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CASE REPORTS

MILIARY GENERALIZED TUBERCULOSIS WITH SUBACUTE EVOLUTION – CASE REPORT

Ruxandra Laza, A.Crişan, Emilia Nicoară

Department of Infectious Diseases, University of Medicine and Pharmacy "Dr. V.Babeş" Timişoara Romania

Abstract. Tuberculosis continues to be "the most lethal disease caused by a single pathogen". The patient that we presented displayed a lot of factors involved in maintaining or re-emerging of tuberculosis infection as a disease (the presence of a low socio-economic level, lack of medical supervision and subsequently extension of a tuberculosis process). The initial clinical diagnosis was meningo-encephalitis syndrome, taken as a probably tuberculosis meningo-encephalitis based on CSF examination. It finally proved to be an extensive tuberculosis: meningeal, pulmonary, urogenital, endocrine. Death occurred on the tenth day of hospitalization and specific treatment, and it was preceded by the appearance of a purpuric syndrome, hepatic cytolysis and azotemia, interpreted as iatrogenic drug reaction.
Keywords: tuberculous meningo-encephalitis, iatrogenic drug reaction, rifampicin

Background

The modern era of tuberculosis infection, that started with streptomycin's efficiency (in 1946), isoniazid and pyrazinamide (1952) and rifampicin (1966), has not proved to be up to the initial estimations. Presently it can be said that the early optimism of the beginning of the era was premature and unrealistic. The tuberculosis infection – as a disease – was not significantly influenced; moreover, WHO considers that „tuberculosis epidemic grows increasingly and becomes more dangerous every year." Although the disease is curable, the annual number of deaths is up to millions. In 2008, WHO recorded 9.4 million of new TB cases and 1.8 million of deaths.

Ruxandra Laza
"Dr. Victor Babeş" Hospital
13 Gh. Adam Str., Timişoara
email: ruxi_martincu@yahoo.com

Increasing incidence of tuberculosis is secondary to:

- deteriorating public health infrastructure (lack of effective strategies, lack of national programs that prevent and fight against tuberculosis);
- the socio-economical status of some poor populations (inadequate housing conditions, nutrition, chronic consumption of tobacco, alcohol, drugs);
- co-existence of HIV/AIDS;
- an increasing number of resistant and multi-resistant strains of M. tuberculosis (440,000 cases in 2008, with 150,000 deaths);
- immigration from geographic areas with a severe endemic level, with an annual number of bacillus carriers that reaches 100-150 $^{0}/_{0000}$ [1,2].

The presented patient displayed a lot of factors involved in maintaining or re-emerging of tuberculosis infection as a disease: the presence of a low socio-economical level, lack of medical supervision and subsequent enlargement of a tuberculosis process.

Clinical evolution of the patient

The patient D.S., 31 years old, C.C. 3831, 06/23 - 07/03/2009, was hospitalized in the Clinical Hospital of Infectious Diseases and Pneumology Dr. "Victor Babeş" Timişoara, without relatives, without data about the disease development, without possibilities of getting a personal history and family history.

On physical examination: afebrile, altered general condition, patient on a gurney, disoriented in time and space, giving monosyllabic answers, responds with pauses, periodically half-open eyes, blank stare; objective signs of meningeal irritation well expressed, without injury of cranial nerves; painful stimuli cause extension of the leg or flexion of the forearms; poor nutritional status, significantly underweight, with constitutional melanic hyperpigmentation of the skin, with no rash, normal peripheral lymph nodes, osteoarticular system without modifications, lungs, heart without modification upon auscultation, 20 breaths/min, heart rate 100 beats/minute, BP 100/60 mmHg, clear abdomen, palpable liver 2 cm below costal edge, spleen palpable on inspiration, globe bladder (Foley catheter inserted).

CSF dynamics are illustrated in Table I.

negative, HIV 1,2 serology negative.

Objective data: *Chest X-ray* (06/23/2009) Multiple homogeneous opacifications of millet size, disseminated bilaterally, apical-basal. No fluid collections in the lateral sinuses. *Abdominal ultrasound scan* (24/06/2009): hyperechoic liver with homogenous structure, gallbladder with increased volume, empty, slim walls, the main bile duct free, right kidney with increased volume, with 22 mm cortical, irregular outline, with moderate stasis and some hyperechoic images without of a *cone*-shaped *shadow* in the basin, left kidney: 146 mm, the same structure, cortical 24 mm, without stasis, empty bladder, without ascites in Douglas bottom bag; spleen 118 mm.

From the first day of hospitalization tuberculostatic treatment was started, along with electrolyte and acid-base correction, glucocorticoids, gastric protectors.

In the fourth day of admission the patient presented a purpuric syndrome, well expressed on the torso and inferior limbs; the therapy was supplemented with hemostatic agents and plasma. Investigations revealed hepatocytolysis and azotemia at significant values (TGP 756 U/l, TGO 666 U/L, urea 210 mg%, creatinine 3.5 mg%) without

CSF	23.06.2009	24.06.2009	1.07.2009
Appearence	Slightly turbid	turbid	Slightly turbid
Pandy	++++	++++	+
Protein	3.08	4.8	1.42
Chlorine	6.77	6.8	7.1
Glucose	76	23	90
Cell count/mm^3	80	150	140
Cell differential	90% lymphocytes 10% PMN	90% lymphocytes 10% PMN	92% lymphocytes, 8% PMN
Microscopic examination	absent	absent	
Culture	sterile	sterile	
directly BK	negative	negative	
BK Culture	positive	positive	

Table I. Cyto-biological and bacteriological data of CSF

Biological examination data are presented in table II.

Bacteriological: urine: 25/06/2009: sterile.

Serology: HBsAg positive, anti HCV antibodies

cholestasis.

The altered general status was maintained, he became comatose, and jaundice of the sclera appeared; the medication needed to be administered

	24.06.2009	28.07.2009	2.07.2009	3.07.2009
White blood cells/mm^3	13530		7430	
Differential	N95%, L3%, M2%		N89% L5% M6%	
Hemoglobin g%	15.1		15.2	
Hematocrit %	45.3		47.5	
Platelets/mm^3	593000		293000	
ESR mm/h/2h	25/60		5/10	
Fibrinogen g%	7.57		3.9	
ALT U/l	13	756		1322
AST U/l	9	666		3120
BD/BT mg/dl	0.54/1	0.41/0.81		2.19/3.08
Glucose mg%	111	112		80
Blood urea mg%	83.9	210		193
Creatinine mg%	1.34	3.51		2.79
Serum uric acid mg%	8.19	19.23		17.63
Cholesterol mg%	219			
Triglycerides mg%	96			
GGT U/l	53			
Alkaline phosphatase U/l	211			
Quick time seconds	11.8		17.7	
INR	0.9		1.49	
Sodiu mmol/l	119	126		
Potassium mmol/l	5.3	4.1		
Chlorine mmol/l	78	82		
EB mmol/l	-8	-3		
Total protein g/l	8.63		7.62	
Urine exam	25.06.2009		1.07.2009	
pH	6		6.5	
Density	1020		1015	
Erythrocytes/ul	250		250	
Proteins g/l	1		1	
Microscopic examination	Microscopic hematuria		Microscopic hematuria	

Table II. Biological constants

by nasogastric tube.

Death, by cardio-respiratory arrest, occurred on the tenth day of hospitalization.

Anatomic-pathological examination showed:

- mostly white exudate in the basal and anterior brain – figure 1;
- pleural adhesions bilaterally, increased lung consistency, miliary conformation, spread bilaterally, 0.5 cm in diameter nodule in the upper lobe of the right lung – figure 2;
- soft-looking dystrophic liver, empty gallbladder;
- right kidney with ulcerative caseous tuberculosis conformation, with whitish creamy contents; the same look on the right ureter – figure 3;
- the prostate contains small nodules with yellowish white, sandy contents;
- increased adrenal volume, white-yellow appearance when cut;
- BK positive at direct exam (meninges, right kidney, prostate).

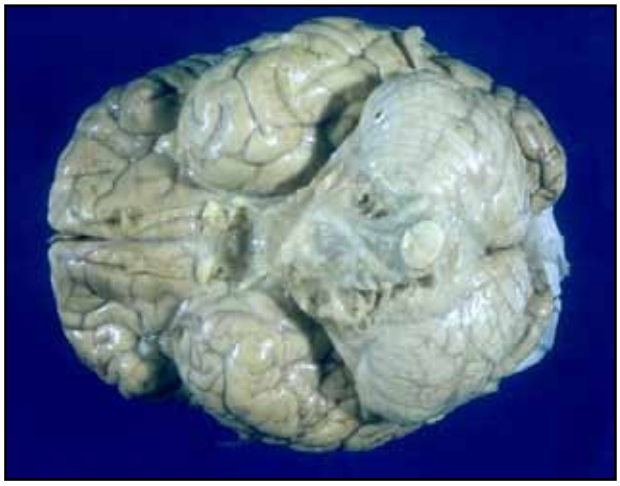

Figure 1. Meningo-encephalitis tuberculosis

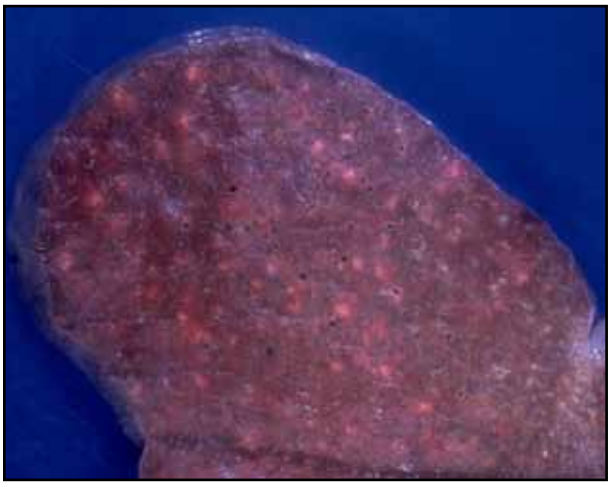

Figure 2. Lung tuberculosis

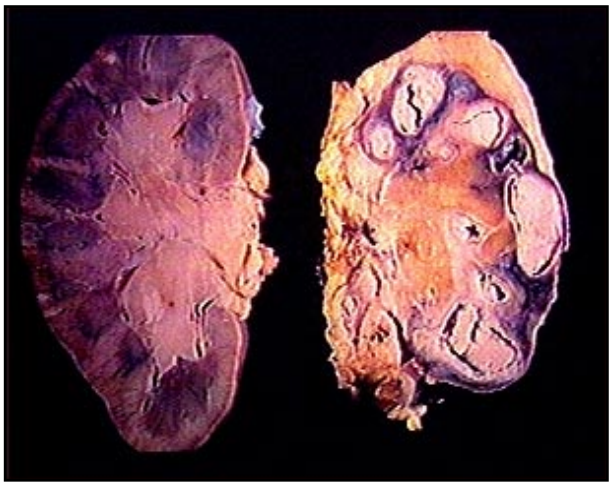

Figure 3. Renal tuberculosis

Discussions

The presented patient shows, on the one hand, the evolution of untreated tuberculosis, on the other hand, the difficulty of interpreting some biological data in the absence of some data about disease evolution, or its own features suggested by knowledge of past medical history and family history.

In our case, the only reliable information was that the patient belonged to a segment of socio-economical disadvantaged population.

Since the first contact with the patient, the diagnosis of meningoencephalitis of possible tuberculous etiology was suspected. The diagnosis was supported by CSF examination data (slightly opalescent appearance, moderate pleocytosis with predominance of lymphocytes), altered sensory and pulmonary changes evident on chest X-ray.

Altered sensory perception was an element in determining the appropriate therapeutic time, and it determined the use of tuberculostatics medication.

Brief exploration of biological and laboratory data were left without „covering" renal changes (moderate azotemia, significant proteinuria, right kidney volume increased, with irregular outline).

Also in relation to the subsequent development of the disease was the presence of HBsAg positive note, the concomitance of normal levels of alanine amino-transferase, the aspartate amino transferase and a normal prothrombin time.

The purpuric syndrome developed on the fourth day of tuberculostatic administration; hemostasis laboratory data did not reveal changes in the platelet component, global coagulation or fibrinolysis (number of platelets, BT, Howell T, fibrinogen, degradation products of fibrinogen).

Aggravation of azotemia, the appearance of hepatocytolysis and purpuric syndrome made us interpret them as manifestations of iatrogenic pathology, as an expression of interference between therapeutic and adverse effects of tuberculostatics medication [3].

The start of this iatrogenic process in the foreground is explained by the mechanism of cytotoxicity induced by unstable and toxic metabolites, formed during the process of tuberculostatics biotransformation. The excessively formed metabolites (especially in the context of a diminished inactivation capacity), once fixed – through covalent bonds – to the cell structures, can cause damage that goes from functional impairment to cell necrosis [4].

The toxic mechanism of the mentioned manifestation has a supporting element in the 4 days in-

terval between administration and onset of adverse reactions. Immuno-allergic mechanism triggering implies a period of 4-6 weeks of treatment and type I immune mechanism is installed in a short period (hours) from the administration of medication [5].

The presence of this latter model reaction (anaphylactoid type), which may be responsible for installing the clinical picture of acute kidney failure would require clinical laboratories equipped with kits to detect antibodies anti rifampicin in order to be confirmed. The azotemia and proteinuria reported at hospitalization were interpreted as part of the normal biological morphopathologic development of renal tuberculosis during the four steps of evolution:

- parenchymal phase (with cortical localization, involving the glomerulus);
- caliceal phase (caseous material migrates along the renal tubules ultimately leading to ulceration on papillae);
- the phase of mixed lesions, ulcerative, caseous and fibrous;
- the expansion phase in the urinary tract [6].

Locating the tuberculosis process at the adrenal glands' level, in the absence of the history and some hormonal determinations (cortisol, 17-SC, 17-OHCS), allows us only to make the following comments:

- adrenal tuberculosis and Addison's disease (chronic corticospinal adrenal insufficiency) – a direct correlation;
- Addison's disease incidence varies in direct relation to the magnitude of endemic tuberculosis [7].

Reported hyponatremia at admission may be associated with limiting reabsorption of sodium, potassium and hydrogen protons removal at the kidney level, respectively with the process of reduced synthesis of mineralocorticosteroids.

Conclusions

Tuberculosis continues to be „the most lethal disease caused by a single pathogen".

Incidence and prevalence of tuberculosis worldwide recorded a significant resurgence.

Endemic TB evolution overcomes the well organized and responsible involvement of the medical act. Control cannot be achieved without influencing the socio-economic factors, education, health and cultural factors. Faced with a clinical suggestive picture, specific therapy should be instituted early, even without the evidence of Koch bacillus presence.

Untreated tuberculosis leads to expansion of the lesions, to worsening of the general condition and even death.

Tuberculostatics, especially rifampicin, hydrazide, can cause organic damages through toxic or immuno-allergic type I immune mechanisms.

Routine determination of anti rifampicin antibodies may prevent the installation of severe side effects (renal failure) at the resumption of treatment with rifampicin.

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