Boutonneuse fever with malignant evolution

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Abstract

A case of boutonneuse fever in an apparently healthy male aged 48 is described. After a typical presentation there was a rapidly progressive systemic involvement, with hepatobiliary, central nervous system and respiratory manifestations. Lung involvement presented as adult respiratory distress syndrome, radiologically manifested by extensive bilateral infiltrate, leading to the need of respiratory intensive care support. In spite of all therapeutic measures the evolution was fatal, suggesting a generalized and abnormally severe vasculitis, which was confirmed post-mortem.

Key words: boutonneuse fever, adult respiratory distress syndrome.

Introduction

Traditionally, Boutonneuse fever is a benign, self-limited disease.1,2 However, it is important to note that its evolution is not always linear, and one should be on the lookout for possible complications, which can be particularly severe.3 The clinical case presented here is an example of this, as it brought up successive problems in terms of diagnosis and therapeutic decision.

Case report

A 47-year-old Caucasian male, married and working at a tire plant in France (emigrant), born in Oleiros, where he was on vacation when he was hospitalized due to exanthema and jaundice. He was apparently healthy until 6 days before admission to hospital, at which point he developed fever (38.5-39ºC), preceded by chills, myalgia and odynophagia. He was seen by a physician and medicated with the anti-inflammatory drugs cefatrizine and nonsteroidal. Generalized, non-itchy exanthema appeared three days later, prompting the visit to ER. The antibiotic was suspended, and the patient was discharged, with referral to outpatient hematology due to thrombocytopenia detected in the analyses.

On the day of admission to hospital the patient once again visited the ER, complaining of accentuated asthenia, anorexia and general malaise; he had been febrile since the previous evening. He had also been suffering from choluria and acholia for about 3 days. He denied other symptoms, namely urinary, gastrointestinal, respiratory or joint disorders.

Twenty-one years earlier he had contracted malaria while in Africa. He denied other relevant diseases, as well as alcoholic or smoking habits or regular consumption of drugs. The epidemiological survey revealed recent consumption of "natural spring water" and having stayed in the countryside for the previous 3 weeks, where he had contact with dogs. He was not aware of any tick bites and had not engaged in promiscuous sexual behavior.

Upon arrival, he was in a good general state and his vital signs were normal (body temperature 36.8ºC; blood pressure 114/ 75 mmHg; heart rate 88 ppm, regular; eupnoeic). He had jaundice of the skin and mucosa. The skin presented maculopapular erythematous lesions spread all over the body, with palmoplantar involvement. He also had petechiae on the legs. The oropharynx showed slight hyperemia and presented lesions suggestive of herpes labialis. The cardiopulmonary observation was normal. The abdominal examination revealed hepatomegaly of about 2cm below the costal margin, at the level of the right midclavicular line, smooth and slightly painful. There were no other abnormalities on objective examination, i.e. cutaneous stigmata of chronic liver disease, palpable adenopathies or splenomegaly, osteoarticular abnormalities or evident neurological

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TABLE I

Leucocytes	9 930/mm^3 (N 85.3%; E 0.05%; B 0.7%; L 6.2%; M 7.5%; Stimulated lymph. -neg.)
Erythrocytes	4 540 000/mm^3
Hemoglobin	14.2 g/dL
Platelets	66 200/mm^3
Glycaemia	7 mmol/l
Na+ /K+	139/3.9 mEq/l
Urinalysis	Prot.++, Hb+, Urobilinogen+, Bilirubin+
TGO/TGP	168/211 U/l
CPK / CK-MB	149/21 U/l
LDH	613 U/l
Total Bilirubin	96 mmol/l
Urea	8.2 mmol/l
Creatinine	55 mmol/l

TABLE II

Liver of normal dimensions, with diffusely heterogeneous echo structure compatible with steatosis and/or hepatocellular lesion. Gallbladder full, with signs of lithiasis and sludge. Dilated portal vein and main bile duct at the upper limit of normal and with considerably thickened walls. Symmetrical kidneys without morphological alterations. Pancreas without alterations. Normal spleen.

TABLE III

TGO/TGP	206/200 U/l
ALP	104 U/l
g-GT	141 U/l
Total/direct bil.	142/104 mmol/L
LDH	944 U/l
ESR	8 mm/h
CRP	18.1 mg/dl
Rickettsia conorii	1/80
Q Fever	< 1/80
Leptospira	neg.
Legionella	neg.
Widal reaction	neg.
VDRL	neg.
HIV 1 and 2	neg.
EBC, CMV, HAV, HBV, HCV	IgM neg.

TABLE IV

Hyperechoic liver, without nodular formations. Without alterations of the intra- or extrahepatic bile ducts. Suprahepatic veins, portal vein, pancreas and spleen all normal. Gall bladder without lithiasis or other endoluminal alterations, with only sight thickening of the gall bladder wall, in accordance with the hepatic alterations.

disorders. *Table 1* shows the analyses carried out in the emergency room. He also underwent a chest x-ray and electrocardiogram, both without alterations, and was hospitalized to clarify the situation. On the 3rd day in hospital, he remained afebrile, but the signs of cholestasis were more accentuated; the exanthema was attenuated. He was observed by the Dermatology department, where he was diagnosed with a "mononucleosis-like viral syndrome caused by the Epstein-Barr or another virus (adenovirus, coxsackie)". Abdominal echography was normal - the report shown in *Table 2*.

The analyses requested at that time are transcribed in *Table 3*. The complete blood count, serum protein electrophoresis, and biochemical parameters already carried out in the ER were all within normal limits, therefore they are not mentioned. The bacteriological exams were also negative, including blood cultures in vital aer and tryptase broths, urine sample and sputum examinations. Tumor markers were requested, and their values were found to be within the normal limits.

On day 4 the fever reappeared, and stayed at 39-40ºC, preceded by chills and exacerbation of the exanthema, this time with a purple tinge. A lesion suggestive of inoculation eschar was detected on the posterior surface of the upper left thigh, and the skin rash was typical of boutonneuse fever, so the patient was started on oral doxycycline at a dose of 200 mg/day. A second abdominal echography was requested (*Table 4*).

Two days later (day 6) there was considerable improvement of the jaundice and exanthema, but the patient remained febrile; conjunctivitis appeared together with extensive pharyngeal irritation, manifested by permanent "sniffing" and odynophagia;

TABLE V

Bilateral diffuse pulmonary condensation, with hemorrhagic areas; necrotizing lesion with hemorrhage and cavities at the base of the right upper lobe, with probable solution of continuity of the pleura; intense tracheobronchitis (vasculitis? pneumonia?). Status Post-thoracic drainage for pneumothorax status. Dispersed punctiform hemorrhagic focuses in the cerebral parenchyma; segmental hemorrhagic mucosal necrosis of the thin intestine (probable vasculitis?). Thrombosis of the periprostatic venous plexuses. Pulmonary embolisms in peripheral branches of the right pulmonary artery. Hypertrophy of the wall of the right ventricle. Hepatic steatosis. Hemorrhagic erosions in the gastric mucosa.

the oropharynx had an intense purple tinge. The patient was observed in Otorhinolaryngology, where atrophic rhinitis was diagnosed. On day 7, although there were no other respiratory symptoms, pulmonary auscultation revealed inspiratory crackles in both lung bases. On day 9 of hospitalization, the patient developed a tickly cough, worsened by the supine position and dyspnea. The patient had tachypnoea, blood pressure of 140/80 mmHg and heart rate of 100 ppm; pulmonary auscultation revealed rhonchi sounds and crackling in the right hemithorax, and there were subcrepitant rales in the lower 1/3 of the left hemithorax. Chest x-ray showed extensive bilateral pulmonary infiltrates. The arterial blood gas analysis revealed hypoxemia (pO2 52.7mmHg; pCO2 35.8mmHg; pH 7.448; HCO3 24.1; sat. O_2 88.5%), refractory to the administration of O2. The situation was interpreted as probable nosocomial infection, yet it was not possible to rule out etiologies such as Legionella pneumophila or Mycoplasma pneumoniae, and it was decided to suspend the doxycycline and to start therapy with erythromycin (1 g every 6/6 h iv) and ciprofloxacin (200 mg every 12/12 h iv). On the following day, the patient was febrile and polypnoeic, with fleeting periods of mental confusion. Pulmonary auscultation revealed crepitant rales in the lower 2/3 of both hemithoraxes and rare wheezes dispersed bilaterally. There was progressive deterioration of the clinical situation, which was reflected by aggravation of hypoxemia and diminished O2 saturation. On the same day, mechanical ventilation was started in the department, with the patient's consent. The echocardiogram taken at the time showed "hyperkinetic heart, without alterations of the valves or chambers."

Of the bacteriological and serum tests requested, only the indirect immunofluorescence (IFI) for Rickettsia conorii was positive with a titer of 1/2560 (7 days after the first titer). Meanwhile, formal arrangements were made to transfer the patient to the intensive care unit, which was only done on day 12. He was admitted to the PICU (polyvalent intensive care unit), with a diagnosis of boutonneuse fever and global respiratory failure. Evolution in the PICU was marked by:
1) existence of adult respiratory distress syndrome (ARDS) - he had pulmonary capillary pressure of 12 mmHg - and great difficulty in ventilation caused by an accentuated decrease in lung compliance;
2) confirmation of sepsis caused by methicillin-sensitive Staphylococcus aureus, treated with appropriate antibiotic therapy according to the antibiogram;
3) appearance of right pneumothorax with high-debt fistula, prompting the use of several ventilation methods, in particular independent lung ventilation with ventilator synchronization or attempted exclusion of the injured lung with normoventilation of the functioning lung.

Despite the use of supportive measures (dopamine, dobutamine and noradrenaline, with monitoring by Swan-Ganz catheter), various types of ventilation (including controlled volume with permissive hypercapnia and independent ventilation) and correct antibiotic therapy, the patient died of multiple organ failure, on day 8 of hospitalization. An autopsy was requested, and its results are transcribed in *Table 5*.

Discussion

As it is well-known, boutonneuse fever is an infectious disease produced by Rickettsia conorii and transmitted to humans by tick bites. It occurs mainly between July and September (± 90% of cases), affects mostly males (60%), and has no age group preference. In Europe, the highest incidence is observed in countries of the Mediterranean Basin, where there are records of a growing number of cases described in the last 15 years, accompanied by an increase in severity.[1,2,3]

After being bitten by an infected tick, there is a phase of bacteremia followed by the establishment of Rickettsia in the cells of the vascular endothelium, where it multiplies, and produces local inflammatory phenomena reflected by ischemia of the skin and visceral capillaries, and an increase in vascular permeability. It is, therefore, a case of generalized

vasculitis, responsible for the clinical manifestations of the disease. As already mentioned, a number of cases of boutonneuse fever with evolution considered "malignant" have been described by many authors. They are characterized by a more or less typical clinical presentation, followed by complications affecting multiple organs. The appearance of complications such as coma, renal failure and respiratory distress is fatal in about 50% of cases. In laboratory terms, the disease is highly variable, with descriptions of evolution, over time, of the values of platelets (initial thrombocytopenia) and leukocytes (leucopenia, followed by leukocytosis with neutrophilia). The rise in transaminases and lactic dehydrogenase is a habitual occurrence. The appearance of hyponatraemia and hypocalcaemia is associated with a poor prognosis.[4-11]

Factors thought to predispose to greater severity of the disease include advanced age, alcoholism, the existence of underlying diseases (diabetes mellitus, neoplasia, glucose-6-phosphate-dehydrogenase deficiency, for example) and previous treatment with sulphonamides. Delay in the establishment of the adequate therapeutic approach is an important factor, as it has been observed that early treatment can avoid an unfavorable evolution. The possible relevance of the virulence of infectious strains as a determinant of prognosis has also been under discussion recently.

The disease diagnosis is based mainly on the clinical history, epidemiology and serology. At specialized experimental centers, it is possible to make a direct diagnosis by isolating Rickettsia in the plasma or in the skin biopsy, obtaining the result in 48 hours.

As regards the therapeutic approach, tetracyclines are considered first-line drugs, and doxycycline is particularly effective in the dose of 200 mg/day, in adults, for 3 to 5 days in normal cases. In the case of allergy or contraindication, it is possible to opt for chloramphenicol, which is very effective when there is pulmonary involvement (due to good penetration in this organ), or quinolone (ciprofloxacin, for example).[12,13]

In the case presented here, the profile of fever, chills and myalgia, followed 3 days later by the appearance of a generalized rash, including on the palms of the hands and soles of the feet, was highly suggestive of boutonneuse fever, also presenting favorable epidemiology. Tâche noire - which is not mandatory and can be confused with scrapes or boils - was not found initially, and the patient essentially manifested intense cholestasis, which is not common in this situation. Since he was afebrile, the health professionals decided not to medicate him immediately, but wait until they had clarified the situation. Indeed, the previous treatment with antibiotic could have been the cause of toxidermia, justifying the cutaneous and hepatic alterations. Moreover, we could not rule out other infectious diseases, namely Q fever, leptospirosis or a viral infection. The existence of a bile duct condition, manifested after the febrile syndrome, was also considered as a hypothesis.

The first abdominal echography was confusing and was therefore repeated two days later, but the abnormalities initially described were not confirmed. However, with the existing data, the diagnostic hypotheses of boutonneuse fever were maintained (presenting a more "malignant" evolution than usual), versus the existence of another associated hepatobiliary pathology, since there was reappearance of fever and accentuation of the exanthema in a purple tinge (sign of poor prognosis).

The appearance of crepitant rales in both lung bases on day 7 of hospitalization, in a patient who had been bedridden and febrile for several days and without semiology of respiratory distress, was interpreted as being due to stasis. Two days later, when respiratory failure occurred, the professionals reassessed the situation in view of the therapeutic approach. We interpreted the situation as a case of ARDS; it could either correspond to a single disease, integrated in the initial process (due to vasculitis), or else there was a respiratory infection on top of the underlying disease. The introduction of corticosteroid therapy was considered, but not initiated. Later, in the PICU, methicillin-sensitive Staphylococcus aureus was isolated in the bronchial secretions, thought we do not believe this was the initial cause of the condition.

Taking into account the abovementioned aspects, and without other conclusive facts, we believe that it was a severe form of generalized vasculitis, manifested by the successive and rapid involvement of the various organs, a fact confirmed in the autopsy. However, the incontestable increase in the anti-Rickettsia conorii antibody titer (IFI technique) is a sufficient criterion to affirm the diagnosis of boutonneuse fever. ■

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