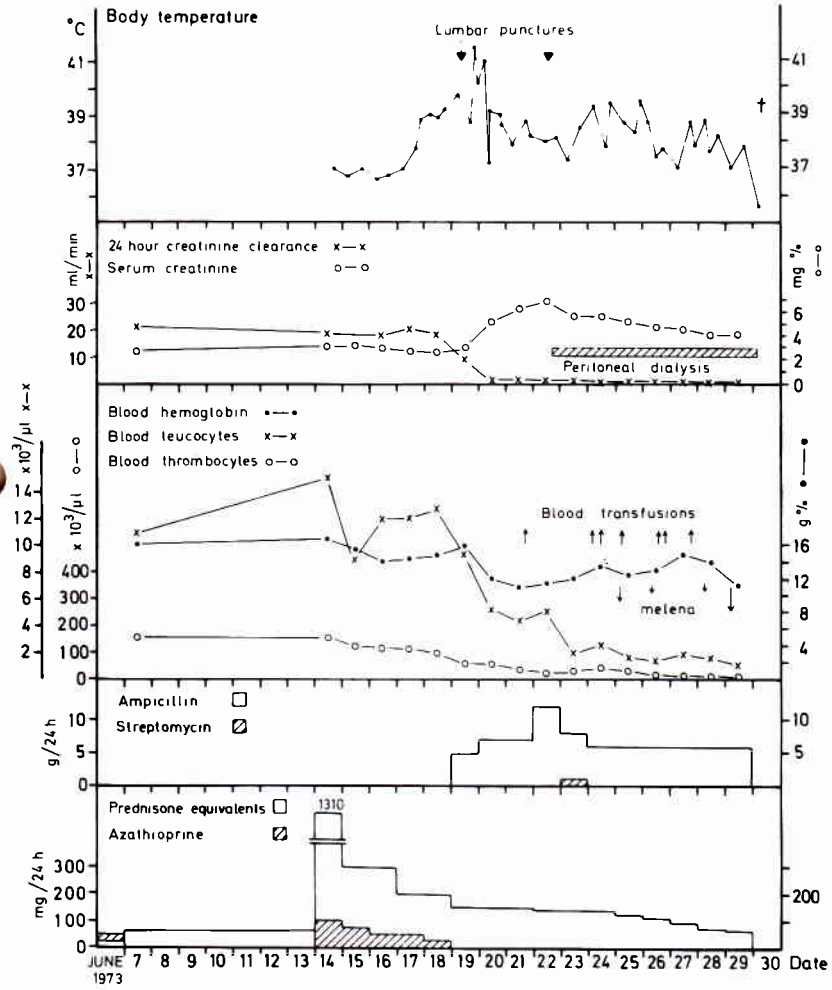

Fig. 2. Temperature, kidney function, Hb, leucocytes, thrombocytes, antibiotic treatment and immunosuppression in case 2.

serum creatinine 3.2 mg/100 ml. Urine cultures were negative. WBC was 15000/mm³, thrombocytes 154000/mm³ and Hb 17 g/100 ml. Rejection of the graft was suspected and 1 g methylprednisolone (Solumedrone®) was administered followed on the next day by 300 mg prednisone, which was thereafter gradually reduced. Azathioprine, which, due to thrombocytopenia, had been discontinued for a week, was now given in a dose of 100 mg/day, being gradually reduced over the next days. Hereby the kidney function improved a little.

On June 18 the temperature rose and at the same time the BP temporarily fell to 105/65 mmHg. Simultaneously the patient got headache and pain in the back. The neck and back were both supple. On June 19 the patient had a stiff neck and back.

Lumbar puncture revealed slightly cloudy spinal fluid under a pressure of 400 mm H_2O. It contained numerous polynuclear and some mononuclear leucocytes, elevated protein and lowered (<30 mg/100 ml) glucose (unfortunately only determined semiquantitatively). Numerous Listeria monocytogenes were demonstrated by microscopy and later in cultures of the spinal fluid. Cultures of the blood grew L. monocytogenes in 7 of 7 glasses.

Treatment with ampicillin, 6 g/day i.v., was started. However the patient became increasingly confused, stuporous and eventually unconscious, the temperature rose to 41°C, the BP fell temporarily to 105/70 mmHg and the urine production decreased permanently to about 5 ml/min. Hb fell from 16 to 12.1 g/100 ml and to 11.0 g/100 ml on the next 2 days, serum bilirubin rose to 1.3 mg/100 ml and plasma Hb was 6.8 mg/100 ml. The leucocytes and the thrombocytes decreased permanently to very low values in spite of the discontinuation of azathioprine. The bleeding and coagulation times, which were normal on admission, were now >15 min and 15 min, respectively. The prothrombin time was normal and did not increase. Several sugillations and petechiae appeared on the skin. Serum GPT, which on admission was 22 U/l, rose to 250 U/l, serum LDH was now also elevated (unfortunately no isoenzyme determination was done).

On June 22 a new lumbar puncture revealed xanthochromatic spinal fluid containing 336 WBC/mm³ with 80% mononuclear and 20% polynuclear cells. Protein

was 234 mg/100 ml and glucose was normal. Some L. monocytogenes were found by microscopy and later in cultures of the spinal fluid. Ampicillin was temporarily increased to 12 g/day and 1 g streptomycin was given.

Due to the reduced kidney function, peritoneal dialysis was started. However, the condition became worse, a grand mal seizure developed followed by cardiac arrest. Both were relieved by relevant treatment. The ventilation now had to be assisted by a respirator. Various cardiac arrhythmias were treated effectively with antiarrhythmic drugs.

During the following days repeated universal epileptic seizures developed, BP fell and increasing pneumonic infiltrations evolved (growth of Klebsiella oxytoca and yeast-like fungi). Relevant treatment was not effective. Urine cultures remained negative. On June 25 the patient had melena and in spite of blood transfusions and other supportive treatment she died on June 30.

At the bacteriologic autopsy numerous Klebsiella oxytoca were cultured from the heart, the lungs, the spleen, and the liver. No Listeria monocytogenes or fungi were cultured. The heart was enlarged. In the posterior wall of the left ventricle a big 10–12-day-old infarction was found. The myocardium was diffusely fibrous. The lungs, specially the lower lobes, contained numerous bronchopneumonic infiltrations. The stomach, the intestine and the colon contained much blood and the mucous membranes were imbibed with blood. In the stomach more acute ulcerations were found. The kidney graft was moderately oedematous and pale, and on the surface two 10–14-day-old infarctions were seen. All anastomoses were sufficient without any reaction. Microscopy revealed chronic vascular rejection. Acute tubular necrosis could not be ruled out because of pronounced autolysis.

The autopsy of the brain revealed a considerable amount of blood in the subarachnoidal space and numerous massive hematomas measuring up to 4 cm in diameter were found in the cerebrum and the cerebellum. No pus was seen on the arachnoid, and the meninges were not thickened.

Microscopically the leptomeninges presented slight patchy perivascular inflammatory reaction and a moderate bleeding beneath the arachnoid. In the white substance marked perivascular edema was present. No microorganisms were demonstrated in Gram-stained sections.

DISCUSSION

Neither of the patients had a history of contact with animals or ill people, nor had they any symptom or sign of gastrointestinal affection, which is supposed to promote the intrusion of Listeria monocytogenes into the organism (1).

Both cases were preceded by an increase in the immunosuppression, which may have activated latent, subclinical infections with L. monocytogenes.

In case 1 stiffness of the neck became apparent 5 days after an increase of the azathioprine dose from 75 to 100 mg/day. The prednisone dose of 30 mg/day was constant throughout the course. No L. monocytogenes were demonstrated in the blood. The bacteriologic diagnosis was established rather late, as a concomitant urinary tract infection was treated for 36 hours with tetracycline, which effectively suppresses the growth of L. monocytogenes. Not until tetracycline had been discontinued for 6 days was it possible to demonstrate L. monocytogenes in cultures of the spinal fluid. Resumed treatment with tetracycline was fully effective.

In case 2 stiffness of the neck appeared 5 days after a massive increase in the steroid dose and administration of a moderate azathioprine dose (Fig. 2) in an attempt to revert a rejection of the kidney graft.

This case was complicated with Listeria sepsis with hemolysis and thrombocytopenia. The latter seems to be due mainly to the depressive action of azathioprine on the bone marrow. Consumption coagulopathy, which, together with hemolysis, has been reported in Listeria sepsis (10), cannot have been present to a significant extent, as the prothrombin time did not increase.

The L. monocytogenes grown were fully sensitive to ampicillin, which is reported to be the drug of choice (4). In spite of the i.v. administration of this drug in high doses, the spinal fluid, after 3 days of treatment, still contained viable L. monocytogenes. Similarly, in a 25-year-old kidney-transplanted woman, in New York, with Listeria meningitis treated with i.v. ampicillin, the spinal fluid still grew L. monocytogenes after 3 days of treatment. However, after 3 weeks of treatment with ampicillin the patient was cured and the spinal fluid had normalized (7).

New in vitro investigations have shown that penicillin or ampicillin in combination with kanamycin or gentamicin kill L. monocytogenes earlier and more effectively than any of the agents alone (3).

The antibiotic treatment given in case 2 seems, however, to have been effective against L. monocytogenes as this microorganism was not demonstrated at autopsy. The characteristic feature of this case was the massive hemorrhages due to the pronounced thrombocytopenia. The meningeal changes were modest and the tissue reaction sparse.

The sudden decrease in kidney function appeared during high fever when the meningeal symptoms evolved and the BP fell; the myocardial infarction must have developed at about this time, when the hemolysis was also demonstrated. These factors seem to have been responsible for the acute renal

failure, whereas acute rejection does not seem to have been present.

From experiments with mice it is known that corticosteroids given at the beginning of the infection with L. monocytogenes, in a dose corresponding to that given in case 2, greatly suppress the production of immunologically committed lymphocytes by depletion of lymphocytes in lymphoid tissue and by inhibition of DNA synthesis in lymphocytes (8). This leads to diminished proliferation and accumulation of macrophages at infective foci in the tissues (8).

At the same time there is an enhanced accumulation, at the infective foci, of polymorphonuclear leucocytes, which cannot neutralize L. monocytogenes. This probably represents an ineffective attempt by the host to compensate for the deficit of macrophages at the infective foci (8).

In this context it is emphasized that the first spinal fluid of case 2, who received a massive steroid dose, revealed polynuclear pleiocytosis. In case 1, who received a comparatively small steroid dose, the spinal fluid was mononuclear pleiocytotic. So it is possible that the pleiocytosis, other things being equal, becomes increasingly polynuclear with increasing steroid immunosuppression.

CONCLUSION

The necessary immunosuppression after renal allotransplantation implies an increased risk of clinical listeriosis. One must therefore be prepared to meet cases of Listeria meningitis among kidney transplanted persons, specially when the immunosuppression has just been increased. The diagnosis should be made rapidly and, as soon as cerebrospinal fluid and peripheral blood have been obtained for culture, antibiotic treatment should be started at once. In view of the seriousness of the infection, it seems justified to increase the resistance of the patient by temporarily discontinuing azathioprine and other cytotoxic drugs and reducing the steroid dose at the height of the infection. This does not necessarily involve rejection of the transplant. The kidney function should, however, be observed carefully.

ADDENDUM

Since the preparation of this manuscirpt we have had two more cases of listeria meningitis among kidney transplanted patients. They appeared shortly after (5 and 11 days, respectively) intensified immunosuppression with methylprednisolone in high doses (1 $^1/_2$ and 3 g given over 2 and 3 days, respectively) carried out to revert rejection of the kidney grafts. In both cases polynuclear pleiocytosis was demonstrated in the spinal fluid. Azathioprine was discontinued temporarily and prednisone was reduced in both patients, who recovered after treatment with ampicillin plus gentamicin.

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