Therapeutic trial with tuberculostatic drugs

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Abstract

The authors emphasize the need, often felt in the clinical practice for a therapeutic trial with tuberculostatic drugs in patients without positive results in the laboratorial tests for mycobacteria. Fever of unknown origin and occurrence of a variety of respiratory complaints are, alone or simultaneously, frequent reasons for starting this therapy. The authors present several clinical cases found in the Pneumology ward and discuss the clinical and laboratory grounds for the therapeutic decision, stressing the possible contradiction between the first clinical suspicion and the final diagnosis.

Keywords: pulmonary tuberculosis, tuberculostatic drugs, therapeutic trial.

Introduction

Mycobacterium tuberculosis infects a third of the world population, being tuberculosis considered the most common infectious disease of mankind. [1] Recently, outbursts of multi-resistant tuberculosis produced a number of victims before laboratorial help regarding susceptibility to anti-bacillary drugs was available. [1]

This is just an extreme example, although a current one, of how inadmissible it is to wait for weeks or months for a sensitivity study to the available drugs, when it is necessary an opportune and efficient therapy.

Tuberculosis diagnosis is suggested by the clinic and image data, but the isolation of the mycobacterium tuberculosis is essential so the existence of tuberculosis can be definitely stated. All biological products can be investigated: sputum, bronchial secretions, bronchoalveolar wash fluid, pleural fluid, cerebral spinal fluid, urine, blood, gastric fluid or products of tissue biopsies of any origin.

The bacilli isolation is achieved, most of the times in the cultural exam, enabling the sensitivity study to anti-bacillary tests to be carried out and starting the most appropriate therapy. The importance of such isolation is as high as higher it is the incidence of non-tuberculosis mycobacteriosis, mainly in immune compromised patients or with AIDS. [2]

Unfortunately, Mycobacterium tuberculosis is a bacillus with a slow replication, growing in colonies in cultural means at present usually takes 2 to 6 weeks, and this can enable colonies to emerge until the 10th week, time in which the absence of growth enables to state the definite negativity of a culture. [2]

New cultural methods have been used in the last few years, searching to reduce the time needed to isolate the Mycobacterium tuberculosis, and consequently the sensitivity study to anti-bacillary drugs. The method as radiometry, using the BACTEC 460 TB system, in which the growth of mycobacteria is quantified by dosing Carbon 14 contained in the CO2 released by the metabolization of the marked palmitic acid, contained in that environment, enables to reduce the time needed to identify mycobacteria for three weeks with an additional 5 to 7 days for sensitivity tests. [2]

The use of DNA probes enables high sensitivity (100%) and specificity (99.1%) in the isolation of Mycobacterium tuberculosis, but demands a previous growth in culture for 2 to 3 weeks. [2]

Other identification means, as the mycobacterial DNA amplification through the polymerase chain reaction, using directly samples of biologic products, enable to shorten the waiting time for just two days but they are still too sophisticated and expensive to be used in the clinical practice, besides they are not very specific, being frequent false positive results. [2]

All this is a consequence of an obvious and frequent inadequacy between the diagnosis means available and the need for a therapeutic guidance which must be appropriate and opportune. Often the clinical situation is so serious that does not allow delays and the suspicion of bacillary aetiology, although

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without a previous guidance of positive direct exam, when all diagnosis means are exhausted, justifies the implementation of trial antituberculosis treatment. [3,4]

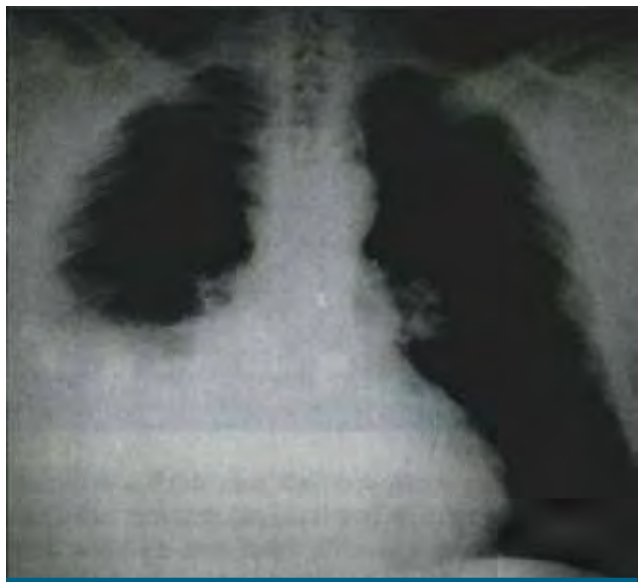
The positivity of the therapeutic trial is based on the clinical and radiologic improvements, being considered as one of two most important criteria fever remission, if it was present. [5] Fever persistence should lead to consider other diagnoses. [5] Anyway, the trial therapy does not prevent the searching of certain diagnoses, not being rare a posterior pneumonia diagnosis of other aetiology, suppuration or neoplasm, whether or not pulmonary. [4,6]

The trial anti-bacillary therapy is used with some frequency in cases of presumed pleuro-pulmonary tuberculosis; however it is the rule and not the exception in the tuberculosis meningitis, due to the emergency of the treatment,[2] in the eruptive forms of cutaneous tuberculosis, due to constant negativity of the bacteriologic study.[8] It should also be remembered the undetermined febrile syndrome, a non rare tuberculosis presentation form, mainly when in extrapulmonary locations justifying with some frequency the onset of anti-bacillary therapy, which in this situation and per definition is always a trial one. [2,9,10]

Material and methods

Five clinical cases of patients admitted in the Pneumology Service of the HUC, to whom was administered a trial anti-bacillary therapy. After a limited anamnesis to the fundamental data, the relevant findings of the objective exam, significant results of the supplementary diagnosing exams, the therapy implemented, the evolution during the admission, the result of cultural exams carried out, with the date of its reception and relevant data obtained from studies performed after discharge, whenever available.

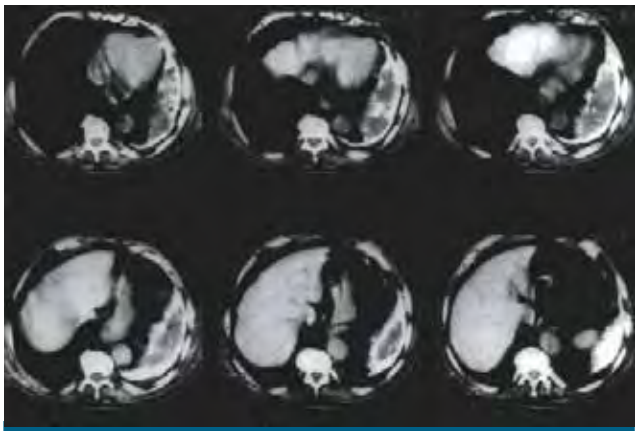
Case 1: JNC, male, 46 years of age, brick worker. Admitted on the 8th July 94, due to pleural effusion on the right. It started insidiously, three weeks before admission, with a sharp thorax pain on the right hemithorax, without any change in the general condition of other following symptoms namely respiratory ones. Background: insulin dependent diabetic, with "bronchopneumonia" for 25 years (sic). Irrelevant family background. Objective exam: apyretic, eupnoeic , good general condition. Semiology of pleural effusion on the lower half of the right hemithorax. Auxiliary diagnosis tests: normal hemogram and blood biochemistry. ESR on the first hour 70 mm,



Clinical Case 1.

FIG. 1

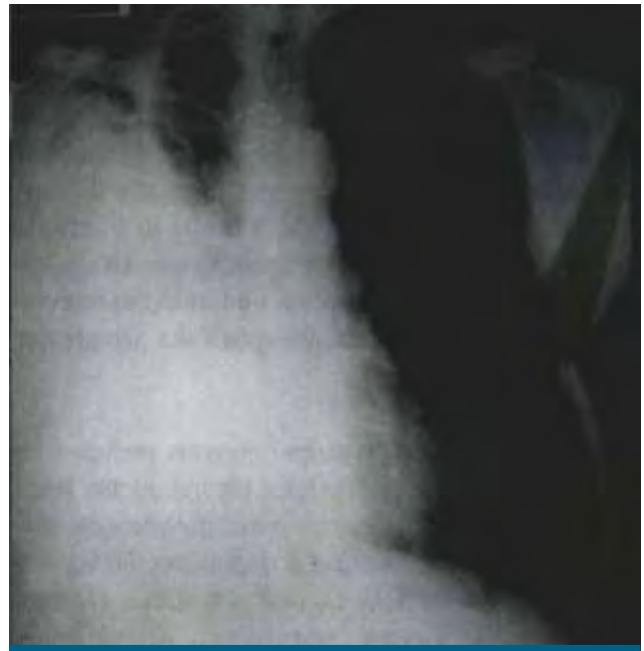
CPR 2.8 mg/dL. PA thorax X-ray with towel opacity on the lower half of the right pulmonary field, with a concave upper limit, compatible with pleural effusion. Diagnostic thoracocentesis: citric-yellow fluid, with exudates biochemistry features and high ADA (6 8 U/L), reaction mesothelial cells without bacilli acid--alcohol resistance (BAAR) to direct exam. Pleural biopsy with pathological anatomy study revealing "unspecific inflammatory infiltrate" and negative BAAR research at direct exam. Intradermal reaction (IDR) to tuberculin (3 U PPD) positive (27 mm, with blister). Optic bronchofibroscopy without any morphologic changes on the bronchial tree; cytology of the brushing and bronchial aspirate revealing only some reactive and inflammatory cells and negative BAAR search in the aspirate direct exam. Therapy: effusion drainage through a catheter; respiratory kinesitherapy. Introduction on the 20 July 94, of trial anti-bacillary therapy with isoniazid 300 mg + rifampicin, 600 mg + pyrazinamide 1500 mg. Favorable progression after starting the anti-bacillary drugs, not redoing the effusion reducing the ESR (9 mm in the first hour on the 10th August 1994); he always kept apyrexia. The discharge was on the 11th August 94, referred to the STDR of Coimbra. Received on the 18th September 94 a positive result of the pleural macerate culture for *Mycobacterium tuberculosis*.



Clinical Case 2.

FIG. 2

Case 2: J.C, male, 79 years of age, retired. Admitted on the 1st August 94 for clarification of the radiology image of condensation on the basis of the left pulmonary field. It had started insidiously at the beginning of 1993 with slight dyspnoea and easy tiredness for medium efforts. Four months before admission, the radiology image of "left pneumonia" (sic), without improvement with antibiotic therapy. A background of transurethral prostatic resection in 1992 and pleurisy on the left around 60 years ago. Irrelevant family background. Objective exam: 36.8°C of axillary temperature, eupnoeic, good general condition. Hypomobility of the left hemithorax on inspection and palpation, with dullness to percussion on the half lower left of such hemithorax, where it can be heard a marked reduction of the vesicular murmur. Rhythmic cardiac auscultation, with apex systolic blow II – III/VI. Diagnostic auxiliary tests: normal hemogram and blood chemistry. ESR on the first hour of 12 mm. Normal prostatic phosphatase (2 U/L). PA Thorax X-Ray with towel opacity on the basis of the left pulmonary field, with a concave upper limit, and some images of calcium density on the periphery and some micro nodes on the reminder of the left pulmonary field. White thoracocentesis. Normal echocardiography. Abdominal ultrasound revealing only an increased prostate volume. Sputum bacilli smear with negative BAAR research at direct exam. IDR to tuberculin (3 U PPD) positive (32 x 20 mm, with vesicles). Optic bronchofibroscopy without morphological changes on the bronchial tree, cytology of the brushing and



Clinical Case 3.

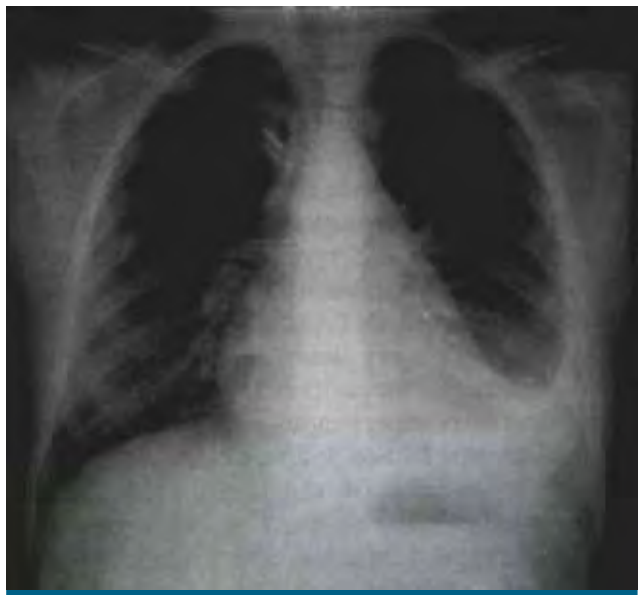
FIG. 3

bronchial aspirates revealing only reactive and inflammatory cells; aspirate negative for BAAR research at direct exam. Requested dosage of IgA anti-KP 90. Respiratory functional study: mixed syndrome with predominant restriction. Thorax CT scan revealing a bulky lesion of productive pleurisy calcified on the left: conditioning a mediastinal deviation towards that side retracting the homolateral hemithorax; several subpleural nodes badly defined on the left with diffuse micro nodulation of the reminder of the lung; the changes mentioned suggest lesions of specific nature as first hypothesis".

Therapy: bronchodilators and respiratory kinesitherapy; introduction of trial anti-bacillary therapy on the 18th August 84, with isoniazid 300 mg + rifampicin 600 mg + pyrazinamide 1500 mg. Evolution: improvement of dyspnoea and tiredness, without a significant change of the laboratory of values, keeping apyrexia. Discharged and referred to Leiria STDR on the 24th August 94. Received on 8th September 94 the positive results of the culture for the tracheobronchial aspirate for *M. tuberculosis*: on the same date, it was received a negative result for IgA anti-KP 90 research in the serum.

Case 3: A.S.O, male, 55 years of age, farmer. Ad-

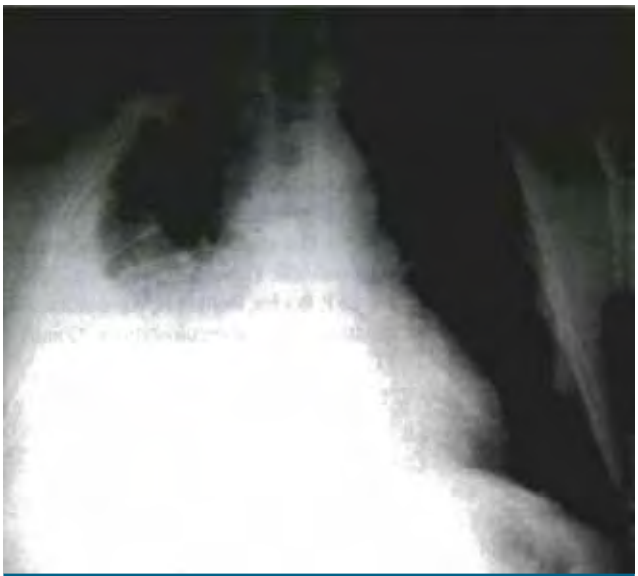
mitted on the 20th January 91, due to cough with bloody sputum and right pleural effusion. It started insidiously, two months before being admitted, with complaints of asthenia, anorexia and moderate weight loss, non-quantified, followed later by chills, abundant night sweating and coughing with bloody sputum. Background of pleurisy six years ago with hospitalization; moderate alcoholic habits. Father deceased by pulmonary tuberculosis. Objective exam: bad general and nutritional condition, high fever (39ºC), polypnoea (30 cycles/minute), quick pulse (120 bpm). Semiology of pleural effusion on the lower two thirds of the right hemithorax. Diagnostic auxiliary tests: anemia (Hb: 10.3 g/dL), leucocytosis (22,800/mm3), high ESR (127 mm in the first hour), hypoalbuminaemia (1.8 mg/dL). PA Thorax X-Ray with towel opacity on the lower two thirds of the right pulmonary field. Diagnostic thoracocentesis with fluid exiting with purulent aspect, biochemistry of exudate compatible with observed characteristics (glucose 1, LDH 11,560), high ADA (77.5 U/L) and cytology with many PMN and pyocytes; negative BAAR research on direct exam. Tuberculin IDR (3 U PPD) positive (20 x 16 mm). Optic bronchofibroscopy without morphological changes of the bronchial tree; brushing cytology and aspirate with reactive cells and many PMN; BAAR research of BAAR through direct exam of the aspirate was negative. Therapy: thoracic drainage by catheter and pleural washes; respiratory kinesitherapy; combined antibiotic therapy (ampicillin plus tobramycin); introduction of trial anti-bacillary therapy on the 1st February 1991, with isoniazid 300 mg + rifampicin 600 mg + pyrazinamide 1200 mg + streptomycin 1 g. Evolution: without apparent response to the initial antibiotic therapy: clinical (with apyrexia and favorable progression of the general condition) and laboratorial (ESR of 62 mm on the first hour, leucocytes 8200/mm3 and albumin 3.8 mg/dL, on the 11th March), after anti-bacillary therapy. Broncho-pleural fistulae on the 14th March 91, solved with drainage under vacuum. Marked subsequent radiologic improvements, with a slight sequelae pleuritis and laboratorial (ESR 33 mm, leucocytes 7200/mm3, albumin 4.1 mg/dL on the 9th April). Discharged and referred to Lamego STDR on the 9th April 91. On the 30th April 91 positive results of the bronchial aspirate culture for M. tuberculosis were received.



Clinical Case 4.

FIG. 4

Case 4: AMD, female, 12 years old, student. Admitted on the 19th September 90, due to left pleural effusion. Insidious start, two months before admission, with asthenia, anorexia, hands arthralgia, dry cough and left thoracalgia not responding to antibiotic therapy with amoxicillin + clavulamic acid. Without relevant personal and family background. Objective exam: apyretic, eupnoeic, good general condition. Semiology of pleural effusion on the basis of the left hemithorax. Diagnostic auxiliary exams: normal haemogram and blood biochemistry; high ESR (90 mm on the first hour). PA thorax X-Ray: occlusion of the left costo-phrenic sinus, rectification of the left edge of the cardiac shadow. Diagnostic thoracocentesis, with the exit of citric-yellow fluid, with biochemistry characteristics of exudate and cytology with reaction or mesothelial cells; negative BAAR research in the direct exam, normal hands X-Ray. Normal echocardiogram. IDR to tuberculin (3 U PPD), positive (35mm). Optic bronchofibroscopy with diffuse inflammatory signs of the bronchial tree; cytology of the brushing and aspirate with reaction cells; BAAR research on the direct exam of the bronchial aspirate was negative. Therapy: respiratory kinesitherapy; introduction of trial anti-bacillary therapy on the 6th October 90, with isoniazid 300 mg + rifampicin 450 mg + pyrazinamide, 1500 mg + prednisolone 20



Clinical Case 5.

FIG. 5

mg (in regressive scheme). Progression: clinical improvement (disappearing thoracalgia and arthralgia improvement), radiology (effusion reabsorbed) and laboratorial (ESR improved : 62 mm on the 11th October). Discharged and referred to STDR of Alcobaça on the 15th October 90. On the 15th November 90 a negative result for BAAR research on the cultural exam of the tracheobronchial aspirates and effusion fluid. After a six-month period where there was again a worsening of the hands arthralgia, involving now also the knees with edema and functional impotence, she was admitted on April 1991, in the Pneumology Service, and the exams carried out presented the following significant results: ESR 105 mm on the first hour, positive ANA, haematuria and proteinuria; kidney biopsy revealing mesangial proliferative glomerular nephritis.

Transferred to the nephrology service on the 7th May 1991 she was diagnosed with lupus nephritis, having started immunosuppressant therapy.

Case 5: MC, male, 70 years old, retired. Admitted on the 5th May 94 due to the right pleural effusion. Sudden onset, 15 days before being admitted with chills, fever and a sharp right thoracalgia, followed by slight productive cough and progressive dyspnoea, without responding to the therapy with amoxicillin + clavulamic acid. Background of pulmonary silicosis, angina pectoris and high blood pressure: irrelevant family background. Objective exam: apyretic, tachypnoeic (25 cycles/minute), normal blood pressure with a good general condition. Semiology of pleural effusion on the lower half of the right hemithorax. Diagnostic auxiliary exams: normal haemogram and blood biochemistry; ESR 70 mm on the first hour, PA thorax X-Ray with towel opacity in the lower half of the right pulmonary field and a concave upper limit; parenchymal nodes of bilateral calcium density. Diagnostic thoracocentesis with citric-yellow fluid exiting, with biochemical features of exudate, increased ADA (52 U/L) and cytology revealing reaction mesothelial cells and cells predominantly lymphocytic; the BAAR research on the fluid direct exam was negative; pleural biopsy revealing only unspecific inflammatory infiltrate. BAAR research on the direct sputum exam was negative. Optic bronchofibroscopy with diffuse inflammatory signs of the bronchial tree; aspirate and brushing cytology revealing reaction all inflammatory cells; the BAAR research in the direct exam after bronchial aspirate was negative. IDR to tuberculin (3 U PPD), negative. Therapy: thorax drainage by catheter; respiratory kinesitherapy; introduction of trial anti-bacillary therapy on the 21st May 94 with isoniazid, 300 mg + rifampicin 600mg + pyrazinamide 2000 mg + streptomycin 750 mg + methylprednisolone, 40 mg (in regressive scheme). Progression: marked clinical improvement; effusion did not reoccur: kept high ESR; discharged on the 29th July 94 for the STDR of Coimbra. Received on the 29th July 94, the positive result for the culture of the bronchial aspirate for *M. Tuberculosis*.

Discussion and conclusions

All cases presented refer to patients with pleurisy and most of them the specific aetiology emerging as likely due to underlying pathologies or favoring habits (diabetes, silicosis, alcoholism), a background of likely tuberculosis, inclusion in higher risk age groups, or existence of classic and exuberant symptomatology.

The IDR existence to tuberculin strongly positive, in most cases, as well as the finding of high ESR and ADA values of pleural fluid above 50, reinforced the suspicion regarding the bacillary aetiology. However the persistent negative direct bacterial exams, the lengthy the cultural exams and, in one of the cases, the serious condition, imposed the decision of implementing a trial anti-bacillary therapy, with a good

apparent result. To be highlighted that in one of the cases, the ulterior study has revealed a basis pathology (disseminated lupus erythematosus), likely to explain the clinical condition leading to hospitalization, and this alone alerts for the need to continue this study after the beginning of trial therapy in an attempt of reaching a definite diagnosis which can be serious and surprising. [3,4,6,11]

The use of new laboratory methods, as well as the systems BACTEC and MB, the detection and dosage of antibodies as Anti-A 60 and IgA anti-KP 90, the use of DNA or polymerase chain reaction probes, can allow a quicker diagnosis, opening a diagnostic hope when the bacillus identification shows itself impossible. [3,4,] In this way, the therapeutic tests in the future may see their role reduced.

In countries with a higher rate of tuberculosis prevalence and incidence, as ours, the trial therapy therefore continues to be justified in a clinical approach. ■

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