LONG-TERM FOLLOW-UP OF PULMONARY DISEASE CAUSED BY MYCOBACTERIUM AVIUM IN A PREVIOUSLY HEALTHY PATIENT

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SUMMARY

A 64-year-old white male with cavitary lung disease is presented. *Mycobacterium avium* was isolated from sputa and gastric lavage and the American Thoracic Society criteria for nontuberculous mycobacterial disease were met. Seven years follow-up and treatment regimens are discussed.

This case illustrates that medical treatment of *M. avium* pulmonary disease can be disappointing and requires regular clinical, radiological, microbiological and haematological reassessment to evaluate efficacy and toxicity of therapy.

Despite in vitro resistance to the standard antimycobacterial agents, prolonged treatment regimens can be successful and are the therapy of choice. Another drug combination, based on in vitro susceptibility patterns, has to be started for patients who fail to respond or who relapse. Lifelong treatment may be necessary to keep the patient stable and to prevent further destruction of lung parenchyma.

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INTRODUCTION

Mycobacterium avium, a slow growing non-chromogenic mycobacterium, has a widespread distribution in natural waters and the soil (1). Transmission to human hosts usually occurs by inhalation of aerosolized mycobacteria or by ingestion (2-4). The risk of becoming infected depends on the intensity of contact with these environmental mycobacteria and the virulence of the different strains. *M. avium* can remain a simple coloniser of the sputum or can cause a benign infection without clinical evidence of disease. Progression of infection to disease also depends on the host's immune status. Typical predisposing conditions are: acquired immune deficiency syndrome (AIDS), diabetes, alcoholism, underlying lung disease, gastrectomy, cystic fibrosis. Recently an increasing number of patients seem to have no evident predisposing conditions or an increased vulnerability due to still unknown factors (4-5).

Medical history, physical examination, chest roentgenogram and skin testing usually do not allow to distinguish *M. tuberculosis* from atypical mycobacteria. A systematic and careful evaluation and isolation by culture remain essential for diagnosis (2).

We present a non-immunocompromised patient with pulmonary *M. avium* disease. Treatment modalities and difficulties are discussed.

CASE REPORT (Table 1)

A 64-year-old white male consulted at the outpatient clinic in June 1985. There were no important medical or surgical events in the past. Since the age of 16 the patient smoked ten cigarettes per day. There was only occasional alcohol

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TABLE 1: CLINICAL EVOLUTION OF THE PATIENT WITH *M. AVIUM* INFECTION

	HISTORY	CHEST X-RAY	DIRECT EXAMINATION	CULTURE	ANTIBIOGRAM	THERAPY
1985	Cough, sputa, night sweats weight loss	Thick-walled cavity LUL suprahilar infiltration	3 sputums: AFB (+)	M. avium	/	INH → 6/86 RMP → 1/86 EMB → 9/85
1986	Clinically stable morning cough	Reduction of the cavities				
...er 1986	Cough↑, sputa↑ fever, night sweats Anorexia	New cavities RUL progression old lesions	3 sputums AFB (+) 1 bronchial lavage AFB (+)	M. avium	/	INH RMP EMB
...r 1986	↑ Dyspnoea	Pneumothorax				
...y 1987	No complaints Stable	Stable		M. avium	R : INH RMP EMB ETH	INH RMP EMB
1987	Stable	Stable		M. avium	S : RBT ERYTHRO KANA	RBT ERYTHRO → 7/87 KANA (2 weeks)
1987	Stable	Stable				INH → 7/89 RBT → 7/89
...ber 1989	Stable	Bilateral nodular fibrotic lesions and pleural thickening		no growth	/	/
...er 1989	Stable	Stable		M. avium	/	/
1990	Cough	Stable		M. avium	S : RBT EMB	RBT EMB → 10/90
1991	Dyspnoea gr II	Stable		M. avium	S : RBT CIPRO	RBT CIPRO
...ber 1991	Stable dyspnoea	New cavities LUL		M. avium	S : RBT CIPRO	RBT CIPRO
June 1992	Stable	Stable		negative, no growth		
...ber 1992	Cough dyspnoea gr III	Stable		M. avium		

: acid fastbacilli

: resistance

: sensitivity

abuse. He was a retired professional soldier. Two months before referral there was a history of progressive worsening cough with expectoration of yellow sputa. There was no haemoptysis. The patient lost 5 kilograms of body weight despite good appetite, and complained of severe night sweats. There were two recent episodes of diarrhoea. He did not complain of dyspnoea or thoracic pain. His outpatient treatment consisted of doxycycline for ten days.

Physical examination revealed a lean man, otherwise looking well. There was no fever, the pulse rate was 72 and the blood pressure 130/70. Examination of head and neck, extremities, pulsations, heart and abdomen were normal. Lung auscultation showed bilateral wheezing and coarse rales, more pronounced on the right side. Enlarged lymph nodes could not be detected. Haematological and biochemical investigation revealed an inflammatory pattern with an eleva-

ted ESR of 52 mm after one hour and 74 mm after the second hour. Blood count was normal. Liver and renal function were normal. Iron was low (37 µg/dl) with a normal iron binding capacity. Total protein was 7.35 g/dl, electrophoresis showed an elevated α1 and α2 globulin fraction.

A chest roentgenogram revealed emphysematous lung fields with relatively thick-walled cavitary structures in the left upper lung zones (LUL) and patchy suprahilar infiltration. The right lung showed some condensations in the axillary regions.

On three consecutive days, sputum and gastric tubage samples were analysed. All three sputa were found positive for acid fast bacilli (AFB). Due to this positive direct examination the patient was assumed to have tuberculosis and therefore treatment with isoniazid (INH) 300 mg daily, rifampicin (RMP) 600 mg daily, ethambutol (EMB) 1200 mg daily and pyridoxine 250 mg twice a week was initiated. An antibiogram was not performed.

Two months later, the isolates were identified as *M. avium*. Skin testing with seven different sensitins (Tween 80 - Statens Seruminstitute Copenhagen) revealed a maximal response for *M. avium* (weak induration of 35/25 mm following 48 hours after intradermal injection of 0.1 µg sensitin). Ophthalmoscopy revealed no abnormalities. Spirometry showed a mild obstructive ventilatory pattern, not reversible after administration of bronchodilators.

Three months later, EMB was discontinued and in January 1986 the patient stopped RMP because of gastrointestinal intolerance. Until June 86 he continued INH and pyridoxine. After one year of conventional treatment, the patient's clinical status was satisfactory. A morning cough persisted. Radiologically there was a slight reduction of the cavitary lesions in the left apex. ESR was 22 mm/ 66 mm.

In November 86, the patient started again to complain of productive cough, dyspnoea, anorexia, night sweats and fever. Chest X-ray revealed progression of the cavitary lesions with newly formed cavities in the right apex (RUL) and air-fluid levels. Three sputum samples and one bronchial lavage were AFB positive on direct examination. Conventional triple therapy was restarted. The next month patient developed a tension pneumothorax and was successfully treated with continuous suction.

In February 87 *M. avium* susceptibility testing revealed resistance for INH, RMP, EMB and ethionamide (ETH). Therapy was continued until May 87 because the patient remained clinically stable. Afterwards, new bronchial samples were taken, cultured and tested for other non-conventional drugs. Then, following the antibiogram, a therapy with rifabutin (RBT) 450 mg daily, erythromycin 3x500 mg daily and kanamycin 1g daily was started. The patient refused to continue the IM injections with kanamycin after two weeks. Erythromycin was stopped after three months. Thereafter, INH was given in combination with RBT until June 89 (24 months).

Three months after discontinuing the RBT INH therapy, sputum cultures were negative. Laboratory results normalised and chest X-ray showed multiple bilateral nodular, fibrotic lesions and pleural thickening.

Six months after therapy was stopped, sputum cultures became positive again for *M. avium* (December 1989). Clinically, biochemically and radiologically the patient remained stable.

In June 1990, after a medication free interval of one year, the patient started coughing again and RBT plus EMB were started (following the previous antibiogram). EMB was stopped in October 90 and the patient continued to take RBT. In March 91 ciprofloxacin 250 mg twice daily was added (a higher dose was not tolerated). In September, sputum culture was again positive for *M. avium*. After September 91 and until June 92 sputum cultures remained negative. Except for a mild exertional dyspnoea, the

were no complaints. Chest X-ray however showed progression of the cavitary lesions in the left apex (Fig. 1).

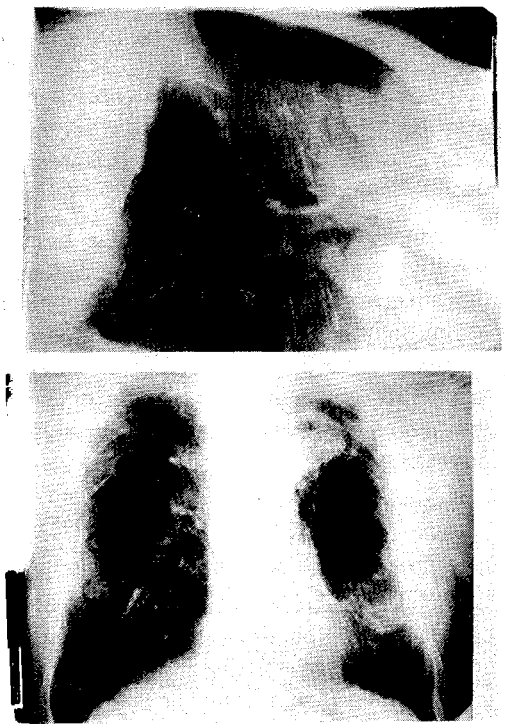

Fig. 1: Chest x-rays of September 1991.

In September 1992, *M. avium* was again isolated from a sputum sample. Chest X-ray remained stable but the patient started to complain again of worsening cough and dyspnoea.

During his follow-up, the patient was screened for anti-HIV twice, and found negative.

MICROBIOLOGICAL ASPECTS: ISOLATION, IDENTIFICATION AND SUSCEPTIBILITY TESTING

The mycobacterial isolates were identified as described by Jenkins et al (6). All the isolates were identified as *M. avium*. The identity of the strains was also confirmed using a commercially available DNA probe (Gen Probe, San Diego, California) which allows differentiation between *M. avium* and *M. intracellulare*. Antimicrobial sensitivity tests were performed by the method of Canetti et al (7).

DISCUSSION

Our case deals with a patient with cavitary infiltrates on chest radiograph, nine positive sputum cultures for *M. avium* (from 1985 until 1992) and no other plausible cause for the disease process. Restriction Fragment Length Polymorphism (RFLP) analysis (data not presented) suggests that the patient remained infected by the same RFLP type. According to the recommended diagnostic criteria of the American Thoracic Society (ATS) (1990), this means that *M. avium* disease is definite (2). For patients with cavitary lung disease the presence of two or more sputum specimens (or sputum and a bronchial washing) that are acid-fast bacilli smear-positive and/or result in moderate to heavy growth of *M. avium* on culture means that *M. avium* infection is established provided that other reasonable causes for the disease process (fungal disease, malignancy, tuberculosis ...) have been excluded.

For patients presenting with non-cavitary lung disease, failure of sputum cultures to clear with bronchial toilet or within two weeks of institution of specific mycobacterial drug therapy is an additional diagnostic criterion.

In the presence of non diagnostic sputum evaluation, diagnosis can only be established by transbronchial or open-lung biopsy yielding the organism and showing mycobacterial histopathologic features. Transbronchial or open lung biopsy that shows mycobacterial histopathologic features but fails to yield the organism requires two or more positive cultures of sputum. A recently published study of Tsukamura (8) confirms the necessity for correct diagnosis of

two or more isolations of the same species in the presence of a new cavitary lesion.

Initially, antibiograms were not performed and blind treatment was started. Two years later, susceptibility testing showed resistance to INH, EMB and RMP. Despite these data conventional triple therapy kept our patient clinically and radiologically stable for almost two years, but sputum cultures remained positive and the inflammatory blood pattern persisted. Only two years of continuous treatment with RBT converted the sputum cultures to negative, normalised blood chemistry and resulted in healed radiologic lesions. Six months later however there was a relapse and since then, the patient is treated following the antibiogram with combinations of RBT and EMB or RBT and ciprofloxacin.

In vitro resistance of *M. avium* to the standard antimycobacterial agents in the relatively low concentrations used for testing *M. tuberculosis* is well known (9). Paradoxically, therapeutic successes are regularly obtained with prolonged treatment regimens. This suggests that resistance criteria for *M. tuberculosis* can not be extrapolated to non-tuberculous mycobacteria. An alternative hypothesis is that some drug combinations show synergistic effects. Ozenne et al. (10) confirmed the results of Heifets (11) about synergistic effects of combinations of RMP-INH, RMP-EMB, EMB-SM, INH-EMB, ETH-INH. Banks and Jenkins (9) found the in vitro combination of EMB-RMP to be most effective. Tsukamura et al. (12) found triple therapy regimens with RMP-INH-enviomycin and RMP-INH-SM, to be superior to the regimen with RMP-INH-EMB. Therapeutic regimens combining more than three antibiotics never proved significantly higher efficacy than triple regimens (10).

Treatment with ETH and cycloserine, which often show good in vitro action, is poorly tolerated (13, 14)

Rifabutin (ansamycin LM427), a still experimental rifamycin derivative, given in a high dose of 450 mg daily, is well tolerated and might improve clinical outcome, when given in combination with other drugs to which the organisms are susceptible (15).

Some new macrolides e.g. roxithromycin and clarithromycin exhibit in vitro bacteriostatic activity against *M. avium* and have similar activities to RBT (16). Controlled clinical trials with new combinations including clarithromycin need to be done.

Changes in the treatment on the basis of sensitivity results should be avoided as long as the patient remains clinically stable. Susceptibility testing may be useful however for modifying treatment regimens in patients who fail to respond to initial chemotherapy or relapse, or in life threatening *M. avium* illness (e.g. disseminated disease in AIDS)(2,3).

Susceptibility of *M. avium* to antibiotics must always be interpreted with knowledge of intracellular and tissue levels and activity. Quinolones, macrolides and rifamycins become concentrated within tissues, so that they may be active in vivo even when the minimum inhibitory concentration (MIC) is higher than the serum drug levels. A second consideration that must be kept in mind is that the results of in vitro sensitivity testing are method-dependent. Isolates are more sensitive when tested in broth than when tested by dilution in agar. Third, drug concentrations required for bactericidal activity can be much higher than for bacteriostatic activity (5).

SAMENVATTING

Een 64 jarige man met cavitaire longletsels wordt voorgesteld. Uit sputa en maagtubages werd *Mycobacterium avium* geïsoleerd en de patiënt beantwoordde aan de diagnostische criteria voor atypische mycobacteriële pathologie van de «American Thoracic Society». Follow-up en behandeling gedurende 7 jaar worden besproken.

Deze casus illustreert dat de medicamenteuse

behandeling van longletsels door *M. avium* zeer onbevredigend blijft en regelmatige klinische, radiologische, bacteriologische en hematologische controles vergt om effect en toxiciteit te beoordelen, en bij te sturen.

Ondanks in vitro resistentie tegen de klassieke tuberculostatica, blijven zij de eerste keuzebehandeling voor langdurige therapieschema's. Andere combinatie therapieschema's, gebaseerd op gevoeligheidsbepalingen in vitro, worden gestart bij (therapie)resistente patiënten en bij recidief onder conventionele behandeling. Levenslange behandeling kan aangewezen zijn om een patiënt te stabiliseren en verdere weefseldestructie te voorkomen.

RESUME

Le cas d'un homme de 64 ans avec une maladie pulmonaire cavitaire est présenté. *Mycobacterium avium* fut isolé de crachats et de tubages gastriques. Le patient répond aux critères de l'American Thoracic Society pour la définition d'une maladie mycobactérienne non tuberculeuse. Sept années de traitement et de suivi sont discutés.

Ce cas illustre les problèmes du traitement médical de la maladie pulmonaire causée par *M.avium.* Un suivi intensif au niveau clinique, radiologique, microbiologique et hématologique est indispensable pour évaluer l'efficacité et la toxicité de la thérapie.

Même si la résistance in vitro aux antibiotiques habituels est démontrée, un traitement classique de longue durée peut être efficace et devrait rester le premier choix. Seul chez les patients dont l'état ne se stabilise pas, ou chez ceux qui font une rechute, la thérapie devrait se baser sur les résultats de l'antibiogramme. Le traitement antibiotique devrait dans certains cas être poursuivi à vie afin de maintenir la stabilité clinique du patient et d'éviter la destruction du parenchyme pulmonaire.

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