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FRENCH REPUBLIC

Ministry for Defence

Service
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HÔPITAL D'INSTRUCTION DES ARMEES PERCY Clamart, 18 November 2004
Anaesthesia/Intensive Care Department

HOSPITALISATION REPORT

Re: Mr Yasser ARAFAT born on 04/08/1929
Arrived on 03/11/2004 Died on 11/11/2004 at 03:30

REASON FOR HOSPITALISATION:

Patient transferred from the haematology department of the HIA Percy for coma.

HISTORY:

- Medical:
  - Hiatus hernia with oesophagitis
  - Gastritis with *Helicobacter pylori* treated in October 2003
  - Essential tremor treated with Avlocardyl 160 LP for 10 years, currently stabilised
- Surgical:
  - Subdural haematoma after an air accident in 1990 treated surgically
- Family:
  - Married, one daughter aged 9 in good health
  - Cancer of the colon in a brother and a sister
- Allergies: unknown
- Transfusions: transfusions of platelets and fresh frozen plasma (FFP) in haematology without problems
- Anaesthetics: at least one general anaesthetic without known problem
- Lifestyle: according to the patient's neurological consultant, he had lived for over 3 years in a cramped space and has apparently encountered episodic difficulties with eating and hygiene
- Toxic habits: no smoking, no alcohol consumption, no drugs

TREATMENTS upon arrival in the department:

- Oflocet® 200 mg x 2/day
- Bactrim® 400 mg x 3/day
- Solumedrol® 60 mg/day
- Eupantol® 40 mg/day
- Heparin 150 Ul/kg/day

HISTORY OF THE ILLNESS

The patient was hospitalised on 29/10/2004 in the haematology department of HIA Percy for exploration of thrombopaenia in a context of alteration of the general condition with digestive problems having arisen suddenly since 13/10/04.

The haematology assessment showed:

- a haematological abnormality with a biological picture of disseminated intravascular coagulation (DIC) and hyperleukocytosis at 40,000 GB (85% PN). A myelogram highlighted a medullary hemophagocytosis (1%), a rich marrow with no abnormal cells; the medullary immunophenotyping did not reveal any phenotypical gap that could suggest a T cell disorder; no schizocytosis was found on the blood counts.
- a digestive abnormality with watery diarrhoea and malabsorption syndrome, associated on the abdominal pelvic tomodensitometry with images of thickening of the gastroduodenal and colic wall without tumour or ganglion or hepatosplenomegaly. Upon arrival there was jaundice with moderate abnormality of the hepatic assessment, this jaundice increased during the stay.
- A neurological abnormality with a stuporous clinical picture, a fluctuating level of consciousness, without signs of coning or meningeal symptoms; the encephalic imaging (TDM and MRI) did not show any abnormality.
- An absence of fever, an absence of biological inflammatory signs (PRC <5 mg/l)

In Haematology the patient benefited from the following treatments: platelet transfusions, intake of FFP and heparin for the DIC, empirical antibiotics with Tazocilline® and Ciflox® in the hypothesis of infectious enterocolitis, and prescription of Zovirax® and corticosteroids in the hypothesis of a macrophage activation syndrome of viral origin. Faced with the increase in the jaundice, drugs that could be hepatotoxic were stopped (Tazocilline®, Ciflox® and Zovirax®); antibiotic treatment was maintained by Oflocet®.

In the night of 2 to 3/11/2004 an agitation of the patient was noted with episode of hypertonia of the left hemicorpus, a doubt over anisocoria, without motor deficit or signs of pyramidal irritation. A non-injected cranial TDM was then carried out and it proved unchanged in comparison to the previous one.

During the day of 3/11/2004, the neurological picture worsened with the onset of a coma in the early afternoon. An EEG showed signs of non-specific encephalopathy (slow diffuse waves without lateralisation), without epileptic aspect or periodic activity.

The patient was then transferred into the intensive care department of the HIA Percy.

UPON ARRIVAL IN THE INTENSIVE CARE DEPARTMENT

Clinical examination:

Skin temperature: 37.5º, weight measured at 68kg (previous estimate at 60kg).

Neurological: the Glasgow score was 7 (E=2, V=1, M=4), the examination of the pupils showed a poorly reactive left meiosis, a poorly reactive right pupil in intermediate position. There was no motor deficit upon painful stimulation. There were no spontaneous movements of the upper and lower limbs. An elastic hypertonia was noted in flexion of the upper limbs. There was a complete areflexia of the upper and lower limbs, a bilateral Babinski sign.

In the cranial nerves spontaneous horizontal pendulum movements of the eyes were noted, with doubt as to paresis of the left VI owing to the absence of movement of the left eye in abduction. There was no facial paralysis; a tendency for the tongue to deviate to the left was noted. The nausea reflex was not tested.

Cutaneous membrane: the patient was jaundiced (conjunctive). An infiltrated aspect of the lowest areas (loins) was noted in favour of a hydrosodic overload, particularly since there was certain weight gain in a context of hypoalbuminaemia. The lesions of the bottom with phlyctena, which had been noted upon arrival in the haematology department, and a few erythematous lesions of the occiput were found. Cutaneous haematomas were noted in the areas where blood was taken, but no cutaneous membrane haemorrhage or cutaneous signs of ischaemia/necrosis. The presence of vitiligo was noted.

Cardiovascular: Cardiac frequency (CF) = 73 bpm, Blood pressure (BP) = 161/77 mm Hg; the extremities were hot, the recirculation time was normal and no mottling was noted. The auscultation was within normal limits without cardiac or vascular murmur; all peripheral pulses up to the pedial areas were perceived; there was a pitting pretibial oedema.

Respiratory: RF = 21 cycles/min, SpO2 = 98% under 6 l/min O2 via mask; auscultation was within normal limits.

Abdomen: soft, bloated, without defence or grimace upon palpation (disappearance of the painful reactions upon palpation noted upon admission to haematology); there was no hepatosplenomegaly, no hydroaeric noises were noted. Rectal palpation was not undertaken.

Paraclinical examinations:

Pulmonary radiography: appearance of interstitial infiltrates without systematic opacity

ECG: sinus rhythm, auriculogram normal, QRS axis = +30º, auriculoventricular and intraventricular conductions normal, flattening of the T waves in V2 and V3, repolarisation normal elsewhere, QT segment normal.

Biology:
GB = 15,000/mm³ (neutro = 88%, lymphocytes 3%, monocytes 8%), haemoglobin = 11.1 g/dl, Platelets = 30,000 mm³, TP 41%, APTT = 112/33, fibrinogen = 0.6 g/l, FDP > 20 µg/ml, D-Dimers = 3.94 µg/ml, soluble complexes negative, Factor II = 35%, Factor V = 89%, Factor VII = 63%, Factor X = 36%, anti-thrombin III = 21%, C Protein = 15%.

Biochemistry:
Arterial gasometry (under oxygen via mask at 6 l/min): PaO2 = 248 mm Hg, pH = 7.53, PaCO2 = 29 mm Hg, HCO3 = 23.8 mmol/l, ABE = 2.1 mM/l, SaO2 = 97.8%, arterial lactates = 3 mmol/l.
Creatinine = 79 µmol/L, urea = 6.9 mmol/L, glycaemia = 9.6 mmol/L, Total bilirubin = 268 µmol/l (normal <17), conjugated bilirubin = 193 µmol/L (normal <5), Na = 138 mmol/l, K = 3.9 mmol/l, Cl = 102 mmol/l, Total CO2 = 24.1 mmol/l, total proteins = 51.5 g/l (normal: 68-83), Ca = 1.94 mmol/l, Corrected Ca = 2.23 mmol/l (normal: 2.3-2.6), P = 0.63 mmol/l (normal: 0.8-1.3), Mg = 0.96 mmol/l (normal: 0.75-1.8), Triglycerides = 0.62 mmol/l (normal: 0.6-1.8), GT = 126 Ul/l (normal: 8-61), ASAT = 73 Ul/l (normal: <60), ALAT = 47 Ul/l (normal <60), LAP = 105 Ul/l (normal: 40-129), LDH = 718 Ul/l (normal: 230-440), ammoniemia = 64 µmol/l (normal <50), CPK = 146 Ul/l (normal <200), myoglobin = 142 µg/l (normal <90), amylase = 50 Ul/l (normal <100), lipase = 54 (normal <60), PRC = 6 mg/L, ferritin = 535 µg/l (normal: 18-464).

Urine sample: glycosuria = 0.3 g/l (normal <0.5), proteinuria = 0.69 g/l (normal <0.1), Urinary Ca = 1.82 mmol/l (normal: 2.5-7), Urinary creatinine = 1.3 mmol/l (normal: 9-16), Urinary urea = 94.5 mmol/l (normal: 250-500), Urinary Na = 68 mmol/l (normal: 100-300), Urinary K = 12 mmol/l (normal: 25-150)

Encephalic MRI and angioMR of the supra-aortic vessels (Prof Jeanbourquin):
Absence of encephalic, meningeal or vascular notable abnormality.

Thoracic/abdominal/pelvic TDM (Prof Jeanbourquin):
Bilateral pleural effusion of average abundance with underlying parenchymatous ventilation problems. Regression of the inflammatory or infectious antro-pyloric duodenal lesions and the colic frame with simple persistence of a parietal thickening with inflammatory reaction in the ascending colon. Isolated vesicular lithiasis with no sign of complication. Ascites of average abundance. Overall hypodense appearance of the hepatic parenchyma.

To sum up:
Patient aged 75 presenting in a coma (Glasgow score = 7) preceded by a stuporous state, associated with the persistence of biological DIC, without additional etiological argument connected to the hospitalisation in the Haematology department. Regression of the clinical and paraclinical digestive symptoms present initially on arrival in Haematology, but aggravation of the jaundice.

INITIAL PRACTICAL APPROACH

On a treatment level:

- Owing to the depth of the coma, the patient was intubated and put under artificial ventilation (FiO_2 = 0.5, Vt = 600 ml, RF – 14 cycles/min, PEP = 5 cm H_2O).
- Temporary sedation via Diprivan® was instigated in order to conduct etiological explorations under good technical conditions and conditions of comfort for the patient while they were carried out.
- Transfusions of FFP and platelets owing to the realisation of invasive procedures.
- Withdrawal of heparin owing to the performance of invasive procedures.
- Continuation of antibiotic treatment instituted in haematology (Oflocet®, Bactrim®).
- Prescription of a gastric protector (Eupantol®)
- Suspension of corticosteroids in consultation with the Haematologists (Prof de Revel, Dr Fagot) owing to fear of infection linked to the stay in intensive care, since they hadn't led to any improvement.

On an etiological testing level:

- Performance of a lumbar puncture (LP): liquid "rock water", 3 white elements (mature lymphocytes), no red cell, proteinorrachia = 0.75 g/l, glycorrhachia = 3.4 mmol/l, chlorurorrachia = 123 mmol/l, procalcitonin was normal in the cerebrospinal fluid (CSF), immunofixation of the immunoglobulins of the CSF proved negative. As a matter of principle, a test for the protein of prion diseases in the CSF was requested (the result came back negative).
- Performance of auditory evoked potentials (AEP) (Dr Raynal): these showed well-structured right and left curves with normal latencies of the I waves, a slight lengthening of the latency of the III wave on the right side, a lengthening of the latencies of the V wave. Conclusion: retrocochlear AEP.
- Performance of an electromyogram (EMG) owing to the areflexia noted in the patient upon his arrival in intensive care (Prof Tailla): the conclusions suggested an aspect of polyradiculoneuritis (lengthened distal latency > 120% of the norm, abolition of more than 2 F waves, reduction of more than 2 motor conduction speeds < 80% of the norm, motor conduction block)
- Performance of a Doppler of the supra-aortic and transcranial stems (Dr Baccialone): Normal appearance of the internal and external carotid flows and the vertebral flows. The ophthalmic flows were normal anterograde, normal aspect of the subclavical flows. Normally modulated appearance of the anterior and posterior intracranial arterial flows.
- Performance of a bone marrow biopsy (BMB) and a myelogram (Dr Fagot): the bone marrow biopsy showed no invasion by a tumoral process with an absence of macrophage infiltrate within the limit of the slides examined. The myelogram showed a rich marrow with an average representation of the megakaryocyte lineage and an absence of excess of blasts and abnormal cells of extramedullary origin. Cytological appearance of marrow reactive with macrophages presenting aspects of hemophagocytosis.

- Performance of high and low digestive endoscopies (Dr Rimlinger) owing to the initial digestive symptomatology and the TDM images on arrival at the hospital: aspect of chronic atrophic gastritis without other abnormality (in particular no oesophageal varices or hypertensive gastropathy); realisation of duodenal and antro-fundal biopsies; uncomplicated sigmoid diverticulosis; sessile polyp in the rectosigmoid junction left in place; no other abnormality in the rectum or sigmoid explored.
- Performance of an abdominal echography (Dr Baccialone) owing to the jaundice: the digestive barrier was abundant, the examination was difficult, the gallbladder was empty, its wall was difficult to assess but did not seem significantly thickened; absence of peri-vesicular effusion; absence of obvious dilation of the bile ducts.

EVOLUTION

The patient's case has been subject to multidisciplinary staff meeting involving:

For the HIA Percy: Prof Pats, Prof Lenoir, Prof Perez and Dr Auroy (anaesthesia / intensive care department)
Prof de Revel and Dr Fagot (haematology department)
Dr Berets (internal medicine department)
Dr Hervé, Dr Foissaud, Dr Samson and Dr Vest (laboratories)
Prof Jeanbourquin (medical imaging department)

For the Ensemble Hospitalier Militaire Parisien (EHMP):
Prof Algayres of the HIA Val de Grâce (internal medicine, gastroenterology department)
Prof Cordoliani of the HIA Val de Grâce (medical imaging department)
Prof Debord of the HIA Bégin (infectious and tropical diseases department)
Prof Joussemet (Army Blood Transfusion Centre)

The following also participated in the discussions:
Dr Boyer-Neumann, Hôpital Béclère (haemostasis laboratory)
Prof Bricaire, Hôpital de la Pitié Salpétrière (infectious diseases department)
Prof Conso, Hôpital Cochin (occupational medicine department)
Dr Garnier, Hôpital Fernand Widal (toxicology department)
Principal Pharmacist Dorandeu (CRSSA)
Prof Hermine, Hôpital Necker (clinical haematology department)
Chief Pharmacist Huart, Institut de medicine aéronautique du service de santé des armées (IMASSA)
Prof Ozier, Hôpital Cochin (anaesthesia and intensive care department)
Prof Piette, Hôpital de la Pitié Salpétrière (internal medicine department)
Chief Doctor Laroche, Service de Protection Radiologique du Service de Santé des Armées (SPRA)
Prof Renaudeau, Chair of pharmaceutical sciences, toxicology and expertise in the army
Prof Ricordel, toxicology laboratory of the Paris Police Headquarters
Chief Pharmacist Perrin and Lieutenant Colonel Tourron of the Institut de Recherche Criminologique de la Gendarmerie Nationale (IRCGN)
Chief Pharmacist Vidal (CRSSA)

In accordance with the wishes of the patient's wife, the information has been sent throughout the stay in the intensive care department to Dr Daka, personal doctor of the patient, and Prof Hentati, personal consultant neurologist of the patient, and also to Dr M Hassoun, haematologist, and Dr P Hassoun, intensive care pneumologist, both brothers-in-law of the patient's wife.

Evolution on a haematological level

The coagulopathy remained stable throughout the evolution of the patient in intensive care, with variations, according to the FFP and platelet concentrate transfusions, in the level of prothrombin (between 41% on arrival and 66% maximum on 05/11/2004), fibrinogen (between 0.6 g/l on arrival and 1.9 g/l on 10/11/04), and platelets (varying between 19,000 on 09/11/2004 and 116,000 on 05/11/2004). The fibrin degradation products (FDP) and the D-Dimers always remained very high, with the absence of soluble complexes not ruling out the diagnosis of DIC owing to the hypofibrinogenaemia.

The hypothesis used was that of an association with DIC firstly and hepatic impairment secondly.

The hepatic impairment was suggested on the measurement of the factor VIII that was initially very high (237% on admission to the hospital) and on the generalised fall in all other coagulation factors. During hepatopathies in general, the clearance deficiency of factors IIa and Xa contributes to making a consumption coagulopathy permanent. The hepatopathy was however moderate in the circumstances because the factor V remained at over 50% throughout the stay in the hospital and the factor VII did not collapse (41%).

A third mechanism could participate in the coagulopathy: a degree of vitamin K deficiency objectified by the fall in vitamin K dependent factors (II, VII, IX, X) and partially corrected by the administration of vitamin K. The concomitant administration of FFP however does not make it possible to conclude.

Furthermore the presence of an imbalance in favour of procoagulant factors in relation to the physiological inhibitors (AT III, C Protein, S Protein), respectively measured on average at 50% and 20%, could result in the risk of thrombosis. This motivated the indication of heparin treatment at 150 Ul/kg/day. This heparin treatment was restarted in intensive care after the invasive explorations conducted on arrival, stopped after the episode of digestive haemorrhage of 05/11/04 (cf. infra), restarted after the cardiovascular event of 08/11/04 (cf. infra) and stopped again after the neurological evolution of 09/11/2004 (cf. infra).

Faced with the absence of fever, the absence of hypertriglyceridemia, the absence of inflammatory syndrome and the normalisation of the ferritin level on 04/11/2004, the diagnosis of systemic macrophage activation syndrome was dismissed and the systemic corticosteroid treatment instigated in haematology was not restarted.

Faced with the absence of major anaemia in spite of the biological signs of haemolysis (haptoglobin < 0.3 g/l, but LDH slightly increased), the absence of acute renal insufficiency upon arrival in intensive care, the absence of schizocytosis > 0.5% in this patient, in spite of the preceding digestive signs on admission and the thrombopaenia, the diagnosis of thrombotic microangiopathy was dismissed.

An intravascular lymphoma would have been a possible etiology, leading us to conduct a second bone marrow biopsy the conclusions of which were identical to the first, with in particular the absence of epithelioid and giant cell granuloma; a hepatic biopsy puncture (HBP) could not be conducted (cf. infra).

The administration of Solumedrol® at the dose of 1 g/day for 3 days was decided by the multidisciplinary staff meeting of 05/11/2004 to try firstly to "break" the intramedullary macrophage reaction assumed to intervene on the DIC and to act moreover on any auto-immune pathology with vascularity, particularly since the measurements taken in haematology of factors C3 and C4 of the complement were low. A response to this treatment was expected 72 hours after the last dose.

The instigation of a plasmapheresis was discussed at multidisciplinary staff meetings but was not undertaken owing to the risk/benefit ratio against it: low probability of diagnosis of thrombotic microangiopathy, risks linked to the activation of coagulation, to the foreseeable platelet consumption and to the fitting of a large calibre catheter required by the absence of sufficient peripheral venous capital.

Evolution on a neurological level

The following etiological hypotheses were mainly suggested:

Whipple's disease: empirical antibiotic treatment with Bactrim® was then instigated pending the results of the tests requested to confirm the diagnosis (PCR of *tropheryma whippelii* on CSF blood and duodenal biopsy, anatomo-pathological examination of the duodenal biopsies). Faced with the negativity of these, treatment with Bactrim® was stopped on 05/11/2004.

Bickerstaff's encephalitis (encephalitic variation of Miller Fisher polyradiculoneuritis). The following elements pleaded in favour of this etiology: clinical picture, albumin-cytological dissociation of the CSF confirmed by a 2nd lumbar puncture, then the electromyogram (EMG). The test for anti-GM1 and anti-GQ1b antibodies was requested (it came back negative on 08/11/04). Faced with this hypothesis of encephalitis and possible vascularity, the multidisciplinary staff meeting of 05/11/2004 proposed the prescription of immunoglobulins (Tegeline®) in spite of the coincidence between an episode of neurological aggravation at home and the prior administration of immunoglobulins (45g in total). A dose of 0.4 g/kg/day for 5 days was prescribed from 05/11/2004, with a response to the treatment expected 7 days after the last dose. However this treatment had to be stopped on 07/11/2004 owing to the onset of acute renal insufficiency (cf. infra).

The clinical neurological evolution was marked by a relative clinical improvement from 07/11/2004 with a patient more responsive to care and to pain, with the reappearance of a right bicipital reflex, absent upon his entry into intensive care, but without however regaining consciousness.

A third encephalic MRI was conducted on 08/11/2004 to seek elements that could explain the persistence of the coma. This then showed the presence in the peduncular and thalamic regions of symmetrical signal abnormalities, on diffusion sequences, without enhancement after injection of contrast product. This new imaging data did not make it possible to offer decisive elements with regard to the etiology of the coma.

On 09/11/2004, although the neurological examination of 4 o'clock in the morning was encouraging (strong reaction to care, opening of the eyes upon tactile or verbal stimulation by those around him), at 5 o'clock in the morning a lack of responsiveness was noted with pupils in unreactive anisocoria. An emergency cranial TDM was conducted which showed intra-axial cerebellar right haemorrhagic lesions, vermian, of the brain stem, and thalami associated with a haemorrhagic flood of the ventricular cavities, a meningeal haemorrhage and a disappearance of the cisterna of the base. Faced with this picture, a neurosurgical opinion was requested of Prof Pernot, head of the neurosurgical department of the HIA Percy: considering the clinical condition (unreactive , absence of oculo-cardiac, corneal or corneo-mandibular reflexes, absence of reaction to painful stimuli), a surgical approach appeared illusory. We could only discuss an external ventricular shunt which, considering the haemorrhagic picture, also comprised an additional risk of haematoma for a minimal clinical benefit. A transcranial Doppler conducted after the scan did not highlight abolition of the cerebral circulation. The electroencephalogram (EEG) (Dr Denis) highlighted a very flat trace with an average amplitude of the microvolt order; a highly degraded electrogenesis persisted in the form of theta and alpha activity in the right temporal region of low amplitude ≠2 microV. A notice of deterioration was given to the wife of the patient and to his personal doctors on 09/11/2004 at 08:15 by Prof Perez, Prof Pats and Dr Auroy

Evolution on a renal level

The patient presented an acute renal insufficiency from 06/11/2004 with plasma creatinine at 110 µmol/l, plasma urea at 11 mmol/l. This renal insufficiency with diuresis was protected under Lasilix® at modulated dose with an objective of diuresis. In the hypothesis of responsibility of the immunoglobulins, these were stopped. The responsibility of the DIC in this renal insufficiency was considered plausible. This renal insufficiency was not accompanied by an increase in the number of schizocytes (1/1000 on 05/11/2004, 1/1000 on 07/11/2004) and the LDH was 763 Ul/l on 06/11/2004. The diuretic treatment was able to be stopped in the morning of 10/11/2004 faced with a spontaneous diuresis at over 1000 ml/day. The plasma creatinine remained stable at 378 µmol/l on 09 and 10/11/2004.

Evolution on a haemodynamic level

Owing to the weight gain estimated to be considerable since the start of hospitalisation, the presence upon arrival in intensive care of diffuse oedema and radiological images of pleural and intra-abdominal effusions on the thoracic-abdominal-pelvic scans, a low dose of diuretics was prescribed in order to correct the hydrosodic balance.

The patient remained stable on a haemodynamic level until 08/11/2004, date on which the ECG problems appeared (sinus tachycardia, modification to the QRS axis, incomplete right branch block, diffuse problems with repolarisation in the precordium), and a rise in the Ic troponin up to 1.33 µg/l. These new elements, after the opinion of Dr Plotton, head of the cardiology department, led to the reintroduction of beta-blocker treatment in the hypothesis of a coronaropathy

unveiled by stopping the long term treatment with Avlocardyl® (essential tremor), particularly since the cardiac frequency was high and the level of blood pressure enabled it. Thus, Tenormine® (2.5 mg IV x 2/day) was begun on 08/11/2004 after a transthoracic cardiac echography (TTE) was conducted by Dr Rigollaud. This TTE showed the absence of left ventricular failure, with a left ventricular ejection fraction (LVEF) estimated at 68%, without abnormality of the segment kinetics, an MI grade 1 and an AI grade 1.

On the other hand, a dilation of the right ventricle with pulmonary arterial hypertension (PAHT) estimated at 75 mm Hg was highlighted.

The association of electrical and echographic signs was judged in favour of an acute pulmonary heart, the origin of which could be imputed to the artificial ventilation (PEP < 5 cm H2O, low insufflation pressures) but could be explained by a pulmonary embolism in the context of the disseminated intravascular coagulation, particularly since the haemostasis assessment suggested a deficiency of the coagulation inhibitors. The patient could not benefit from a spiral pulmonary TDM with injection of contrast product to confirm the diagnosis, owing to the renal insufficiency contemporary to the onset of the problems.

Evolution on an infectious level

During his stay in intensive care, the patient was never febrile at over 37.8ºC, the PRC never rose above 12 mg/l. The whole infection test up to the PCR RNA 16S remained negative, no haemoculture (including isolator) came back positive, no surface sample isolated any germ or yeast. Tests for multi-resistent bacteria were negative. No PCR or viral, bacterial, mycological or parasite serology came back positive. The test for mycobacteria by direct examination or GENPROBE remained negative, the cultures are in progress. Empirical antibiotic treatment with Clamoxyl® was started on 08/11/2004 in the hypothesis of an atypical form of meningitis with *Listeria monocytogenes*.

Evolution on a respiratory level

The oxygenation of the patient was always correct with a PaO2 / FiO2 ratio > 300 and a FiOs < 0.5 throughout his stay in intensive care. The pulmonary radiography showed a deterioration with the appearance of diffuse alveolar opacities that could be overload owing to the renal insufficiency and the weight gain; but owing to the context, a broncho-alveolar lavage was conducted on 08/11/2004 to test for nosocomial pneumopathy: this did not show infected polymorphonucleocytes and highlighted a few gram-positive cocci in a cluster which were identified as *Staphylococcus epidermidis* sensitive to oxacillin and would not be treated. The test for *Legionnella pneumoniae* by antigenuria and initial serology was negative.

Evolution on a hepato-digestive level

The jaundice with conjugated bilirubin increased during the stay, without major abnormality of the hepatic assessment (ASAT maximum 88 Ul on 06/11/2004, ALAT < normal during the stay, regression of the GT and LAP during the stay). To assess this jaundice and look for a hepatopathy, a transjugular hepatic biopsy was envisaged by the multidisciplinary staff meeting of 06/11/2004, within a timeframe to be determined, in spite of the possible haemorrhagic risks. This hepatic biopsy had the objective of eliminating a possible intravascular lymphoma and reviewing the icteric cholestasis and the macrophage activation. This hepatic biopsy was offered on 07/11/2004 to the family, which refused it.

The patient had an episode of digestive haemorrhage with melenas and deglobulisation (haemoglobin at 8.4 g/dl on 04/11/2004) which required the transfusion of 2 erythrocyte concentrates and the withdrawal of heparin, and melenas. A further high digestive endoscopy was conducted in the morning of 05/11/2004 and highlighted the presence of red haematic residues in the second duodenum, 2 round lesions of around 5mm diameter eroding at the bottom and with purplish red edges in the distal part of the second duodenum, with a small haemorrhagic weeping in the most distal lesion. The injection of 6ml adrenalin at 1/1000 to the edges and within the lesion stopped the weeping. These lesions seemed to correspond to post-biopsy scars. There was no blood initially in the stomach. The other biopsy scars, antro-fundal, were fully visible and were not haemorrhagic. There was no digestive haemorrhagic relapse during the stay.

The patient benefited from attempts at enteral nutrition attempts via Normoreal® adapted to the measurement of gastric residues without obtaining an enteral nutrition output of over 500 ml/day. Also parenteral nutrition by Kabiven® 1600 Kcal/day had to be instigated owing to the duration of the digestive problems preceding the hospitalisation and the finding of trophic problems of the bottom and the occiput.

No pancreatic abnormality was noted at any time, biological or radiological.

On a toxicological level

At the HIA Percy, the blood test for barbiturates, benzodiazepines, tricyclic antidepressants, salicylates, paracetamol and lithium proved negative. The test in the urine for barbiturates, benzodiazepines, tricyclic antidepressants, opiates, cannabis, cocaine, amphetamine, methamphetamine, methylene dioxymethamphetamine and methadone proved negative.

At the Institute de Recherche Criminelle de la Gendarmerie Nationale, samples of blood, urine, stools and cerebrospinal fluid were analysed. For xenobiotics, the results corresponded to the presence of the treatments taken by the patient (ciprofloxacin, propranolol, metoclopramide, lidocaine and amantadine). With regard to metals there was no difference found, for the elements tested, with the controls. The results of these tests have already been passed on to the patient's wife.

At the radio-toxicological control laboratory of the Service de Protection Radiologique des Armées (SPRA) a test was conducted for contamination by radioelements. This test proved negative. The results are appended.

The multidisciplinary meetings and the examinations conducted did not suggest intoxication to explain the condition of the patient.

Terminal evolution

The patient died on 11/11/2004 at 03:30 of the consequences of a cerebral engagement secondary to the haemorrhagic vascular accident.

IN CONCLUSION

On the 13th day of his hospitalisation at the Hôpital d'Instruction des Armées Percy, and on the 8th day of his hospitalisation in the intensive care department, Mr Y. ARAFAT died of a massive haemorrhagic cerebrovascular accident. This cerebral haemorrhage was complicated by a clinical picture including:

- An inaugural digestive syndrome having occurred 30 days earlier, suggesting enterocolitis.
- A haematological syndrome associating serious DIC and isolated medullary hemophagocytosis without systemic macrophage activation syndrome.
- Cholestatic jaundice
- A neurological syndrome with fluctuating stuporous state then coma.

The consultation of a large number of experts of multiple specialities and the results of the examinations conducted did not make it possible to find a nosological framework explaining the combination of syndromes.

[signature]

B PATS Services Chief Doctor
Associate Professor of Val-de-Grâce
Head of Anaesthesia/Intensive Care Department
HIA PERCY – 92141 CLAMART
Tel 01 41 46 62 21 – Fax 01 41 46 64 67
Adeli Code: 961007622